Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content

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Goodpaster, Bret H., David E. Kelley, F. Leland Thaete, Jing He, and Robert Ross. Skeletal muscle attenuation determined by computed tomography is associated with skeletal muscle lipid content. J Appl Physiol 89: 104–110, 2000.—The purpose of this investigation was to validate that in vivo measurement of skeletal muscle attenuation (MA) with computed tomography (CT) is associated with muscle lipid content. Single-slice CT scans performed on phantoms of varying lipid concentrations revealed good concordance between attenuation and lipid concentration ($r^2 = 0.995$); increasing the phantom’s lipid concentration by 1 g/100 ml decreased its attenuation by ~1 Hounsfield unit (HU). The test-retest coefficient of variation for two CT scans performed in six volunteers was 0.51% for the midthigh and 0.85% for the midcalf, indicating that the methodological variability is low. Lean subjects had significantly higher ($P < 0.01$) MA values (49.2 ± 2.8 HU) than did obese nondiabetic (39.3 ± 7.5 HU) and obese Type 2 diabetic (33.9 ± 4.1 HU) subjects, whereas obese Type 2 diabetic subjects had lower MA values that were not different from obese nondiabetic subjects. There was also good concordance between MA in midthigh and midcalf ($r = 0.60, P < 0.01$), psoas ($r = 0.65, P < 0.01$), and erector spinae ($r = 0.77, P < 0.01$) in subsets of volunteers. In 45 men and women who ranged from lean to obese (body mass index = 18.5 to 35.9 kg/m²), including 10 patients with Type 2 diabetes mellitus, reduced MA was associated with increased muscle fiber lipid content determined with histological oil red O staining ($P = -0.43, P < 0.01$). In a subset of these volunteers ($n = 19$), triglyceride content in percutaneous biopsy specimens from vastus lateralis was also associated with MA ($r = -0.58, P = 0.019$). We conclude that the attenuation of skeletal muscle in vivo determined by CT is related to its lipid content and that this noninvasive method may provide additional information regarding the association between muscle composition and muscle function.

triglyceride; body composition; obesity; Type 2 diabetes mellitus

LIPID CONTAINED WITHIN SKELETAL muscle plays an important role in its function, as demonstrated in recent studies linking muscle triglyceride (TG) content to a reduced insulin-stimulated glucose uptake (9, 21, 23) and to reductions in glycogen synthase activity (21) within muscle. An increased muscle lipid content has also been noted in older persons (5, 26) and in association with muscle wasting diseases (13, 18, 19). However, muscle TG are capable of providing a substantial proportion of energy to exercising muscles (12, 25, 27). Additional data concerning lipid contained within muscle will provide a better understanding of its role in both normal and impaired muscle function. Unfortunately, the majority of studies concerning TG content in human muscle have employed the invasive percutaneous muscle biopsy procedure for the measurement of TG within a small sample (12, 21, 23). Thus the recent interest in the implications of skeletal muscle lipid content has been an impetus to develop noninvasive methods such as magnetic resonance spectroscopy (1) and computed tomography (CT) (8, 9) for in vivo determination of skeletal muscle lipid.

CT is capable of distinguishing different tissue types in vivo on the basis of their attenuation characteristics, which, in turn, are a function of tissue density and chemical composition (2). Attenuation values determined by CT are expressed in Hounsfield units (HU), on the basis of a linear scale using water as the reference (0 HU). For example, CT can clearly discern fat from muscle because fat displays negative attenuation values, whereas attenuation for muscle is positive, and CT attenuation is sensitive to proton content per unit mass, which is high in adipose tissue. The detailed spatial maps of attenuation coefficients provided by CT can be used to quantify tissue areas within a specific range of attenuation values and the mean tissue attenuation. A few earlier studies have realized the quantitative potential of CT to describe muscle composition and have found association between a reduced skeletal muscle attenuation on CT and diminished muscular strength in patients suffering from neurological disease (20) and Duchenne muscular dystrophy (18). Our laboratory has observed that the mean attenuation within skeletal muscle is reduced in obesity and Type 2 diabetes mellitus (15); that there are strong associa-
tions among reduced muscle attenuation and low aerobic capacity (9), a diminished oxidative enzyme capacity within muscle (28), insulin resistance (9, 28), and a blunted lipolytic response by insulin (14); and that weight loss increases the mean attenuation value of muscle (8).

On the basis of these observations, and considering the chemical basis of attenuation characteristics, we have hypothesized that reduced attenuation of skeletal muscle in obese subjects represents an increased lipid content. The aim of this investigation was to ascertain whether the CT measurement of muscle attenuation is an indicator of muscle lipid content in vivo. Collateral aims were to determine the methodological variance in muscle attenuation and to determine the variance in muscle attenuation within and between different muscle groups.

RESEARCH DESIGN AND METHODS

CT attenuation of lipid emulsion phantoms. All scans of lipid emulsion phantoms were performed with either a CT-Hi Speed Advantage or HiSpeed CT/i CT scanner (General Electric, Milwaukee, WI). Phantoms containing 0, 2, 4, and 6 g/100 ml lipid emulsion (Baxter, Deerfield, IL) were placed in 700-ml plastic containers and scanned individually. Scan parameters were set at 120 kVp for 1 s (170 mA) by using a 25-cm field of view (FOV) and a 512 × 512 matrix. Four scans were performed on each phantom to determine the test-retest reliability of the attenuation measurement.

Recent advances in CT technology have stimulated interest in helical CT scanning, resulting in faster imaging and potentially providing more information about tissue with less radiation exposure. A set of helical CT scans was performed in another set of lipid phantoms to compare attenuation values in single-slice and helical CT and to determine the variability of attenuation values within the solution. To this aim, a series of helical and single-slice CT scans was performed on six phantoms containing varying lipid concentrations with a constant concentration of NaI to approximate the attenuation of skeletal muscle (~60 HU). For the helical scans, five images were collected on each phantom at 120 kVp for 1 s (340 mA), a FOV of 25 cm, and a matrix of 512 × 512, by using 10-mm continuous slices spaced 10 mm apart.

Clinical studies. Forty-five men and women between the ages of 25 and 49 yr were recruited to this study. Before participation, all potential research volunteers underwent a medical screening evaluation, including a 2-h 75-g oral glucose tolerance test. Ten volunteers were patients who had Type 2 diabetes mellitus and were not receiving insulin or oral hypoglycemic medications. All volunteers were normotensive and had fasting plasma TG and cholesterol levels <300 mg/dl. None of the subjects was taking antihypertensive or lipid-lowering medications, and women taking oral contraceptives were excluded. None of the subjects was currently engaged in exercise training, and all were weight stable for a period not <3 mo. The study was approved by the University of Pittsburgh Institutional Review Board, and informed written consent was obtained from each subject.

CT. CT imaging (CT-Hi Speed Advantage, General Electric) was conducted at ~7:00 PM for each subject. With the subject supine, a 10-mm cross-sectional scan of both legs in each subject was obtained at the midpoint between the anterior superior iliac crest and the patella. Scans were obtained by using 170 mA, a 512 × 512 matrix, and 48-cm FOV, thereby attaining a pixel resolution of 0.94 mm. Skeletal muscle attenuation was measured for each subject as the mean attenuation value from all pixels within the range of 0–100 HU as previously described (9), thereby excluding most of the intermuscular, or “marbled,” adipose tissue in the analysis. Because of the limited resolution of CT, however, depots of extracellular adipose tissue smaller than the pixel’s resolution were not completely excluded.

Variability in muscle attenuation within and between muscle groups. To examine the variation in muscle attenuation within the mid thigh, a series of three CT scans was performed in 20 nondiabetic volunteers. The first scan was obtained at the midpoint of the thigh as described in CT. The second and third images were obtained at exactly 40 and 80 mm inferior of the first image, respectively, and the mean muscle attenuation was determined in each image.

Associations between mean attenuation values from the mid thigh and other distinct muscle groups were assessed by performing CT scans of the mid thigh and mid calf in 15 subjects and of the psoas and erector spinae muscles in another subset of 45 volunteers. Scan parameters for both thigh and calf were the same as described in CT, and the location of the mid thigh image was the same as before. The 10-mm midcalf CT scan was located at the point of the largest girth determined by external measurement. Both psoas and erector spinae muscle groups were located in cross-sectional scans centered at the L4-L5 vertebral disk. Mean muscle attenuation values were calculated for each muscle group.

Test-retest reliability of in vivo muscle attenuation. To appreciate the degree to which CT is able to determine the biological variability of muscle attenuation, it is important to examine the potential methodological variability of muscle attenuation in vivo. Therefore, we performed two separate single-slice CT scans of the mid thigh and mid calf in three women and three men. The first set of scans was performed as described in CT; immediately afterward, the volunteer was removed from the scanner and repositioned, and landmarks were redefined for the second scan of both mid thigh and mid calf.

Association between muscle attenuation and lipid content. To test the hypothesis that CT attenuation characteristics of skeletal muscle reflect muscle lipid content, CT scans of the mid thigh and percutaneous muscle biopsies of the vastus lateralis were performed in 45 volunteers who ranged from lean to obese (body mass index = 18.5–35.9 kg/m²). Subjects were instructed not to perform physical exercise 48 h before the muscle biopsy procedure to help prevent acute effects of exercise on muscle TG (12). Subjects were admitted to the General Clinical Research Center where they were fed a standardized dinner (42 kJ/kg; 50% carbohydrate, 30% fat, 20% protein), had CT scans of the mid thigh, and then fasted overnight. The following morning, ~12 h after completion of the CT scans, muscle biopsies were obtained from the middle region of the vastus lateralis (15 cm above the patella) and ~2 cm away from the fascia by the percutaneous needle-biopsy technique (4). Muscle specimens were trimmed of all visible fat and connective tissue, mounted, and frozen in isopentane cooled at ~160°C by liquid nitrogen and stored at ~80°C for histochemical analysis. Another sample from 19 subjects was frozen immediately in liquid nitrogen for lipid extraction and subsequent TG determination by using a chloroform-ethanol method to extract TG from the muscle biopsy specimen samples (6). Briefly, extracts were dried under nitrogen and hydrolyzed in KOH and ethanol, and TG content was determined spectrophotometrically by using a commercially available method (Sigma Chemical, St. Louis, MO).
Objective quantification of skeletal muscle lipid staining was performed on the entire cohort of 45 volunteers by using the oil red O soluble dye, which stains neutral lipid (mainly TG) with an orange-red tint (17), as previously described (10). Briefly, the lipid content was determined on light-microscopic micrographs of 8-μm-thick transverse cryostat sections (model HM505E, Micron, Walldorf, Germany). Cryosections were mounted on glass slides, air dried for 15 min, then immersed in a working solution of oil red O (Fisher Scientific, Fair Lawn, NJ) for 10 min, rinsed with water, and then allowed to dry. An Olympus light microscope (Provis, Toyko, Japan), was used to examine the stained muscle sections, by using a ×40 oil-immersion objective and bright-field settings. Images were digitally captured by using a charge-coupled device camera (Sony, Toyoko, Japan). Eight contiguous FOVs within the biopsy section that were free from artifact were analyzed for lipid content; quantitative image analysis was then carried out on at least 80 fibers, or on ~10 contiguous fibers per field, by using National Institutes of Health Image software (rsb.info.nih.gov/nih-image). Muscle sectioning, staining, and image analysis were done in a blinded manner with respect to group. Skeletal muscle lipid content was measured as the area occupied by lipid staining, and a lipid accumulation index (LAI) was calculated as follows: LAI = total area occupied by lipid droplets of muscle fiber ×100/total cross-sectional area of a muscle fiber. The LAI was calculated for each of eight fields within the biopsy section, and a mean LAI was then calculated for each volunteer. A negative-control section treated with acetone and subsequently stained revealed no background staining.

Statistical analysis. Association between lipid concentration in lipid-emulsion phantoms or muscle with mean attenuation was determined with simple linear regression. Between-group differences in mean muscle attenuation were determined with one-way analysis of variance. Probability was set at an α level of P = 0.05.

RESULTS

CT attenuation of lipid emulsion phantoms. The attenuation of various concentrations of lipid emulsions is presented in Fig. 1. There was nearly perfect linear agreement between the CT attenuation value and lipid content of the phantoms (r = 0.997). Alteration of the lipid content changed the mean attenuation value ~1 HU · 1 g⁻¹ · 100 l lipid⁻¹. The low SD (0.3 HU) and coefficient of variation (CV; 9%) for four repeated attenuation measures of the same solution indicates that the attenuation within a homogenous phantom of lipid and water can be measured reliably.

Data obtained from helical CT scans of six lipid emulsions of 0, 2, 4, 6, 8, and 10 g/100 ml (Table 1) revealed that the CV for attenuation among five contiguous 10-mm slices was 0.06, 0.17, 0.35, 0.13, 0.22, and 0.45%, respectively. This indicates that the variability in measuring attenuation within a homogenous lipid emulsion is very low. Moreover, these data indicate that single-slice and helical CT scanning provide nearly identical values for attenuation within a homogenous solution. Data in Fig. 1 also reveal that attenuation of lipid phantoms measured by helical CT scanning is highly correlated with their lipid concentration (r = 0.995).

Variability in muscle attenuation within and between muscle groups. Biological variability in muscle attenuation was examined to determine whether this method is sensitive enough to detect potential between-subject differences in this measurement. The mean muscle attenuation values in 15 lean, 20 obese, and 10 obese diabetic subjects (body mass index = 23.3 ± 0.8, 34.1 ± 0.7, and 36.2 ± 1.0 kg/m², respectively) are presented in Fig. 2. Lean subjects had attenuation values that were significantly higher than those of obese nondiabetic and obese diabetic subjects, whereas attenuation values were not different between obese diabetic and obese nondiabetic subjects. These data demonstrate that the CT method used in the present study is capable of detecting differences in mean muscle attenuation between groups of obese and lean subjects.

Fig. 1. A: plot of computed tomography attenuation values for water and 3 lipid-emulsion phantoms, representing 0, 2, 4, and 6 g/100 ml lipid (r = 0.997). Error bars, SD of Hounsfield unit (HU) measurement from 4 separate computed tomography scans of each phantom. B: plot of mean computed tomography attenuation values of 5 helical computed tomography slices in 6 phantoms containing 0, 2, 4, 6, 8, and 10 g/100 ml lipid (r = 0.995). Phantoms consisted of a constant concentration of NaI to approximate attenuation of muscle in combination with lipid emulsion to arrive at precise lipid concentration. Error bars, SD of attenuation value among 5 helical slices.
The variance in mean midthigh muscle attenuation within three slices located 40 mm apart is demonstrated in Fig. 3. Muscle attenuation values ranged from 31 to 54 HU across the groups of subjects, yet the within-subject variance (SD) was only 1.3 HU (CV 3.3%). Performance of CT scans of the midthigh, psoas, erector spinae, and midcalf muscle revealed that there was good concordance in muscle attenuation values between distinct muscle groups (Fig. 4).

Test-retest reliability of in vivo muscle attenuation. The methodological variability in muscle attenuation in vivo is presented in Table 2. The SD and CV observed for test-retest variability in attenuation values for both the midthigh (SD = 0.2 HU, CV = 0.51%) and midcalf (SD = 0.4 HU, CV = 0.85%) in six volunteers were low. These data indicate that, if the patient is carefully repositioned and landmarks are redefined, any variability in muscle attenuation is almost certainly biological.

Association between muscle attenuation and muscle lipid content. Muscle attenuation determined in vivo with CT was associated with muscle lipid content determined in muscle biopsy specimens of vastus lateralis (Fig. 5). Lipid contained within muscle fibers as determined with histochemical staining of lipid was negatively associated with muscle attenuation (r = -0.43, P < 0.01). The TG content of muscle was also negatively associated with muscle attenuation (r = -0.58, P = 0.019). These results concur with those from the histological staining data and suggest that muscle attenuation varies as a function of muscle lipid content.

**DISCUSSION**

There has been a renewed interest in the health implications of lipid stored within skeletal muscle with respect to energy metabolism (3, 7, 11, 12, 16), obesity, and diabetes mellitus.

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<th>Lipid content, g/100 ml</th>
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<td>CV, %</td>
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Values are means ± SD for computed tomography attenuation within each phantom. Phantoms consisted of solutions containing NaI in water (no lipid) and NaI in water with various concentrations of lipid. CV, coefficient of variation in the attenuation among 5 consecutive helical computed tomography slices.
(8–10, 21), insulin resistance (9, 21, 23), and Type 2 diabetes mellitus (15, 29). Whereas much of the data concerning muscle lipid in humans have resulted from biopsies, few investigations have used noninvasive in vivo methods to quantify lipid contained within muscle. Our laboratory (8, 9, 15, 28) and others (13, 18, 19, 26) have utilized CT to quantify the composition of skeletal muscle. The question that arises is whether reduced attenuation in muscle reflects an increase in lipid content.

The primary findings of the present study confirm previous observations (19) that an increase in skeletal muscle lipid content is associated with a decrease in the CT attenuation values within muscle. The results from the lipid-emulsion phantom experiments demonstrate that the decrease in attenuation within a series of homogeneous solutions occurs as a linear function of increasing lipid content. Increasing the lipid content within the solution by 1 g/100 ml decreased the mean attenuation by $\sim$1 HU. These data are entirely consistent with the fact that attenuation coefficients determined by CT are based on a linear scale of tissue attenuation values relative to water, with the later as the reference set to 0 HU. Furthermore, the phantom studies demonstrate that the attenuation measurement is sensitive to small changes in lipid content. This point deserves further attention, because the absolute difference in muscle attenuation between lean and moderately obese subjects is relatively small (39.2 ± 0.8 vs. 35.9 ± 0.8 HU, respectively) (8). Data from the phantom studies suggest that this range of attenuation values may represent as much as a 3% difference in muscle fat content. No other studies have attempted to determine the direct association between muscle lipid content and attenuation determined by CT, and only one study has estimated the lipid content within muscle on the basis of the mean attenuation of muscle (13). Other evidence supporting the concept that attenuation is a marker of lipid contained within muscle comes from clinical weight-loss studies. Our laboratory found that identical calorie restriction-induced weight-loss programs reduced the lipid content within muscle by 1.3% (10) and increased the mean muscle attenuation by $\sim$2 HU (8). Although the association between the change in lipid and the change in attenuation is similar to that observed in the present lipid emulsion experiments, additional intervention studies are needed to examine the concomitant changes in attenuation and muscle lipid content.

Another goal of the present study was to determine the methodological variability in muscle attenuation and the variability of muscle attenuation within and between muscle groups in vivo. The test-retest study found that the variance in muscle attenuation at three locations within the mid thigh was only 1.3 HU. In addition, within the same individual, there was good correlation between attenuation in the mid thigh and that of other distinct muscle groups. Although no other studies have compared the fat content in different muscle groups of the same individual, these results demonstrate that the variance in muscle attenuation in association with lipid content is consistent both within and between muscle groups.

The use of chemical phantoms represents a rigorous means to establish a criterion for direct comparison of attenuation and lipid concentration, and, in the present study, muscle tissue was also used. Muscle attenuation determined with CT was significantly as-

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**Fig. 4.** Associations between MA in mid thigh and that in psoas (A), erector spinea (B), and mid calf (C). Correlation coefficients were $r = 0.65$ for A (n = 45), $r = 0.77$ for B (n = 45), and $r = 0.60$ for C (n = 15) (all $P < 0.01$).
associated with skeletal muscle lipid content measured by both biochemical extraction of TG and staining for neutral lipid within muscle fibers. These data indicate that reduced muscle attenuation determined by CT is partly due to lipid contained within the muscle fibers. The finding that an increasing muscle TG was also associated with decreased muscle attenuation corroborates these findings. Nevertheless, the amount of TG or lipid staining within the biopsy specimen accounted for only ~34 and 18%, respectively, of the variance in CT attenuation. Several reasons may explain the lack of strength in correlating muscle attenuation determined by CT and the muscle biopsy measurement of lipid content. First, extrapolation of lipid contained within a small biopsy specimen containing ~80 fibers to the lipid content of whole muscle is arduous, particularly because variability in the TG content in different biopsy samples from the same individual is quite high (31). Second, a careful attempt was made to exclude the extracellular lipid from the biopsy specimens, and, because of its limited resolution, CT is not capable of excluding all extracellular lipid. Thus muscle attenuation determined by CT likely reflected lipid contained in both extracellular and intracellular depots, whereas the lipid contained within the biopsy samples was assumed largely to reflect intracellular depots. Moreover, a pixel determined by CT that contains both adipose tissue and muscle will exhibit attenuation values intermediate of the two tissues. Factors such as an alteration in muscle protein, perfusion, or extracellular water content might also affect muscle attenuation; thus it is unlikely that muscle lipid content is the only factor that contributes to altered muscle attenuation.

The primary limitation of this CT method is that a direct measurement of muscle lipid content is not possible. Moreover, it is not possible with this technique to assess whether the lipid within muscle is intracellular or outside the myocyte. Other noninvasive imaging methods such as magnetic resonance imaging could provide a direct quantification of muscle lipid content in vivo without the exposure to ionizing radiation. In addition, it has been recently demonstrated that proton magnetic resonance spectroscopy is capable of discerning intra- and extracellular lipid in vivo (1, 22, 24, 30). Nevertheless, the radiation exposure in conventional single-slice or multislice helical CT scanning as performed in the present investigation is relatively low, and the speed, cost, and availability of CT make it suited for large-scale clinical investigation.

In summary, this study has determined that skeletal muscle attenuation determined by CT is associated with lipid contained within muscle. These data support the claims made by several investigations that de-

<table>
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Values for muscle attenuation are given in Hounsfield units for 6 subjects. CV is for mean muscle attenuation for 2 separate computed tomography scans.
creased muscle attenuation is indicative of an increased lipid content. This CT method represents a noninvasive means to determine the relative lipid content within muscle between subjects or in individual subjects as a result of clinical intervention. Skeletal muscle attenuation measured with CT may provide further insight into the implications of skeletal muscle lipid with respect to energy metabolism, obesity and insulin resistance. Studies using this method may also provide knowledge regarding the effects of fatty infiltration of muscle in association with aging and impaired muscle function.

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