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REVIEW

# The role of DXA in sarcopenia

**Giuseppe Guglielmi[1,2] · Federico Ponti[3,4] · Margherita Agostini[3] · Michele Amadori[3] · Giuseppe Battista[3] · Alberto Bazzocchi[4]**

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**Abstract** Sarcopenia is a condition characterized by progressive and generalized reduction in skeletal muscle mass and muscle strength, associated with an increased risk of adverse outcomes (disability, hospitalization, death). The growing attention in the last years, aiming to establish a consensus definition and treatment, reflects the interest of the scientific community toward this complex condition, which has many implications in clinical practice and public health. Dual-energy X-ray absorptiometry (DXA) is the gold-standard technique in the analysis of body composition at molecular level, providing assessment and quantification of fat mass, lean mass and bone mineral content, both in a single body region of interest and at whole-body level. In particular, through the assessment of non-bone lean mass parameters, such as appendicular lean mass adjusted for BMI or height (ALM/BMI and ALM/ht$^2$, respectively), it is possible to discriminate subjects with "physiological" loss of muscle mass from those with "pathological" impoverishment of this compartment, referring to specific cutoff values validated in the literature, but keeping in mind the lack of standardization of DXA measures. In addition, it is useful in treatment planning, estimating resting energy expenditure, and in follow-up, because it allows quantifying with high reproducibility the modifications in BC, distinguishing when the change is biological (deterioration due to a progression of the disease or improvement due to treatment). Due to DXA favorability in terms of accuracy, simplicity, availability, low cost and low radiation exposure, its role in sarcopenia diagnosis is becoming increasingly important, emerging as reference assessment technique in muscle mass evaluation.

**Keywords** Sarcopenia · Aging · Absorptiometry · Photon · Muscle · Body composition · Diagnosis

✉ Giuseppe Guglielmi
giuseppe.guglielmi@unifg.it

[1] Department of Radiology, University of Foggia, Viale Luigi Pinto 1, 71100 Foggia, Italy

[2] Department of Radiology, Scientific Institute "Casa Sollievo della Sofferenza" Hospital, Viale Cappuccini 1, 71013 San Giovanni Rotondo, Foggia, Italy

[3] Department of Specialized, Diagnostic, and Experimental Medicine, Sant'Orsola - Malpighi Hospital, University of Bologna, Via G. Massarenti 9, 40138 Bologna, Italy

[4] Diagnostic and Interventional Radiology, The "Rizzoli" Orthopaedic Institute, Via G. C. Pupilli 1, 40136 Bologna, Italy

## Introduction

Sarcopenia is a condition increasingly recognized as an extremely important public health issue. Due to its widely demonstrated association with poor quality of life [1–3], greater risk of mortality [4, 5], mobility disability [6, 7] and risk of hospitalization [8], sarcopenia currently has, and will have even more in the future, a dramatic impact on public health, both at the patient level, as it impairs quality of life and it is associated with several adverse outcomes, and at the social level, as it results in higher healthcare costs in terms of days of hospitalization, nursing home placement, home and ambulatory care [9]. Since the number of people around the world aged $\geq$60 years is expected to increase approximately from 600 million in the year 2000 to 1.2 billion by 2025 and 2 billion by 2050 (according to the World Health Organization), this implies that sarcopenia will become an ever-increasing problem for the healthcare expenditures. In 2004, Jansen et al., carried out a cross-sectional survey in order to estimate the

economic impact of sarcopenia in the USA, assessing how it could be limited by reducing sarcopenia prevalence; in 2000, the costs of sarcopenia in terms of hospitalization, home care and outpatient treatment, affected health burden for a total of 10.8 billion dollars, which represented 1.5 % of total healthcare expenditure. It was estimated that a 10 % reduction in sarcopenia prevalence would result in savings of 1.1 billion dollars per year in US healthcare costs [10]. Nevertheless, since sarcopenia is an operational definition, which still has no broadly accepted consensus definition, an accurate assessment of its actual prevalence remains a challenge [9]. The term "sarcopenia" was first proposed by Irwin Rosenberg [11], from the Greek root "sarx" (meaning flesh) and "penia" (meaning loss) to indicate the age-related decrease in muscle mass with aging, concept which was already been investigated in some studies [12] as part of the structural and functional age-related decline, but which had not yet been framed as a disease phenomenon able to induce a disability. Actually, since then, the concept of sarcopenia was investigated in an increasing number of studies, to determine a focused definition, epidemiology, etiology and therapy. Over the past decades, several authors proposed definitions of sarcopenia. Among these, the study of Baumgartner [13] is of particular importance, where the author suggested useful indices of skeletal muscle mass and cutoff values of reference for sarcopenia diagnosis (Table 1). Recently, various studies showed [14, 15] that the loss of lean mass is not a critical factor by itself in determining poorer physical function, impaired quality of life and physical disability, but it is the combination of both loss of strength and mass to be a strong predictor of loss of physical performance with consequent adverse outcomes. The importance of a clinically relevant decrease in muscle mass (the presence of a decline in skeletal mass able to determine a muscle weakness) has become a key element in the more recent studies on sarcopenia: Nowadays, it is globally shared that the concepts of low lean mass and decreased muscle function should necessarily be incorporated both into its definition. According to this trend line, several

**Table 1** Main proposed operational definitions of sarcopenia using DXA for assessment of body composition

| Study group | Definition | Criteria | | | |
|---|---|---|---|---|---|
| | | Muscle mass | | Muscle function | |
| | | | Tool suggested for assessment of body composition | Muscle strength | Physical performance |
| Baugmarter et al. [13] | "Muscle mass decreases with age, leading to 'sarcopenia,' or low relative muscle mass, in elderly people" | ASM/ht$^2$ >2SD below the sex-specific mean in a young healthy reference population | DXA | X | X |
| IWGS [16] | "Sarcopenia is the age-associated loss of skeletal muscle mass and function. Sarcopenia is a complex syndrome that is associated with muscle mass loss alone or in conjunction with increased fat mass" | ALM/ht$^2$<br>Men $\leq$7.23 kg/m$^2$<br>Women $\leq$5.67 kg/m$^2$<br>(i.e., less than 20 % tile of values for healthy young adults) | DXA | X | Gait speed <1.0 m/s |
| EWGSOP [17] | "Sarcopenia is a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death" | Presarcopenia<br>Reduced muscle mass[a] | DXA or BIA | X | X |
| | | Sarcopenia<br>Reduced muscle mass[a] | DXA or BIA | Reduced muscle strength[a] | OR Gait speed <0.8 m/s |
| | | Severe sarcopenia<br>Reduced muscle mass[a] | DXA or BIA | Reduced muscle strength[a] | AND Gait speed <0.8 m/s |
| FNIH [18] | "Clinically relevant weakness and low lean mass" | $ALM_{BMI}$<br>Men <0.789<br>Women <0.512 | DXA | Grip strength<br>Men <26 kg<br>Women <16 kg | Gait speed <0.8 |

*ASM* appendicular skeletal mass, *ALM/ht$^2$* ratio of appendicular lean mass over height squared, *SD* standard deviation, *$ALM_{BMI}$* ratio of appendicular lean mass over body mass index

[a] Several cutoff points indicated

international working groups have published in recent years new consensus definitions of sarcopenia; in most of them, the suggested technique for assessment of muscle mass is DXA. The main operational definitions of sarcopenia, proposed by the International Working Group on Sarcopenia (IWGS) [16], the European Working Group on Sarcopenia in Older People (EWGSOP) [17] and the Foundation for the National Institutes of Health (FNIH) [18] Sarcopenia Project, are summarized in Table 1. Nevertheless, several techniques are available for assessment of body composition: Table 2 shows main advantages and disadvantages of each technique, while Table 3 presents the cutoff points for the diagnosis of sarcopenia in the literature.

## Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) is the standard technique in the analysis of BC at molecular level, and it is based on a three-compartment model: fat mass, lean mass and body mineral content (FM, LM and BMC, respectively) [19, 20]. DXA is based on physical principle of measurement of the X-ray transmission in crossing tissues of the human body at two different energy levels. The radiation energies are variably attenuated (absorbed or scattered) by anatomical structures, depending on the intensity of energy and on the density and thickness of human tissues.

Attenuation of X-ray beam decreases with increasing photon energy. Low-density materials (i.e., soft tissue)

**Table 2** Main advantages and disadvantages of each technique in assessment of body composition

| Technique | Advantages | Disadvantages |
|---|---|---|
| DXA | High precision, accuracy and reproducibility | Variability of instrument calibration procedures, hardware and software version between manufacturers |
| | Quick and noninvasive | Requires specific technical skills and operator experience |
| | Good availability | Contraindicated in pregnancy |
| | Low radiation exposure | Body thickness and hydration status may influence the measurements |
| | Able to differentiate FM, LM and BMC | Inability to discriminate the different types of fat (visceral, subcutaneous and intramuscular) |
| | Possibility of obtaining regional measures (e.g., ALM) | |
| BIA | Quick and noninvasive | Results based on population-specific regression equations, not always available |
| | Good availability | Variation in hydration status of the patient, in the positioning of the electrodes and in numerous other variables may alter consistently the results |
| | No radiation exposure | |
| | Ease of use | |
| CT | High accuracy and reproducibility | Requires specific technical skills and operator experience |
| | High image resolution | High cost |
| | Able to discriminate the different tissues at anatomical level, also estimating the degree of fat infiltration into the muscle | High radiation exposure |
| | | Not always available |
| | | Requires high patient compliance |
| MRI | High accuracy and reproducibility | Requires specific technical skills and operator experience |
| | High image resolution | High cost |
| | Most accurate technique able to discriminate the different tissues at anatomical level | Scarcely available |
| | | Requires high patient compliance |
| | Most accurate estimation of the degree of fat infiltration into the muscle | |
| US | Quick and noninvasive | Requires specific technical skills and operator experience |
| | Good availability | Requires high patient compliance |
| | No radiation exposure | Low reproducibility (operator-dependent results) |
| | Able to estimate the degree of fat infiltration into the muscle | Experience in evaluation of body composition is still limited |
| | Low cost | |
| Anthropometry | Quick and noninvasive | Significant interobserver variability. |
| | Easily obtained | Low reproducibility and vulnerability to error |
| | Inexpensive | Absence of consistent cutoff values |
| | | No assessment of body composition |

**Table 3** Review of main cutoff points suggested in the literature

| Technique | Cutoff points | Reference population | Study group |
|---|---|---|---|
| Muscle mass | | | |
| DXA | ASM/height$^2$ | Based on 2SD below mean of young adults (Rosetta study), using Lunar DPX | Baugmarter et al. [13] |
| | Men <7.23 kg/m$^2$ | | |
| | Women <5.45 kg/m$^2$ | | |
| | SMI (ASM/height$^2$) | Based on sex-specific lowest 20th percentile (Health ABC study), using QDR 4500A, Hologic | Newman et al. [104] |
| | Men <7.23 kg/m$^2$ | | |
| | Women <5.67 kg/m$^2$ | | |
| | ALM/height$^2$ | Based on sex-specific lowest 20th percentile in a population of young adults, using QDR 4500A, Hologic | International Working Group on Sarcopenia (IWGS) [16] |
| | Men ≤7.23 kg/m$^2$ | | |
| | Women ≤5.67 kg/m$^2$ | | |
| | ALM/height$^2$ | Based on best available data in sarcopenia researches from Asian countries | Asian Working Group for Sarcopenia (AWGS) [105] |
| | Men <7.0 kg/m$^2$ | | |
| | Women <5.4 kg/m$^2$ | | |
| | $ALM_{BMI}$ | Based on data from nine sources of community-dwelling older persons ($n$ = 26,625), using 4500 Hologic, 2000 Hologic, Lunar Prodigy | Foundation for the National Institutes of Health (FNIH) [18] |
| | Men <0.789 | | |
| | Women <0.512 | | |
| Muscle strength | | | |
| Handgrip strength | Men <26 kg | Based on best available data in sarcopenia researches from Asian countries | Asian Working Group for Sarcopenia (AWGS) [105] |
| | Women <18 kg | | |
| | Men <26 kg | Based on data from nine sources of community-dwelling older persons ($n$ = 26,625) | Foundation for the National Institutes of Health (FNIH) [18] |
| | Women <16 kg | | |
| Physical performance | | | |
| Usual gait speed | ≤0.8 m/s | Based on available data defining sarcopenia cutoff points | European Working Group on Sarcopenia in Older People (EWGSOP) [17] |
| | <1 m/s | Consensus of an international group of geriatricians and scientists | International Working Group on Sarcopenia (IWGS) [16] |
| | <0.8 m/s | Based on best available data in sarcopenia researches from Asian countries | Asian Working Group for Sarcopenia (AWGS) [105] |
| | <0.8 m/s | Based on data from nine sources of community-dwelling older persons ($n$ = 26,625) | Foundation for the National Institutes of Health (FNIH) [18] |
| SSPB | <8 | Based on data from Established Populations for the Epidemiologic study of the Elderly (ESPESE) | Guralnik et al. [6] |

*ASM* appendicular skeletal mass, *SMI* skeletal mass index, *ALM* appendicular lean mass, *DXA* dual energy X-ray absorptiometry, *BMI* body mass index, *SSPB* short physical performance battery

allow more photons to pass through; thus, they attenuate the X-ray beam lesser than materials with higher density as bone. The difference in the attenuation of the two X-ray energy peaks is specific for each tissue. DXA estimates the *R*-value, which is the ratio of attenuation coefficients at the two different energy levels. *R*-value of soft tissue varies depending on subject's soft tissue composition (the lower are *R*-values, the higher is fat percentage), while it is constant for bone and fat in all patients. Although DXA provides three BC measurements (FM, LM and BMC—regionally and whole body), it does not measure directly the three components. In pixels containing bone, which are about 40–45 % of total pixels in a total-body scan, DXA distinguishes bone from soft tissue (FM + LM) [21–23]: The quantity of FM and LM is deducted on the basis of the FM/LM calculated in neighboring bone-free pixels, assuming therefore that the amount of fat over bone is the same as that over the adjacent bone-free tissues. Densitometers may use different kinds of X-ray beams. Pencil beam densitometers are characterized by a singular beam of X-ray and a single detector. Although the pencil beam is considered the gold standard for precision, the scan time is increased for the single beam to cover the body. In the fan beam DXA (wide-angle fan beam), the X-ray tube emissions are received by multiple detectors, which are swept across the region under investigation. These systems provide shorter scan times and better resolution, but there is a minimal image distortion due to magnification of the tissue and a higher radiation exposure. Third-generation DXA is the narrow-angle fan beam (micro-angle fan beam):

Although it is still a fan beam, the narrow angle uses multiple passes to acquire multiple images. Image reconstruction combines these images to mesh the precision of pencil beam and the speed of a fan beam system [23].

In conclusion, the latest generation densitometers allow the evaluation of BC with a single whole-body scan (that means low radiation exposure and fast acquisition time), providing high-resolution images (almost comparable to a radiological image) and very accurate and precise data (thanks to a minimal magnification of image) [24–28].

## Methodological aspects

DXA measurements are susceptible of various pitfalls and errors that can be distinguished in technical errors (incorrect positioning of the patient and inaccuracies in image post-processing) and biological variation (hydration status influenced by exercise and diet), which should be considered for the development of adequate standardized protocols of acquisition and for proper selection of patients to be examined. It is necessary to ensure that the patient does not wear clothes that could attenuate the X-ray beam, such as zippers, buttons, buckles and other metal objects.

The patient's body is placed at the center of the table scan, using the center line on the table as a reference for proper alignment, with the head in a neutral position, avoiding any hyperflexion and hyperextension, about 3 cm below the upper horizontal line of the scan area. The patient's arms are positioned along the body If possible, the hands must not touch the legs, and there should be a gap of minimum 1 cm between arms and trunk without exceeding the lines of the scan [29, 30]. To reduce any patient movement that may affect the accuracy of the examination, Velcro straps are used to tie thumbs with fingers, knees and ankles together [29, 30]. If the patient is too high or too wide to fit in the scan area, some tricks may be used. When the height of the subjects exceeds the scan area, they can be positioned so that the feet are included in the scan, eventually leaving out the skull. The composition of the head in fact is assumed to be constant, differently to that of the lower limbs. It is necessary, however, to ensure that jaw is not excluded, since the lowest line that delimits the area of the head is a reference in the determination of the other ROIs [29]. Alternative options may be to perform the examination with a knee-bent position or to sum two examinations [31]. When the width of the subject exceeds the scan area, a trick to include the entire body in the scan field may be to change the position of the hands, placing them vertically to the densitometer. If even in this case the patient's body is not completely comprised within the limits of the scan area, another adjustment allows an estimation of the not imaged body side on the basis of the examined body half, assuming that body symmetry may be to perform ("half-body analysis") [29, 32].

It has been shown that the recent intake of a meal may produce an increase in total and trunk lean mass of both males and females [33]. Also, exercise or substantial physical activity may affect the reliability of DXA estimates due to expansion or reduction in body fluid compartments determined by dehydration and/or increased blood flow and capillary dilation [34], especially reducing total-body LM (because of dehydration) and increasing trunk LM (because of the exercise-induced distribution of blood volume to the limbs). Moreover, environmental factors such as the ambient temperature and the extent of water consumption may affect the hydration status and therefore the evaluation of BC [34].

Standardization of methodology (patient fasting, rested, euhydrated with standardized positioning and scanning) is an important expedient to obtain measurements the best possible reproducible, allowing a confident detection of any small but potentially "real" change, reducing potential confounding factors associated with the technical and biological variability.

### *Clinical aspects*

According to the ISCD Official Positions for adults, total-body (without head) values of BMI, BMD, BMC, total mass, total lean mass, total fat mass and percent fat mass should appear on all reports.

Other more specific measures of adiposity and lean mass are optional and include lean mass index (LMI: total lean mass/ht$^2$), appendicular lean mass (ALM: arms LM + legs LM), appendicular lean mass index (ALMI: appendicular lean mass/ht$^2$), skeletal muscle mass index (SMI: ALM/ht$^2$), visceral adipose tissue (VAT), android/gynoid percent fat mass ratio, trunk to leg fat mass ratio, fat mass index (FMI: fat mass/ht$^2$). As already explained, SMI, ALM, ALMI and ALMI$_{BMI}$ have been proposed as parameters in the assessment of a reduction in muscle mass, which, as already seen, is a key element in the diagnosis of sarcopenia.

In addition, LMI determined with DXA may be a potentially useful indicator of nutritional status, and it may have an important role also when studying socioeconomic status in children [35]. Furthermore, it has been demonstrated an association of a low LMI with certain pathological conditions, like osteoporosis [36], low bone mass and low BMD [37, 38], polycystic ovarian syndrome [39], lung pathologies [40] and chronic kidney disease [41]. In obese patients, where an excess of body fat may be associated with a reduced muscle mass and/or strength (sarcopenic obesity), SMI can be a useful indicator for

identification of subjects with increased risk of sarcopenic obesity or of metabolic syndrome [42].

Therefore, according to the ISCD "the utility of reporting ALMI in every patient referred for DXA BC should be assessed" [43].

*Why use DXA instead of other body composition techniques?*

CT and MRI are still considered, at the present moment, the "gold standard" for body composition studies [44, 45].

Both techniques allow discriminating the different tissue types, providing measurements at compartmental tissue level of skin, skeletal muscle and adipose tissue (with its attendant nonfat components) [45], whereas DXA, as already explained, allows the analysis of BC at the molecular level, assessing FM, LM and BMC.

Computed tomography allows discriminating the different tissue types on the basis of their characteristics of attenuation on the X-ray beam, also estimating the degree of fat infiltration into the muscle and quantifying the fat-free skeletal muscle. CT is able to supply, therefore, information on the "muscle quantity" [46] (the decline with aging is a central aspect of sarcopenia), as well as information on muscle composition (fatty infiltration into skeletal muscle is widely recognized to contribute to the reduction in muscular strength and quality) [47–49]. MRI is another imaging technique able to provide high-resolution body images, clearly identifying the different tissue types and estimating the intramuscular adipose tissue on the basis of the chemical molecular properties of the different anatomical compartments.

Differently, DXA-derived FM is a chemical compartment (triglycerides), which differs from the adipose tissue meant as an anatomical compartment, constituted by adipocytes, collagenous and elastic fibers, fibroblast and capillaries [50], measured by MRI or CT. Thus, DXA-derived FM is lower than CT- or MRI-derived adipose tissue, being closer to adipose tissue minus its protein, mineral and water content [51]. Similarly, DXA-derived LM is higher than skeletal muscle mass measured by CT or MRI, because it includes the sum of body water, total-body protein, carbohydrates, nonfat lipids and soft tissue mineral [50]. It is therefore closer to skeletal muscle tissue plus skin, connective tissues, lean components of the adipose tissue and organ lean tissues [51, 52].

Despite differences in absolute values between FM and LM measured with DXA and skeletal muscle tissue and adipose tissue measured with CT or MRI, studies have found a strong correlation between fat mass assessed by DXA and adipose tissue evaluated by CT or MRI; the same correlation was observed between lean mass assessed by DXA and skeletal muscle tissue evaluated by CT or MRI. Therefore, DXA is an accurate and feasible technique in predicting skeletal muscle mass and fat mass compartments [45, 51, 53, 54].

In particular, ALM has proved to be the best predictor for skeletal muscle mass, according to the high correlation between DXA-derived ALM and MRI-derived skeletal muscle mass for the total body as evaluated by Chen et al. ($r = 0.95$) [51].

Nevertheless, despite their accuracy and precision, CT and MRI have a number of disadvantages compared to DXA.

First of all, CT determines a very high radiation exposure compared to DXA.

Both CT and MRI require a high patient compliance: Lying on a flat table for a few minutes (CT) or more (MRI) may be uncomfortable, the closed and small MRI gantry may lead to feelings of claustrophobia, breath holding is often necessary to minimize motion artifacts associated with breathing, wearing earplugs is usually indispensable due to the MRI system noise and the presence of implants with ferromagnetic components such as pacemaker or metallic prosthesis may be a contraindication in MRI.

Furthermore, both CT and MRI are very expensive systems, which are not always available in small hospitals, clinics and research centers.

The ultrasound imaging (US) is a noninvasive and highly available technique that can be useful in the evaluation of muscle quantity and quality.

It allows to display the muscle morphology and to estimate the degree of fatty infiltration and interstitial fibrosis on the basis of the increase in muscle echo intensity.

Numerous studies have been made in this regard [55, 56] also with the aid of computer-assisted gray-scale analysis of muscle echo intensity [57], but the experience in the field of sarcopenia is still limited.

Furthermore, US requires significant patient compliance (breath holding, need to assume uncomfortable positions for the examination), and the results are operator dependent, resulting in a very low measurement reproducibility.

Bioelectrical impedance analysis (BIA) and anthropometry are the today most applied and relevant alternatives to DXA and imaging methods, in the clinical practice of body composition assessment.

The BIA is a noninvasive and well-validated technique for BC measurement, characterized by speed of execution, ease of use and low cost [58].

BIA measures the impedance offered by a body to the passage of an alternating electric current of low intensity and fixed frequency. Since the conduction capacity is directly proportional to the amount of water and the electrolytes content of the tissue, BIA allows the calculation of total muscle mass, which is the largest water-rich tissue in

the body [59], using population-specific regression equations.

However, it is burdened by being conditioned by the hydration status of the patient and by numerous other variables: Presence of edema, the environment temperature, recent physical activity, assumption of a large meal in the hours preceding the examination, as well as small variations in the positioning of the electrodes and of the limbs during the detection, or an incorrect calibration of the device, in fact, may alter consistently the results.

It is therefore of utmost importance to perform these measurements in as much as possible standardized conditions.

Furthermore, BIA prediction equations proposed in the literature are numerous, and there is no consensus agreement on which is the most reliable, especially in certain patient populations (such as elderly or overweight people), for which a well-validated equation may be not available [60–62].

Anthropometric measures (especially skinfold thickness measurement and limb circumferences) represent another method able to provide information about fat and muscle mass.

Several studies showed the association of a smaller arm circumference with higher mortality risk and functional decline in the elderly [63, 64], but no cutoff values indicative of this risk or validated for the prediction of sarcopenia presence have been yet established.

A study of Rolland et al. [65] investigated the calf circumference as a possible indicator of sarcopenia, finding that a cutoff point of 31 cm is characterized by high specificity (91.4 %) but low sensitivity (44.3 %), and therefore, it has limited usefulness in sarcopenia assessment.

The significant interobserver variability, the poor repeatability, the vulnerability to error, the age-related changes in the distribution of body fat and the loss of elasticity of the skin in the elderly and the absence of consistent cutoff values make the anthropometric measures, although useful in clinical practice, poorly recommended for an accurate assessment of muscle mass.

The main features of the above-mentioned methods for assessment of muscle and fat mass are summarized in Table 4.

## Contraindications and limitations

The effective dose to an adult from whole-body examinations, acquired with last generation DXA equipments, is about 4.7μSv depending on the manufacturer, model and scan mode used.

Whereas the natural background radiation provides approximately 6.7 μSv per day, a total-body DXA scan corresponds to an effective radiation exposure lower than the natural daily dose (for comparison, a chest CT scan submits the patient to an exposure amounting to many years of exposure to natural background radiation) [23, 66, 67].

Radiation exposure for the technical operators is also minimal, provided that the manufacturer's guidelines in the execution of the procedure are respected; thus, it is usually not necessary a lead shielding for the walls of the room of DXA examination [67, 68]. In the literature, there are no specific contraindications to perform a DXA whole-body scan.

International Society of Clinical Densitometry (ISCD) does not recommend to perform total-body DXA in pregnant women because there is not sufficient justification of radiation exposure [69], even if the effective radiation dose of the DXA is extremely low and fetal risks from radiation doses <50 mGy are negligible [70].

The presence in the body of contrast media (iodine-based or barium) or radioactive isotopes, due to a recent radiological investigation or nuclear medicine test, may interfere in some cases with the accuracy of the DXA causing artifacts. Because of the potential confounding effects, in these situation DXA examination should be postponed, with a delay depending on the specific pharmacodynamics of contrast or isotope in question, to allow excretion from the body clearance [71, 72].

Furthermore, each device has a specific table reporting weight limitation and directions to ensure adequate X-ray penetration and accurate measures in patients with certain weights.

**Table 4** Features of the main tools in muscle mass assessment

| | DXA | BIA | Anthropometry | CT | MRI | US |
|---|---|---|---|---|---|---|
| Accuracy | ++ | + | − | +++ | +++ | / |
| Simplicity | ++ | ++ | +++ | − | − | + |
| Reproducibility | +++ | + | − | +++ | +++ | − |
| Availability | ++ | ++ | +++ | + | − | +++ |
| Low cost | + | + | +++ | − | − | ++ |
| Radiation exposure | + | − | − | +++ | − | − |

*DXA* dual-energy X-ray absorptiometry, *BIA* bioimpedance analysis, *CT* computed tomography, *MRI* magnetic resonance imaging, *US* ultrasound

In conclusion, the presence of contrast medium or radioactive isotope not yet excreted, or a patient's weight exceeding weight limits shown in the table are relative contraindications. The only absolute contraindication is represented by pregnancy, due to the risk (albeit low) of fetal exposure to radiation [69].

In very obese subjects, the accuracy of measurements may be affected by a phenomenon of beam hardening. It results from the fact that when a multienergy X-ray beam passes through the body, photons are variably attenuated depending on their energy, and those with lower energy are attenuated much more than those with higher energy. Thus, the higher is tissue thickness, the more is attenuation of the low energy photons, causing a deformation of the spectrum to a greater average energy (beam hardening).

In most cases, this effect is minimized by a proper calibration of the densitometer, but in subjects with very high body sizes studies have shown that it may result in underestimation of body fat [73–76].

Variations in soft tissue hydration may determine errors in estimation of BC: A DXA fundamental assumption is in fact a "constancy" of fat-free body mass hydration [77, 78], even if small changes (in a range from 68.2 to 78.2 %) do not affect the accuracy of fat tissue estimation. Differently, conditions of severe overhydration, such as edema or ascites, may determine significant errors [21, 79]. Experimental models showed how a soft tissue overhydration with normal saline solution or with water determines underestimation or overestimation of actual fat percent, respectively [21].

Simulated experiments suggest DXA fat errors of 1 % with hydration changes of 1–5 %. The possibility of fat estimation errors in the range of several percent, however, exists when soft tissue overhydration is severe, perhaps in the range of 20–25 % of total soft tissue mass [21]. Such severe alterations in hydration status are not common in clinical practice; thus, under normal or even most clinical conditions, the anticipated magnitude of this error is small and this should not pose any substantial limitations to the accuracy of the DXA technique [21].

As previously described, in pixels containing bone, FM and LM, DXA does not directly measure all the three components, but the quantity of FM and LM is determined on the basis of the FM/LM calculated in neighboring bone-free pixels, therefore assuming that the amount of fat over bone is the same as that over the adjacent bone-free tissues.

Thus, in regions where few bone-free pixels are available for direct measurement of FM and LM, such as legs, arms and chest, the accuracy of the determination of the soft tissue may be slightly lower than in bone-free regions [22, 80].

An infiltration of muscle tissue by lipid components, both at intermyocellular level, at interstitium, and at intramyocellular level [81, 82], is a morphologic aspect of aging skeletal muscle. Several studies have shown that fatty infiltration of skeletal muscle is associated with reduced strength and functional status, explaining how infiltration affects muscle function [46, 47, 83]. Contractility, motor unit recruitment and oxidative muscle metabolism are reduced in the presence of fat infiltration [46], and the excess of fatty acids within muscle fibers interferes with the normal cellular signaling [84].

Therefore, the evaluation of intramuscular adipose tissue (IMAT) may be useful in the diagnosis of sarcopenia. However, DXA does not discriminate the different types of fat (visceral, subcutaneous and intramuscular), since DXA provides an assessment of fat mass at molecular level and not at compartmental tissue level [50].

Currently, IMAT is measured on the basis of the tissue density of an area by CT or on the chemical properties of fat and muscle by MRI.

However, new software options are emerging in DXA supporting the opportunity of visceral and intramuscular fat estimation. Very recently, for example, a new application designed to estimate the intramuscular fat with DXA has been developed and is currently under investigation. This system is based on the placement of two ROIs on a DXA whole-body scan, usually at the location of the subject's limb.

A first region, wider, 5 cm high, is placed from side to side of the limb. A second region, 5 cm high but smaller, is placed centered inside the first and extends across the muscle.

The ROIs are usually positioned automatically by a software tool: the larger on the basis of anatomical landmarks, and the smaller using an algorithm based on the percentage of fat inside the larger region. The algorithm detects in fact the "inflection point" of the % fat, that is where the % fat decreases due to the passage from the subcutaneous fat area to the muscle area, setting at this level the boundaries of the smaller region.

However, the ROIs can also be placed manually by the operator with a visual assessment of the image.

The larger ROI then provides a measurement of the total fat mass of the limb in a region of 5 cm, while the smaller ROI provides a measurement of the fat mass of the muscle plus whatever subcutaneous fat is present above and below the muscle region in the two-dimensional DXA projection.

These measurements are combined in a linear equation, together with constants that correlate the results with intramuscular adipose tissue measured by quantitative computed tomography, obtaining an estimate of intramuscular adipose tissue.

Even if DXA examinations are precise, noninvasive and quick, specific technical skills and experience of the operators and calibration procedures are required, in order

to minimize potential confounding factors due to operator or machine variability [85].

An adequate quality assurance program consisting of quality control procedures both of the instrument and of the operator is usually able to guarantee good accuracy, precision and repeatability of the results. Recent studies have shown a high precision of BC measurements with last generation densitometers, specifically for whole-body BC assessment, whose precision has been demonstrated to be higher than regional BC measurements. In particular, a coefficient of variation of 0.5 % has been reported for total-body lean mass assessment, 1.6 % for arms LM, 1.1–1.3 % for legs LM and 1.0 % for trunk LM [23].

Nevertheless, the variability of instrument calibration procedures, hardware and software version between manufacturers may reduce the comparability of measurements between different machines, and this may represent a limit in epidemiological studies and research field. A standardization of methodologies as much as possible on a large scale is therefore a current need [50, 86].

In particular, in clinical practice as regards sarcopenia, there is not interchangeability of measures between manufacturers, different machines and software versions of several parameters used for assessment and follow-up of muscle mass as ALM/height$^2$ (kg/m$^2$) [87–89].

Moreover, it was found that the whole-body BMC was approximately 10 % higher on GE systems compared to Hologic. However, total-body lean soft tissue mass was 7.7 % lower and ALM was approximately 3 % lower on GE systems compared to Hologic [Shepherd 2016].

In a multinational study, Shepherd et al. [90] derived cross-calibration equations to develop universal standardization of whole-body measures between GE Healthcare Lunar and Hologic DXA systems, concluding that the cutoff points of muscle mass are not interchangeable in the definition of sarcopenia.

## Therapy and follow-up

Several studies have investigated the therapeutic options in sarcopenic patients. Treatment possibilities (summarized in Table 5) can be classified in four categories: exercise and physical therapy, drug treatment, diet and nutrition and combination of these.

No unanimous treatment for sarcopenia has been established yet, but combined intervention of exercise, pharmacological therapy and diet demonstrated a potential efficacy [91].

Since the physiological variations or the therapy-induced changes in BC are often small, it is of utmost importance, especially in patients who undergone serial BC tests, to discriminate whether the modifications detected are real (due to an actual biological change) or attributable to precision error inherent to the examination itself [92].

**Table 5** Main therapeutic options for sarcopenia

| Interventions | |
|---|---|
| Exercise and physical therapy | |
| Exercise | PRT |
| | Aerobic (running) |
| Physical therapy | ES (electrical stimulation) |
| Drug treatment | |
| Hormone replacement | Testosterone |
| | GH |
| | DHEA |
| | SARMs |
| Pharmacological intervention | CR mimetics (for example, rapamycin) |
| | ACE inhibitor (for example, enalapril) |
| | Inhibitors of myostatin |
| Diet and nutrition | |
| | Protein |
| | EAAs |
| | HMB |
| | Fatty acids (α-linolenic acid) |
| | Vitamin D |
| | Antioxidants (vitamins E and C) |
| Combination | Diet and exercise |

*PRT* progressive resistance exercise training, *GH* growth hormone, *CR* caloric restriction, *SARMs* selective androgen receptor modulators, *EAAs* essential amino acids, *HMB* β-hydroxy β-methylbutyric acid, *DHEA* dehydroepiandrosterone

In this regard, the clinical significance of a change can be assessed by referring to the "least significant change" (LSC), which represents the smallest difference between successive measurements that can be attributable to a real change (with 95 % confidence) [93].

Thus, if the change noted in the measurement is equal or greater than LSC, it can be attributable to a genuine biological change, while if it is below the LSC values, it can be considered not clinically significant, as due to chance or random errors in measurement [92, 93].

The LSC for 95 % confidence can be defined as:

$$\text{LSC} = 2.77 \times \text{precision error}.$$

Precision error can be expressed as the root-mean-square standard deviation (RMS SD) in g/cm$^2$ of a set of measurements (recommended by ISCD), or as coefficient of variation percent (% CV), i.e., the root-mean-square standard deviation divided by the mean and expressed as a percentage [92].

LSC may vary according to the DXA instrument used, the measurement site, the patient population examined, the technologist's experience (for example, in positioning the patient).

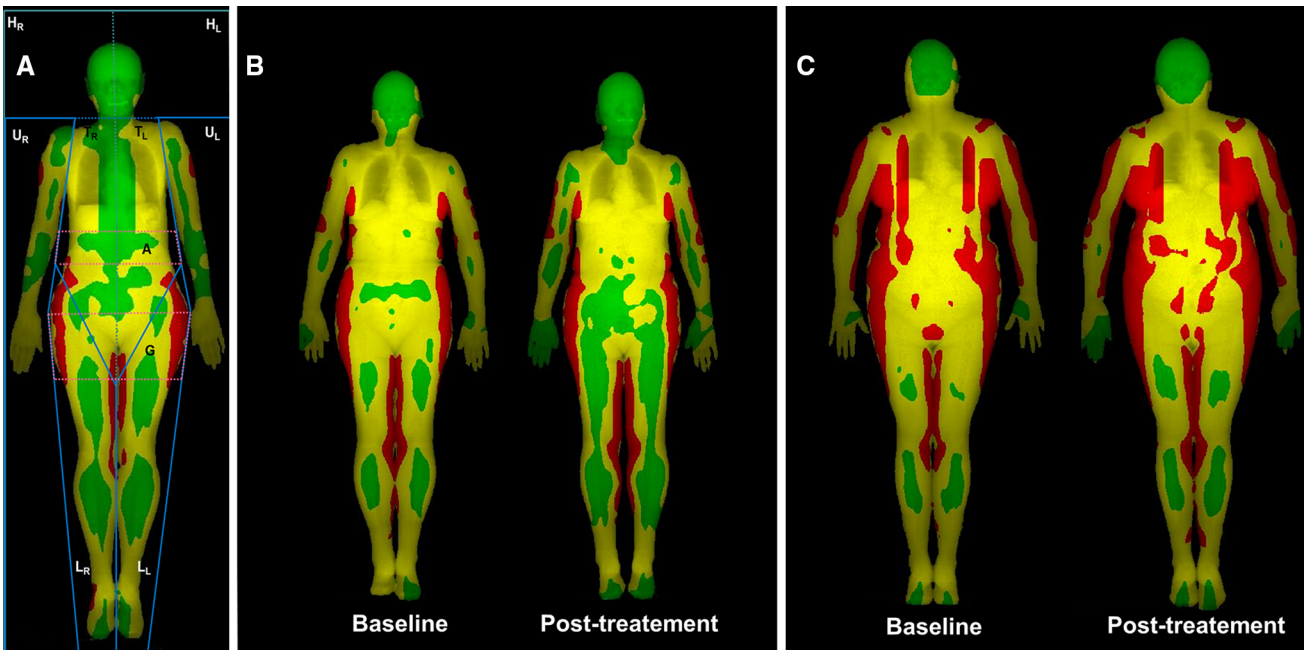


**Fig. 1** **a** An example of *colored* soft tissues map of whole-body scan by DXA highlights the standard ROIs specifics for body composition assessment (head—H, trunk—T, upper limbs—U, lower limbs—L), with the two regions representing by gynoid (G) and android (A) regions, the latter included in the trunk %). In particular, appendicular lean mass (ALM: arms LM + legs LM) is highlighted in *blue* in the figure. The *different colors* represent the fat percentage in the different body areas (*red*, high fat percentage—conventionally >60 %; *yellow*, medium fat percentage—conventionally ≤60 and ≥25 %, *green*, low fat percentage—conventionally <25 %). **b** Significant response to treatment: a 67-year-old woman, weight 65 kg, with a severe sarcopenia (SMI <5.67 kg/m$^2$; handgrip test <16 kg; gait speed test <0.8 m/s) started on a treatment regimen (physical and nutritional therapy + vitamin D supplement). Baseline SMI (ALM/total height squared): 5.66 kg/m$^2$; one year later post-treatment SMI: 6.01 kg/m$^2$; difference is 6 %; LSC = 2.77 × (CV % SMI) = 2.77 × 1 % = 2.77 %; CV % SMI at our DXA center is = 1 %; conclusion: The least significant change (2.77 %) has been exceeded (the SMI has increased of 6 %), leading to the conclusion that there was statistically significant therapeutic response. **c** Non-significant response to treatment: a 71-year-old woman, weight 72 kg, with a severe sarcopenia, (SMI <5.67; kg/m$^2$ and handgrip test <16 kg and gait speed test <0.8 m/s); started on a treatment regimen (physical and nutritional therapy + vitamin D supplement). Baseline SMI (ALM/total height squared): 5.15 kg/m$^2$; one year later post-treatment SMI: 5.27 kg/m$^2$; difference is 2 %; conclusion: The SMI has increased of 2 %, but the LSC (2.77 %) has not been exceeded, leading to the conclusion that there was no statistically significant therapeutic response

In the literature, CV is estimated between 1 and 2 % for the total lean mass, reaching 0.5 % for the better equipments, while precision error of the regional lean mass (upper or lower limbs) presents worst CV values (from 1 to 10 %) [94].

ISCD recommends therefore a precision assessment of each DXA operator, a LSC evaluation for every measurement site and densitometer used [92, 95, 96].

LSC is important also in the sarcopenia assessment with DXA, especially in the follow-up, in order to discriminate when a possible change in LM parameters is actually due to a real worsening or improvement (response to therapy) of the disease. Two examples are shown in Fig. 1.

The LSC has been further used in adults to derive the monitoring time interval (MTI): the time needed to pass between two measures expecting to identify a change that exceeds the LSC. The MTI is simply the ratio of the LSC to the median annual change in LM for a specific age and sex group and specific measurement site. Half of the population will experience a change in LM equal to the LSC for measures taken in the time interval defined by the MTI. MTI can be therefore defined as: MTI = LSC (g)/expected rate of chance (g/years) * years [97] (Fig. 2).

Furthermore, given that the fat-free mass is a major determinant of resting metabolic rate, especially in sedentary people [98], it follows that, in sarcopenic patients, since there is a loss of muscle mass, resting metabolic rate (RMR) also decreases significantly [12, 99–101].

DXA is able to evaluate the resting energy expenditure (REE), which is, according to the American Council on Exercise, synonymous with the RMR, and corresponds at almost the 70 % of the total energy expenditure, representing the minimum amount of energy that a body requires when lying in physiological and mental rest.

DXA estimates the predict REE using the tissue–organ level model developed by Hayes et al. [102], which consist in the summed heat productions from the weights of the brain, skeletal muscle mass, adipose tissue, bone and tissue organs.

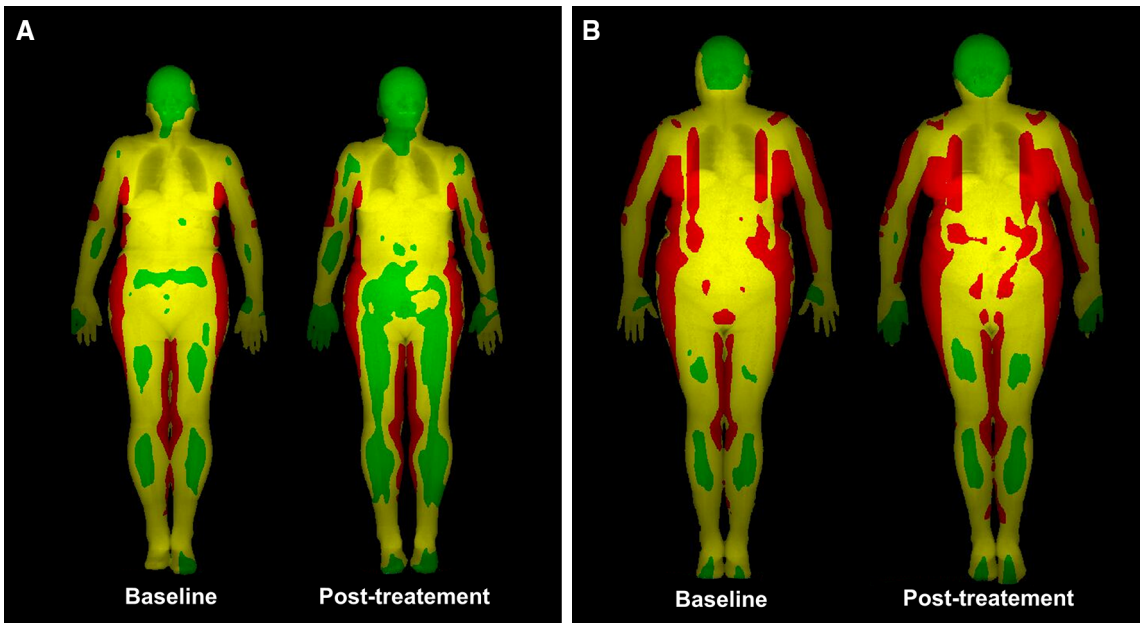


**Fig. 2** **a**, **b** An example of colored soft tissues map of whole-body scan by DXA showing a significative change from baseline to post-treatment images

$$\text{REE} = k_{\text{AT}} \times \text{AT} + k_{\text{SM}} \times \text{SM} + k_{\text{Bone}} \times \text{Bone} + k_{\text{Brain}} \times \text{Brain} + k_{\text{RM}} \times \text{RM} \; [102]$$

where AT is adipose tissue, SM is skeletal muscle mass, residual mass (RM) is the difference between body mass and the four remaining estimated components, and k is the specific resting metabolic rate of individual organs and tissues.

The assessment of REE by DXA may be another important tool in management of sarcopenic subjects, because this offers "a bridge" to effective prevention, treatment and care with the dietary management and exercise regimen for life style-related diseases [103].

## Conclusions

Today, sarcopenia is a clinical problem of major importance for global health, which greatly affects the survival and quality of life of older people. Considering the aging of the world population, its prevalence is growing. Therefore, it will be increasingly important to prevent or postpone the onset of this condition as much as possible. To reach this target, it is essential to know the modifications that aging determine on BC and function, in particular on muscle mass. Several techniques are available in this field, in both clinical practice and research. Dual-energy X-ray absorptiometry is emerging as "gold-standard" method in the diagnosis and characterization of sarcopenia, since it provides with low cost, easy to use and wide availability an accurate and precise evaluation of BC. The distinction of subjects with "physiological" loss of muscle mass from those with "pathological" impoverishment of this compartment, through the assessment of non-bone lean mass parameters, such as appendicular lean mass adjusted for BMI or height (ALM/BMI and ALM/ht$^2$, respectively), is essential. This process should rely on specific cutoff values validated in the literature, however considering the problem of standardization of DXA measures. In addition, DXA can be useful in treatment planning, estimating resting energy expenditure, and in follow-up, for its high reproducible evaluation of modifications in BC.

**Compliance with ethical standards**

**Conflict of interest** The authors declare that they have no conflict of interest.

**Ethical approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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