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

J. Aubrey, N. Esfandiari, V. E. Baracos, F. A. Buteau, J. Frenette, C. T. Putman and V. C. Mazurak

Faculty of Physical Education and Recreation, University of Alberta, Edmonton, AB, Canada
Department of Oncology, University of Alberta, Edmonton, AB, Canada
Département de Réadaptation, Faculté de Médecine, Centre Hospitalier Universitaire de Québec–Centre de Recherche du Centre Hospitalier de l’Université Laval (CHUQ-CRCHUL), Université Laval Quebec City, Quebec City, QC, Canada
Division of Human Nutrition, University of Alberta, Edmonton, AB, Canada

Abstract
Skeletal muscle contains intramyocellular lipid droplets within the cytoplasm of myocytes as well as intermuscular adipocytes. These deposits 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 intramuscular adipose tissue. MRS can be used to separately detect and quantify intramuscular 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 intramuscular 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 pre-defined HU ranges to demarcate intramuscular 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.
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

![Figure 1](image-url)

**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.
Variation in skeletal muscle attenuation

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 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), Pohlmian 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) |
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; −3.3) |
| 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
Variation in skeletal muscle attenuation · J Aubrey et al.

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 (Miljikovic & Zmuda 2010, Miljikovic 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 spondylololisthesis (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.

Funding for this study was provided by Natural Sciences and Engineering Research Council (NSERC) and Canadian Institutes for Health Research (CIHR). CT Putman is a Senior Scholar of Alberta Innovates Health Solutions.

References

Airaksinen, O., Herno, A., Kaukanen, E., Saari, T., Siivonen, T. & Suomalainen, O. 1996. Density of lumbar muscles 4 years after decompressive spinal surgery. *Eur Spine J* 5, 193–197.

Anderson, D.E., D’Agostino, J.M., Bruno, A.G., Demissie, S., Kiel, D.P. & Bouxsein, M.L. 2013. Variations of CT-based trunk muscle attenuation by age, sex, and specific muscle. *J Gerontol A Biol Sci Med Sci* 68, 317–323.

Antoun, S., Lanoy, E., Lacovelli, R., Alblides-Sauvin, L., Loriot, Y., Merad-Taoufik, M., Fizazi, K., di Palma, M., Baracos, V.E. & Escudier, B. 2013. Skeletal muscle density predicts prognosis in patients with metastatic renal cell carcinoma treated with targeted therapies. *Cancer* 119, 3377–3384.

Baumgartner, R.N. 2000. Body composition in healthy aging. *Ann N Y Acad Sci* 904, 437–448.

Berg, H.E., Tedner, B. & Tesch, P.A. 1993. Changes in lower limb muscle cross-sectional area and tissue fluid volume after transition from standing to supine. *Acta Physiol Scand* 148, 379–385.

Brochu, M., Starling, R.D., Tchernof, A., Matthews, D.E., Garcia-Rubi, E. & Poehlman, E.T. 2000. Visceral adipose tissue is an independent correlate of glucose disposal in older obese postmenopausal women. *J Clin Endocrinol Metab* 85, 2378–2384.

Bulcke, J.A., Termote, J.L., Palmers, Y. & Crolla, D. 1979. Computed tomography of the human skeletal muscular system. *Neuroradiology* 17, 127–136.

Chabowski, A., Zendzian-Piotrowska, M., Nawrocki, A. & Gorski, J. 2012. Not only accumulation, but also saturation status of intramuscular lipids is significantly affected by PPARgamma activation. *Acta Physiol* 205, 145–158.

Cheema, B., Abas, H., Smith, B., O’Sullivan, A., Chan, M., Parwardhan, A., Kelly, J., Gillin, A., Pang, G., Lloyd, B. & Singh, M.F. 2007. Progressive exercise for anabolism in kidney disease (PEAK): a randomized, controlled trial of resistance training during hemodialysis. *J Am Soc Nephrol* 18, 1594–1601.

Conroy, M.B., Kwoh, C.K., Krishnan, E., Nevitt, M.C., Boudreau, R., Carbone, L.D., Chen, H., Harris, T.B., Newman, © 2014 The Authors. Acta Physiologica published by John Wiley & Sons Ltd on behalf of Scandinavian Physiological Society, doi: 10.1111/apha.12224
Acta Physiol 2014, 210, 489–497

A.B. & Goodpaster, B.H. 2012. Muscle strength, mass, and quality in older men and women with knee osteoarthritis. *Arthritis Care Res (Hoboken)* 64, 15–21.

Delmonico, M.J., Harris, T.B., Visser, M., Park, S.W., Conroy, M.B., Velasquez-Meyer, P., Boudeau, R., Manini, T.M., Nevitt, M., Newman, A.B. & Goodpaster, B.H. 2009. Longitudinal study of muscle strength, quality, and adipose tissue infiltration. *Am J Clin Nutr* 90, 1579–1585.

Deriaz, O., Dumont, M., Bergeron, N., Despres, J.P., Brochu, M. & Prud’homme, D. 2001. Skeletal muscle low attenuation area and maximal fat oxidation rate during submaximal exercise in male obese individuals. *Int J Obes Relat Metab Disord* 25, 1579–1584.

Driscol, S.D., Meininger, G.E., Ljungquist, K., Hadigan, C., Torriani, M., Kibanski, A., Frontera, W.R. & Grinspoon, S. 2004. Differential effects of metformin and exercise on muscle adiposity and metabolic indices in human immunodeficiency virus-infected patients. *J Clin Endocrinol Metab* 89, 2171–2178.

Dube, M.C., Joannis, D.R., Prud’homme, D., Lemieux, S., Bouchard, C., Perusse, L., Lavoie, C. & Weisnagel, S.J. 2006. Muscle adiposity and body fat distribution in type I and type II diabetes: varying relationships according to diabetes type. *Int J Obes (Lond)* 30, 1721–1728.

Fairfield, W.P., Treat, M., Rosenthal, D.I., Frontera, W., Stanley, T., Corcoran, C., Costello, M., Parlm, K., Schoenfeld, D., Kibanski, A. & Grinspoon, S. 2001. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. *J Appl Physiol* 90, 2166–2171.

Froholdt, A., Holm, L., Keller, A., Gunderson, R.B., Reikeras, O. & Brox, J.I. 2011. No difference in long-term trunk muscle strength, cross-sectional area, and density in patients with chronic low back pain 7 to 11 years after lumbar fusion versus cognitive intervention and exercises. *Spine* 11, 718–725.

Goodpaster, B.H., Thaete, F.L., Simoneau, J.A. & Kelley, D.E. 1997. Subcutaneous abdominal fat and thigh muscle composition predict insulin sensitivity independently of visceral fat. *Diabetes* 46, 1579–1585.

Goodpaster, B.H., Kelley, D.E., Wing, R.R., Meier, A. & Thaete, F.L. 1999. Effects of weight loss on regional fat distribution and insulin sensitivity in obesity. *Diabetes* 48, 839–847.

Goodpaster, B.H., Kelley, D.E., Thaete, F.L., He, J. & Ross, R. 2000a. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. *J Appl Physiol* 89, 104–110.

Goodpaster, B.H., Thaete, F.L. & Kelley, D.E. 2000b. Composition of skeletal muscle evaluated with computed tomography. *Am N Y Acad Sci* 904, 18–24.

Goodpaster, B.H., Thaete, F.L. & Kelley, D.E. 2000c. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type II diabetes mellitus. *Am J Clin Nutr* 71, 885–892.

Goodpaster, B.H., Carlson, C.L., Visser, M., Kelley, D.E., Scherzinger, A., Harris, T.B., Stamm, E. & Newman, A.B. 2001. Attenuation of skeletal muscle and strength in the elderly: the health ABC study. *J Appl Physiol* 90, 2157–2165.

Heymsfield, S.B., Gallagher, D., Visser, M., Nunez, C. & Wang, Z.M. 1995. Measurement of skeletal muscle: laboratory and epidemiological methods. *J Gerontol A Biol Sci Med Sci* 50, 23–29.

Hicks, G.E., Simonsick, E.M., Harris, T.B., Newman, A.B., Weiner, D.K., Nevitt, M.A. & Tylavsky, F.A. 2005a. Trunk muscle composition as a predictor of reduced functional capacity in the health, aging and body composition study: the moderating role of back pain. *J Gerontol A Biol Sci Med Sci* 60, 1420–1424.

Hicks, G.E., Simonsick, E.M., Harris, T.B., Newman, A.B., Weiner, D.K., Nevitt, M.A. & Tylavsky, F.A. 2005b. Cross-sectional associations between trunk muscle composition, back pain, and physical function in the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 60, 882–887.

Hultman, G., Nordin, M., Saraste, H. & Ohlsen, H. 1993. Body composition, endurance, strength, cross-sectional area, and density of MM erector spine in men with and without low back pain. *J Spinal Disord* 6, 114–123.

Hutchison, S.K., Teede, H.J., Rachon, D., Harrison, C.L., Strauss, B.J. & Stepto, N.K. 2012. Effect of exercise training on insulin sensitivity, mitochondria and computed tomography muscle attenuation in overweight women with and without polycystic ovary syndrome. *Diabetologia* 55, 1424–1434.

Imamura, K., Ashida, H., Ishikawa, T. & Fuji, M. 1983. Human major psoas muscle and sacrospinalis muscle in relation to age: a study by computed tomography. *J Gerontol* 38, 678–681.

Jones, D.A., Round, J.M., Edwards, R.H., Grindwood, S.R. & Tofts, P.S. 1983. Size and composition of the calf and quadriceps muscles in Duchenne muscular dystrophy. A tomographic and histochemical study. *J Neurol Sci* 60, 307–322.

Kalichman, L., Hodges, P., Li, L., Guermazi, A. & Hunter, D.J. 2010a. Changes in paraspinal muscles and their association with low back pain and spinal degeneration: CT study. *Eur Spine J* 19, 1136–1144.

Kalichman, L., Kim, D.H., Li, L., Guermazi, A. & Hunter, D.J. 2010b. Computed tomography–evaluated features of spinal degeneration: prevalence, intercorrelation, and association with self-reported low back pain. *Spine* 10, 200–208.

Katsiaras, A., Newman, A.B., Kriska, A., Brach, J., Krishnaswami, S., Feingold, E., Kritchevsky, S.B., Li, R., Harris, T.B., Schwartz, A. & Goodpaster, B.H. 2005. Skeletal muscle fatigue, strength, and quality in the elderly: the Health ABC study. *J Appl Physiol* 99, 210–216.

Katzman, W., Cawthon, P., Hicks, G.E., Vittinghoff, E., Shepherd, J., Cauley, J.A., Harris, T., Simonsick, E.M., Strotmeyer, E., WOMAC, C. & Kado, D.M. 2012. Association of spinal muscle composition and prevalence of hyperkyphosis in healthy community-dwelling older men and women. *J Gerontol A Biol Sci Med Sci* 67, 191–195.

Keller, A., Gunderson, R., Reikeras, O. & Brox, J.I. 2003. Reliability of computed tomography measurements of paraspinal muscle cross-sectional area and density in patients with chronic low back pain. *Spine* 28, 1455–1460.
Keller, A., Brox, J.L., Gunderson, R., Holm, I., Friis, A. & Reikeras, O. 2004. Trunk muscle strength, cross-sectional area, and density in patients with chronic low back pain randomized to lumbar fusion or cognitive intervention and exercises. *Spine (Phila Pa 1976)* 29, 3–8.

Kelley, D.E., Slasky, B.S. & Janosky, J. 1991. Skeletal muscle density: effects of obesity and non-insulin-dependent diabetes mellitus. *Am J Clin Nutr* 54, 509–515.

Kelley, D.E., McKolanski, T.M., Hegazi, R.A., Kaluhi, L.H. & Kalhan, S.C. 2003. Fatty liver in type II diabetes mellitus: relation to regional adiposity, fatty acids, and insulin resistance. *Am J Physiol Endocrinol Metab* 285, E906–E916.

Komiya, H., Mori, Y., Yokose, T., Kurokawa, N., Horie, N. & Tajima, N. 2006. Effect of intramuscular fat difference on glucose and insulin reaction in oral glucose tolerance test. *J Atheroscler Thromb* 13, 136–142.

Lang, T., Cauley, J.A., Tylavsky, F., Bauer, D., Cummings, S., Harris, T.B. & ABC Health Study. 2010. Computed tomographic measurements of thigh muscle cross-sectional area and attenuation coefficient predict hip fracture: the health, aging, and body composition study. *J Bone Miner Res* 25, 513–519.

Larson-Meyer, D.E., Smith, S.R., Heilbronn, L.K., Kelley, D.E., Ravussin, E., Newcomer, B.R. & Look AHEAD Adipose Research Group. 2006. Muscle-associated triglyceride measured by computed tomography and magnetic resonance spectroscopy. *Obesity* 14, 73–87.

Lee, S., Kuk, J.L., Davidson, L.E., Hudson, R., Kilpatrick, K., Graham, T.E. & Ross, R. 2005. Exercise without weight loss is an effective strategy for obesity reduction in obese individuals with and without type II diabetes. *J Appl Physiol* 99, 1220–1225.

Liefers, J.R., Bathe, O.F., Fassbender, K., Winget, M. & Baracos, V.E. 2012. Sarcopenia is associated with postoperative infection and delayed recovery from colorectal cancer resection surgery. *Br J Cancer* 107, 931–936.

Lo, J., Bernstein, L.E., Canavan, B., Torriani, M., Jackson, M.B., Ahima, R.S. & Grinspoon, S.K. 2007. Effects of TNF-alpha neutralization on adipocytokines and skeletal muscle adiposity in the metabolic syndrome. *Am J Physiol Endocrinol Metab* 293, E102–E109.

MacDonald, A.J., Greig, C.A. & Baracos, V. 2011. The advantages and limitations of cross-sectional body composition analysis. *Curr Opin Support Palliat Care* 5, 342–349.

Martin, L., Birdsell, L., MacDonald, N., Reiman, T., Clendinnen, M.T., McCargar, L., Murphy, R., Ghosh, S., Mb, S. & Baracos, V.E. 2013. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol* 31, 1539–1547.

Mayer, T.G., Vanharanta, H., Gatchel, R.J., Mooney, V., Barnes, D., Judge, L., Smith, S. & Terry, A. 1989. Comparison of CT scan muscle measurements and isokinetic trunk strength in postoperative patients. *Spine* 14, 33–36.

Miljkovic, I. & Zmuda, J.M. 2010. Epidemiology of myosteatosis. *Curr Opin Clin Nutr Metab Care* 13, 260–264.

Miljkovic, I., Cauley, J.A., Wang, P.Y., Holton, K.F., Lee, C.G., Sheu, Y., Barrett-Connor, E., Hoffman, A.R., Lewis, C.B., Orwoll, E.S., Stefanick, M.L., Strotmeyer, E.S., Mar-shall, L.M. & the Osteoporotic Fractures in Men (MrOS) Research Group. 2013. Abdominal myosteatosis is independently associated with hyperinsulinemia and insulin resistance among older men without diabetes. *Obesity (Silver Spring)* 21, 2118–2125.

Murphy, R.A., Mourtzakis, M., Chu, Q.S., Baracos, V.E., Reiman, T. & Mazurak, V.C. 2011. Nutritional intervention with fish oil provides a benefit over standard of care for weight and skeletal muscle mass in patients with non-small cell lung cancer undergoing chemotherapy. *Cancer* 117, 1775–1782.

Pochlmann, E.T., Dvorak, R.V., DeNino, W.F., Brochu, M. & Ades, P.A. 2000. Effects of resistance training and endurance training on insulin sensitivity in nonobese, young women: a controlled randomized trial. *J Clin Endocrinol Metab* 85, 2463–2468.

Rasch, A., Bystrom, A.H., Dalen, N. & Berg, H.E. 2007. Reduced muscle radiological density, cross-sectional area, and strength of major hip and knee muscles in 22 patients with hip osteoarthritis. *Acta Orthop* 78, 505–510.

Rasch, A., Bystrom, A.H., Dalen, N., Martínez-Carranza, N. & Berg, H.E. 2009. Persisting muscle atrophy two years after replacement of the hip. *J Bone Joint Surg* 91, 583–588.

Ross, R., Freeman, J., Hudson, R. & Janssen, I. 2002. Abdominal obesity, muscle composition, and insulin resistance in premenopausal women. *J Clin Endocrinol Metab* 87, 5044–5051.

Rouffet, D., Villars, C., Fissoune, R., Sappey-Mariner, D., Laville, M., Ibarrola, D., Sothier, M., Monnet, M.F., Ovize, M., Bonnefoy, M., Boesch, C. & Canet-Soules, E. 2013. Intramyocellular lipid variations in active older men: relationship with aerobic fitness. *Acta Physiol* 207, 516–523.

Sabel, M.S., Lee, J., Cai, S., Englesbe, M.J., Holcombe, S. & Wang, S. 2011. Sarcopenia as a prognostic factor among patients with stage III melanoma. *Ann Surg Oncol* 18, 3579–3585.

Schafer, A.L., Vittinghoff, E., Lang, T.F., Sellmeyer, D.E., Harris, T.B., Kanaya, A.M., Strotmeyer, E.S., Cawthon, P.M., Cummings, S.R., Tylavsky, F.A., Scherzinger, A.L. & Schwartz, A.V. 2010. Fat infiltration of muscle, diabetes, and clinical fracture risk in older adults. *J Clin Endocrinol Metab* 95, E368–E372.

Sipila, S. & Suominen, H. 1995. Effects of strength and endurance training on thigh and leg muscle mass and composition in elderly women. *J Appl Physiol* 78, 334–340.

Stephens, N.A., Skipworth, R.J., MacDonald, A.J., Greig, C.A., Ross, J.A. & Fearon, K.C. 2011. Intramyocellular lipid droplets increase with progression of cachexia in cancer patients. *J Cachexia Sarcopenia Muscle* 2, 111–117.

Storheim, K., Holm, I., Gunderson, R., Brox, J.I. & Bo, K. 2003. The effect of comprehensive group training on cross-sectional area, density, and strength of paraspinal muscles in patients sick-listed for subacute low back pain. *J Spinal Disord Tech* 16, 271–279.

Strandberg, S., Wretling, M.L., Fredmark, T. & Shanab, A. 2010. Reliability of computed tomography measurements in assessment of thigh muscle cross-sectional area and attenuation. *BMC Med Imaging* 10, 18–25.
Taaffe, D.R., Newman, A.B., Haggerty, C.L., Colbert, L.H., de Rekeneire, N., Visser, M., Goodpaster, B.H., Nevitt, M.C., Tylavsky, F.A. & Harris, T.B. 2005a. Estrogen replacement, muscle composition, and physical function: the Health ABC Study. *Med Sci Sports Exerc* 37, 1741–1747.

Taaffe, D.R., Sipila, S., Cheng, S., Puolakka, J., Toivanen, J. & Suominen, H. 2005b. The effect of hormone replacement therapy and/or exercise on skeletal muscle attenuation in postmenopausal women: a yearlong intervention. *Clin Physiol Funct Imaging* 25, 297–304.

Taaffe, D.R., Henwood, T.R., Nalls, M.A., Walker, D.G., Lang, T.F. & Harris, T.B. 2009. Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. *Gerontology* 55, 217–223.

Torriani, M., Hadigan, C., Jensen, M.E. & Grinspoon, S. 2003. Psoas muscle attenuation measurement with computed tomography indicates intramuscular fat accumulation in patients with the HIV-lipodystrophy syndrome. *J Appl Physiol* 95, 1005–1010.

Visser, M., Kritchevsky, S.B., Goodpaster, B.H., Newman, A.B., Nevitt, M., Stamm, E. & Harris, T.B. 2002. Leg muscle mass and composition in relation to lower extremity performance in men and women aged 70 to 79: the health, aging and body composition study. *J Am Geriutr Soc* 50, 897–904.

Visser, M., Goodpaster, B.H., Kritchevsky, S.B., Newman, A.B., Nevitt, M., Rubin, S.M., Simonsick, E.M. & Harris, T.B. 2005. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. *J Gerontol A Biol Sci Med Sci* 60, 324–333.

Wronska, A. & Kmiec, Z. 2012. Structural and biochemical characteristics of various white adipose tissue depots. *Acta Physiol* 205, 194–208.

Yeo, S.E., Hays, N.P., Dennis, R.A., Kortebein, P.M., Sullivan, D.H., Evans, W.J. & Coker, R.H. 2007. Fat distribution and glucose metabolism in older, obese men and women. *J Gerontol A Biol Sci Med Sci* 62, 1393–1401.