Chapter 3
Muscle Mass, Quality, and Composition Changes During Atrophy and Sarcopenia

Yosuke Yamada

Abstract Skeletal muscle mass (SMM) and muscle strengh reach their peak in 20s to 40s of age in human life and then decrease with advancing age. The decrease rate of muscle strength or power was twice to four times as large as that of the SMM. Thus, the normalized muscle force (muscle strength divided by SMM) also decreases in aging. It depends on the number of factors in skeletal muscle tissues and neuromuscular system. In human study, SMM cannot be measured directly without dissection so that all of the methodologies are indirect methods to assess SMM, even computing tomography or magnetic resonance imaging. Dual-energy X-ray absorptiometry, ultrasonography, anthropometry, and bioelectrical imped-ance analysis (BIA) are used as secondary indirect methods to estimate SMM. Recent researches show muscle composition changes in aging, and in particular, the ratio of muscle cell mass (MCM) against SMM decrease and relative expansion of extracel-lular water (ECW) and extracellular space is observed with advancing age and/or decrease of physical function. The intracellular water (ICW) and ECW estimated by segmental bioelectrical impedance spectroscopy or multifrequency BIA are good biomarkers of the ratio of MCM against SMM in limbs. The BIS and other state-of-the-art technology for assessment of muscle mass, quality, and composition are use-ful to fully understand the muscle atrophy in a living organism.

Keywords CT · MRI · DXA · BIS · BIA · Frailty · Cachexia · Muscle cell mass · Lateral force transmission

Y. Yamada (✉)
National Institute of Health and Nutrition, National Institutes of Biomedical Innovation, Health and Nutrition Tokyo, Tokyo, Japan
e-mail: yamaday@nibiohn.go.jp

3.1 Introduction

Muscle strength generally reaches its peak in 20s to 40s of age in human life and then decreases with age. Skeletal muscle mass (SMM) also decreases with age (Figs. 3.1 and 3.2). The study of Allen et al. (1960) was probably the first scientific report about SMM decrease with age [1]. Allen et al. reported that muscle mass is decreasing with age by calculating total body potassium (TBK) via whole body counter, using the fact that a small amount of radioisotope ^{40}K exists naturally. In this method, based on the hypothesis that the potassium volume (concentration) in body cell mass (BCM) is constant, the BCM was estimated from the TBK, and then the BCM was used as an index for skeletal muscle mass [2, 3].

Since then, various methods such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI) have been invented (Figs. 3.1 and 3.2). Using these methods, the SMM change with age in the human body has been examined in many researches. In the systemic review for the SMM change with age by various measurement methods [4], the SMM decreased only 0.37% per year in female and 0.47% per year in male when compared with the young adult (18 to 45 years old) to the elderly (65 years old or over). The decrease rate of muscle mass per 10 years drops more steeply after a certain age (i.e., 50 to 65 years old) than younger age; the longitudinal study that assessed in older adults (65 years old or over) over 5 to 12.2 years showed that the decrease rate was approximately 0.51% [4]. The decrease rate is much lower than muscle strength.

The longitudinal study with the elderly showed the muscle strength decreased 2.5 to 3% in female and 3 to 4% in male in a year. In the cohort that muscle mass and muscle strength were measured at the same time (e.g., Baltimore Longitudinal Study and Health ABC study), the decrease rate of muscle strength was twice to four times as large as that of the SMM [5, 6] (Fig. 3.3). Furthermore, it is clear that low muscle strength rather than low SMM is a risk factor for mobility disability and mortality [7–9]. In consideration of the above, the meaning of muscle mass or strength measurement has become a controversial topic; it has been discussed that "dynapenia," which focuses on age-related loss of muscle function, is probably more useful than "sarcopenia" which is mainly considered on age-related loss of SMM [10, 11].

The term "sarcopenia" was originally created by Rosenberg at a meeting summary (1989) [12] of "Epidemiologic and methodologic problems in determining nutritional status of older persons (Albuquerque, New Mexico, USA, October 19–21)" in 1988. In its proceedings, Rosenberg mentioned that "the prevention and/or attenuation of decreasing lean mass with age" is one of the most important public health issues for exercise and nutrition for older adults and coined sarcopenia from Greek words σάρξ sarx, "flesh," and πενία penia, "poverty." Rosenberg summarized the meeting to introduce what the meeting was like and what the sentence meant [12].

One out of 25 persons was the elderly population (65 years old or over) in 1900, 1 out of 9 in 1989, and then 1 out of 5 in the twenty-first century. Drs. Samet, Rhyne,
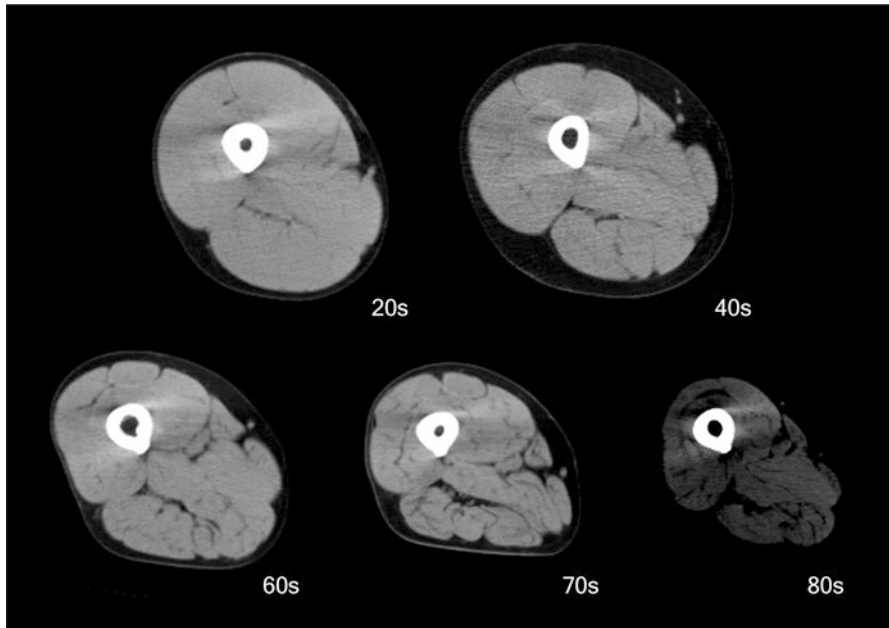
Fig. 3.1 Typical example of mid-thigh cross-sectional area (CSA) obtained by X-ray computed tomography (CT) in each age individual. Skeletal muscle CSA (gray area) is decreased with advancing age. In addition, the signal intensity of muscle area became low with advancing age. (The figure is reprinted from Yamada 2015 [2] with permission (see detail in Sect. 6 in this chapter))

Fig. 3.2 Relationship between age and whole-body skeletal muscle mass assessed by magnetic resonance imaging (MRI). (The figure was created based upon Table 1 of Janssen et al. 2000 [3] for the present article by Yamada)
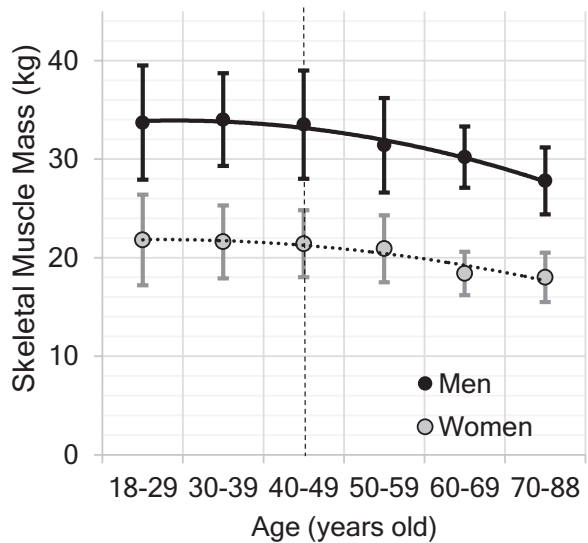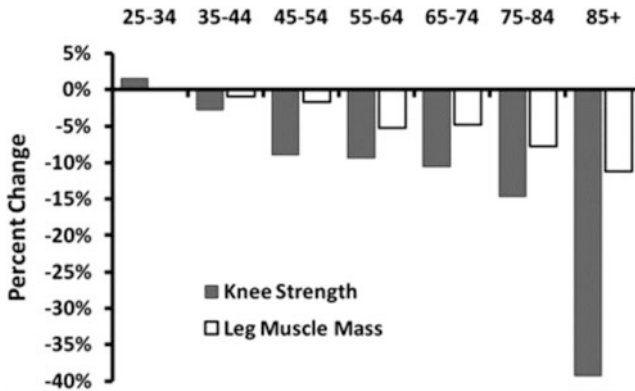
Fig. 3.3 Changes of knee extension strength (KES) and leg muscle mass (LMM) in Baltimore Longitudinal Study of Aging. KES was measured by isokinetic dynamometry, and LMM was assessed by dual-energy X-ray absorptiometry (DXA). The rate of decline for both parameters is steeper with older age (in particular, 45+ and 75+); the decrease rate of muscle strength was twice to four times as large as that of the muscle mass. (The figure is reprinted from Ferrucci et al. 2012 [5] with permission)

Harris, Hegsted, and Goodwin et al. [13–17] emphasized the diversity of elderly in the meeting; there is not only non-negligible differences between a 65-year-old and an 80-year-old person (chronological age) but also inter-individual variation of aging (biological age) which is different from chronological age. There are also difference in races, ethnicity, and sex. Furthermore, the activity level of elderly varies: some are independent and active, some cannot leave home, and others stay in the nursing home. Some uses multiple medications, which affects to the body and mental functions. We must conduct research for all those elderly since we cannot evaluate the populations of "normal aging" or "normal nutritional status" if we use the cohort of only elderly who visit a hospital, excluding active healthy elderly, or the cohort of elderly excluding persons who are charged in the nursing home or cannot leave home. Therefore, the method we should use is to evaluate various old population including a marathon runner and a person who needs nursing care, to clarify the effect of decreased function of each organ with age to food and nutritional conditions, and to have better understanding for the influence of food and nutrition to the maintenance or decreased function of each organ. From the NHANES, National Health and Nutrition Examination Survey, III (from 1988 to 1994), Harris and Kuczmarski et al. [15, 18] revealed these problems applying oversampling technique for 5000 elderly including 1300 who were older than 80.

Drs. Kuczmarski, Chumlea, Heymsfield, and Schoeller [18–21] lectured about body composition assessment method in the meeting, which is essential for nutritional status assessment. Each method has both advantages and disadvantages. Because of recent drastic progress of body composition assessment method, it is possible to evaluate various compositions instead of using a traditional two-composition model (fat and lean mass). Thus, using these methods, it is necessary

to have a wide variety of data including the abovementioned race and ethnic differences. Rosenberg asseverated that there is no important dramatic functional change with age other than lean mass change. Decreased lean body mass influences on various aspects such as mobility ability, physical functions, energy (calorie) intake and expenditure, nutrient consumption, nutritional condition, independence (nursing care requirement), cardiovascular function and/or respiratory function. To pay more attention to lean mass decrease, Rosenberg proposed the term sarcomalacia/sarcopenia and suggested that more research should be conducted for the relationship lean mass decrease and exercise. Muscle mass would be increased even in the elderly, and the elderly with frailty would drastically improve physical function.

In summary, Rosenberg [12] picked up Dr. Hegsted's topic related to recommended dietary allowance (RDA) [16]. What is the role of RDA for elderly with wide variety of characteristics? When it comes to the recommended food to maximize one's healthy living and to maintain activities in one's life cycle, it is necessary to understand the diversity and variability in young and old women and men.

Sarcopenia was originally the proposed term to proceed the research about loss of lean mass during age considering appropriate nutrition and exercise for each old person with understanding of variety of old people in the meeting summary comment. However, as it is mentioned above, from the results that many researches had proceeded focusing on muscle mass and strength since 1990, the risk for mortality and/or loss of physical function and independence cannot be fully explained by only muscle mass.

Therefore, the European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 [22], the International Working Group on Sarcopenia (IWGS) in 2011 [23], the Asian Working Group for Sarcopenia (AWGS) [24], and the Foundation for the National Institutes of Health (FNIH) Biomarkers Consortium Sarcopenia Project [25] in 2014 defined sarcopenia as low muscle strength and/or low physical function in addition to SMM.

In those consensus, muscle strength and physical function are important components of sarcopenia, but the assessment of muscle strength and/or physical function is not sufficient to apply a medical diagnosis under the precedent of the medical diagnosis of osteoporosis or metabolic syndrome. The SMM is still used as a primary marker, which is a more objective parameter than voluntary force production or conducting physical function test [26–31].

It is, however, not easy to assess human's SMM *in vivo* accurately, and its definition is needed to be reconsidered. Especially, I would like to explain the concept of in vivo SMM is different from that of "muscle cell mass" (MCM). The ratio of MCM against SMM (MCM/SMM) changes with advancing age.

All methods of assessing SMM are indirect methodology since human body composition cannot be measured directly except for cadaver. As they are indirect methods, there are always hypotheses. The results of any indirect methods have systematic and/or random bias from those of direct measurement [32]. Therefore, when body composition is mentioned, the term "estimate, assess, or calculate" is used; avoid using the term "measure" in this article.

3.2   Estimate of Skeletal Muscle Mass (SMM) in Human Body

It has been tried to estimate SMM as one of the body compositions along with the fat and bone mass [1, 33]. In relation with obesity, the amount of body fat or percent body fat against body mass has been focused along with visceral fat, ectopic fat, hyperglycemia, hypertension, and hyperlipidemia. Bone mass and bone mineral content has been given attention with bone density, bone metabolism markers, and spine morphology because of its relationship with osteoporosis and risk of fracture. The SMM has been given importance in complex metabolic disorder syndrome (cachexia) that is characterized by the loss of muscle mass observed with drastic weight decrease in patients with chronic disease and myopathy such as muscular dystrophy and amyotrophic lateral sclerosis (ALS); however, the establishment of its clinical meaning in non-disease adult is delayed in comparison with body fat amount (obesity) and bone mass (osteoporosis).

On the other hand, in sports science area or exercise physiology, skeletal muscle mass assessment has been conducted relatively early because skeletal muscle mass has strong correlation with muscle strength or power which is one of the essential sport performance factors [34]. After various imaging methods and other estimation methods are invented, the research using assessment of muscle mass or muscle mass distribution has been performed strenuously [3, 34–44]. Especially, CT and MRI are currently considered as standard methods to estimate whole-body skeletal muscle volume or mass (e.g., skeletal muscle tissue density, 1.041 g/cm^3 [45]) since they can estimate the total volume of whole-body skeletal muscle tissue by filming the whole body and extracting signal from skeletal muscle tissue. Dual-energy X-ray absorptiometry (DXA) is considered an alternative method to separate bone mass, adipose mass, and other soft lean tissues. It does not estimate whole-body SMM itself that is different from MRI and CT; however, appendicular lean soft tissue (ALST) estimated by DXA can be converted to SMM measured by MRI (at least in American) using the equation by Kim et al. [46].

3.3   The Difference of Age-Related Decreases Between Muscle Mass and Strength

In consideration with the above, muscle strength decreases 2.5 to 4% in a year, but SMM decreases only 0.5 to 1% [4]. To scrutinize Janssen et al. [3] research which measured skeletal muscle mass by MRI in 468 females and males with age from 18 to 88, the SMM difference of 20s to 70s in the upper body is approximately 8%. The SMM difference of 20s to 70s in the lower body is ~26% in male and ~23% in female; the decrease rate of lower body is about three times as high as that of the

Fig. 3.4 Relationship between age and skeletal muscle mass (SMM) in the lower body and upper body in 268 men (**a**) and 200 women (**b**) aged 1888 years old. The SMM was assessed by MRI, and its difference of 20s to 70s in the upper body is approximately 8%. The SMM difference of 20s to 70s in the lower body is ~26% in male and ~23% in female; the decrease rate of the low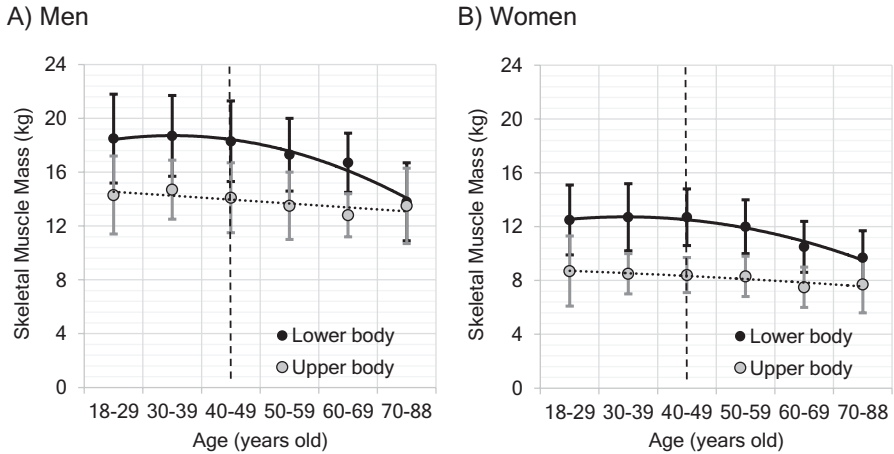er body is about three times as high as that of the upper body, but it is still only about 0.5% decrease in a year. (The figure was created based upon Table 1 of Janssen et al. 2000 [3])

upper body, but it is still only about 0.5% decrease in a year. It is worth noting that there is a significant difference in decrease rate between muscle groups even in the lower body muscles. Assessing for muscle thickness change of each body part with age, ultrasound imaging device has been especially used for many previous researches [34, 44, 47–53]. For example, when it is measured by ultrasound imaging, the decrease rate of the front thigh is greater than that of the back thigh [42, 43, 54, 55]; the decrease ratio of 20s to 70s in the front thigh muscle thickness is ~30%. These values are very similar to the direct measurement of cross-sectional area (CSA) of the vastus lateralis muscle in the cadavers by Lexell et al. [56]; the decrease ratio of 20s to 70s was ~26% (Fig. 3.4).

With all the above considered, the measurement sensitivity of muscle mass change is higher in using MRI or CT than in using traditional two-component method of lean mass estimation. Furthermore, the measurement of muscle groups, which atrophy rate is large, such as muscle mass in the lower body, is seemingly more useful than that of the whole-body muscle mass for the relationship with physical function. However, this explains only 20 to 50% of muscle force or its decrease rate, and the rest of 50 to 80% can be explained by, what we call, "factors other than SMM decrease" [4]. For these "factors other than SMM decrease," "neural factors" that include from central nerve to neuromuscular junction have been considered as major factors. Various researches have been proceeded, however, and other potential factors of neural factors are also discussed recently as described in the following sessions.

3.4   Concept About Skeletal Muscle Cell Mass (MCM)

In the abovementioned cadaver research by Lexell et al. [56], in addition to measurement of vastus lateralis CSA, myofiber number, myofiber size, and the ratio of fast muscle fiber to slow-twitch fiber were also measured under the microscope (Fig. 3.5a and b). Scrutinizing this research data brings about significant meanings. The CSA decrease rate of 20s to 70s was ~26%, but the myofiber number decrease ratio was up to 41%. The decrease rate of mean CSA of one myofiber was ~11% (Type I myofiber, ~0% decrease; Type II myofiber, ~25% decrease). Thus, from the values in literature, when I calculate "total myofiber CSA" using the equation of myofiber number multiplied by mean one myofiber CSA, the decrease rate of 20s to 70s is ~48% [57, 58]. This shows that the proportion of myofiber (cell) area to whole-muscle CSA is decreased with advancing age. SMM decrease rate with age is different from MCM decrease rate (Fig. 3.5c). As implied by Fig. 3.1a, this is because intercellular gap becomes large. Intercellular gap includes connective tissue, adipose outside of muscle cell, and extracellular water (ECW) (Fig. 3.5).

Normal imaging methods, like MRI, CT, or DXA, cannot evaluate this intercellular gap, and this results in overestimating muscle cell mass. Skeletal muscle is not a homogeneous tissue and composed of MCM, extracellular space (ECS), and adipose tissue mass (ATM) in its cell level (Fig. 3.2) [59]. Since the MCM gives tension, the assessment of MCM and/or the ratio of MCM/SMM is essential. It is well known that the proportion of ATM to SMM increases with advancing age; except for this, the MCM/SMM changes if ECS and MCM ratio changes. The ratio of solid to liquid in the MCM (intracellular water, ICW), the ratio of solid to liquid in the ECS (extracellular water, ECW), and the ratio of water in the ATM (adipose tissue water, ATW) are not always constant but can be considered to be relatively stable as 0.72, 0.97, and 0.14 in normal hydration status of homeostasis, respectively. Therefore, in this case, the ratio of intracellular water to total water (TW) in the skeletal muscle tissue (ICW/TW) can be considered an index for the MCM/SMM (Fig. 3.6).

3.5   Estimation Method of MCM/SMM

Segmental bioelectrical impedance spectroscopy (BIS) or multifrequency bioelectrical impedance analysis (MF-BIA) is useful to assess the ratio of ICW/TW that is related to the MCM/SMM. The detailed explanation for BIS and MF-BIA was described in our previous articles [60, 61] (Fig. 3.8), which is briefly summarized below. Muscle cell membrane is composed of phospholipid bilayer and works as a capacitor on the alternating current circuit. The alternating current with low frequency (e.g., 5 kHz) cannot pass through inside of cells and mainly pass through extracellular space. On the other hand, the alternating current with high frequency (e.g., 250 kHz or 500 kHz) can pass through inside of cells [62] (Fig. 3.4a). Since
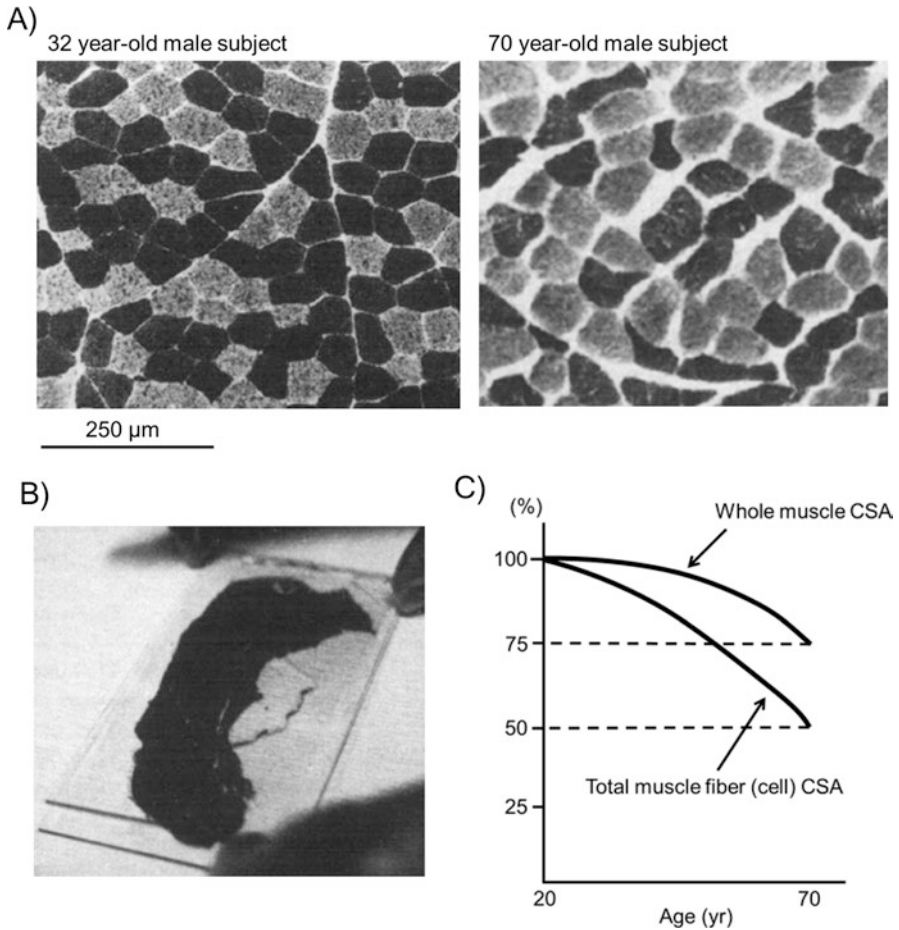
Fig. 3.5 (**a**) Micrographic picture of cross section of m. vastus lateralis from a young (left) and an old (right) individual. (Originally from Lexell et al. 1988. The scale of the picture from old individual was modified to match into the scale of the younger one by Yamada.) (**b**) The picture of prepared cross section of m. vastus lateralis for measurement of cross-sectional area (CSA). (**c**) The rate of loss of whole-muscle CSA and total muscle fiber (cell) CSA. Total muscle fiber CSA was calculated as muscle fiber number multiplied by mean fiber size by Yamada 2015. (Figures A and B are reprinted from Lexell et al. 1988 [56] and Fig. C is reprinted from Yamada 2015 [32] with permission)

the ICW/TW is relatively stable in normal young adults and there is strong correlation among TBW, ICW, and ECW [63, 64], single-frequency bioelectrical impedance analysis (SF-BIA) using 50 kHz is sufficient to evaluate skeletal muscle mass [65, 66]. For example, Miyatani et al. research [65] in young adults showed that, with impedance value at 50 kHz (Z_{50}), the impedance index (L^2/Z_{50}; L, segment length), which is an index related to muscle mass in the upper leg, lower leg, upper
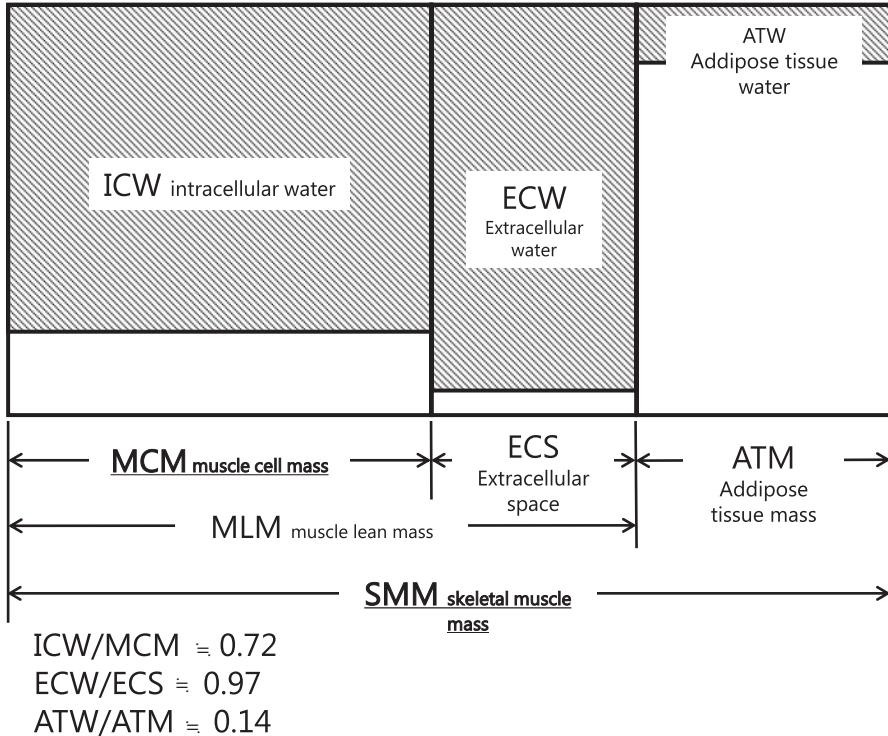
Fig. 3.6 Model of muscle composition (Mingrone et al. 2001). Skeletal muscle contains not only "contractile" tissue but also "non-contractile" tissue. Inter-muscular adipose tissue and intramuscular fat and extracellular water are "non-contractile" components in muscle tissue. (The figure is reprinted from Yamada 2015 [32] with permission)

arm, and forearm, was highly correlated to SMM obtained by MRI and maximal voluntary joint torques of corresponding muscle groups (Fig. 3.7).

On the other hand, in our research with 405 old female and male participants aged 65 to 90 years old [60], the impedance index of 50 kHz in the upper leg segments (L^2/Z_{50}) was just moderately correlated to maximal voluntary knee extension strength. This means the muscle mass must be evaluated in consideration with the ICW/TW change with age in the elderly [67]. Actually, the relative expansion of ECW and decrease of ICW/TW were observed in older adults compared with younger adults (Fig. 3.8). We, therefore, proposed to use the segmental MF-BIA for skeletal muscle mass evaluation and validated it against CT [68]. While the traditional method overestimates muscle mass in the people who have larger ECW/ICW ratio, the newly developed segmental MF-BIA can evaluate muscle mass properly in the elderly since the impedance value combination of 250 kHz and 5 kHz can discriminate ICW from ECW. In addition, this method shows more significant correlation in muscle strength in the elderly in comparison with the traditional method [60]. This index is also correlated to walking speed in the elderly [69] (Fig. 3.9).
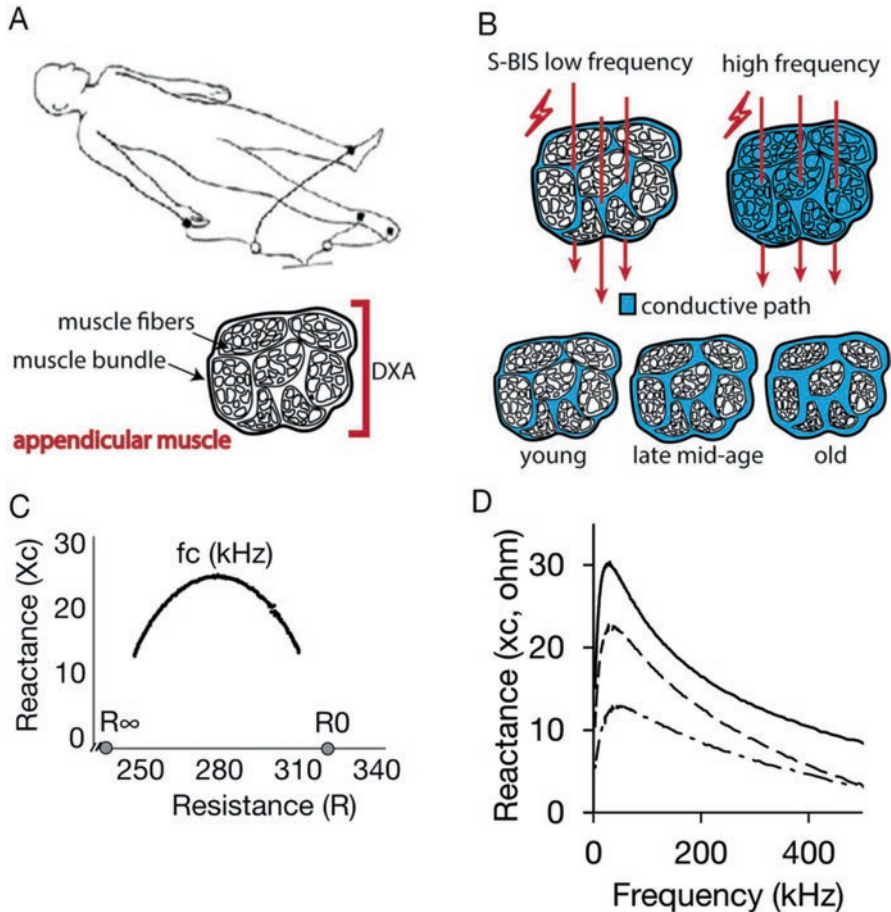
Fig. 3.7 (**a**) Upper panel: electrode placements of segmental bioelectrical impedance spectroscopy (S-BIS) measurement for a single leg. Lower panel: schematic representation showing muscle mass detection by dual-energy X-ray absorptiometry (DXA) and S-BIS. DXA measures appendicular lean mass and cannot inform about lean mass composition. (**b**) S-BIS takes advantage of the partitioning of contents in appendicular skeletal muscle between intracellular and extracellular pools. (**c**) Representative Cole-Cole plot of resistance versus reactance measures obtained by leg S-BIS from one individual from the study cohort. The intracellular resistance (R_I) was calculated using $1/[(1/R_\infty) - (1/R_0)]$. (**d**) Representative frequency versus reactance measures obtained by leg S-BIS from 29-, 56-, and 76-year-old female adults (solid line, dashed line, and chain line, respectively). Older adults tended to have lower reactance. (The figure is reprinted from Yamada et al. 2017 [61] with permission)

While this method used fixed frequencies of 250 kHz (or 500 kHz) and 5 kHz [63, 70], various frequency currents ranging from 1 to 1000 kHz (BIS; Fig. 3.4b) were used in the other method [71, 72]. Resistance values (R_0 and R_∞) at 0 kHz (direct current) and infinite frequency (∞ kHz) obtaining from Cole-Cole plot of resistance (R) vs. reactance (Xc) resulting in a semicircular arc, BIS characterizes
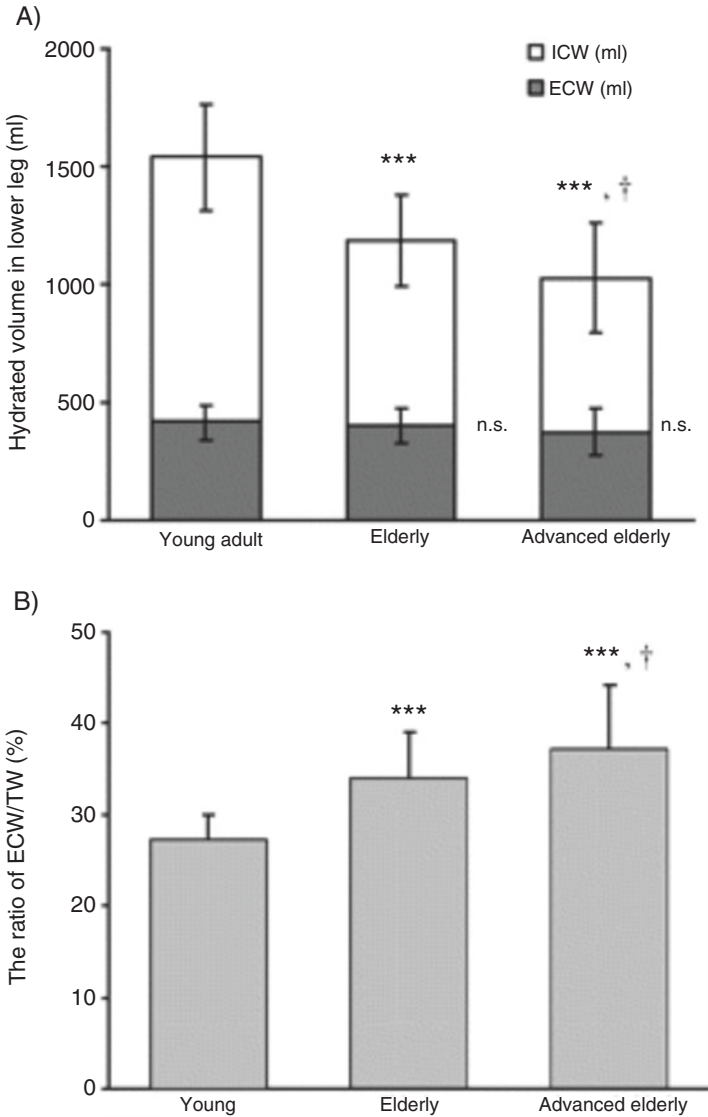
Fig. 3.8 Water distribution in the lower leg estimated by S-BIS (mean ± SD). (**a**) ***significantly lower intracellular water (ICW) than young adult ($p < 0.001$); †significantly lower ICW than elderly adults. No significant main effect was observed in extracellular water (ECW). The total bar shows the sum of ICW and ECW (total water [TW]). (**b**) The ECW/TW ratio increased significantly with aging. ***significantly higher than young adult ($p < 0.001$); †significantly higher than elderly adults. (The figure is reprinted from Yamada et al. 2010 [67] with permission)

the measurement segment for ECW and ICW. There is another model that is the combination of this model with the emulsion electrochemical model [64, 72] by Dr. Tetsuya Hanai (Hanai mixing theory) [73]; this is beyond scope of this article.
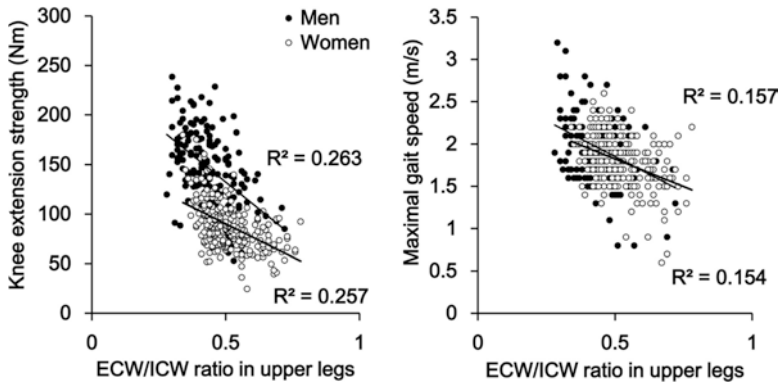
Fig. 3.9 The relationships between the ratio of extra- and intracellular water (ECW/ICW) in the upper legs as assessed by segmental bioelectrical impedance spectroscopy (S-BIS) and isometric knee extension strength (**a**) and maximal gait speed (**b**). ○ women and ● men. (The figure is reprinted from Yamada et al. 2017 [69] with permission)

The BIS method is theoretically reflected to ECW and ICW more precisely [64]. But when there is correlation coefficients with the muscle strength or power were compared between MF-BIA and BIS, there is no significant difference between MF-BIA and BIS. Although BIS is more strictly stick to the theory but reactance measurement is difficult especially at lower or higher frequency, R_0 and R_∞ that are calculated by extrapolation method of curve regression may have a large margin of error. It is, therefore, meaningful to directly use impedance at 250 kHz or 5 kHz that has less error cause [60]. Note that there is an alternative way for SF-BIA to use Xc and phase angle information to obtain body compositions [74, 75] and electrical characteristics of BIS are related to muscle function [61]. Additionally, most recent study shows that appendicular ICW estimating BIS have interesting information for sarcopenia [76].

Impedance is influenced not only by the amount of water but ion concentration in the fluid; thus, it is required to use assumption for the specific resistance of ICW and ECW. In relationship K^+ ion and BCM or ICW in the elderly [77], TBK/FFM or TBK/TBW decreases with age in the whole-body measurement, but TBK/BCM and TBK/ICW are constant [78]; this is supported by the data in rat exenterate skeletal muscle [79]. Therefore, ICW can be considered the index to reflect MCM. As another issue, the change of ICW/TW in the limbs with age obtained by BIS or MF-BIA is seemingly greater than that of ICW/TBW in the whole body in physiology field. This may be partly because few research has been conducted in elderly with age over 80; it is necessary to perform the investigation of skeletal muscle compositions in various ages. It is also necessary to evaluate edema, inflammation, body fluid shift after exercise or posture change, or the influence on various diseases [80–82].

3.6   Relationship Between Muscle Composition and Muscle Function

Whenever BIS or MF-BIA is used, ICW in the limbs, which is reflected to MCM, decreases with age [67], especially the elderly who require nursing care shows low ICW in the limbs [77]. In comparison with a traditional muscle mass index, ICW shows stronger correlation to muscle strength, muscle power, and ability to stand up from the chair; it is possible to discriminate the requirement of nursing care with good sensitivity and specificity. In addition, ICW/TW, which is a biomarker of MCM/SMM, also decreases with age and especially shows low value in the elderly who require nursing care. Interestingly, ICW/TW, being independent of skeletal muscle index of ICW, is also statistically significantly correlated to muscle strength, muscle power, and ability to stand up from the chair. ICW/TW decrease reflects the decrease of the ratio of muscle cells per unit volume; it is also the index for relative expansion of ECW or dilatation of extracellular matrix, connective tissue, or adipose tissue between muscle cells. The relationship between this index and the increase of adipose tissue mass and connective tissue must be scrutinized; if the density of muscle fiber is low (low muscle density), the decrease of lateral transmission of force can happen [83].

It is possible to evaluate muscle composition or muscle quality by not only relative increase of ECW by BIS but CT, MRI, diffusion tensor MRI (DT-MRI), Dixon MRI, or ultrasonic image echo intensity [84]. For example, Hounsfield unit (HU), signal strength of CT, is the degree of X-ray attenuation with the following conditions: distilled water at standard pressure (1000 hPa) (STP defined by IUPAC) and standard temperature (0 °C) is defined as 0 HU; the radiodensity of air is defined as −1000 HU. The HU value of the fat tissue is negative (approximately -100 to -50HU) while that of the muscle tissue is positive (approximately 0 to 100HU). Mean HU value of muscle tissue area decreases with age; the proportion of normal-density muscle area (30 to 100HU) decreases, and that of low-density muscle area (0 to 30HU) increases. This fact especially reflects to adipose tissue mass [85, 86]. However, since HU value of water is 0 HU and that of solid mass in the skeletal muscle shows high, mean HU value decreases even if the MCM/SMM decreases. Thus, the low HU value in the elderly possibly also reflects relative ECW increase in addition to adipose tissue mass increase. It is known that adipose tissue mass measured by MRI or a non-contraction factor is high in the elderly [87], the λ value of diffusion tensor MRI changes with age [88], and T2 value of the skeletal muscle at rest is high in the elderly [89]. In addition, in recent years, it is clear that ultrasonic image shows brighter in the elderly than in the young, and its echo intensity is negatively correlated to muscle force [52, 90–92]. Most recent study suggests that ultrasonic image echo intensity is correlated to muscle strength independent of the ratio of intracellular fluid to extracellular by BIS in the elderly [93] (Fig. 3.10).

As it is mentioned above, while muscle force decreases 2.5 to 4% in a year, the SMM decreases only 0.5 to 1% in a year [4]. In contrast, the actual decrease rate of
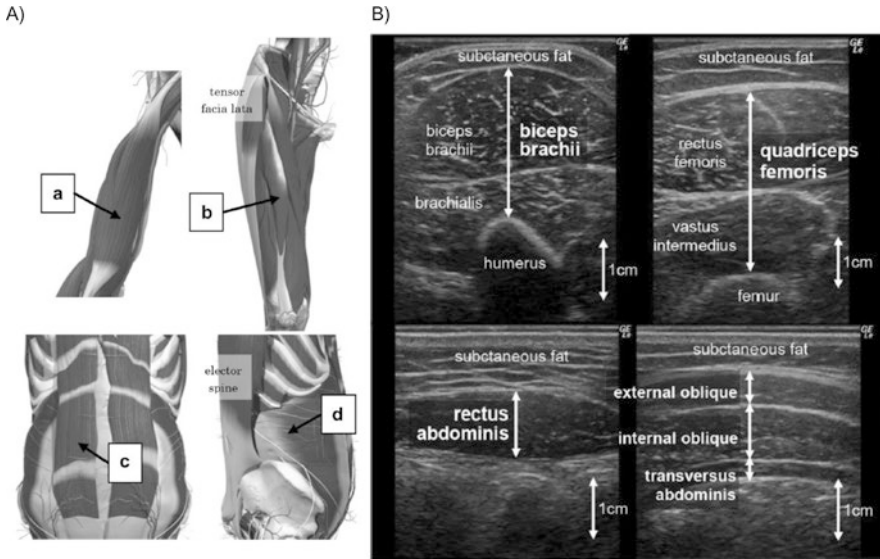
Fig. 3.10 (**a**) Ultrasound sites for each muscle. *a.*. Biceps brachii, two-thirds of the way between the acromion and the antecubital crease. *b*. Quadriceps femoris, midway between the anterior superior iliac spine and the proximal end of the patella. *c*. Rectus abdominis, 3 cm lateral to the umbilicus. *d*. External oblique, internal oblique, and transversus abdominis, 2.5 cm anterior to the midaxillary line, at the midpoint between the inferior rib and the iliac crest. (**b**) Representative ultrasound images. Echo intensity (EI) can be assessed by computer-assisted 8-bit gray-scale analysis using the standard histogram function in Adobe Photoshop Elements (Adobe Systems, San Jose, CA, USA) or other image software as an index of muscle quality. (The figure is reprinted from Fukumoto et al. 2015 [52] with permission)

MCM is thought to be as twice as that of SMM since the composition of muscle changes drastically. However, MCM decrease rate does not explain fully about the muscle force decrease. For this part, as it is mentioned above, ICW/TW (or MCM/ SMM) is the factor to explain muscle force independent of ICW; the decrease of myofiber density is probably related to the decrease of lateral transmission of force [83]. But, in addition to this, various changes happen to the muscle tissue and the neuromuscular system [4]. Muscle tissue factors are as follows: the decrease of pennation angle and muscle fascicle length with age [94], selective atrophy of fast muscle fiber with change of its cross-sectional shape (e.g., a crushed shape) [56], qualitative and quantitative changes of extracellular matrix (ECM) [83, 95], decrease in the number of satellite cells relative to the total number of nuclei of muscle fibers [96], increased occurrence of coexistence of myosin heavy chain iso- forms in single fibers [97], increased myonuclear domain (MND) size variability [98], and the decrease of Ca^{2+} sensitivity and the reduction of Ca^{2+} release [99]. Age-related change in the tendon tissue also occurred [100]. Neuromuscular sys- tem factors are as follows: decrease in the number of motoneurons and the remain- ing intact motoneurons sprouting to innervate the denervated fibers [101], decrease in α-motoneuron excitability [102, 103], excitability of the motor cortex to the

spine [104, 105], decrease of nerve conduction velocity [106], co-contraction of the antagonistic muscle [107], and elaborated muscle synergy adjustment [108]. However, exhaustive research is required to determine how much degree these factors influence to the decrease of muscle force with aging since there is a literature stating antagonist torques cannot explain the observed torque declines at the knee joint, for example [109].

At any rate, skeletal muscle cell mass in the body may change more drastically than it used to be considered. Ikenaga et al. reported that ICW at the thigh increased when slightly weighted (+200 g) shoe interventions were given to the elderly and the lower and long-term low degree burden (average 10,000 step walking for 100 min a day) was given to the lower limbs [110]. Also, ICW increase in the thigh was observed when weekly 90- to 180-min/wk moderate intermittent slow jogging interventions for 12 weeks were given, although the total muscle CSA obtained by CT was not changed [111].

3.7 Frailty, Sarcopenia, Skeletal Muscle Cell Mass, and Muscle Composition

World turns into the aging, aged or super-aged society, and life expectancy is increasing worldwide. The population of elderly over 75 is drastically increasing. The elderly gradually decreases physical function, daily activity level, and independence with advancing age [112]. This process is called frailty [113, 114]. According to Fried et al. criteria, if one has the presence of three or more of the following five components, one is frail: "shrinking: weight loss, unintentional," "grip strength weakness," "poor endurance and energy," "slowness," and "low physical activity level." "Poor endurance and energy" is included because it is a good indicator of VO$_2$max and is a predictive indicator of cardiovascular disease. Depending on cohort design, it is possible to determine frailty by just asking all questions, but basic concept of Fried criteria is to use actual measurement values since it consists of "weight (muscle mass) decrease," "grip strength," "aerobic capacity," "walking speed," and "daily physical activity." The concept of this type of frailty seems to be based on factors measured in exercise physiology area [113, 114]. Other several types of frailty indices were also proposed [115–117]. The frailty with or without muscle atrophy is a research topic for healthy life span from rodents [118–122], nonhuman primates [123], and human [114, 115, 124, 125].

The concept of frailty and sarcopenia is overlapped currently, and central component of frailty is considered to be sarcopenia. Since EWGSOP proposed the definition of sarcopenia with advancing age and its diagnosis criteria in 2010 [22, 26], active discussion is ongoing like IWGS [23, 27], FNIH sarcopenia project [28–31, 126], and AWGS [24]. In addition, the concept between sarcopenia, cachexia, and muscle wasting disorders is complex and sometimes confused in research or clinical settings [127–130]. One of the current important issues is that it is difficult to reach international consensus because the prevalence of sarcopenia is different depending
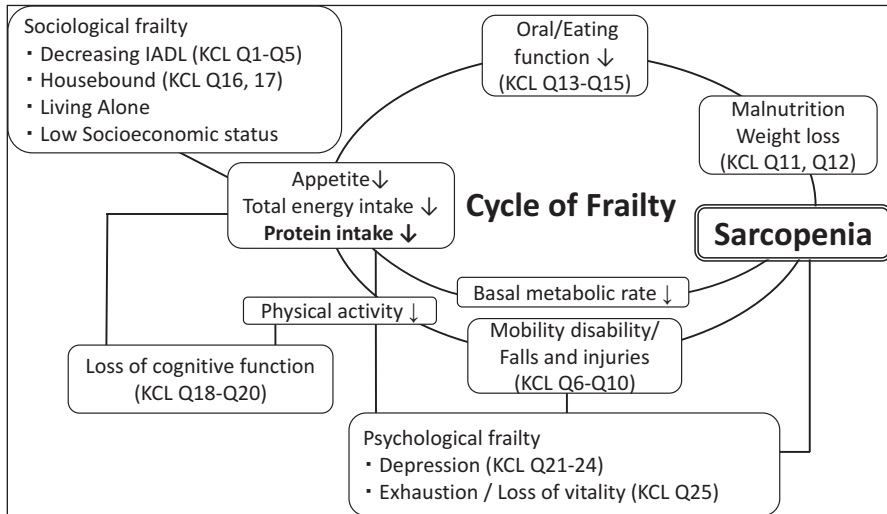
Fig. 3.11 Schematic diagram of the cycle of frailty by the Kihon Checklist (KCL) and its relationship to protein intake. *IADL* Instrumental activities of daily living, *KCL Q* question number of KCL. (This figure is reprinted from Nanri et al. [137] with permission)

on what guidelines and which SMM assessment techniques are used [131–133]. One of the biggest problems is that there is no consensus about how to assess "skeletal muscle mass (SMM)" quickly and easily in clinical settings [134]. For example, since it is not feasible to measure skeletal muscle mass in the whole body by CT or MRI in clinical environments and the measurement by DXA or BIA is device-dependent, there is no absolute method [135, 136]. Furthermore, SMM or CSA by CT that is estimated by ALST via DXA is moderately or poorly correlated to physical function decrease or total death risk [7–9]. To solve this, it is necessary to reconstruct the definition of "skeletal muscle mass." Most recent 4-year longitudinal study found that association of physical activity with age-related changes in quadriceps femoris muscle thickness and echo intensity in older adults [137]. As it is mentioned above, it is necessary to reconsider skeletal MCM and muscle compositions by paying attention to SMM compositions and their quality. In addition, the researches about effects of exercise, physical activity, nutritional status on MCM or SMM and complex frailty cycle are needed for future direction (Fig. 3.11) [138].

References

1. Allen TH, Anderson EC, Langham WH (1960) Total body potassium and gross body composition in relation to age. J Gerontol 15:348–357

2. Yamada Y (2015) Assessment of skeletal muscle mass, strength and frailty. In: Shimada H (ed) Prevention and rehabilitation of the frailty (FUREILU NO YOBOU TO RIHABIRITESHON). Ishiyaku Publishers, Inc., Tokyo

3. Janssen I, Heymsfield SB, Wang ZM, Ross R (2000) Skeletal muscle mass and distribution in 468 men and women aged 18–88 year. J Appl Physiol (1985) 89(1):81–88

4. Mitchell WK, Williams J, Atherton P, Larvin M, Lund J, Narici M (2012) Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front Physiol 3:260. https://doi.org/10.3389/fphys.2012.00260

5. Ferrucci L, de Cabo R, Knuth ND, Studenski S (2012) Of Greek heroes, wiggling worms, mighty mice, and old body builders. J Gerontol A Biol Sci Med Sci 67(1):13–16. https://doi.org/10.1093/gerona/glr046

6. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M, Newman AB (2006) The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. J Gerontol Ser A Biol Med Sci 61(10):1059–1064

7. Lauretani F, Russo CR, Bandinelli S, Bartali B, Cavazzini C, Di Iorio A, Corsi AM, Rantanen T, Guralnik JM, Ferrucci L (2003) Age-associated changes in skeletal muscles and their effect on mobility: an operational diagnosis of sarcopenia. J Appl Physiol 95(5):1851–1860. https://doi.org/10.1152/japplphysiol.00246.2003

8. Newman AB, Kupelian V, Visser M, Simonsick EM, Goodpaster BH, Kritchevsky SB, Tylavsky FA, Rubin SM, Harris TB (2006) Strength, but not muscle mass, is associated with mortality in the health, aging and body composition study cohort. J Gerontol A Biol Sci Med Sci 61(1):72–77 doi:61/1/72 [pii]

9. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, Simonsick EM, Harris TB (2005) Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci 60(3):324–333 doi:60/3/324 [pii]

10. Clark BC, Manini TM (2008) Sarcopenia =/= dynapenia. J Gerontol A Biol Sci Med Sci 63(8):829–834

11. Manini TM, Clark BC (2012) Dynapenia and aging: an update. J Gerontol A Biol Sci Med Sci 67(1):28–40. https://doi.org/10.1093/gerona/glr010

12. Rosenberg IH (1989) Summary comments for the meeting of epidemiologic and methodologic problems in determining nutritional status of older persons. Am J Clin Nutr 50(5):1231–1233. https://doi.org/10.1093/ajcn/50.5.1231

13. Garry PJ, Hunt WC, VanderJagt DJ, Rhyne RL (1989) Clinical chemistry reference intervals for healthy elderly subjects. Am J Clin Nutr 50 (5 Suppl):1219–1230; discussion 1231-1215. https://doi.org/10.1093/ajcn/50.5.1219

14. Goodwin JS (1989) Social, psychological and physical factors affecting the nutritional status of elderly subjects: separating cause and effect. Am J Clin Nutr 50 (5 Suppl):1201–1209; discussion 1231-1205. https://doi.org/10.1093/ajcn/50.5.1201

15. Harris T, Woteki C, Briefel RR, Kleinman JC (1989) NHANES III for older persons: nutrition content and methodological considerations. Am J Clin Nutr 50 (5 Suppl):1145–1149; discussion 1231-1145. https://doi.org/10.1093/ajcn/50.5.1145

16. Hegsted DM (1989) Recommended dietary intakes of elderly subjects. Am J Clin Nutr 50 (5 Suppl):1190–1194; discussion 1231-1195. https://doi.org/10.1093/ajcn/50.5.1190

17. Samet JM (1989) Surrogate measures of dietary intake. Am J Clin Nutr 50 (5 Suppl):1139–1144; discussion 1231-1135. https://doi.org/10.1093/ajcn/50.5.1139

18. Kuczmarski RJ (1989) Need for body composition information in elderly subjects. Am J Clin Nutr 50 (5 Suppl):1150–1157; discussion 1231-1155. https://doi.org/10.1093/ajcn/50.5.1150

19. Chumlea WC, Baumgartner RN (1989) Status of anthropometry and body composition data in elderly subjects. Am J Clin Nutr 50 (5 Suppl):1158–1166; discussion 1231-1155. https://doi.org/10.1093/ajcn/50.5.1158

20. Heymsfield SB, Wang J, Lichtman S, Kamen Y, Kehayias J, Pierson RN, Jr. (1989) Body composition in elderly subjects: a critical appraisal of clinical methodology. Am J Clin Nutr 50 (5 Suppl):1167–1175; discussion 1231-1165. https://doi.org/10.1093/ajcn/50.5.1167

21. Schoeller DA (1989) Changes in total body water with age. Am J Clin Nutr 50 (5 Suppl):1176–1181; discussion 1231-1175. https://doi.org/10.1093/ajcn/50.5.1176

22. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel J-P, Rolland Y, Schneider SM, Topinkova E, Vandewoude M, Zamboni M (2010) Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing 39:412–423. https://doi.org/10.1093/ageing/afq034

23. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Abellan van Kan G, Andrieu S, Bauer J, Breuille D, Cederholm T, Chandler J, De Meynard C, Donini L, Harris T, Kannt A, Keime Guibert F, Onder G, Papanicolaou D, Rolland Y, Rooks D, Sieber C, Souhami E, Verlaan S, Zamboni M (2011) Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. J Am Med Dir Assoc 12(4):249–256. https://doi.org/10.1016/j.jamda.2011.01.003

24. Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M, Arai H (2014) Sarcopenia in Asia: consensus report of the Asian working Group for Sarcopenia. J Am Med Dir Assoc 15(2):95–101. https://doi.org/10.1016/j.jamda.2013.11.025

25. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam TT, Vassileva MT (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 69(5):547–558. https://doi.org/10.1093/gerona/glu010

26. Cruz-Jentoft AJ, Landi F, Schneider SM, Zuniga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T (2014) Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 43(6):748–759. https://doi.org/10.1093/ageing/afu115

27. Cesari M, Fielding RA, Pahor M, Goodpaster B, Hellerstein M, van Kan GA, Anker SD, Rutkove S, Vrijbloed JW, Isaac M, Rolland Y, M'Rini C, Aubertin-Leheudre M, Cedarbaum JM, Zamboni M, Sieber CC, Laurent D, Evans WJ, Roubenoff R, Morley JE, Vellas B (2012) Biomarkers of sarcopenia in clinical trials-recommendations from the International Working Group on Sarcopenia. J Cachexia Sarcopenia Muscle 3(3):181–190. https://doi.org/10.1007/s13539-012-0078-2

28. Alley DE, Shardell MD, Peters KW, McLean RR, Dam T-TL, Kenny AM, Fragala MS, Harris TB, Kiel DP, Guralnik JM, Ferrucci L, Kritchevsky SB, Studenski SA, Vassileva MT, Cawthon PM (2014) Grip strength Cutpoints for the identification of clinically relevant weakness. J Gerontol Ser A Biol Med Sci 69(5):559–566. https://doi.org/10.1093/gerona/glu011

29. Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam T-TL, Kenny AM, Fragala MS, Harris TB, Kiel DP, Guralnik JM, Ferrucci L, Kritchevsky SB, Vassileva MT, Studenski SA, Alley DE (2014) Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. J Gerontol Ser A Biol Med Sci 69(5):567–575. https://doi.org/10.1093/gerona/glu023

30. Dam T-T, Peters KW, Fragala M, Cawthon PM, Harris TB, McLean R, Shardell M, Alley DE, Kenny A, Ferrucci L, Guralnik J, Kiel DP, Kritchevsky S, Vassileva MT, Studenski S (2014) An evidence-based comparison of operational criteria for the presence of sarcopenia. J Gerontol Ser A Biol Med Sci 69(5):584–590. https://doi.org/10.1093/gerona/glu013

31. McLean RR, Shardell MD, Alley DE, Cawthon PM, Fragala MS, Harris TB, Kenny AM, Peters KW, Ferrucci L, Guralnik JM, Kritchevsky SB, Kiel DP, Vassileva MT, Xue Q-L, Perera S, Studenski SA, Dam T-TL (2014) Criteria for clinically relevant weakness and low lean mass and their longitudinal association with incident mobility impairment and mortality: the Foundation for the National Institutes of Health (FNIH) sarcopenia project. J Gerontol Ser A Biol Med Sci 69(5):576–583. https://doi.org/10.1093/gerona/glu012

32. Yamada Y (2015) New approach focused on muscle cell mass and muscle composition for the definition of skeletal muscle mass and sarcopenia. Jpn J Phys Fitness Sports Med (TAIRYOKUKAGAKU) 64(4):461–472 in Japanese

33. Heymsfield SB, Lohman TG, Wang ZW, Going SB (2005) Human Body Composition, second edition

34. Ikai M, Fukunaga T (1968) Calculation of muscle strength per unit cross-sectional area of human muscle by means of ultrasonic measurement. Int Z Angew Physiol 26(1):26–32

35. Heymsfield SB, Smith R, Aulet M, Bensen B, Lichtman S, Wang J, Pierson RN, Jr. (1990) Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. Am J Clin Nutr 52 (2):214–218

36. Heymsfield SB, Gallagher D, Visser M, Nunez C, Wang ZM (1995) Measurement of skeletal muscle: laboratory and epidemiological methods. J Gerontol A Biol Sci Med Sci 50 Spec No:23–29

37. Wang ZM, Gallagher D, Nelson ME, Matthews DE, Heymsfield SB (1996) Total-body skeletal muscle mass: evaluation of 24-h urinary creatinine excretion by computerized axial tomography. Am J Clin Nutr 63(6):863–869

38. Wang ZM, Visser M, Ma R, Baumgartner RN, Kotler D, Gallagher D, Heymsfield SB (1996) Skeletal muscle mass: evaluation of neutron activation and dual-energy X-ray absorptiometry methods. J Appl Physiol (1985) 80(3):824–831

39. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R (1998) Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. J Appl Physiol (1985) 85(1):115–122

40. Pietrobelli A, Morini P, Battistini N, Chiumello G, Nunez C, Heymsfield SB (1998) Appendicular skeletal muscle mass: prediction from multiple frequency segmental bioimpedance analysis. Eur J Clin Nutr 52(7):507–511

41. Moritani T, deVries HA (1979) Neural factors versus hypertrophy in the time course of muscle strength gain. Am J Phys Med 58(3):115–130

42. Abe T, Loenneke JP, Thiebaud RS, Fukunaga T (2014) Age-related site-specific muscle wasting of upper and lower extremities and trunk in Japanese men and women. Age (Dordr) 36(2):813–821. https://doi.org/10.1007/s11357-013-9600-5

43. Abe T, Sakamaki M, Yasuda T, Bemben MG, Kondo M, Kawakami Y, Fukunaga T (2011) Age-related, site-specific muscle loss in 1507 Japanese men and women aged 20 to 95 years. J Sports Sci Med 10(1):145–150

44. Sanada K, Kearns CF, Midorikawa T, Abe T (2006) Prediction and validation of total and regional skeletal muscle mass by ultrasound in Japanese adults. Eur J Appl Physiol 96(1):24–31. https://doi.org/10.1007/s00421-005-0061-0

45. Snyder WS, Cook MJ, Nasset ES, Karhansen LR, Howells GP, Tipton IH (1975) Report of the task group on reference men. Pergamon Press, Oxford

46. Kim J, Wang Z, Heymsfield SB, Baumgartner RN, Gallagher D (2002) Total-body skeletal muscle mass: estimation by a new dual-energy X-ray absorptiometry method. Am J Clin Nutr 76(2):378–383

47. Ikezoe T, Mori N, Nakamura M, Ichihashi N (2012) Effects of age and inactivity due to prolonged bed rest on atrophy of trunk muscles. Eur J Appl Physiol 112(1):43–48. https://doi.org/10.1007/s00421-011-1952-x

48. Abe T, Loenneke JP, Young KC, Thiebaud RS, Nahar VK, Hollaway KM, Stover CD, Ford MA, Bass MA, Loftin M (2015) Validity of ultrasound prediction equations for total and regional muscularity in middle-aged and older men and women. Ultrasound Med Biol 41(2):557–564. https://doi.org/10.1016/j.ultrasmedbio.2014.09.007

49. Miyatani M, Kanehisa H, Fukunaga T (2000) Validity of bioelectrical impedance and ultrasonographic methods for estimating the muscle volume of the upper arm. Eur J Appl Physiol 82(5–6):391–396

50. Ohata K, Tsuboyama T, Ichihashi N, Minami S (2006) Measurement of muscle thickness as quantitative muscle evaluation for adults with severe cerebral palsy. Phys Ther 86(9):1231–1239. https://doi.org/10.2522/ptj.20050189

51. Masaki M, Ikezoe T, Fukumoto Y, Minami S, Tsukagoshi R, Sakuma K, Ibuki S, Yamada Y, Kimura M, Ichihashi N (2015) Association of sagittal spinal alignment with thickness and echo intensity of lumbar back muscles in middle-aged and elderly women. Arch Gerontol Geriatr 61:197. https://doi.org/10.1016/j.archger.2015.05.010

52. Fukumoto Y, Ikezoe T, Yamada Y, Tsukagoshi R, Nakamura M, Takagi Y, Kimura M, Ichihashi N (2015) Age-related ultrasound changes in muscle quantity and quality in women. Ultrasound Med Biol 41(11):3013–3017. https://doi.org/10.1016/j.ultrasmedbio.2015.06.017

53. Midorikawa T, Sanada K, Yoshitomi A, Abe T (2009) Is the use of ultrasound-derived prediction equations for adults useful for estimating total and regional skeletal muscle mass in Japanese children? Br J Nutr 101(1):72–78 S000711450899440X [pii]10.1017/S000711450899440X [doi]

54. Loenneke JP, Thiebaud RS, Abe T (2014) Estimating site-specific muscle loss: a valuable tool for early sarcopenia detection? Rejuvenation Res 17(6):496–498. https://doi.org/10.1089/rej.2014.1611

55. Miyatani M, Kanehisa H, Azuma K, Kuno S, Fukunaga T (2003) Site-related differences in muscle loss with aging. "A cross-sectional survey on the muscle thickness in Japanese men aged 20 to 79 years.". Int J Sport Health Sci 1:34–40

56. Lexell J, Taylor CC, Sjostrom M (1988) What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. J Neurol Sci 84(2–3):275–294

57. Yamada Y (2014) Assessment methods of skeletal muscle mass and strength. J Clin Exp Med (IGAKU NO AYUMI) 248(9):670–678 in Japanese

58. Yamada Y (2014) Current issue of body composition research: Tissue, organ, cell level approach from fat to muscle. J Health Phys Educ Recreat (TAIIKU NO KAGAKU) 64(3):149–155

59. Mingrone G, Bertuzzi A, Capristo E, Greco AV, Manco M, Pietrobelli A, Salinari S, Heymsfield SB (2001) Unreliable use of standard muscle hydration value in. Obesity 280, 2

60. Yamada Y, Watanabe Y, Ikenaga M, Yokoyama K, Yoshida T, Morimoto T, Kimura M (2013) Comparison of single- or multifrequency bioelectrical impedance analysis and spectroscopy for assessment of appendicular skeletal muscle in the elderly. J Appl Physiol (Bethesda, Md : 1985) 115(6):812–818. https://doi.org/10.1152/japplphysiol.00010.2013

61. Yamada Y, Buehring B, Krueger D, Anderson RM, Schoeller DA, Binkley N (2017) Electrical properties assessed by bioelectrical impedance spectroscopy as biomarkers of age-related loss of skeletal muscle quantity and quality. J Gerontol Ser A Biol Med Sci 72(9):1180–1186. https://doi.org/10.1093/gerona/glw225

62. Yamada Y, Yamagata E, Kimura M (2012) Frailty, sarcopenia, and long-term care prevention. J Kyoto Prefectural Univ Med 121(10):535–547 in Japanese with English abstract

63. Segal KR, Burastero S, Chun A, Coronel P, Pierson RN Jr, Wang J (1991) Estimation of extracellular and total body water by multiple-frequency bioelectrical-impedance measurement. Am J Clin Nutr 54(1):26–29

64. Gudivaka R, Schoeller DA, Kushner RF, Bolt MJG (1999) Single- and multifrequency models for bioelectrical impedance analysis of body water compartments. J Appl Physiol 87(3):1087–1096

65. Miyatani M, Kanehisa H, Masuo Y, Ito M, Fukunaga T (2001) Validity of estimating limb muscle volume by bioelectrical impedance. J Appl Physiol 91(1):386–394

66. Tanaka NI, Miyatani M, Masuo Y, Fukunaga T, Kanehisa H (2007) Applicability of a segmental bioelectrical impedance analysis for predicting the whole body skeletal muscle volume. J Appl Physiol 103:1688–1695. https://doi.org/10.1152/japplphysiol.00255.2007

67. Yamada Y, Schoeller DA, Nakamura E, Morimoto T, Kimura M, Oda S (2010) Extracellular water may mask actual muscle atrophy during aging. J Gerontol Ser A Biol Med Sci 65A(5):510–516

68. Yamada Y, Ikenaga M, Takeda N, Morimura K, Miyoshi N, Kiyonaga A, Kimura M, Higaki Y, Tanaka H (2014) Estimation of thigh muscle cross-sectional area by single- and multi-frequency segmental bioelectrical impedance analysis in elderly. J Appl Physiol 116(2):176–182

69. Yamada Y, Yoshida T, Yokoyama K, Watanabe Y, Miyake M, Yamagata E, Yamada M, Kimura M (2017) The extracellular to intracellular water ratio in upper legs is negatively associated with skeletal muscle strength and gait speed in older people. J Gerontology Ser A Biol Sci Med Sci 72(3):293–298. https://doi.org/10.1093/gerona/glw125

70. Deurenberg P, Schouten FJ (1992) Loss of total body water and extracellular water assessed by multifrequency impedance. Eur J Clin Nutr 46(4):247–255

71. Cole KS (1972) Membranes, ions and impulses: a chapter of classical biophysics. University of California Press, Berkeley

72. De Lorenzo A, Andreoli A, Matthie J, Withers P (1997) Predicting body cell mass with bio-impedance by using theoretical methods: a technological review. J Appl Physiol 96:161–166

73. Hanai T (1968) Electrical properties of emulsions. In: Sherman PH (ed) Emulsion science. Academic Press Inc, London, pp 354–477

74. Piccoli A, Rossi B, Pillon L, Bucciante G (1994) A new method for monitoring body fluid variation by bioimpedance analysis: the RXc graph. Kidney Int 46(2):534–539

75. Piccoli A, Piazza P, Noventa D, Pillon L, Zaccaria M (1996) A new method for monitoring hydration at high altitude by bioimpedance analysis. Med Sci Sports Exerc 28(12):1517–1522

76. Siglinsky E, Buehring B, Krueger D, Binkley N, Yamada Y (2018) Could bioelectric impedance spectroscopy (BIS) measured appendicular intracellular water serve as a lean mass measurement in sarcopenia definitions? A pilot study. Osteoporos Int 29:1653–1657. https://doi.org/10.1007/s00198-018-4475-z

77. Yamada Y, Matsuda K, Bjorkman MP, Kimura M (2014) Application of segmental bioelectrical impedance spectroscopy to the assessment of skeletal muscle cell mass in elderly men. Geriatr Gerontol Int 14(Suppl 1):129–134. https://doi.org/10.1111/ggi.12212

78. Wang Z, St-Onge MP, Lecumberri B, Pi-Sunyer FX, Heshka S, Wang J, Kotler DP, Gallagher D, Wielopolski L, Pierson RN Jr, Heymsfield SB (2004) Body cell mass: model development and validation at the cellular level of body composition. Am J Physiol Endocrinol Metab 286(1):E123–E128. https://doi.org/10.1152/ajpendo.00227.2003

79. Lustyik G (1986) Age-dependent alterations of the intracellular water and electrolyte content of heart and muscle cells. Arch Gerontol Geriatr 5(4):291–296

80. Shiose K, Yamada Y, Motonaga K, Takahashi H (2018) Muscle glycogen depletion does not alter segmental extracellular and intracellular water distribution measured using bio-impedance spectroscopy. J Appl Physiol (Bethesda, Md : 1985). https://doi.org/10.1152/japplphysiol.00666.2017

81. Shiose K, Yamada Y, Motonaga K, Sagayama H, Higaki Y, Tanaka H, Takahashi H (2016) Segmental extracellular and intracellular water distribution and muscle glycogen after 72-h carbohydrate loading using spectroscopic techniques. J Appl Physiol (1985) 121(1):205–211. https://doi.org/10.1152/japplphysiol.00126.2016

82. Shiose K, Yamada Y, Motonaga K, Takahashi H (2017) Circadian variation of extracellular and intracellular resistance of the leg, arm, and trunk in healthy humans: a segmental bioimpedance spectroscopy study. Biomed Phys Eng Express 3(6):065007. https://doi.org/10.1088/2057-1976/aa87c0

83. Zhang C, Gao Y (2014) Effects of aging on the lateral transmission of force in rat skeletal muscle. J Biomech 47(5):944–948. https://doi.org/10.1016/j.jbiomech.2014.01.026

84. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J (2015) Skeletal muscle mass and quality: evolution of modern measurement concepts in the context of sarcopenia. Proc Nutr Soc 74:1–12. https://doi.org/10.1017/s0029665115000129

85. Goodpaster BH, Carlson CL, Visser M, Kelley DE, Scherzinger A, Harris TB, Stamm E, Newman AB (2001) Attenuation of skeletal muscle and strength in the elderly: the health ABC study. J Appl Physiol 90(6):2157–2165

86. Goodpaster BH, Kelley DE, Thaete FL, He J, Ross R (2000) Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol 89(1):104–110

87. Kent-Braun JA, Ng AV, Young K (2000) Skeletal muscle contractile and noncontractile components in young and older women and men. J Appl Physiol 88(2):662–668

88. Galban CJ, Maderwald S, Stock F, Ladd ME (2007) Age-related changes in skeletal muscle as detected by diffusion tensor magnetic resonance imaging. J Gerontol A Biol Sci Med Sci 62(4):453–458

89. Ploutz-Snyder LL, Yackel-Giamis EL, Rosenbaum AE, Formikell M (2000) Use of muscle functional magnetic resonance imaging with older individuals. J Gerontol A Biol Sci Med Sci 55(10):B504–B511

90. Watanabe Y, Yamada Y, Fukumoto Y, Ishihara T, Yokoyama K, Yoshida T, Miyake M, Yamagata E, Kimura M (2013) Echo intensity obtained from ultrasonography images reflecting muscle strength in elderly men. Clin Interv Aging 8:993–998. https://doi.org/10.2147/CIA.S47263

91. Fukumoto Y, Ikezoe T, Yamada Y, Tsukagoshi R, Nakamura M, Mori N, Kimura M, Ichihashi N (2012) Skeletal muscle quality assessed from echo intensity is associated with muscle strength of middle-aged and elderly persons. Eur J Appl Physiol 112(4):1519–1525. doi. https://doi.org/10.1007/s00421-011-2099-5

92. Akagi R, Suzuki M, Kawaguchi E, Miyamoto N, Yamada Y, Ema R (2018) Muscle size-strength relationship including ultrasonographic echo intensity and voluntary activation level of a muscle group. Arch Gerontol Geriatr 75:185–190. https://doi.org/10.1016/j.archger.2017.12.012

93. Taniguchi M, Yamada Y, Fukumoto Y, Sawano S, Minami S, Ikezoe T, Watanabe Y, Kimura M, Ichihashi N (2017) Increase in echo intensity and extracellular-to-intracellular water ratio is independently associated with muscle weakness in elderly women. Eur J Appl Physiol 117(10):2001–2007. https://doi.org/10.1007/s00421-017-3686-x

94. Narici MV, Maganaris CN, Reeves ND, Capodaglio P (2003) Effect of aging on human muscle architecture. J Appl Physiol (1985) 95(6):2229–2234. https://doi.org/10.1152/japplphysiol.00433.2003

95. Nishimura T, Ojima K, Hattori A, Takahashi K (1997) Developmental expression of extracellular matrix components in intramuscular connective tissue of bovine semitendinosus muscle. Histochem Cell Biol 107(3):215–221

96. Kadi F, Charifi N, Denis C, Lexell J (2004) Satellite cells and myonuclei in young and elderly women and men. Muscle Nerve 29(1):120–127. https://doi.org/10.1002/mus.10510

97. Klitgaard H, Zhou M, Schiaffino S, Betto R, Salviati G, Saltin B (1990) Ageing alters the myosin heavy chain composition of single fibres from human skeletal muscle. Acta Physiol Scand 140(1):55–62. https://doi.org/10.1111/j.1748-1716.1990.tb08975.x

98. Cristea A, Qaisar R, Edlund PK, Lindblad J, Bengtsson E, Larsson L (2010) Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. Aging Cell 9(5):685–697. https://doi.org/10.1111/j.1474-9726.2010.00594.x

99. Delbono O, O'Rourke KS, Ettinger WH (1995) Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. J Membr Biol 148(3):211–222

100. Kubo K, Ishida Y, Komuro T, Tsunoda N, Kanehisa H, Fukunaga T (2007) Age-related differences in the force generation capabilities and tendon extensibilities of knee extensors and plantar flexors in men. J Gerontol A Biol Sci Med Sci 62(11):1252–1258

101. Luff AR (1998) Age-associated changes in the innervation of muscle fibers and changes in the mechanical properties of motor units. Ann N Y Acad Sci 854:92–101

102. Moritani T, deVries HA (1980) Potential for gross muscle hypertrophy in older men. J Gerontol 35(5):672–682

103. Kamen G (2005) Aging, resistance training, and motor unit discharge behavior. Can J Appl Physiol 30(3):341–351
104. Kido A, Tanaka N, Stein RB (2004) Spinal excitation and inhibition decrease as humans age. Can J Physiol Pharmacol 82(4):238–248. https://doi.org/10.1139/y04-017
105. Oliviero A, Profice P, Tonali PA, Pilato F, Saturno E, Dileone M, Ranieri F, Di Lazzaro V (2006) Effects of aging on motor cortex excitability. Neurosci Res 55(1):74–77. https://doi.org/10.1016/j.neures.2006.02.002
106. Lauretani F, Bandinelli S, Bartali B, Di Iorio A, Giacomini V, Corsi AM, Guralnik JM, Ferrucci L (2006) Axonal degeneration affects muscle density in older men and women. Neurobiol Aging 27(8):1145–1154. https://doi.org/10.1016/j.neurobiolaging.2005.06.009
107. Klein CS, Rice CL, Marsh GD (2001) Normalized force, activation, and coactivation in the arm muscles of young and old men. J Appl Physiol (1985) 91(3):1341–1349
108. Shinohara M, Latash ML, Zatsiorsky VM (2003) Age effects on force produced by intrinsic and extrinsic hand muscles and finger interaction during MVC tasks. J Appl Physiol (1985) 95(4):1361–1369. https://doi.org/10.1152/japplphysiol.00070.2003
109. Billot M, Duclay J, Simoneau-Buessinger EM, Ballay Y, Martin A (2014) Is co-contraction responsible for the decline in maximal knee joint torque in older males? Age (Dordr) 36(2):899–910. https://doi.org/10.1007/s11357-014-9616-5
110. Ikenaga M, Yamada Y, Mihara R, Yoshida T, Fujii K, Morimura K, Hirano M, Enishi K, Shindo M, Kiyonaga A (2012) Effects of slightly-weighted shoe intervention on lower limb muscle mass and gait patterns in the elderly. Jpn J Phys Fitness Sports Med (TAIRYOKUKAGAKU) 61(5):469–477 (in Japanese with English abstract)
111. Ikenaga M, Yamada Y, Kose Y, Morimura K, Higaki Y, Kiyonaga A, Tanaka H (2017) Effects of a 12-week, short-interval, intermittent, low-intensity, slow-jogging program on skeletal muscle, fat infiltration, and fitness in older adults: randomized controlled trial. Eur J Appl Physiol 117(1):7–15. https://doi.org/10.1007/s00421-016-3493-9
112. Yamada Y, Nanri H, Watanabe Y, Yoshida T, Yokoyama K, Itoi A, Date H, Yamaguchi M, Miyake M, Yamagata E, Tamiya H, Nishimura M, Fujibayashi M, Ebine N, Yoshida M, Kikutani T, Yoshimura E, Ishikawa-Takata K, Yamada M, Nakaya T, Yoshinaka Y, Fujiwara Y, Arai H, Kimura M (2017) Prevalence of frailty assessed by fried and Kihon checklist indexes in a prospective cohort study: design and demographics of the Kyoto-Kameoka longitudinal study. J Am Med Dir Assoc 18:733.e7. https://doi.org/10.1016/j.jamda.2017.02.022
113. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA (2001) Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56(3):M146–M156
114. Xue QL, Bandeen-Roche K, Varadhan R, Zhou J, Fried LP (2008) Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's health and aging study II. J Gerontol A Biol Sci Med Sci 63(9):984–990
115. Rockwood K, Andrew M, Mitnitski A (2007) A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci 62(7):738–743
116. Arai H, Satake S (2015) English translation of the Kihon checklist. Geriatr Gerontol Int 15(4):518–519. https://doi.org/10.1111/ggi.12397
117. Satake S, Senda K, Hong YJ, Miura H, Endo H, Sakurai T, Kondo I, Toba K (2016) Validity of the Kihon checklist for assessing frailty status. Geriatr Gerontol Int 16(6):709–715. https://doi.org/10.1111/ggi.12543
118. Arum O, Rasche ZA, Rickman DJ, Bartke A (2013) Prevention of neuromusculoskeletal frailty in slow-aging ames dwarf mice: longitudinal investigation of interaction of longevity genes and caloric restriction. PLoS One 8(10):e72255. https://doi.org/10.1371/journal.pone.0072255
119. Feridooni HA, Sun MH, Rockwood K, Howlett SE (2015) Reliability of a frailty index based on the clinical assessment of health deficits in male C57BL/6J mice. J Gerontol A Biol Sci Med Sci 70(6):686–693. https://doi.org/10.1093/gerona/glu161

120. Kane AE, Hilmer SN, Boyer D, Gavin K, Nines D, Howlett SE, de Cabo R, Mitchell SJ (2016) Impact of longevity interventions on a validated mouse clinical frailty index. J Gerontol A Biol Sci Med Sci 71(3):333–339. https://doi.org/10.1093/gerona/glu315

121. Liu H, Graber TG, Ferguson-Stegall L, Thompson LV (2014) Clinically relevant frailty index for mice. J Gerontol A Biol Sci Med Sci 69(12):1485–1491. https://doi.org/10.1093/gerona/glt188

122. Whitehead JC, Hildebrand BA, Sun M, Rockwood MR, Rose RA, Rockwood K, Howlett SE (2014) A clinical frailty index in aging mice: comparisons with frailty index data in humans. J Gerontol A Biol Sci Med Sci 69(6):621–632. https://doi.org/10.1093/gerona/glt136

123. Yamada Y, Kemnitz JW, Weindruch R, Anderson RM, Schoeller DA, Colman RJ (2018) Caloric restriction and healthy life span: frail phenotype of nonhuman primates in the Wisconsin National Primate Research Center Caloric Restriction Study. J Gerontol A Biol Sci Med Sci 73(3):273–278. https://doi.org/10.1093/gerona/glx059

124. Mitnitski A, Rockwood K (2015) The rate of aging: the rate of deficit accumulation does not change over the adult life span. Biogerontology 17:199. https://doi.org/10.1007/s10522-015-9583-y

125. Mitnitski A, Song X, Rockwood K (2013) Assessing biological aging: the origin of deficit accumulation. Biogerontology 14(6):709–717. https://doi.org/10.1007/s10522-013-9446-3

126. Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, Ferrucci L, Guralnik JM, Fragala MS, Kenny AM, Kiel DP, Kritchevsky SB, Shardell MD, Dam T-TL, Vassileva MT (2014) The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol Ser A Biol Med Sci 69(5):547–558. https://doi.org/10.1093/gerona/glu010

127. Evans WJ (2010) Skeletal muscle loss: cachexia, sarcopenia, and inactivity. Am J Clin Nutr 91(4):1123s–1127s. https://doi.org/10.3945/ajcn.2010.28608A

128. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, Jatoi A, Loprinzi C, MacDonald N, Mantovani G, Davis M, Muscaritoli M, Ottery F, Radbruch L, Ravasco P, Walsh D, Wilcock A, Kaasa S, Baracos VE (2011) Definition and classification of cancer cachexia: an international consensus. Lancet Oncol 12(5):489–495. https://doi.org/10.1016/s1470-2045(10)70218-7

129. Muscaritoli M, Anker SD, Argiles J, Aversa Z, Bauer JM, Biolo G, Boirie Y, Bosaeus I, Cederholm T, Costelli P, Fearon KC, Laviano A, Maggio M, Rossi Fanelli F, Schneider SM, Schols A, Sieber CC (2010) Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG) "cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr 29(2):154–159. https://doi.org/10.1016/j.clnu.2009.12.004

130. Yamada Y (2017) Assessment and definition of sarcopenia: general concept and importance at digestive surgery. Gastroenterol Surg (SHOKAKIGEKA) 40(7):1009–1024 in Japanese

131. Lee WJ, Liu LK, Peng LN, Lin MH, Chen LK (2013) Comparisons of sarcopenia defined by IWGS and EWGSOP criteria among older people: results from the I-Lan longitudinal aging study. J Am Med Dir Assoc 14(7):528 e521–528 e527. https://doi.org/10.1016/j.jamda.2013.03.019

132. Cooper R, Bann D, Wloch EG, Adams JE, Kuh D (2015) "Skeletal muscle function deficit" in a nationally representative British birth cohort in early old age. J Gerontol A Biol Med Sci 70(5):604–607. https://doi.org/10.1093/gerona/glu214

133. Wen X, An P, Chen WC, Lv Y, Fu Q (2015) Comparisons of sarcopenia prevalence based on different diagnostic criteria in chinese older adults. J Nutr Health Aging 19(3):342–347. https://doi.org/10.1007/s12603-014-0561-x

134. Buehring B, Siglinsky E, Krueger D, Evans W, Hellerstein M, Yamada Y, Binkley N (2017) Comparison of muscle/lean mass measurement methods: correlation with functional and biochemical testing. Osteoporos Int 29(3):675–683. https://doi.org/10.1007/s00198-017-4315-6

135. Yamada Y, Nishizawa M, Uchiyama T, Kasahara Y, Shindo M, Miyachi M, Tanaka S (2017) Developing and validating an age-independent equation using multi-frequency bioelectri-

cal impedance analysis for estimation of appendicular skeletal muscle mass and establishing a cutoff for sarcopenia. Int J Environ Res Public Health 14(7). https://doi.org/10.3390/ijerph14070809

136. Yamada M, Yamada Y, Arai H (2016) Comparability of two representative devices for bioelectrical impedance data acquisition. Geriatr Gerontol Int 16(9):1087–1088. https://doi.org/10.1111/ggi.12647

137. Fukumoto Y, Yamada Y, Ikezoe T, Watanabe Y, Taniguchi M, Sawano S, Minami S, Asai T, Kimura M, Ichihashi N (2018) Association of physical activity with age-related changes in muscle echo intensity in older adults: a 4-year longitudinal study. J Appl Physiol [Epub ahead of print]. https://doi.org/10.1152/japplphysiol.00317.2018

138. Nanri H, Yamada Y, Yoshida T, Okabe Y, Nozawa Y, Itoi A, Yoshimura E, Watanabe Y, Yamaguchi M, Yokoyama K, Ishikawa-Takata K, Kobayashi H, Kimura M, Kyoto-Kameoka Study Group (2018) Sex difference in the association between protein intake and frailty: assessed using the Kihon checklist indexes among older adults. J Am Med Dir Assoc 19(9):801–805. https://doi.org/10.1016/j.jamda.2018.04.005