Muscle MRI in Duchenne and Becker muscular dystrophy

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Chapter

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Comparison of Dixon and T1-weighted MR methods to assess the degree of fat infiltration in Duchenne muscular dystrophy patients

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ABSTRACT

Purpose

To compare different lipid multi-peak spectral models to the single peak model in Dixon based fat-water separation and to evaluate differences between visually scored MR images and quantitatively assessed fat fractions in muscle of Duchenne muscular dystrophy patients.

Materials and methods

T1-weighted and 3-point Dixon imaging of the upper and lower leg was performed in thirteen Duchenne patients and six healthy controls. Three-, four- and five peak lipid spectrum models were compared to a single peak model and to each other. T1-weighted images were visually scored by two radiologists and quantitative fat fractions were obtained from Dixon images.

Results

Differences between the multiple-peak spectral models were minimal. The three-peak model was used for subsequent comparisons. Although there was high correlation between quantitative and visual scores, visual scores were consistently higher than quantitative values of the same muscles.

Conclusion

There are minor differences between the various lipid spectral models in terms of quantifying fat fraction in a large number of skeletal muscles in the legs of Duchenne patients and healthy controls. Quantitative 3-point Dixon MRI is more precise and reliable than visual radiological methods for evaluation of fat fractions for potential longitudinal follow-up or therapy evaluation of Duchenne patients.

INTRODUCTION

Muscle MRI is increasingly being used in the evaluation of disease severity in neuromuscular diseases such as Duchenne muscular dystrophy (DMD) [98, 99, 109, 116]. DMD is a progressive muscle disease affecting young males and results in a severely reduced life expectancy of ~30 years. Skeletal muscles of DMD patients show hypertrophy, inflammation, progressive fatty infiltration and fibrosis. The level of fatty infiltration is considered to be a useful parameter to quantify the effect of new therapeutic interventions, and can potentially be measured accurately using non-invasive MRI protocols [77, 78, 117].

Chemical shift based water-fat separation methods such as the Dixon method use the phase difference between water and fat to separate these two components. As such, they can give a quantitative measure of the signal fraction of both water and fat. The first goal of our study was to compare the performance of different lipid spectrum models (three-, four- and five- peaks) to the single peak model of the lipid spectrum in fatty infiltrated muscles of DMD patients, using images acquired with a three-point Dixon method [98, 118-121]. In its most basic form, processing of the Dixon data models the fat signal as a single spectral peak, although the fat signal in fact contains multiple peaks from different saturated methyl and methylene protons, as well as unsaturated methyne groups. Previous studies have shown both in vitro and in liver, that modelling of the fat signals as multiple peaks significantly improves the fit and performs better in tissue with higher fat fractions [119, 122]. However, it is unknown how the multipeak spectral model behaves in much more spatially inhomogeneous tissues such as fatty infiltrated muscle.

There are various “semi-quantitative” visual-assessment scales available to describe the fatty infiltration in the muscle [101, 123-126]. However, although such scales are very quick to implement for the practicing radiologist, a recent study shows that semi-quantitative assessment of the fat fraction in muscles of patients with diabetes overestimates the fatty infiltration when compared to quantitative MRI methods [127]. Most patients in this previous study had relatively low levels of fatty infiltration and it is currently not known if this overestimation is still present if the muscle fat fraction is very high, as is often observed in DMD patients. Additionally, in patients with increased levels of fatty infiltration in the muscles, visual assessment of the fatty infiltration, especially in intermediate fat ranges, is likely to be less sensitive in detecting small changes [102]. Therefore, these methods could be less suitable for longitudinal follow up or therapy assessment. The second aim of our study was to compare “semi-quantitative” fat fractions obtained with an accepted neurological visual scoring method with those obtained using the quantitative MRI method outlined in the first part of the paper [123].

METHODS

Patients and controls

In total thirteen DMD patients (mean age 10.8 ± 2.0 years; range 8-14 years) and six healthy controls (mean age 11 ± 0.9 years; range 10-12 years) participated in this study. For the reconstruction with a different number of peaks, raw data are needed. As they were not present for all subjects data sets of nine patients (mean age 10.6 years ± 1.9; range 8-14 years) and six healthy controls (mean age 11 years ± 0.9; range 10-12 years) were used for the comparison of single- versus multipeak modelling. For the comparison of the semi-quantitative and quantitative analysis the images of ten patients (mean age 10.3 ± 1.9 years; range 8-13 years) were analysed using the three-peak model [122].
Patients were recruited from the Dutch dystrophinopathy database. Diagnosis of DMD was confirmed by DNA testing or muscle biopsy showing absence of dystrophin. Patients had no history of illness other than DMD. Healthy subjects were recruited from local schools. The local medical ethics committee approved the study and all subjects or their legal representative gave written informed consent.

MRI

MR images were acquired on a 3T scanner (Achieva, Philips Healthcare, Best, The Netherlands) from the left upper and lower leg using a 14-cm diameter two-element receive coil and body coil excitation. The receive coils were positioned on the anterior and posterior side of the leg; directly below the patella for lower leg imaging and directly above the patella for upper leg imaging. The left leg was imaged since this allowed optimal positioning of the coil in all patients, even those with some contractures, with respect to the patient table and the coil. The scanning protocol consisted of a T1-weighted spin echo (SE) sequence (25 five mm slices, 0.5 mm gap, repetition time (TR) 600ms, echo time (TE) 16ms) and a 3-point gradient echo Dixon sequence of the same region of interest (25 five mm slices identical to the T1- weighted slices, 0.5 mm gap, TR 400 ms, first TE 4.41 ms, echo spacing 0.71 ms, flip angle 8°). The TR of 400 ms and low flip angle of 8° were chosen to produce minimal T1 weighting. The total scanning protocol, including positioning of the patients, was performed in 20 minutes.

Quantitative analysis

The 3-point Dixon images were reconstructed with the lipid spectrum modelled as a single peak or multiple peaks using three different lipid spectrum models. The first model was a three peak model with frequencies $f_{p=}$[94, -318, -420] Hz and amplitudes $A_{p=}$[0.08, 0.15, 0.78] and was based on the model proposed by Yu et al. [122]. The four peak model resolves the peak from the terminal CH3 group from the large aliphatic peak with $f_{p=}$[94, -318, -418, -470] Hz and $A_{p=}$[0.08, 0.15, 0.72, 0.04], and it was obtained by a weighted average of the signals at -300 and -325 Hz from the five peak model. Finally, a five peak model with $f_{p=}$[94, -300, -325, -418, -470] Hz and $A_{p=}$[0.08, 0.05, 0.1, 0.72, 0.04] was implemented [128]. The five peak model separates the α-methylene protons of the COO and C=C bonds into two separate signals. To obtain fat fractions per muscle, regions of interest (ROIs) were manually drawn using Medical Image Processing, Analysis and Visualization software package (www.mipav.cit.nih.gov) on co-registered T1 images on every other slice provided that the muscle was clearly identifiable. The fat fraction was modelled as $SI_{fat}/(SI_{fat}+cSI_{water})$, with SI representing the signal intensity and the factor *c* (1.41) correcting for differences in the proton densities of water and fat, as well as the differences in the T2 values of water (38 ms) and fat (150 ms). In order to obtain realistic proton density and T2 values, these were measured in one healthy control. T2 values were measured by using a single slice multi-echo experiment. The proton densities were estimated using a single slice spin echo sequence with TR/TE 5000 ms/6 ms, and then back-calculating the signal intensity for a virtual echo time of 0 ms using the T2 values measured previously.

Visual scoring

T1-weighted images of the left upper and lower leg of ten patients (mean age 10.3 years ± 1.9; range 8-13) were scored in consensus by two experienced musculoskeletal radiologists. For the scoring the available slices within the entire field-of-view, which was identical to the Dixon images, were used. A visual 4-point scale classified muscle as: 1-normal muscle, 2-mild changes of less than 30% estimated fatty infiltration, 3-moderate changes of 30-60% estimated fatty infiltration, and 4-severe changes of more than an estimated 60% showing an increased signal intensity [123]. The following muscles were scored in the upper leg: rectus femoris, vastus lateralis, vastus intermedius, vastus medialis, short head of the biceps femoris, long head of the biceps femoris, semitendinosus, semimembranosus, adductor longus, adductor magnus, gracilis and sartorius, and in the lower leg: medial and lateral head of the gastrocnemius, soleus, flexor digitorum longus, flexor hallucis longus, posterior tibialis, extensor hallucis longus, peroneus, anterior tibialis and extensor digitorum longus.

Statistical analysis

The SPSS statistical package Version 17.0 for Windows (SPSS Inc., Chicago, IL) was used for all analyses. A box plot was used to visualize differences between the visual and quantitative scoring methods and a Spearman correlation was used to compare the two methods. To evaluate differences between the different multipeak models a Bland-Altman plot was used. Statistical significance was set at $p<0.05$. Values are shown as mean ± one standard deviation (SD).

RESULTS

Single versus multipeak analysis

Figure 1 shows the comparison of the three different multipeak models to the single peak model. In the range of 0-70% fatty infiltration the multipeak models consistently show higher fat fractions than the single peak model. The difference between the models is most prominent in the range of 20-50% fatty infiltration and negligible in the very high ranges. Subtracted images of the single peak and the three peak model (Figure 2a.) show a clear difference between these two models, which is much less evident between the three- and the five peak model (Figure 2b), showing predominantly noise.

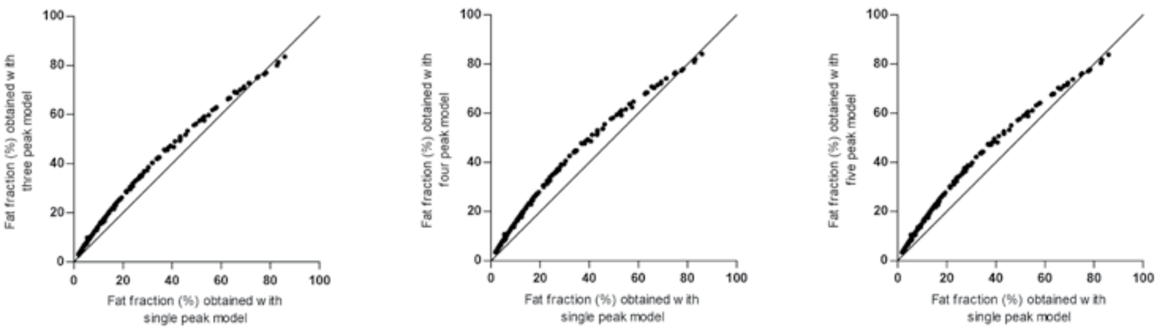

Figure 1. Single peak model versus three peak, four peak and five peak spectral model.
The four peak model deviates most from the single peak model. For all three models the differences are most apparent in the mid-range of the fat fraction.

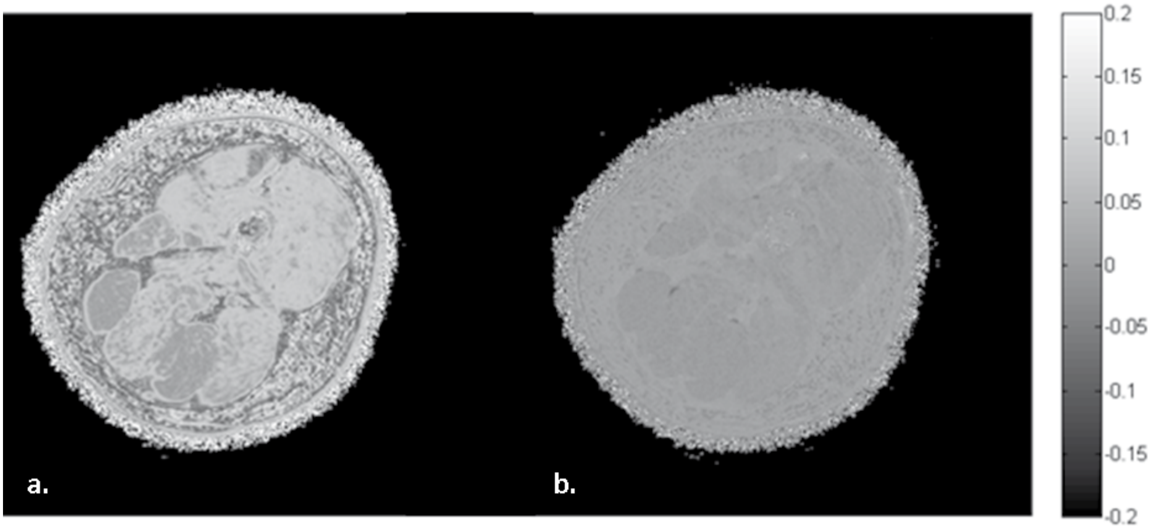

Figure 2. Subtracted images of the different spectral peak models.
The three peak minus the single peak model (a) shows a clear difference between the fat fractions of the two models. The five peak minus the three peak model (b) shows much smaller differences and mainly noise.

Figure 3 shows the difference between the four and the five peak model as compared to the three peak model. Both the four and the five peak model show very slightly higher fat fractions than the three peak model, with the four peak model showing less variability in the data. Nevertheless, the differences between the models were so small that in the subsequent comparisons the three peak model was used.

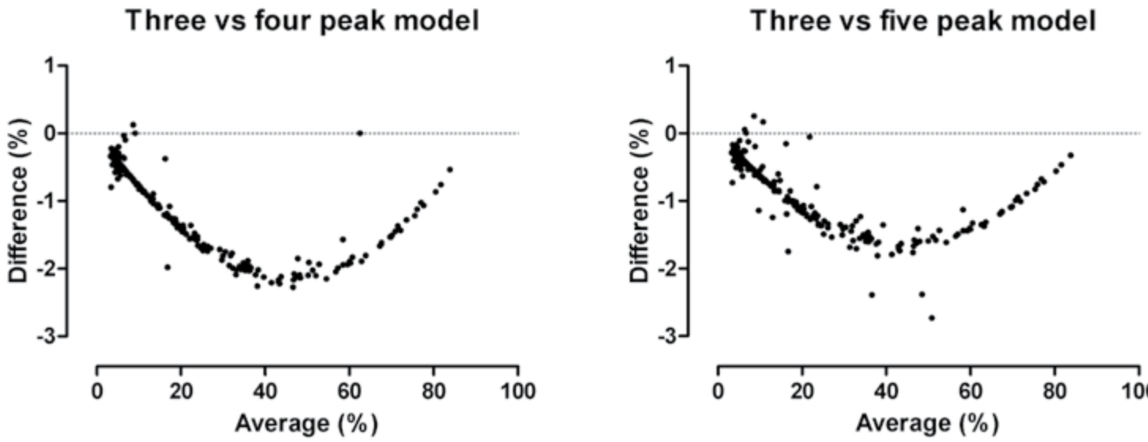

Figure 3. Bland-Altman plot showing the differences between the four and five peak model compared to the three peak model for the average fat fraction.
The four peak model shows less variation in the values which would make the model more precise than the five peak model.

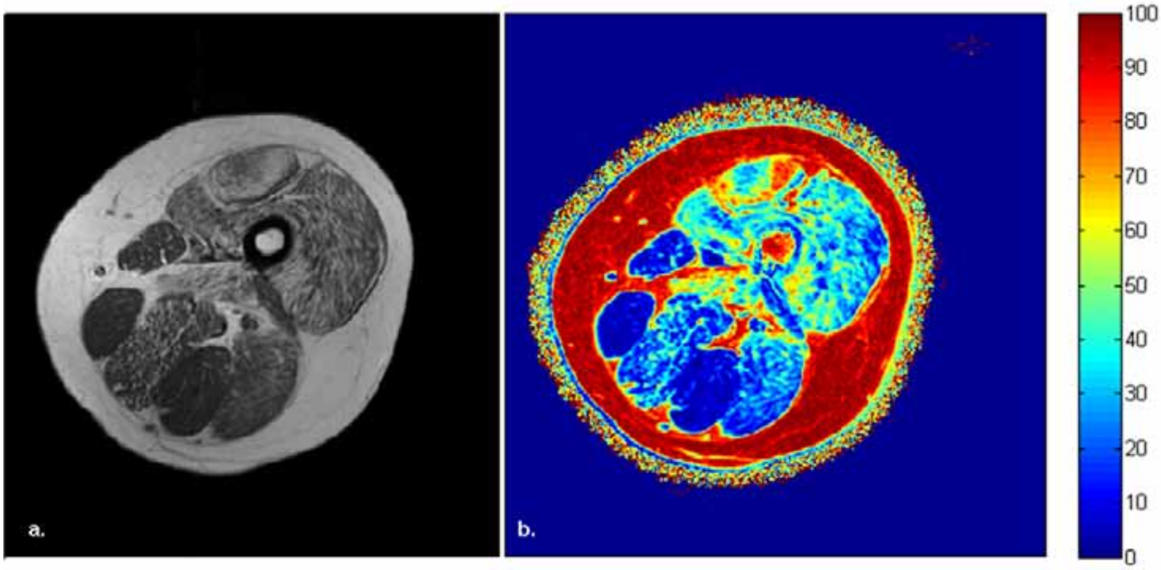

Figure 4. Upper leg of DMD patient showing the T1 weighted image (a) and a color representation of the fat fraction in the Dixon image (b).

Visual scoring and quantitative analysis

In ten patients fat fractions from a total of 201 muscles were scored on the 4-point scale. Of these, 17 (8.5%) were scored as normal, 62 (30.8%) as mildly affected, 34 (16.9%) as moderately affected and 88 (43.8%) as severely affected. The same muscles were analysed using the data from the 3-point Dixon scans (Figure 4).

There was a significant correlation between the two scoring methods, Spearman r=0.89, p<0.0001. Figure 5 shows how the quantitative Dixon values relate to the visual scores. Two main differences were noted. First, the visually scored fat fractions were higher than their quantitative equivalents, except for normal appearing muscle (Figures 5 and 6). Second, the variation in the values of the quantitative fat fraction scores was higher with increasing visually scored values. The variation was most evident in the visually scored group of severely affected muscles, defined as more than 60% fatty infiltration. Quantitative fat values in this group ranged from a minimum of 16% up to a maximum of 86%.

Overall, in healthy controls the mean quantitative fat fraction was 5.3 ± 0.98% ranging from 3 to 10%. The mean quantitative fat fraction in the patients was 29.7 ± 13.2% ranging from 5 to 86%.

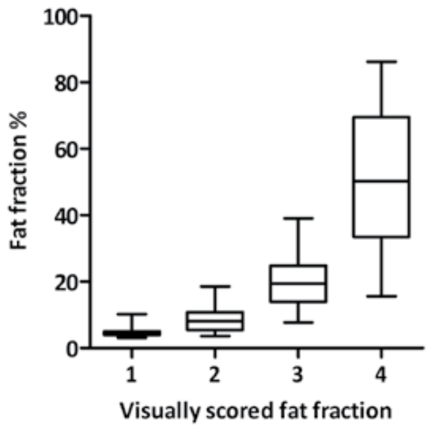

Figure 5. Visually scored versus quantitative fat fractions.

With visually scored fat scores as 1: normal appearing muscle, 2: mildly affected muscle (<30%), 3: moderately affected muscle (30-60%) and 4: severely affected muscle (>60%). Especially in the third and the fourth group of the semi-quantitative values there is large variation of the quantitative values.

DISCUSSION

The first aim of our study was to evaluate the performance of the multipeak models of the lipid spectrum in chemical shift-based water-fat separation over the entire range of healthy to severely affected muscles. Several previous in vitro and in vivo liver studies have shown that accounting for multiple peaks (up to six) of the lipid spectrum results in a more accurate measurement of the fat fraction. In this paper we have shown that in muscle of healthy controls and DMD patients with varying disease severity multipeak models shows consistently higher fat fractions in the range of 0-70% fatty infiltration. Compared to the multipeak models, single peak modeling underestimates the fat fraction in the range of these values, and this underestimation is a non-linear function of fat fraction. Overall there were very minor differences in the estimate of fat fraction using a three-, four- or five peak model. The difference between these results, and those acquired in phantoms and in liver, could be that the lipid spectrum depends significantly upon muscle fiber orientation. This results in a shift of the lipid peaks and consequently increases the sensitivity of the model to the specific frequency of the spectral peaks [129], whereas there is no such variation in either homogenous phantoms or liver tissue.

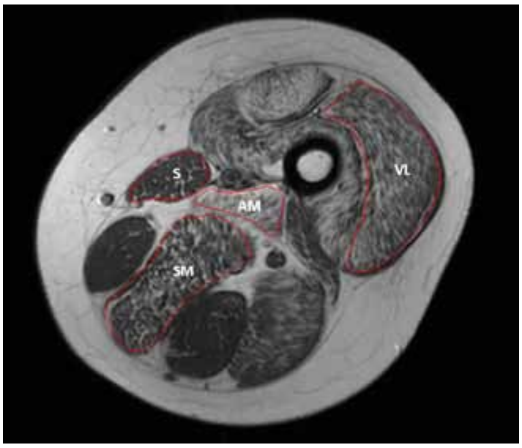

Figure 6. T1 weighted image of upper leg of DMD patient comparing visually scored and quantitative values.
The vastus lateralis visual score was 4 (severely affected) with a quantitative fat fraction of 33%. The adductor magnus (AM) visual score 4 with fat fraction 47%, sartorius (S) visual score 2 (mild changes) and fat fraction 10% and for the semimembranosus (SM) the visual score was 4 with a fat fraction of 24%.

Accurate fat quantification in chemical shift-based water-fat separation can also be influenced by other factors such as the difference in T1 values between fat and water (which itself is dependent upon the fat/water fraction in a particular voxel) if the images are T1-weighted [122, 129-131]. By choosing a low flip angle and a long TR in this study T1 effects were minimized [130]. Additionally, as mentioned above, the lipid spectrum depends significantly upon muscle fiber orientation and this could also affect its quantification. However, as in multi echo acquisitions with a low number of echoes and a short range of echo times the influence of these shifts on the resulting signal is relatively small [129].

The second aim of our study was to compare a radiological visual scoring method of the fat fraction with quantitative MRI values in both healthy and fatty infiltrated muscles. The mean quantitative fat fraction in our healthy volunteers was in agreement with a recent study [132]. In muscle of healthy controls and DMD patients with relatively low fat fractions, the visual scores were highly correlated with the quantitatively obtained fat fractions. However, the visual scores for the fat fractions in the muscle were generally higher than their corresponding quantitative values. This finding implies that the visual scoring measurements overestimate the fat fraction in affected muscles. Alizai et al. showed a similar finding in the muscle of diabetes patients: in this study most patients were only relatively mildly affected [127]. Our data shows large variation between the visually scored and quantitative values, specifically in the severely affected muscles. The large variability of the visually-scored method illustrates that these methods are less sensitive for the recognition of subtle changes, as could be present in longitudinal follow up of DMD patients or in therapy evaluation [133]. The overestimation and possibly also the variation of the fat fraction with the visually scored methods could partly be explained by the difficulty in visually differentiating between a moderate and severely fatty infiltrated voxel, which has also been suggested by Alizai [127]. Secondly it might be difficult to consistently estimate the amount of muscle left in a diffusely fatty infiltrated muscle as frequently observed in the DMD patients. In the radiological literature the Goutallier classification is commonly used, (normal muscle, fatty streaks, less fat than muscle, as much fat as muscle and more fat than muscle) [125]. This might be easier to use in scoring fatty infiltration of muscle by the human eye. However, the largest differences are seen in the most severely fatty infiltrated muscles. Both the overestimation of the fat fraction and the large variability in visually scored DMD muscle can influence the assessment of possible changes in the muscles in longitudinal follow up of or in the evaluation of therapy effects. Therefore, in these situations quantitative evaluation of the fat fraction seems more precise and reliable than visual radiological methods.

There were also some limitations to our study; most importantly no validation of the data with histology was made. A previous study has shown that values obtained with chemical shift-based water-fat separation methods are generally in accordance with data obtained from muscle biopsy [134]. The multipeak approach has previously been validated with in vitro measurements and MR spectroscopy and we therefore assume that any of our multipeak models are more representative of the actual fat fraction than a single peak model [119, 122, 135]. Another limitation of our study could be that a relatively low number of subjects were included. However, as a total of 201 different muscles were scored, the number of data points used for the comparison was very high.

In conclusion our results show that visually scored assessment of the fat fraction generally correlates with quantitative values, but overestimates the fat fraction and shows higher variability. Quantitative MRI methods such as chemical shift-based water-fat separation produce a more accurate estimation of the fat fraction, especially in the more severely affected muscle. Correcting for the multiple peaks of the lipid spectrum contributes to obtaining more precise fat fractions. These findings further stress the importance of quantitative evaluation of the fat fraction to accurately demonstrate changes in the muscle.