Sarcopenia: Beyond Muscle Atrophy and into the New Frontiers of Opportunistic Imaging, Precision Medicine, and Machine Learning

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Abstract

As populations continue to age worldwide, the impact of sarcopenia on public health will continue to grow. The clinically relevant and increasingly common diagnosis of sarcopenia is at the confluence of three tectonic shifts in medicine: opportunistic imaging, precision medicine, and machine learning. This review focuses on the state-of-the-art imaging of sarcopenia and provides context for such imaging by discussing the epidemiology, pathophysiology, consequences, and future directions in the field of sarcopenia.

Keywords

- sarcopenia
- myosteatosis
- osteoporosis
- computed tomography
- dual X-ray absorptiometry

Currently ~ 50 million people worldwide have sarcopenia.[1] Broadly conceived, sarcopenia is a significant loss of skeletal muscle mass and function.[1,2] On imaging studies, sarcopenia most commonly manifests as generalized muscle atrophy and fatty infiltration. Yet for patient health and for population health, sarcopenia is much more than fatty muscle atrophy. The clinical significance of sarcopenia cannot be overstated, especially in the context of aging and cancer, where its association with increased morbidity and mortality is well established.[2–7]

Because the worldwide population of people > 60 years of age is projected to double by 2050, the impact of chronic musculoskeletal disorders on the health of the population will be substantial.[8,9] Along with osteoporosis and osteoarthritis, sarcopenia will be such an important determinant of health that both clinicians and radiologists will be expected to contribute to its accurate and timely diagnosis.

At the same time, broad trends in medicine and in imaging are promising to change patient care. In medicine, the current standard of treating a so-called average patient is being replaced by a new trend, called precision treatment, based on individual patient characteristics (phenotypes and genotypes).[10] In imaging, the current standard of making qualitative, often subjective, diagnoses will be increasingly augmented (and even superseded) by the use of quantitative approaches to diagnoses.[11,12] These trends will help determine how the diagnosis of sarcopenia is made and how subsequent patient care is delivered.

In this review, we focus on the state-of-the-art imaging of sarcopenia and provide context for such imaging by discussing the epidemiology, pathophysiology, consequences, and future directions in the field of sarcopenia. Our goal is to provide radiologists with the foundation needed to help evaluate patients affected by this clinically relevant and increasingly common diagnosis.

Epidemiology of Sarcopenia

Early studies on the epidemiology of sarcopenia primarily focused on the loss of muscle mass with aging, usually measured with dual X-ray absorptiometry (DXA).[13] In the past decade, however, that focus has expanded in many directions: from measuring only muscle mass to measuring muscle quality and function; from studies in older adults to

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studies in cancer patients and other populations at risk; and from using DXA to using computed tomography (CT), magnetic resonance imaging (MRI), and ultrasound (US).[14–17]

A fundamental question of how many people have sarcopenia is surprisingly difficult to answer owing to the wide range of diagnostic methodologies and study populations. Prevalence figures are typically based on measures of muscle mass (e.g., DXA-measured appendicular lean mass [ALM]), muscle strength (e.g., grip strength), physical performance (e.g., gait speed), or some combination of the three.

In older adults, such an approach is justified by the fact that weaker grip strength and slower gait speed are associated with adverse health outcomes including increased mortality.[18] A considerable effort has been made to standardize the approach to diagnosing sarcopenia, taking both muscle mass and muscle function into account. ►**Table 1** presents the three most widely used approaches: the European Working Group on Sarcopenia in Older Persons (EWGSOP), the International Working Group on Sarcopenia (IWGS), and the Foundation for the National Institutes of Health (FNIH) Sarcopenia Project.[1,19–21]

In a landmark analysis of 7,113 men and 2,950 women, $\geq$ 65 years of age, using these three methods, the prevalence of sarcopenia varied from 0.5% to 5.3% in men and from 1.8% to 13.3% in women.[22] These data from the FNIH Sarcopenia Project provide robust prevalence figures by pooling data from nine different studies with a broad representation of community-dwelling adults. However, those figures underestimate true prevalence because they exclude multiple vulnerable populations (e.g., individuals in assisted living facilities, nursing homes, or hospitals), where prevalence rates may be much higher.[22]

In cancer patients, the prevalence of sarcopenia has usually been estimated based on CT, rather than DXA, and without functional testing. A meta-analysis of 38 studies of adults with solid tumors reported a prevalence range of 15 to 74%.[23] Another recent systematic review of 26 studies of 5,936 cancer patients before treatment reported a prevalence of 24.6% in men and 13.1% in women.[5]

Regardless of diagnostic methodology and study population, the prevalence of sarcopenia in men and women increases with age. Importantly, as the worldwide population continues to get older, the overall impact of sarcopenia on public health will continue to grow.

Pathophysiology of Sarcopenia

The pathophysiology of sarcopenia is multifactorial, encompassing genetic components, decreased physical activity, poor nutrition, hormonal dysregulation, increased inflammation, and other factors. ►**Table 2** summarizes the common causes of sarcopenia.

Sarcopenia results from an imbalance of anabolic and catabolic pathways that regulate muscle protein synthesis. The most important anabolic muscle pathway is activation of the Akt mammalian target of rapamycin, resulting in increased muscle protein synthesis.[24–26] The most important catabolic pathway is the activation of the ubiquitin-proteasome pathway and calpain and caspases, controlled by the transcription factors forkhead box O and nuclear factor κB, resulting in decreased muscle protein synthesis.[24–26]

Table 2 Common causes of muscle depletion

Age related	Sex hormones
	Apoptosis
	Mitochondrial dysfunction
Disuse	Immobility
	Low physical activity
Cachexia	Cancer
	Chronic illness
Nutrition	Malabsorption
Endocrine	Corticosteroids
	Thyroid hormone
	Growth hormone
	Insulin resistance (insulin-like growth factor 1)
Neurodegenerative	Motor neuron loss

Table 1 Diagnosis of sarcopenia using DXA and functional testing

Definition	Sex	Muscle mass	Muscle function
EWGSOP Moderate sarcopenia	**Women**	ALM/ht^2 < 5.67 kg/m^2	Gait speed < 0.8 m/s or grip strength < 20 kg
	Men	ALM/ht^2 < 7.23 kg/m^2	Gait speed < 0.8 m/s or grip strength < 30 kg
EWGSOP Severe sarcopenia	**Women**	ALM/ht^2 < 5.67 kg/m^2	Gait speed < 0.8 m/s and grip strength < 20 kg
	Men	ALM/ht^2 < 7.23 kg/m^2	Gait speed < 0.8 m/s and grip strength < 30 kg
IWGS Sarcopenia	**Women**	ALM/ht^2 < 5.67 kg/m^2	Gait speed < 1 m/s
	Men	ALM/ht^2 < 7.23 kg/m^2	Gait speed < 1 m/s
FNIH Sarcopenia	**Women**	ALM/BMI < 0.512	Gait speed < 0.8 m/s and grip strength < 16 kg
	Men	ALM/BMI < 0.789	Gait speed < 0.8 m/s and grip strength < 26 kg

Abbreviations: ALM, appendicular lean mass; BMI, body mass index; DXA, dual X-ray absorptiometry; EWGSOP, European Working Group on Sarcopenia in Older Persons; FNIH, Foundation for the National Institutes of Health Sarcopenia Project; IWGS, International Working Group on Sarcopenia.

Aging is generally accompanied by decreased physical activity and protein intake, decreased concentrations of anabolic hormones including testosterone, growth hormone, and insulin-like growth factor 1, increased concentrations of proinflammatory cytokines, and increased muscle fiber denervation that results in downregulation of the anabolic pathway.[25,26] In patients with cancer, the pathophysiology of sarcopenia includes many of the same factors seen with aging including decreased physical activity and increased inflammation. In cancer, increased activity of the ubiquitin-proteasome system is a major factor in muscle catabolism.[27] Various determinates of cachexia, including chronic illness, malnutrition, and chemotherapy, contribute to muscle depletion in patients with cancer.[28]

Considerable research has recently focused on the interaction of muscle, bone, and fat tissues.[29,30] Various studies point to the value of using the terms "sarcopenic obesity," "osteosarcopenia," and "osteosarcopenic obesity" to define combined phenotypes.[29,31,32] These phenotypes not only help elucidate the pathophysiology of sarcopenia but help place it in a broader context. The combination phenotypes also help determine patient prognosis. Similarly, frailty syndrome, cachexia syndrome, and more recently "dysmobility" syndrome associate sarcopenia with multiple other clinical and imaging phenotypes to characterize specific patient populations, help determine prognosis, and improve treatment strategies.[33–37] ►**Table 3** summarizes the diagnostic criteria for syndromes that include muscle depletion.

Table 3 Syndromes that include muscle depletion

Syndrome	Diagnostic criteria
Frailty (Fried et al[33])	Three or more of the following:
	• Unintentional weight loss (10 lb in past year)
	• Self-reported exhaustion
	• **Low grip strength**
	• **Slow walking speed**
	• Low physical activity
Cachexia (Fearon[34])	• Weight loss $>$ 5% in past 6 mo without starvation and/or
	• Weight loss $>$ 2% and BMI $<$ 20 and/or
	• Weight loss $>$ 2% and **sarcopenia**
Cachexia (Evans et al[35])	• Weight loss $>$ 5% in past 12 mo and underlying chronic disease or • BMI $<$ 20 And three of these criteria: • Abnormal biochemistry
	• CRP $>$ 5 mg/L
	• Hb $<$ 12 g/dL
	• Albumin $<$ 3.2 g/dL
	• Fatigue • Anorexia
	• **Decreased muscle strength**
	• **Lean tissue depletion**
Dysmobility (Binkley et al[36])	Three or more of the following:
	• **Low muscle mass**
	• **Slow gait speed**
	• **Low grip strength**
	• High fat mass
	• Osteoporosis
	• History of falls within 1 y

Abbreviations: BMI, body mass index; CRP, C-reactive protein; Hb, hemoglobin.

Consequences of Sarcopenia

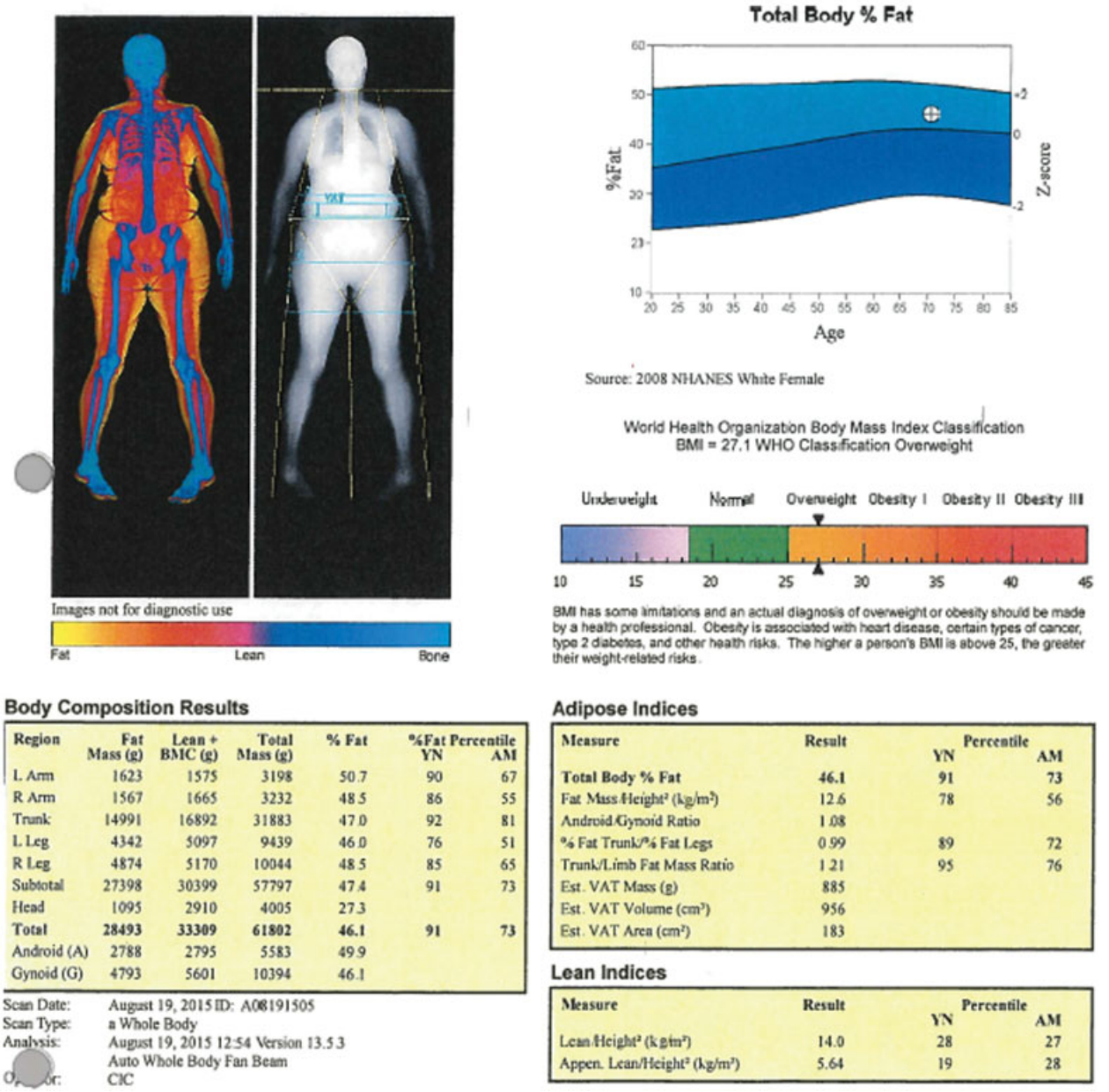
Important consequences of sarcopenia include increased falls, increased physical disability, longer hospital stays, increased number of hospital readmissions, higher rates of postoperative complications, lower quality of life, and higher mortality.[38–43]

In older adults, a recent meta-analysis of health outcomes in 17 prospective studies that defined sarcopenia using EWGSOP criteria (DXA or bioelectrical impedance analysis [BIA]) reported increased mortality in community-dwelling (odds ratio [OR]: 3.39), nursing home (OR: 3.32), and hospital (OR: 4.73) settings.[6] The same study also reported an association of sarcopenia with functional decline (OR: 3.03), increased falls (OR: 3.23), and increased hospitalizations (OR: 1.57).[6]

In cancer patients, a meta-analysis of 38 studies containing 7,843 participants (nonhematologic solid tumors) reported an association between CT-measured sarcopenia and overall survival (hazard ratio: 1.44).[23] A recent systematic review of 22 studies ($n = 5{,}351$), reported an association between pretreatment CT-measured sarcopenia and overall decreased survival in 19 of 22 studies.[5] The authors also reported an association of sarcopenia with chemotoxicity in 5 of 6 studies and with postoperative complications in 8 of 11 studies. The evidence for decreased survival in patients with sarcopenia is most established for urothelial, colorectal, hepatocellular, and pancreatic cancers.[7]

In noncancer patients, CT-measured sarcopenia was associated with increased mortality in patients with chronic liver disease, chronic renal disease, pneumonia, and sepsis as well as in intensive care unit (ICU), trauma, vascular surgery, general surgery, orthopaedic surgery, and transplant patients.[44–56] In a cohort of 450 trauma patients age $\geq$ 65 years admitted to the ICU, CT-measured sarcopenia was associated with 1-year mortality.[15] In our study of 274 hip fracture patients followed for 8 years, lower paraspinous muscle density at the T12 level on chest and abdomen CT was associated with increased all-cause mortality.[57]

The consequences of syndromes associated with sarcopenia (e.g., frailty, cachexia, and dysmobility) are beyond the scope of this discussion. However, these syndromes combined with sarcopenia generally confer a worse prognosis for patients, compared with sarcopenia diagnosed by imaging alone.



Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	%Fat Percentile AM
L Arm	1623	1575	3198	50.7	90	67
R Arm	1567	1665	3232	48.5	86	55
Trunk	14991	16892	31883	47.0	92	81
L Leg	4342	5097	9439	46.0	76	51
R Leg	4874	5170	10044	48.5	85	65
Subtotal	27398	30399	57797	47.4	91	73
Head	1095	2910	4005	27.3		
Total	**28493**	**33309**	**61802**	**46.1**	**91**	**73**
Android (A)	2788	2795	5583	49.9		
Gynoid (G)	4793	5601	10394	46.1		

Scan Date: August 19, 2015 ID: A08191505
Scan Type: a Whole Body
Analysis: August 19, 2015 12:54 Version 13.5.3
Auto Whole Body Fan Beam
Operator: CIC

Measure	Result	Percentile YN	Percentile AM
Total Body % Fat	**46.1**	**91**	**73**
Fat Mass/Height² (kg/m²)	12.6	78	56
Android/Gynoid Ratio	1.08		
% Fat Trunk/% Fat Legs	0.99	89	72
Trunk/Limb Fat Mass Ratio	1.21	95	76
Est. VAT Mass (g)	885		
Est. VAT Volume (cm³)	956		
Est. VAT Area (cm²)	183		

Measure	Result	Percentile YN	Percentile AM
Lean/Height² (kg/m²)	14.0	28	27
Appen. Lean/Height² (kg/m²)	5.64	19	28

Fig. 1 A 70-year-old woman presents for sarcopenia evaluation. Dual X-ray absorptiometry of the whole body shows that the appendicular lean mass, adjusted for height, is 5.64 kg/m^2. Based on the International Working Group on Sarcopenia cut point for women (< 5.67 kg/m^2), she meets the diagnostic criterion for sarcopenia.

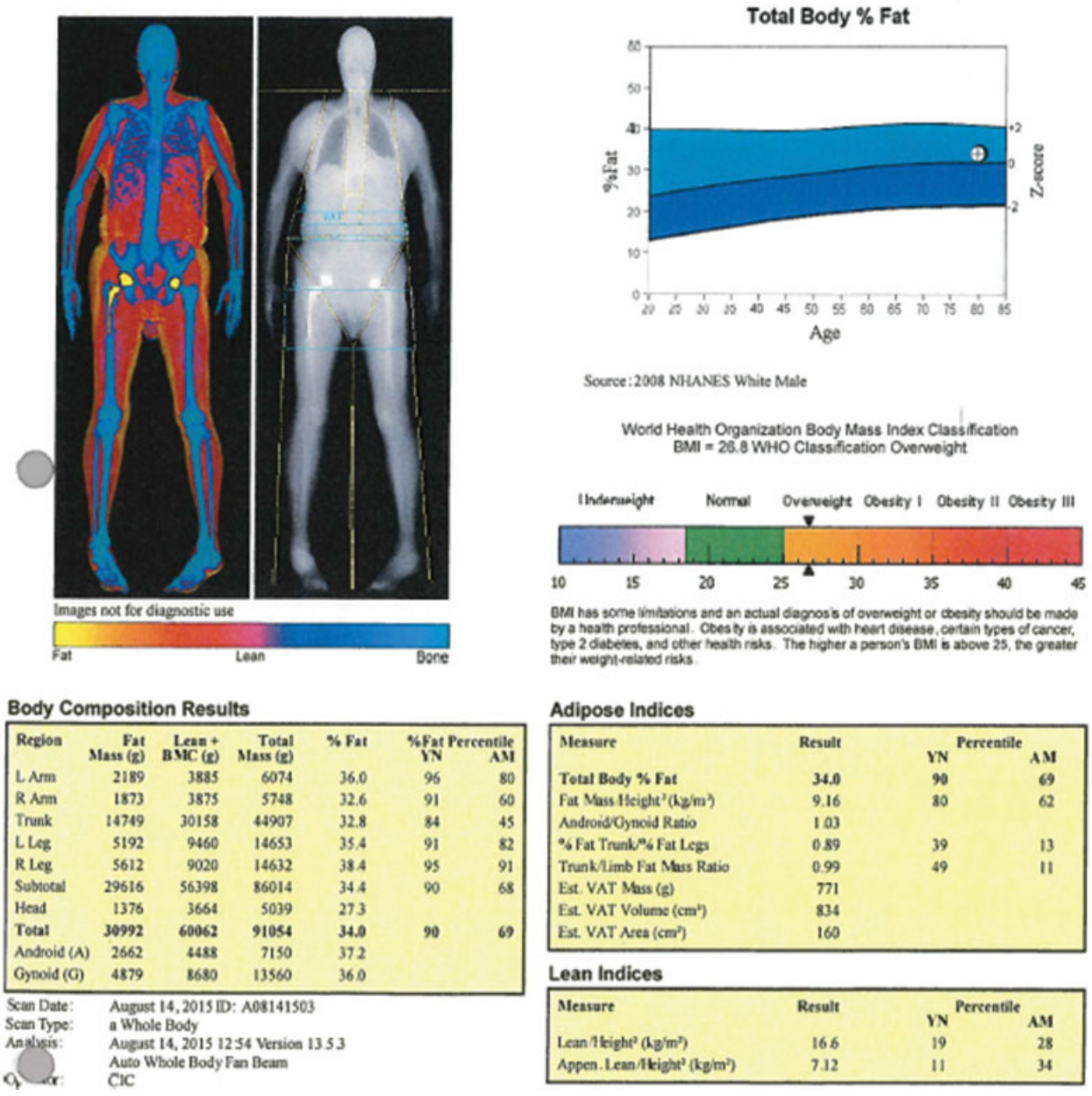
Diagnosis of Sarcopenia

Clinical evaluation of patients for sarcopenia usually includes measurements of grip strength and/or walking speed. Additional tests that may be used include the chair stand test and the short physical performance battery (SPBB). The SPBB uses tasks that mimic daily activities to examine three aspects of lower extremity function: balance, gait speed, and getting in and out of a chair.[58]

Most consensus groups, including EWGSOP, IWGS, and FNIH, recommend functional testing before muscle mass measurements. Focused on older adults, these groups consider the diagnosis of sarcopenia to require both low muscle function and low muscle mass. In cancer patients, however, such consensus is lacking, and the role of functional testing as a supplement to muscle mass measurements is not well defined. In fact, the relationship between muscle mass, strength, and mobility may not be the same in community-dwelling older adults compared with more vulnerable populations.

Role of Imaging

Today, imaging of sarcopenia may be done using DXA, CT, MRI, or US. There are some important similarities and differences in how these modalities are used to evaluate patients for



Region	Fat Mass (g)	Lean + BMC (g)	Total Mass (g)	% Fat	%Fat Percentile YN	AM
L Arm	2189	3885	6074	36.0	96	80
R Arm	1873	3875	5748	32.6	91	60
Trunk	14749	30158	44907	32.8	84	45
L Leg	5192	9460	14653	35.4	91	82
R Leg	5612	9020	14632	38.4	95	91
Subtotal	29616	56398	86014	34.4	90	68
Head	1376	3664	5039	27.3		
Total	**30992**	**60062**	**91054**	**34.0**	**90**	**69**
Android (A)	2662	4488	7150	37.2		
Gynoid (G)	4879	8680	13560	36.0		

Measure	Result	Percentile YN	AM
Total Body % Fat	**34.0**	**90**	**69**
Fat Mass Height² (kg/m²)	9.16	80	62
Android/Gynoid Ratio	1.03		
% Fat Trunk/% Fat Legs	0.89	39	13
Trunk/Limb Fat Mass Ratio	0.99	49	11
Est. VAT Mass (g)	771		
Est. VAT Volume (cm³)	834		
Est. VAT Area (cm²)	160		

Measure	Result	Percentile YN	AM
Lean/Height² (kg/m²)	16.6	19	28
Appen. Lean/Height² (kg/m²)	7.12	11	34

Fig. 2 An 80-year-old man presents for sarcopenia evaluation. Dual X-ray absorptiometry of the whole body shows that the appendicular lean mass, adjusted for height, is 7.12 kg/m^2. Based on the International Working Group on Sarcopenia cut point for men ($<$ 7.23 kg/m^2), he meets the diagnostic criterion for sarcopenia.

sarcopenia. Although each modality provides quantitative information on muscle mass, it is difficult to compare results across technologies. Except for DXA, each modality also provides some information on muscle quality, of which muscle fat infiltration (i.e., myosteatosis) is the most relevant. Again, with the exception of DXA, each modality could benefit from a more standardized approach to muscle measurement, and each poses unique challenges to such standardization.

Radiologists active in sarcopenia research have an opportunity to help move the field forward by determining how to adapt these imaging tools from research environments to clinical settings. In the near future, clinical radiologists will be asked to help diagnose sarcopenia on DXA or CT. On DXA, radiologists will likely use a whole-body scan to measure ALM (►**Figs. 1** and **2**). On CT, they will likely use muscle cross-sectional area and muscle attenuation. With both DXA and CT, increasing consensus on how best to use these technologies for patient care is likely. With MRI and US, the technical challenges (e.g., standardization) as well as clinical implementation are less established. For this reason, we focus our discussion on DXA and CT, the two modalities with the most pressing clinical relevance.

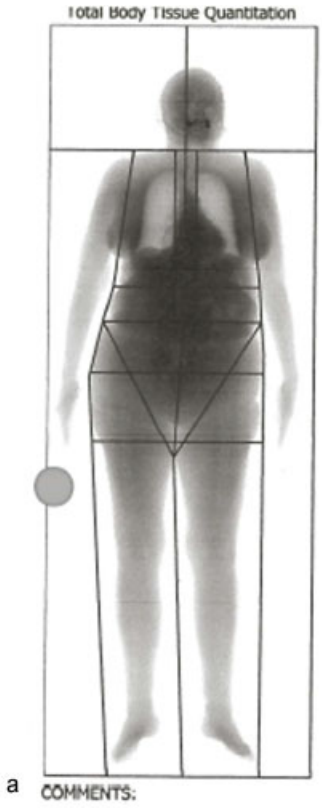
Lessons from Imaging of Osteoporosis

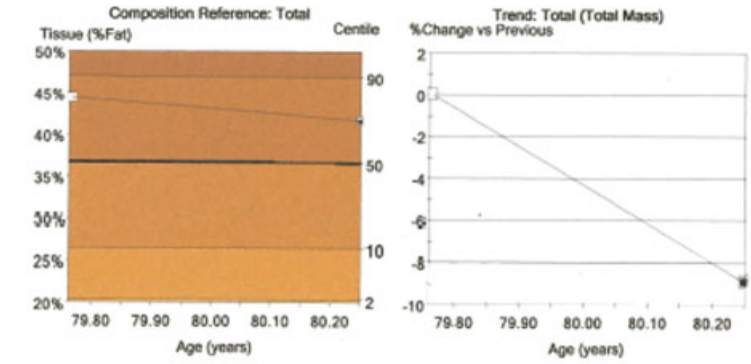
When determining the optimal approach to imaging of sarcopenia with DXA or CT, it is valuable to consider how osteoporosis is imaged using the same modalities. Most radiologists

are familiar with how DXA is used in the clinical evaluation of osteoporosis. In patients with suspected osteoporosis, DXA of the spine and hip helps diagnose osteoporosis, assess fracture risk, determine the need for pharmacologic therapy, and monitor therapy or disease progression. Could a similar approach be used to evaluate sarcopenia?

With osteoporosis, a standardized approach to the diagnosis using DXA helped promote both research and clinical uses of the modality. In 1994, the World Health Organization operationalized the definition of osteoporosis as bone mineral density (BMD) $>$ 2.5 standard deviations (SDs) below young-healthy normal reference.[59] Soon after, the term "T-score" was coined and widely adapted to DXA interpretation and reporting.

With sarcopenia, standardized approaches to diagnosis using DXA were proposed by the EWGSOP in 2010, the IWGS in 2011, the FNIH in 2014, and the Asian Working Group for Sarcopenia in 2014. All are essentially based on the T-score, defining the DXA cut point for sarcopenia as 2 SDs below young normal reference. Unlike the definition of osteoporosis, all consensus definitions of sarcopenia rely on functional measures, as well as DXA-based measurement.





Region	Tissue (%Fat) [1]	Centile [2,3]	Total Mass (lbs)	Fat (lbs) [1]	Lean (lbs) [1]	BMC (lbs)
Legs	40.2	-	54.1	21.05	31.28	1.73
Trunk	44.8	-	84.4	37.20	45.86	1.36
Total	41.8	74	163.5	66.36	92.29	4.84

Trend: Total [1]

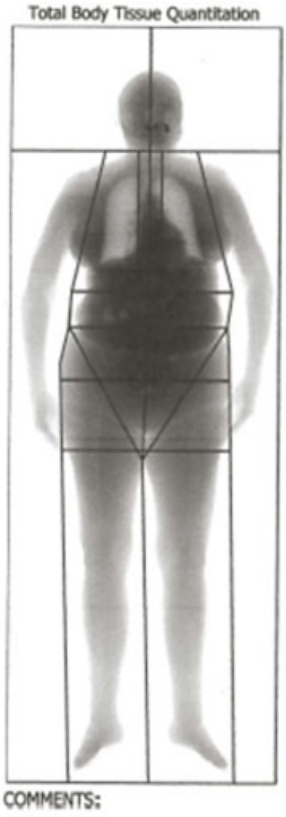
Measured Date	Age (years)	Total Mass (lbs)	Change vs Previous (lbs)	Change vs Previous (%)
02/22/2013	80.2	163.5	-16.0	-8.9
08/29/2012	79.7	179.5	-	-

b

BODY COMPOSITION

Region	Tissue [1] (%Fat)	Region (%Fat)	Tissue [1] (lbs)	Fat [1] (lbs)	Lean [1] (lbs)	BMC (lbs)	Total Mass (lbs)
Left Arm	42.3	40.5	6.96	2.94	4.02	0.30	7.3
Left Leg	40.0	38.7	25.76	10.30	15.46	0.84	26.6
Left Trunk	45.9	45.2	42.59	19.54	23.05	0.66	43.2
Left Total	42.0	40.8	80.97	34.03	46.94	2.53	83.5
Right Arm	42.9	41.3	7.52	3.22	4.30	0.29	7.8
Right Leg	40.5	39.1	26.57	10.75	15.82	0.89	27.5
Right Trunk	43.6	42.9	40.47	17.66	22.81	0.70	41.2
Right Total	41.6	40.4	77.68	32.32	45.35	2.31	80.0
Arms	42.6	40.9	14.48	6.17	8.32	0.59	15.1
Legs	40.2	38.9	52.33	21.05	31.28	1.73	54.1
Trunk	44.8	44.1	83.06	37.20	45.86	1.36	84.4
Android	45.0	44.6	14.21	6.39	7.82	0.11	14.3
Gynoid	45.2	44.4	24.30	10.98	13.32	0.46	24.8
Total	41.8	40.6	158.64	66.36	92.29	4.84	163.5

Fig. 3 An 80-year-old woman evaluated before and after an 18-month period of resistance training. (**a**) Baseline whole-body dual X-ray absorptiometry (DXA) and (**b**) additional DXA results show her appendicular lean mass (left arm + left leg + right arm + right leg) is 39.60 lb. (**c**) Follow-up DXA and (**d**) additional DXA results show her appendicular lean mass is 42.38 lb. During the 18 months of training, she gained 2.78 lb of lean mass.



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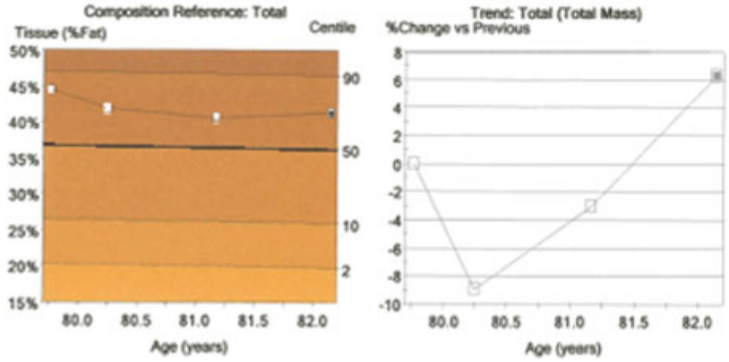


Region	Tissue[1] (%Fat)	Centile[2,3]	Total Mass (lbs)	Fat[1] (lbs)	Lean[1] (lbs)	BMC (lbs)
Legs	39.7	-	55.8	21.50	32.67	1.65
Trunk	44.7	-	86.2	37.90	46.98	1.37
Total	41.4	74	168.6	67.75	96.08	4.74

Trend: Total[1]

Measured Date	Age (years)	Total Mass (lbs)	Change vs Previous (lbs)	Change vs Previous (%)
01/14/2015	82.1	168.6	10.0	6.3
01/22/2014	81.1	158.6	-4.9	-3.0
02/22/2013	80.2	163.5	-16.0	-8.9
08/29/2012	79.7	179.5	-	-

d

BODY COMPOSITION

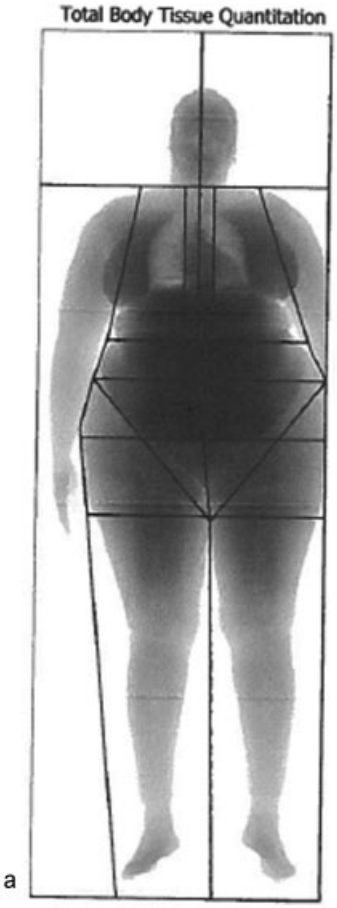
Region	Tissue[1] (%Fat)	Region (%Fat)	Tissue[1] (lbs)	Fat[1] (lbs)	Lean[1] (lbs)	BMC (lbs)	Total Mass (lbs)
Left Arm	39.4	38.0	7.42	2.92	4.49	0.28	7.7
Left Leg	39.7	38.5	27.12	10.76	16.36	0.80	27.9
Left Trunk	45.0	44.3	43.51	19.57	23.94	0.66	44.2
Left Total	41.5	40.4	82.44	34.22	48.22	2.35	84.8
Right Arm	40.4	39.0	8.75	3.53	5.22	0.30	9.1
Right Leg	39.7	38.5	27.05	10.75	16.31	0.85	27.9
Right Trunk	44.3	43.6	41.37	18.33	23.04	0.70	42.1
Right Total	41.2	40.0	81.39	33.53	47.86	2.39	83.8
Arms	39.9	38.5	16.17	6.46	9.72	0.58	16.7
Legs	39.7	38.5	54.17	21.50	32.67	1.65	55.8
Trunk	44.7	43.9	84.88	37.90	46.98	1.37	86.2
Android	45.4	45.0	14.90	6.76	8.14	0.11	15.0
Gynoid	45.9	45.1	25.95	11.90	14.05	0.46	26.4
Total	41.4	40.2	163.83	67.75	96.08	4.74	168.6

Fig. 3 (*Continued*)

In contrast to DXA, the use of CT in the evaluation of osteoporosis has not been uniformly embraced, and in the United States, it is confined mostly to research settings. Traditional clinical quantitative CT (QCT) measurements are performed with the help of specialized software and calibration phantoms. Diagnosis is usually made based on trabecular BMD of the lumbar vertebrae: BMD between 80 mg/cm^3 and 120 mg/cm^3 is used to define osteopenia and BMD $<$ 80 mg/cm^3 is used to define osteoporosis.[60] At L1, trabecular bone attenuation $\leq$ 90 HU appears to represent an optimal threshold for determining significantly increased risk for moderate or severe osteoporotic vertebral compression fractures.[61] Methods based on T-score for diagnosis using CT of the proximal femur have recently gained acceptance. Current use of CT for the evaluation of sarcopenia is similar in that some standardization exists, but it is not as developed as DXA.

DXA for Sarcopenia Evaluation

DXA is currently the most widely used technology for the evaluation of sarcopenia, especially in nonhospitalized patients (►**Fig. 3**).



BODY COMPOSITION

(e) - Estimated

Region	Tissue [1] (%Fat)	Region (%Fat)	Tissue [1] (lbs)	Fat [1] (lbs)	Lean [1] (lbs)	BMC (lbs)	Total Mass (lbs)
(e) Left Arm	48.2	47.0	15.39	7.42	7.97	0.41	15.8
(e) Left Leg	52.2	51.2	51.88	27.10	24.78	1.06	52.9
(e) Left Trunk	57.6	56.6	62.78	36.18	26.60	1.09	63.9
(e) Left Total	53.0	51.8	135.24	71.71	63.53	3.22	138.5
Right Arm	48.2	47.0	15.39	7.42	7.97	0.41	15.8
Right Leg	52.2	51.2	51.88	27.10	24.78	1.06	52.9
Right Trunk	57.6	56.6	62.72	36.15	26.56	1.11	63.8
Right Total	53.2	52.0	134.46	71.52	62.95	3.13	137.6
(e) Arms	48.2	47.0	30.78	14.85	15.93	0.83	31.6
(e) Legs	52.2	51.2	103.76	54.20	49.56	2.13	105.9
(e) Trunk	57.6	56.6	125.49	72.33	53.16	2.20	127.7
(e) Android	61.0	60.9	22.30	13.61	8.69	0.05	22.4
(e) Gynoid	58.6	57.8	49.30	28.87	20.42	0.62	49.9
(e) Total	53.1	51.9	269.70	143.23	126.48	6.35	276.1

FAT MASS RATIOS

b

Fig. 4 A 61-year-old woman presents for sarcopenia evaluation. (**a**) Whole-body dual X-ray absorptiometry (DXA) image shows that the left arm did not fit within the scan window. (**b**) Additional DXA results show that the left arm lean mass (as well as fat and bone mass) was estimated (e) based on the measurement of the right arm.

Technical Considerations

To measure muscle mass using DXA, a whole-body scan is obtained. These scans are obtained on the same scanners used for osteoporosis screening, but they require dedicated software for whole-body analysis.

Before DXA was widely used for the evaluation of osteoporosis, there was general agreement on the measurement sites (i.e., spine, hip, and forearm) and the relevant regions of interest (i.e., L1–L4, total hip, and femoral neck). Similarly, for the DXA-based evaluation of sarcopenia, there is already general agreement on the measurement site (i.e., whole body) and the relevant region of interest (i.e., ALM).

DXA has several important limitations when measuring lean mass (►**Figs. 4** and **5**). Whole-body lean mass includes all tissues that are not bone or fat (e.g., organs) and therefore is not a reliable biomarker for sarcopenia. Consequently, ALM, which combines all not-bone and not-fat tissues of the upper and lower extremities, is the most commonly used phenotype for sarcopenia. In obese individuals, lean mass may be overestimated by as much as 15%.[62,63]

One important benefit of DXA is that the whole-body DXA scan measures fat mass and BMD at the same time it measures lean mass. This may help assess various clinical syndromes that involve muscle depletion (e.g., cachexia and dysmobility).

Clinical Considerations

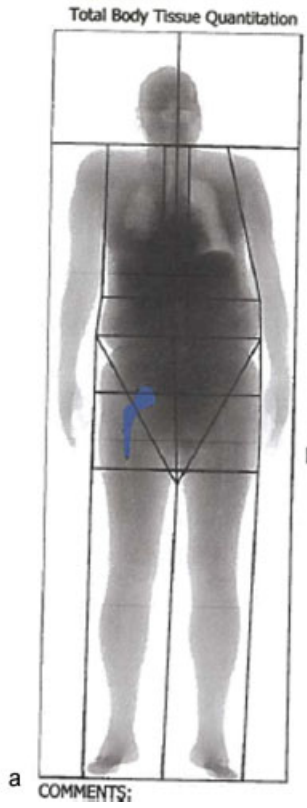
Ideally, obtaining a DXA would help diagnose sarcopenia, assess prognosis, determine the need for intervention, and monitor that intervention or disease progression. Although there is some agreement on the diagnostic thresholds using DXA (►**Table 1**), these have mainly been applied in research rather than clinical environments. For this reason, perhaps the most immediate opportunity for DXA is in helping with prognosis and monitoring disease progression.

Computed Tomography for Sarcopenia Evaluation

CT has been widely used in the assessment of sarcopenia, especially in patients with cancer. Unlike DXA, which only measures muscle quantity, CT measures muscle quantity and muscle quality (e.g., myosteatosis). CT assessment of myosteatosis is possible because increased fat infiltration in muscle results in lower CT attenuation of muscle.

Technical Considerations

Unlike DXA, which typically measures whole-body lean mass or ALM, CT measurements of muscle are usually limited to a particular anatomical region. Sarcopenia is typically defined based on muscle cross-sectional area (often indexed for



BODY COMPOSITION

Region	Tissue [1] (%Fat)	Region (%Fat)	Tissue [1] (lbs)	Fat [1] (lbs)	Lean [1] (lbs)	BMC (lbs)	Total Mass (lbs)
Left Arm	31.9	30.2	9.71	3.09	6.61	0.54	10.2
Left Leg	33.3	31.9	34.74	11.55	23.18	1.50	36.2
Left Trunk	34.9	34.3	67.04	23.40	43.64	1.28	68.3
Left Total	33.8	32.7	114.86	38.77	76.08	3.74	118.6
Right Arm	32.2	30.5	10.01	3.22	6.78	0.56	10.6
Right Leg	31.9	30.6	32.27	10.29	21.98	1.39	33.7
Right Trunk	34.0	33.4	61.61	20.93	40.68	1.13	62.7
Right Total	32.4	31.3	110.79	35.90	74.89	4.00	114.8
Arms	32.0	30.4	19.72	6.32	13.40	1.09	20.8
Legs	32.6	31.2	67.00	21.84	45.16	2.89	69.9
Trunk	34.5	33.8	128.65	44.33	84.33	2.41	131.1
Android	33.5	33.2	21.39	7.16	14.23	0.18	21.6
Gynoid	37.5	36.7	31.93	11.97	19.96	0.66	32.6
Total	33.1	32.0	225.64	74.67	150.97	7.74	233.4

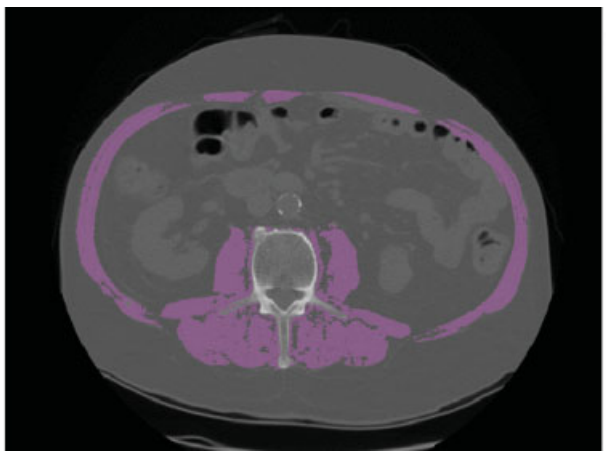
b

Fig. 5 A 66-year-old man presents for sarcopenia evaluation. (**a**) Whole-body dual X-ray absorptiometry (DXA) image shows a right total hip arthroplasty. (**b**) Additional DXA results show that the right leg mass measurement was not adjusted to account for the artifact.

patient height in square meters, referred to as the "skeletal muscle index") and muscle attenuation. Many different approaches have been described.

Abdominal CT examinations have been used to measure sarcopenia in several large prospective epidemiological studies of aging including the Framingham Study and the Osteoporotic Fractures in Men Study.[64,65] Abdominal CT also has been used in the vast majority of cancer studies. Thigh CTs have been used much less often in large cohorts, with a notable exception of the Health Aging and Body Composition study.[66] Several smaller studies have used chest, spine, or neck CTs.[67–70]

Depending on the CT chosen, various muscles and muscle groups have been measured. On abdominal CTs, the region of interest (ROI) used to measure sarcopenia may include the psoas muscles, the paraspinous muscles, and all visualized abdominal muscles (►**Figs. 6** and **7**). There is also variability about where these muscle groups are measured and on how many CT slices. The two most common approaches are to



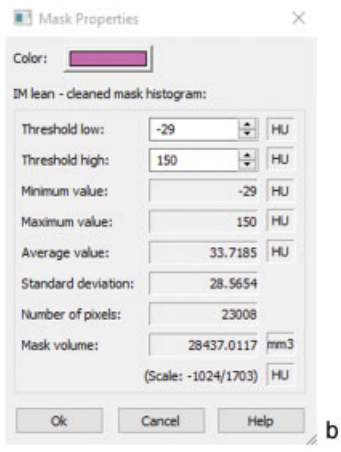


Fig. 6 A 65-year-old woman presents for sarcopenia evaluation. (**a**) Computed tomography image at L3 shows segmented psoas, paraspinous, and abdominal muscles. (**b**) Using − 29 to + 150 HU threshold, the muscle measures 28.4 cm^2. The skeletal muscle index (SMI) = cross-sectional area (CSA)/ht^2 = 113.6/2.3 = 49.4 cm^2/m^2. Based on the SMI threshold for women (< 38.5 cm^2/m^2), she does not meet the diagnostic criterion for sarcopenia.

Fig. 7 A 78-year-old woman presents for sarcopenia evaluation. (**a**) Computed tomography image at L3 shows segmented psoas, paraspinous, and abdominal muscles. (**b**) Using − 29 to + 150 HU threshold, the muscle measures is 19.0 cm^2. The skeletal muscle index (SMI) = cross-sectional area (CSA)/ht^2 = 76/2.8 = 27.1 cm^2/m^2. Based on the SMI threshold for men (< 52.4 cm^2/m^2), he meets the diagnostic criterion for sarcopenia.

measure all visualized muscles at the L3 level or measure just the psoas muscles at the L4 level.

Defining or "segmenting" muscle ROIs usually are performed on a clinical picture archiving and communication system (PACS) workstation or on a separate computer with specialized segmentation software (e.g., Mimics, OsiriX, Image J, Slice-O-Matic, 3D Slicer). Using specialized software allows for standardized thresholding of muscle from − 29 to + 150 HU and fat from − 30 to − 190 HU. In contrast, current PACS-based measurements do not allow for thresholding but are much faster to perform and are more easily incorporated into the clinical radiology workflow (►**Figs. 8** and **9**).

With specialized software, the most commonly obtained measurements are as follows (►**Fig. 10**):

1. Muscle area: the cross-sectional area of tissue contained within the ROI with attenuation between − 29 and + 150 HU
2. Intermuscular adipose tissue area: the cross-section of tissue contained within the ROI with attenuation between − 190 and − 30 HU
3. Muscle density: the mean attenuation of tissue contained within the ROI, after applying attenuation thresholds of − 29 and + 150 HU
4. Intermuscular fat density: the mean attenuation of tissue contained within the ROI with attenuation between − 190 and − 30 HU.

Different CT measurements of muscle (just listed) may have variable associations within the

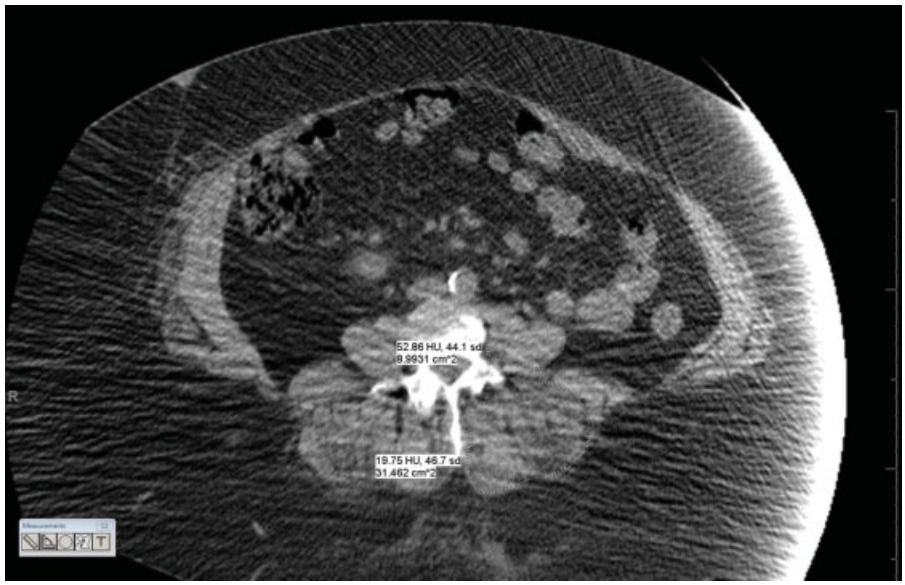


Fig. 8 A 68-year-old woman presents for sarcopenia evaluation. Computed tomography at L4 shows a streak artifact that may invalidate the measurements of psoas and paraspinous muscles.

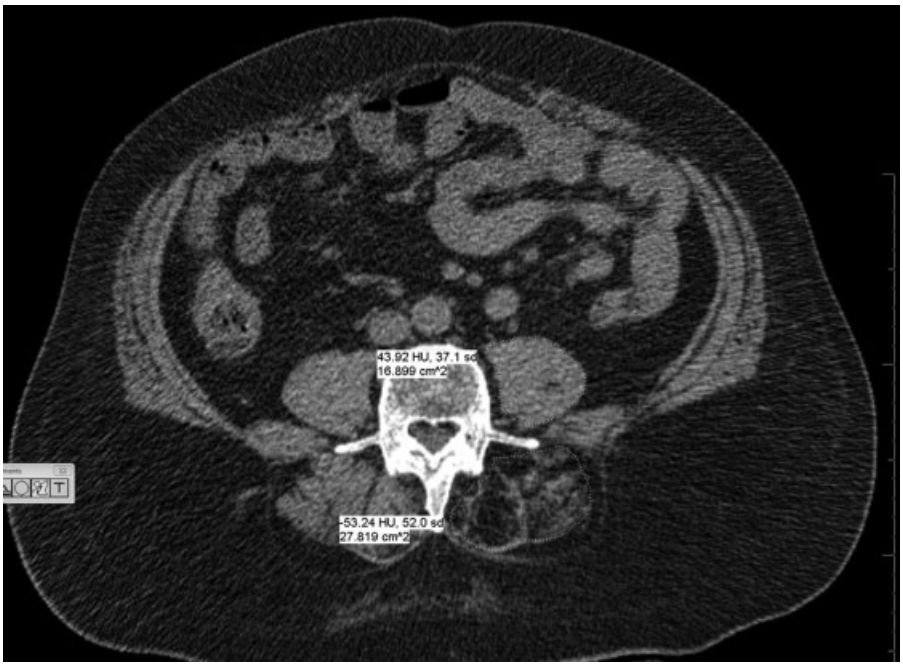


Fig. 9 A 54-year-old woman presents for sarcopenia evaluation. Computed tomography at L4 shows focal atrophy of left paraspinous muscle, possibly related to a prior lumbar spine procedure.

myocytes (intramyocellular lipids) and in between the myocytes (extramyocellular lipids). Determining which approach is best suited for clinical use may require correlating each type of measurement with health outcomes, muscle function, and muscle histochemistry or MR spectroscopy. For now, there is little standardization. But an increasing body of literature supports using PACS-based segmentation to measure intramuscular fat amount or density, without applying any tissue thresholds.[57,64] Such an approach is especially well suited to so-called opportunistic CT screenings.

When measuring muscle metrics on CT, standardized acquisition parameters are important. In particular, studies show that intravenous contrast can impact results.[71] Changes in kilovoltage peak can affect muscle measurements, although much less than for bone measurements. For this reason, some investigators have suggested using calibration phantoms during CT measurements of muscle, analogous to the QCT measurements of bone.[72]

Comparing technical issues related to CT measurement of bone with muscle offers some context. After decades of CT-based evaluation of osteoporosis, there is general agreement on the skeletal sites (vertebra and proximal femur) but little agreement on the size, shape, and placement of the ROIs. The same lack of standardization may affect the CT evaluation of sarcopenia. As with osteoporosis, it is likely that practical clinical imperatives will help drive the field forward.

Clinical Considerations

Before CT measurement of sarcopenia can be widely adapted to clinical practice, further agreement on what output variables are most clinically relevant is warranted. Although muscle cross-sectional area (CSA) and muscle attenuation (MA) are directly measured, many studies have used derived variables including skeletal muscle index (SMI) = CSA/height,[2] skeletal muscle gauge = SMI × MA, and radiographic density ratio = MA × SD of MA. Of these, SMI of total abdominal muscles is the most widely used.

Using the EWGSOP cut point for sarcopenia ($T < -2$), CT-based diagnostic thresholds for sarcopenia have been proposed. The most widely used thresholds to diagnose CT sarcopenia are SMI < 52.4 cm^2/m^2 in men and SMI < 38.5 cm^2/m^2 in women. These thresholds were proposed in seminal work by Prado et al that has now been cited in > 900 subsequent publications.[73] That research specifically analyzed CTs of obese patients being treated for solid tumors of the respiratory or gastrointestinal tract, and it likely included patients with both cancer-related cachexia and other causes of muscle depletion. Another important caveat: These cut points are valid only if the measurement is obtained using abdominal CT at the level of L3 with a ROI that uses total skeletal muscle CSA (including abdominal muscles) and thresholds of -29 to $+150$ HU.

In addition to its use for the diagnosis of sarcopenia, CT may be used to help determine prognosis. The association between CT-derived muscle metrics and adverse patient outcomes has been well documented, especially in cancer patients, surgical noncancer patients, and trauma patients. Increasing evidence also indicates that longitudinal CT measurements may be used to monitor disease progression and as an additional prognostic variable.[66]

Effective integration of CT-based diagnosis of sarcopenia into patient care will require collaboration with referring clinicians, especially geriatricians, oncologists, and surgeons. An incidental finding of age-related sarcopenia in an elderly patient may have different implications than muscle wasting in a patient with cancer cachexia. In an elderly patient,

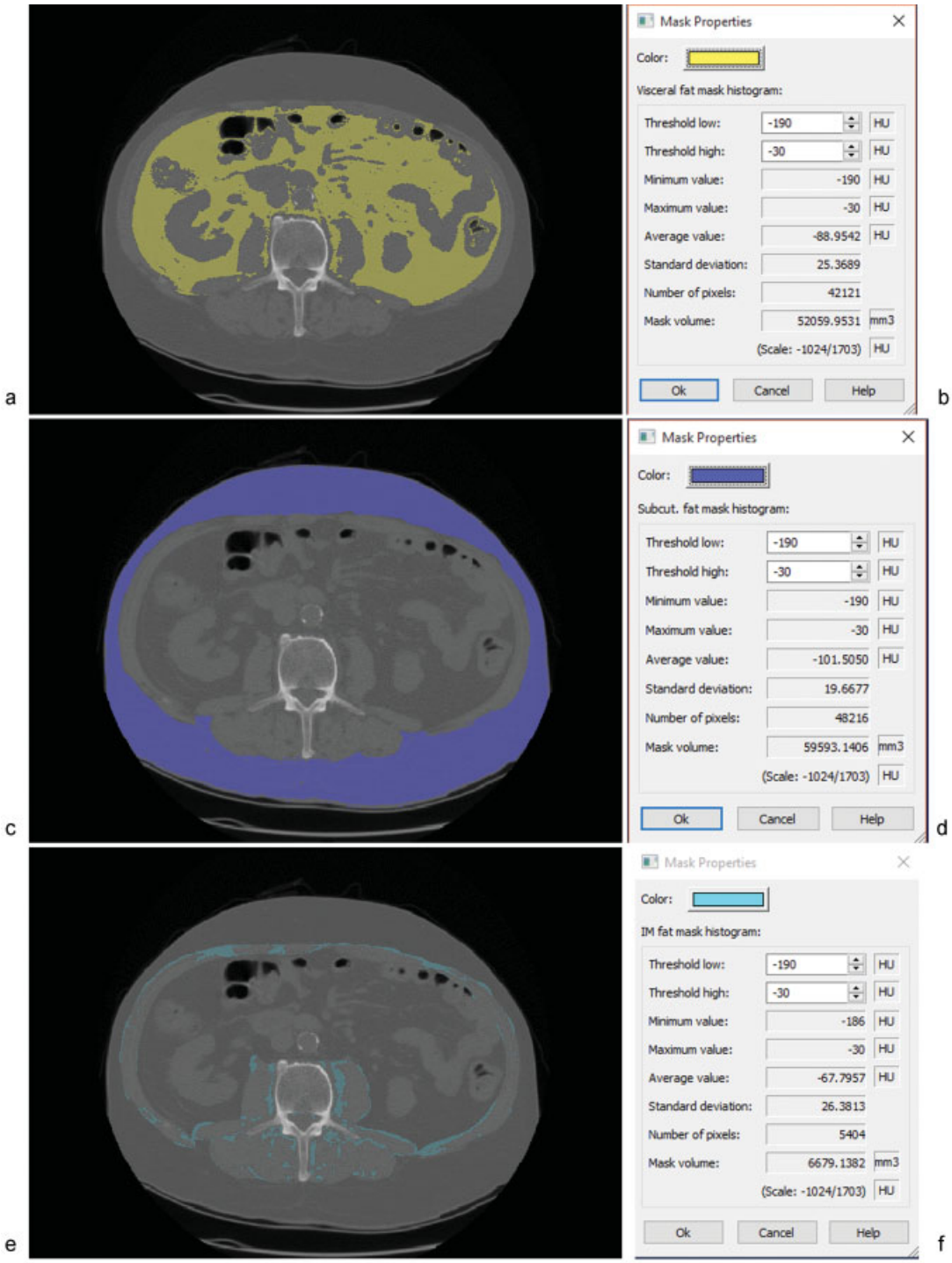


Fig. 10 A 65-year-old woman presents for sarcopenia evaluation. Computed tomography images at L3 show (**a**, **b**) visceral adipose tissue (VAT), (**c**, **d**) subcutaneous adipose tissue (SAT), and (**e**, **f**) intermuscular adipose tissue (IMAT) segmentation using the − 190 to − 30 HU thresholds.

imaging metrics of muscle depletion may be used as a marker of frailty and lead to a more comprehensive assessment to confirm the diagnosis and initiate therapy. In a cancer patient, it may be used as a marker of cachexia and lead to additional testing and targeted management (e.g., preoperative nutritional supplementation, physical therapy). In any case, radiologists should be ready to start using CT measurements of muscle mass and MA to help with the diagnosis, prognosis, and monitoring of sarcopenia.

Prevention and Treatment of Sarcopenia

Because DXA and CT may be used to monitor disease progression or response to intervention, radiologists should have some familiarity with various intervention strategies for sarcopenia.

In older adults, current prevention and treatment strategies are focused on diet and exercise, either alone or in combination. Nutritional supplementation and resistance training may

help promote muscle mass and muscle function.[74,75] Supplementation with protein, amino acids (e.g., branched chain amino acids), and vitamin D seems especially promising and deserves additional study.[76,77] In patients with cancer-related sarcopenia and cachexia, treatment with physical activity and nutritional supplementation are also very promising for optimizing quality of life and other outcomes.[78,79]

Many pharmacologic therapies for sarcopenia are on the horizon, either in phase 2 or phase 3 trials. These include β adrenergic agents, ghrelin, estrogen receptor agents, selective androgen receptor modulators, and myostatin inhibitors.[3] Importantly, these agents are being investigated in older adults as well as cancer patients. As some of these agents reach clinical use, there will be a corresponding need for imaging biomarkers to help identify patients for therapy and help monitor that therapy. For now, both DXA and CT measurements of muscle seem well suited to fill this need.

Controversies

Although functional measures of sarcopenia (e.g., grip strength, SPPB) are cost effective and have been validated in many observational and clinical trials, they are associated with greater variability than muscle mass measurements. For this reason, some experts have advocated for limiting the definition of sarcopenia to low muscle mass alone.[80] Sarcopenia would thus be distinguished from "dynapenia," a term denoting low muscle strength. Unfortunately, such a major shift in terminology appears unlikely.

For radiologists familiar with sarcopenia screening using DXA and CT, it is worth emphasizing that muscle mass could also be measured with BIA. Widely used in epidemiologic studies, BIA measurements of lean mass are fairly well correlated with DXA. However, BIA measurements are more influenced than DXA by patient hydration and recent physical activity. In one study, BIA overestimated fat mass in lean patients and underestimated fat mass in obese patients.[81] Although the sarcopenia field seems to be moving away from BIA toward DXA and CT, some future patients may be measured using all three technologies. For this reason, approaches for comparing results across these three platforms will need to be developed.

Future Directions

The future use of imaging in the evaluation of patients with sarcopenia seems to point away from DXA toward CT. In particular, radiologists should be aware of how trends in opportunistic screening, precision medicine, and machine learning may influence how CT examinations can help improve patient care.

Opportunistic Screening

More than 82 million CTs are performed annually in the United States. Although these examinations allow for quantitative assessment of muscle, bone, and fat phenotypes that have a high impact on health, these measurements are not routinely collected during patient care. There is increasing interest in secondary analysis of CT images to screen opportunistically for sarcopenia, osteoporosis, and visceral adiposity, without additional radiation exposure to patients. On the technical side, an increasing body of literature validates such screenings. On the clinical side, the challenge is for radiologists to work with our clinical colleagues to determine how best to incorporate such screenings into existing patient care algorithms.

Precision Medicine

Precision medicine is becoming widely accepted by patients, clinicians, and government agencies. Imaging has already contributed to precision medicine by providing quantitative measurements used for screening, early diagnosis, prognosis, guiding treatment, evaluating response to therapy, and assessing the likelihood of disease recurrence.

"Radiomics" refers to the conversion of digital medical images to mineable data via quantitative image analyses.[82] Combining imaging phenotypes with genomics has been widely used in cancer research. There is now increasing interest in applying radiomic methodology for noncancerous conditions, such as metabolic disease, Alzheimer's disease, and stroke. Why not sarcopenia? Ideally, CT measurements of muscle would complement genotypic and other phenotypic information for improving patient care.

In the future, CT measures of muscle (possibly combined with measurements of bone and fat) would help classify patients with similar disease manifestations into distinct subgroups. This, in turn, would help improve clinical trial designs, help evaluate interventions, and improve patient outcomes. Many questions in the sarcopenia field still need answers. In particular, it is not known if the associations between muscle mass, muscle function, and disability are similar or different in community-dwelling adults compared with hospitalized patients. Precision medicine, based on opportunistic CT measurements, could help provide the answers and improve the care of patients with sarcopenia.[83]

Machine Learning

The growth of precision medicine will require high-quality, high-volume, real-life patient data to do the modeling. Can the success of precision medicine in cancer be applied to other disorders? There is increasing interest in applying recent advances in machine learning to automate CT segmentation of muscle, bone, and adipose tissues to help improve health outcomes.[84–86]

Currently, quantitative analysis of CT images requires time-consuming manual drawing of ROIs around anatomical structures (e.g., muscles), making broad use to promote population health unrealistic. In the future, automated CT analysis will be used to identify patients at risk for sarcopenia, determine the need for follow-up and potential therapeutic intervention, predict prognosis, and improve patient outcomes, which are the very goals of precision medicine.

Conclusion

Sarcopenia, osteoporosis, and obesity are increasingly prevalent in older adults, and the resulting impact on adverse

health outcomes is immense. In all three areas, research has led to significant improvements in clinical patient care. Clinical obesity screening with BMI and osteoporosis screening with DXA are widely used, and clinical sarcopenia screening with gait speed and grip strength is becoming more common.

CT has shown distinct advantages for assessment of muscle, bone, and adipose tissue, especially for distinguishing visceral from subcutaneous fat, cortical from trabecular bone, and muscle size from muscle density. These CT-derived measurements have been validated as important prognostic biomarkers. Low muscle density, low trabecular bone density, and more recently high visceral fat density have been associated with reduced survival. However, the clinical use of CT for the evaluation of sarcopenia, osteoporosis, and visceral adiposity is still in its infancy.

Although many clinicians and radiologists have been hesitant to make the diagnosis of sarcopenia in the past, there is now a specific International Classification of Disease code (ICD−10 code M62.84) that is important step forward in recognizing sarcopenia as a major disease. The radiology community has an opportunity to help move the sarcopenia field forward, as it did with osteoporosis. In doing so, we will be enhancing the role of quantitative imaging techniques in patient care. More importantly, we will be promoting increasing physical function, quality of life, and health span in our patients.

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