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REVIEW

Measurement of skeletal muscle radiation attenuation and basis of its biological variation

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Abstract

Skeletal muscle contains intramyocellular lipid droplets within the cytoplasm of myocytes as well as intermuscular adipocytes. These depots exhibit physiological and pathological variation which has been revealed with the advent of diagnostic imaging approaches: magnetic resonance (MR) imaging, MR spectroscopy and computed tomography (CT). CT uses computer-processed X-rays and is now being applied in muscle physiology research. The purpose of this review is to present CT methodologies and summarize factors that influence muscle radiation attenuation, a parameter which is inversely related to muscle fat content. Pre-defined radiation attenuation ranges are used to demarcate intermuscular adipose tissue [from −190 to −30 Hounsfield units (HU)] and muscle (−29 HU to +150 HU). Within the latter range, the mean muscle *radiation attenuation* [muscle (*radio*) density] is reported. Inconsistent criteria for the upper and lower HU cut-offs used to characterize muscle attenuation limit comparisons between investigations. This area of research would benefit from standardized criteria for reporting muscle attenuation. Available evidence suggests that muscle attenuation is plastic with physiological variation induced by the process of ageing, as well as by aerobic training, which probably reflects accumulation of lipids to fuel aerobic work. Pathological variation in muscle attenuation reflects excess fat deposition in the tissue and is observed in people with obesity, diabetes type II, myositis, osteoarthritis, spinal stenosis and cancer. A poor prognosis and different types of morbidity are predicted by the presence of reduced mean muscle attenuation values in patients with these conditions; however, the biological features of muscle with these characteristics require further investigation.

Keywords computed tomography, Hounsfield units, muscle attenuation, muscle density, myosteatosis, skeletal muscle.

Lipids in skeletal muscle

Two principal anatomical compartments of white adipose tissue are visceral and subcutaneous. Fat is also associated with skeletal muscles in the form of intramyocellular lipid droplets within the cytoplasm of myocytes as well as intermuscular adipocytes (Wronska & Kmiec 2012). These lipid stores are

thought to provide fuels for skeletal muscle contraction and vary physiologically with aerobic fitness levels and sensitivity to insulin. Amount of intramyocellular stores can be altered through short-term dietary interventions where fat content is varied (Rouffet *et al.* 2013). The excess deposition of triglycerides within cells and organs that normally contain only small amounts of fat (such as liver, pancreas, skeletal and cardiac muscle) is defined as ectopic fat accumulation and is considered to be a pathological phenomenon. In some instances, this is well characterized; abnormal accumulation of fat in the liver (hepatosteatosis) is described by tens of thousands of publications and is a pathological partner of obesity and type II diabetes. A parallel condition, affecting skeletal muscle, myosteatosis, is also associated with diabetes and obesity (Goodpaster *et al.* 2000a,c, Lee *et al.* 2005), reduced muscle activity (Taaffe *et al.* 2009), myositis and cancer (Murphy *et al.* 2011). In contrast to fatty liver, myosteatosis is relatively poorly characterized, however, interest has been raised by its relationship to insulin resistance, poor physical function and most recently, survival. The purpose of this review is to summarize literature on skeletal muscle radiation attenuation, a radiological index of muscle fat content, with a focus on measurement and biological variation.

Measurement of lipids in skeletal muscle

Biopsy of skeletal muscle is a direct, but quite invasive approach to assess muscle triglyceride content and to make morphological examination of inter- and intramyocellular lipids. The advent of non-invasive radiological techniques: magnetic resonance (MR) imaging (MRI), MR spectroscopy (MRS) and computed tomography (CT) has enabled new explorations of the physiological and pathological variations in muscle fat content. It is not the intent of this review to detail the technical aspects and limitations of all of these approaches, but it is helpful to be aware of their overall characteristics. MRI is useful to quantify macroscopic regions of intermuscular adipose tissue. MRS can be used to separately detect and quantify intermuscular adipose tissue and microscopic intramyocellular lipid droplets, which behave uniquely in MRS.

CT imaging is based on the characteristic attenuation of X-rays by different tissues and is now being applied in clinical and experimental muscle physiology research. CT scans are useful to quantify macroscopic accumulations of intermuscular fat as well as muscle radiodensity (also known as muscle radiation attenuation). Goodpaster *et al.* (2000c) demonstrated that the radiodensity of human thigh muscle obtained by CT correlates well with muscle triglyceride content. The purpose of this review is to present CT methodologies and summarize factors that influence muscle radiation attenuation, a parameter which is inversely related to muscle fat content.

Computed tomography is increasingly being applied as a research tool to investigate aspects of skeletal muscle biology *in vivo*. This approach enables segmentation of individual tissues and provides direct measures of tissue cross-sectional area in single images as well as tissue volume in a series of images that encompass an entire organ. These methods have been extensively developed and validated (Heymsfield *et al.* 1995, MacDonald *et al.* 2011). Muscle radiation attenuation is a radiological characteristic. Considering the entire organ, any given skeletal muscle displays radiation attenuation between −190 and +150 Hounsfield units, HU, with a prominent peak near +50 HU. When muscle cross-sectional area and attenuation are reported, the most common practice is to use predefined HU ranges to demarcate intermuscular adipose tissue (usually −190 to −30 HU) and muscle tissue (usually −29 HU to 150 HU).

An illustration of this analysis is useful to understand the range of variation observed in muscle radiation attenuation. CT images of paraspinal/psoas muscles (Fig. 1a,b), annotated CT images (Fig. 1c,d), pie charts (Fig. 1e,f) and histograms (Fig. 1g,h) of radiation attenuation show the percentages of total tissue cross-sectional area within the typical attenuation ranges determined for the respective tissues (Goodpaster *et al.* 2000b). Adipose tissue [*light blue*, −190 to −30 HU], normal attenuation muscle [*red*, +30 to +150 HU (1)] and abnormal (reduced) attenuation muscle in two ranges [*dark blue*, −29 to 0 HU; *yellow*, +1 to +29 HU] are depicted for two subjects. Subject 1 is a 63-year-old male with a normal distribution of muscle attenuation with over 85% of the total cross-sectional area of his muscles falling within the normal attenuation range (red). For Subject 2, there is extensive macroscopic adipose tissue, and less than half of the cross-sectional area of his muscles falls within the normal attenuation range.

A review of the literature on CT – derived measures of muscle attenuation

Published literature was searched up to 31 July 2013 in electronic database(s) using terms identifying skeletal muscle, computed tomography and radiation attenuation. Identified articles were hand-searched for additional citations. A total of 57 articles reporting quantification of skeletal muscle radiation attenuation values were reviewed. For each article, the details of the methodology for measurement of muscle attenuation were abstracted, as well as the specific findings related to muscle attenuation variation.

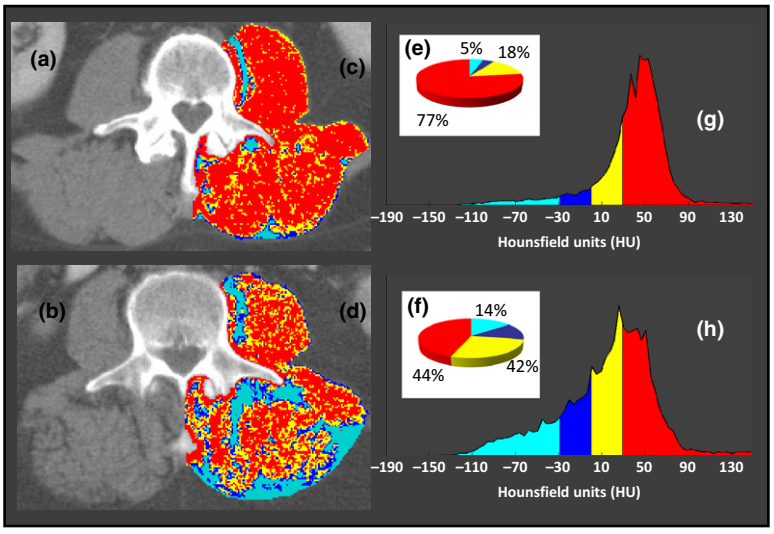

Figure 1 Radiation attenuation map of paraspinal muscles with and without myosteatosis. (a, c, e, g): Subject 1 is a 63-year-old male with a body mass index of 26.0 kg m^{-2}. Paraspinal and psoas muscles of Subject 1 show visible fat within the fascia surrounding skeletal muscle (intermuscular fat, *light blue*) making up 4.6% of total tissue area. Exclusive of the intermuscular fat, the mean overall radiation attenuation is 42.3 HU with 77.2% of the total muscle cross-sectional area falling into the normal attenuation range for muscle [*red*]. (b, d, f, h): Subject 2 is similar in age [65 years] and body mass index [26.7 kg m^{-2}] to Subject 1. Subject 2 exhibits extensive visible regions of intermuscular fat infiltration (*light blue*) comprising 14.1% of total area, a value threefold higher than Subject 1. Exclusive of the macroscopic fat infiltration, paraspinal and psoas muscles show abnormally low overall mean attenuation [20.4 HU]. In this subject, less than half [44.4%; annotated in *red*] of the total tissue cross-sectional area falls within the normal range of muscle radiation attenuation values.

Methodological considerations

Computed tomography provides a new lens for understanding skeletal muscle *in situ*, including quantification of tissue area, volume and attenuation. Current research is focused on the appearance of abnormally low radiation attenuation in muscles of some individuals (see below). However, to unify the findings on this parameter across studies, the criteria for muscle attenuation measurement require further agreement and standardization. Absolute values of radiation attenuation obtained on rigorously calibrated equipment are at best accurate to the nearest 4–5 HU. It is important that this calibration be done regularly and on standard materials with attenuation within the range of soft tissues, water (0 HU), fat (−100 HU) and muscle (50 HU).

There is also a need to agree on cut-offs defining normal and low attenuation muscle. The most common and accepted HU range for adipose tissue is −190 to −30 HU, and these values are quite consistent across studies. When muscle cross-sectional area and attenuation are reported, the common practice is to use pre-defined HU ranges. There was a notable disparity in the literature with respect to the HU range used for muscle, and there was considerable variation in both their upper and lower limit, which starts at either 0 HU or −29 HU and extends to 100, 150 or 200 HU (Table 1). Some reports do not include the range from −29 HU to 0 HU (Table 1), and using that approach, any regions within this attenuation range are regarded as being neither muscle nor adipose tissue. Omission of this HU range would, at least in some individuals, fail to account for a significant proportion of the total muscle cross-sectional area. For example in Fig. 1, Subject 2 has 13.5% of muscle area within the range of −29 HU to 0 HU. Another source of variation between studies is that mean attenuation may be reported for the entire muscle or a selected representative region[s] (Table 1). The generally accepted lower boundary of normal attenuation muscle is 30 HU (Goodpaster *et al.* 2000b, Lee *et al.* 2005), and this was defined as two standard deviations below the mean attenuation value across all pixels of muscles of young healthy persons (Goodpaster *et al.* 2000b). Most of the variation exists in the HU ranges included for low attenuation muscle. Some authors defined low attenuation muscle from 0 to +29 HU (Goodpaster *et al.* 2000b, Deriaz *et al.* 2001, Lee *et al.* 2005), while others included −29 to +30 HU. While the exact constitution and functional capacity of tissue within this range remain to be determined, it would seem advisable to incorporate the entire range from

Table 1 Hounsfield unit (HU) range (lower; upper) used in the quantification of skeletal muscle cross-sectional area and mean attenuation

HU ranges, muscle	HU ranges, adipose tissue	Approach used for reporting mean attenuation	Reference
NR	NR	Circular or square region of interest within the muscle	Berg *et al.* (1993), Bulcke *et al.* (1979), Kalichman *et al.* (2010a,b), Keller *et al.* (2003), Kelley *et al.* (1991), Jones *et al.* (1983), Storheim *et al.* (2003) Torriani *et al.* (2003)
NR	NR	User-defined region of interest around the whole muscle; avoiding bone and adipose tissue	Airaksinen *et al.* (1996), Delmonico *et al.* (2009), Froholdt *et al.* (2011), Hultman *et al.* (1993), Imamura *et al.* (1983), Jones *et al.* (1983), Katzman *et al.* (2012), Keller *et al.* (2004), Lo *et al.* (2007), Mayer *et al.* (1989), Rasch *et al.* (2007), Rasch *et al.* (2009), Schafer *et al.* (2010), Taaffe *et al.* (2009)
Bimodal histogram determination	Bimodal histogram determination	User-defined region of interest around the whole muscle; avoiding bone and adipose tissue	Conroy *et al.* (2012), Goodpaster *et al.* (2001), Hicks *et al.* (2005a,b), Katsiaras *et al.* (2005), Taaffe *et al.* (2005a,b), Visser *et al.* (2002, 2005)
0; 100	NR	Region of interest was characterized as all pixels within muscle HU range	Kelley *et al.* (2003), Larson-Meyer *et al.* (2006), Lee *et al.* (2005), Ross *et al.* (2002), Strandberg *et al.* (2010), Yeo *et al.* (2007)
0; 100	−190; −30	Region of interest was characterized as all pixels within muscle HU range	Brochu *et al.* (2000), Cheema *et al.* (2007), Dube *et al.* (2006), Fairfield *et al.* (2001), Goodpaster *et al.* (1997, 1999, 2000a,b,c), Lang *et al.* (2010), Poehlman *et al.* (2000), Sabel *et al.* (2011)
0; 100	−200; −1	Region of interest was characterized as all pixels within muscle HU range	Kelley *et al.* (1991)
0; 200	−200; −1	User-defined region of interest around the whole muscle; avoiding bone and adipose tissue	Sipila & Suominen (1995)
−29; 150	NR	User-defined region of interest around the whole muscle; avoiding bone and adipose tissue	Strandberg *et al.* (2010)
−29; 150	−190; −30	Region of interest was characterized as all pixels within muscle HU range	Antoun *et al.* (2013), Hutchison *et al.* (2012), Martin *et al.* (2013)
−29; 150	−190; −30	Circular or square region of interest within the muscle	Komiya *et al.* (2006)
−30; 100	NR	Region of interest was characterized as all pixels within muscle HU range	Larson-Meyer *et al.* (2006)
−50; 150	NR	User-defined region of interest around the whole muscle; avoiding bone and adipose tissue	Anderson *et al.* (2013)
NR	−50; −250	User defined region of interest around the whole muscle; avoiding bone and adipose tissue	Driscoll *et al.* (2004)

−29 to +29 HU in the definition of low attenuation muscle. Tissue cross-sectional area within the range of −29 to 0 HU cannot be disregarded. The benefit of a defined range of attenuation values for both muscle and adipose tissue alongside a standardized approach would enable comparison between various studies.

Physiological and pathological variation in muscle attenuation

Disparity in methodologies limits direct comparison of mean attenuation values reported in different papers. It is of interest, however, to evaluate effects of different physiological states and interventions, within any

Table 2 Factors contributing to muscle attenuation values

Factor contributing to muscle attenuation values	Reference	Total subjects (*N*)	Absolute effect on muscle attenuation (HU)*
Age (75 and older vs. 35–50)[†,‡]	Anderson *et al.* (2013)	120	−15.9 (−24.6; −7.4)
Gender (Male)[†,‡]	Anderson *et al.* (2013), Goodpaster *et al.* (2001), Kalichman *et al.* (2010a,b)	2934	+3.8 (−1.5; 14.7)
Obesity[§,‡]	Goodpaster *et al.* (2000a,b), Lee *et al.* (2005)	105	−5.7 (−9.9; −3.3)
Detrained (Strength)[¶,‡]	Taaffe *et al.* (2009)	13	−4.8 (−5.4; −4.2)
Type II diabetes and obesity[‡]	Goodpaster *et al.* (2000a,b), Lee *et al.* (2005), Kelley *et al.* (2003)	161	−7.3 (−15.3; −3.5)
Lumbar back pain[†]	Hicks *et al.* (2005a,b), Hultman *et al.* (1993)	1572	−3.6 (−9; −3.4)
Hip with osteoarthritis[**,†,‡]			
Before hip surgery	Rasch *et al.* (2009)	20	−6.6 (−13.8; −1.3)
2 years after hip surgery	Rasch *et al.* (2009)	20	−3.0 (−10.1; −0.4)
Strength training[‡]	Taaffe *et al.* (2009), Poehlman *et al.* (2000)	40	+2.2 (2.0; 2.7)
Endurance training[‡]	Lee *et al.* (2005), Poehlman *et al.* (2000)	48	+1.9 (0.6; 2)

HU, Hounsfield units.

*All values obtained are from within-paper comparisons of mean values that were significant differences. The ranges are various differences between papers and within papers of various muscle groups (lowest; highest).

[†]Paraspinal muscles and Psoas muscles were used.

[‡]Thigh muscles were used.

[§]Obesity was defined as a BMI ≥ 30.0.

[¶]Detraining period lasted for 24 weeks, after a 24 weeks resistance training period.

**Difference between the muscles of the affected side compared to the muscles of the contralateral healthy hip.

given study (Table 2). When subjects with obesity, diabetes and deconditioning of muscle, either owing to detraining or secondary to degenerative conditions of the spine or joints, are compared to subjects without these conditions, muscle attenuation is reduced. Each one of these conditions is associated with reduced attenuation of the order of 3–6 HU (Table 2). The effects of older age per se are difficult to evaluate, as older individuals are progressively more likely to develop obesity, diabetes and inactivity. By contrast to these influences that tend to lower muscle attenuation values, strength or endurance training as well as surgical correction of bone/joint conditions can partly reverse the effects of deconditioning on muscle attenuation. Standard values for attenuation ranges remain to be established according to gender, age and race.

One of the more recent developments in research on skeletal muscle radiation attenuation in clinical populations is the association of reduced muscle attenuation with the progression and outcomes of cancer. Muscle attenuation is independently prognostic of survival in cancer patients in three reports. The first report by Sabel *et al.* (2011) in melanoma patients showed remarkably poor disease-free survival and distant disease-free survival in patients in the lowest tertile of psoas muscle attenuation. Major complications of surgical resection of the lymph nodes including wound infection requiring intravenous antibiotics, wound dehiscence, haematoma, deep vein thrombosis/pulmonary embolism and lymph leak were significantly more likely in patients exhibiting reduced attenuation in psoas muscle (Sabel *et al.* 2011). Martin *et al.* (2013) reported that reduced muscle attenuation was independently prognostic of poor survival in a large cohort of patients with solid tumours of the lung and gastrointestinal tract. Antoun *et al.* (2013) reported markedly shorter overall survival in patients with metastatic renal cell carcinoma who exhibited skeletal muscle attenuation values below the median. The basis of this predictive value of muscle attenuation for survival is unknown. There is direct evidence that muscles of cancer patients develop increased numbers of intramyocellular lipid droplets (Stephens *et al.* 2011). These authors observed muscle biopsy material using electron microscopy and found that the lipid droplets were significantly more abundant in muscles of patients experiencing progressive cancer-associated weight loss, as compared to weight-stable individuals. Reduced radiation attenuation of muscle is a relatively newly characterized and distinctive abnormality in people with cancer, thus the relationship of reduced attenuation of muscle to clinical outcomes and morbidity in cancer patients remain to be explored.

There is currently little histologic or biochemical description of human muscles that could shed light on the specific identity of the molecular constituents contributing to reduced attenuation, and this awaits further investigation. There have been three suggested

constituents that could cause a marked decrease in attenuation in muscle: lipid, glycogen and water (Deriaz *et al.* 2001). Glycogen and water have been eliminated as possibilities due to theoretical considerations (Deriaz *et al.* 2001); thus, fat infiltration is the most widely accepted cause of reduced attenuation of muscle. Skeletal muscles normally contain only small amounts of fat used as a source of energy during aerobic work. Reduced muscle attenuation has been directly associated with accumulation of lipid (Goodpaster *et al.* 2000a, Larson-Meyer *et al.* 2006), however, little is known about the composition of lipid components. Muscle lipids are comprised of a variety of lipid species, including free fatty acids, diacylglycerol, triacylglycerol and phospholipids. It may be not only the content but also the composition of these components that may be important in the pathological effects of fat accumulation. Recent studies have revealed that the composition of lipid components in muscle may be as important in driving reduced function (or pathology) of muscle as the total amount of fat *per se*. For example, accumulation of diacylglycerols, but not triacylglycerol, is associated with insulin resistance in non-adipose tissues (Chabowski *et al.* 2012).

It is not in the usual repertoire of radiologists to report quantifiable dimensions of muscles such as cross-sectional area or attenuation. There may be merit in quantifying alterations in muscle mass and attenuation with a view to identify individuals affected by muscle wasting and altered attenuation. Wasting of skeletal muscle has been associated with deficits of physical function, and these have been exhaustively characterized (Baumgartner 2000, Visser *et al.* 2002). Muscle wasting also associates with poor clinical outcomes in cancer patient populations, including mortality, treatment toxicity, post-operative infections and extended hospital stay (Lieffers *et al.* 2012). Low attenuating muscle is also related to deficits in physical functioning, altered metabolism and poor prognosis. Excess infiltration of fat in muscle has emerged as an important factor associated with insulin resistance and type II diabetes (Miljkovic & Zmuda 2010, Miljkovic *et al.* 2013). Decreased thigh muscle attenuation has been linked to reduced strength and performance (Goodpaster *et al.* 2001, Visser *et al.* 2002) and increased risk of hip fracture (Lang *et al.* 2010). Loss of trunk muscle strength was reported to associate with reduced muscle attenuation (Mayer *et al.* 1989). Reduced muscle attenuation is related to lower back pain (Hultman *et al.* 1993, Hicks *et al.* 2005a,b), facet joint osteoarthritis, disc narrowing and spondylolisthesis (Kalichman *et al.* 2010a,b).

In summary, reduced radiation attenuation of muscle has been observed in computed tomography images of people with obesity, diabetes, cancer, mobility disorder and muscle disease. This growing area of research would benefit from diagnostic criteria for low attenuation muscle alongside a standardized approach to quantify myosteatosis. Further research is required to characterize and define therapies for myosteatosis.

Conflict of interest

The authors have no potential conflict of interest to declare.

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