PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Measurement of net muscle volume in patients with muscular dystrophy using muscle CT for prospective muscle volume analysis
AUTHORS	Nakayama, Takahiro; Kuru, Satoshi; Okura, Masashi; Motoyoshi, Yoshifumi; Kawai, Mitsuru

VERSION 1 - REVIEW

REVIEWER	Matsubara, Shirou Tokyo Metroporitan Neurological Hospital, Neurology
REVIEW RETURNED	19-Aug-2013

THE STUDY	1. The formula of the estimation function is somewhat difficult to follow. It will be nicer if it is presented in an ordinary form of mathematical formula and explained in a way easier to understand. It will be also helpful to have some explanations for DICOM and MATLAB. 2. The figure of the density map in Fig. 3 is too small to see in detail. Each step of image-processing should be illustrated with due explanation.
RESULTS & CONCLUSIONS	1. It will make presentation more convincing if an example of change in density maps in a case observed over years is attached. 2. The annual decrease rate of muscle volume in a mixture of various conditions with progressive weakness has limited practical meaning. It will be better to present the decrease ratios in certain conditions including both progressive and non-progressive ones.
GENERAL COMMENTS	I appreciated importance of this new method, but feel that it will be still arguable if it is appropriate to name this method “net muscle volumetry”, since the present method gives an estimation of muscle volume in a limited part of the thigh.

REVIEWER	Fischmann, Arne University of Basel Hospital
REVIEW RETURNED	19-Aug-2013

THE STUDY	Abstract: - Net muscle volumetry should be used in the paragraph “Methods 1a” - Methods 2: should be reworded to: “To evaluate longitudinal changes of mucle volumes, net muscle volumetry at the mid thigh level was performed repeatedly over a 4 year period”. Introduction: - Contrary to the authors statements, several groups have performed muscle volumetry in patients with muscular dystrophy on either single muscle or as whole body trials, e.g.: - Hsieh et al. In vivo proton magnetic resonance spectroscopy

	assessment for muscle metabolism in neuromuscular diseases. J Pediatr (2007) vol. 151 (3) pp. 319-21 - Gong et al. Estimation of body composition in muscular dystrophy by MRI and stereology. Journal of magnetic resonance imaging : JMRI (2000) vol. 12 (3) pp. 467-75 However none of these trials included longitudinal measurements of muscle volume. Subjects: - The exact scanner type should be mentioned. - The exact inclusion criteria should be mentioned ("all patients with muscular dystrophy presenting from- to were asked to participate…") Methods: - The exact method how muscle CT-values were obtained, should be described: e.g. ROIs were drawn at prespecified levels including the whole muscle and mean ROI values were reported. - Page 9, line 11 ff: The formula should be written in a dedicated editor, to improve readability. - The term "net muscle volume" should be introduced at page 9, line 56. - The number of scans performed for the prospective volumetry study should be mentioned as well as the mean time from one scan to the next. - The exact statistical calculations (e.g. spearman correlation coefficient?, Bland-Altman blots etc.) should be described Figure Legends: - Page 18, line 9: The previous method to calculate muscle volume should be mentioned. - Figure 4: SD-lines should be included in the Bland-Altman Blot. In addition, the difference of scale between the axes should be emphasized (to highlight the excellent correlation). As this text has been prepared by a non-native speaker, some sentence patterns as well as the wording chosen is detrimental to the readability. There are multiple instances where the translation requires close reading to understand the meaning. These might be improved by editing from a native speaker. Page2, line 34: attached software should be changed to "vendor provided software" Page 6, line 46f: The meaning of this sentence is not clear, the sentence should therefore be rewritten. Page 7, line 19: It is not clear, whether the umbilicus was included in the evaluation. Page 7, Line 38: "Patients gave written informed consent". Page 11, line 44: "In addition, we could demonstrate, that the decrease …." Page 18, line 13: It is not clear, what "to walk obviously" indicates in this sentence.
RESULTS & CONCLUSIONS	Results: - Page 11, line 11 ff: This section should be clarified. It appears, that muscle volume correlated to muscle cross sectional area at mid thigh, however it is difficult to extract this meaning from the text. - Page 11, line 31. This section should be expanded upon. How did the clinical parameters change in these patients compared to the 5 patients without change in gait disturbance. - Page 11, Line 33: This probably was meant to be:" At this rate, a reduction of muscle volume of 41% would be expected over a 10

	year period" Discussion - Emphasis should be given to the fact, that MRI would be preferable in children due to radiation dose. However, in adults with muscular dystrophy and a low life expectancy due to the natural course of the disease, CT might be a valuable alternative. - This method can be automated in a simple way and might therefore be superior to MRI evaluations, where extensive manual segmentation is necessary. This should be emphasized in the text.
GENERAL COMMENTS	This is an important work, as quantitative imaging will be used in clinical practice increasingly. In addition the methods presented in this paper could be translated into clinical practice and even into a commercial product easily. As mentioned previously, the importance of this work should not be hidden due to limited readability. I therefore highly suggest to use a professional editing service or the cooperation of an experienced native speaker to improve this manuscript, which otherwise would qualify for publication after minor alterations.

VERSION 1 – AUTHOR RESPONSE

Reviewer: Shiro Matsubara MD, PhD
1. It will be also helpful to have some explanations for DICOM and MATLAB.
-> We gave explanations for these words

2. The figure of the density map in Fig. 3 is too small to see in detail.
-> We added images for each step of image-processing.

1. It will make presentation more convincing if an example of change in density maps in a case observed over years is attached.
-> We attached the sample of density map for both progressive and non-progressive patients.

2. The annual decrease rate of muscle volume in a mixture of various conditions with progressive weakness has limited practical meaning. It will be better to present the decrease ratios in certain conditions including both progressive and non-progressive ones.
-> We added the decrease ratio for each group.

I appreciated importance of this new method, but feel that it will be still arguable if it is appropriate to name this method "net muscle volumetry", since the present method gives an estimation of muscle volume in a limited part of the thigh.
-> We had titled our manuscript as "measurement of net muscle volume", however we estimated the net volume. Then we rename the title of our manuscript to "estimation of net muscle volume".

Reviewer: Dr. Arne Fischmann, MHBA,
Abstract:
-Net muscle volumetry should be used in the paragraph "Methods 1a"
-Methods 2: should be reworded to: "To evaluate longitudinal changes of mucle volumes, net muscle volumetry at the mid thigh level was performed repeatedly over a 4 year period".
-> We rewrote our article according to the reviewer's comment.

Introduction:
- Contrary to the authors statements, several groups have performed muscle

volumetry in patients with muscular dystrophy on either single muscle or as whole body trials.
-> We added to our article according to the reviewer's comment.

Subjects:
- The exact scanner type should be mentioned.
- The exact inclusion criteria should be mentioned
Methods:
- The exact method how muscle CT-values were obtained, should be described:
-> We added to our article according to the reviewer's comment.

- Page 9, line 11 ff: The formula should be written in a dedicated editor, to improve readability.
-> We rewrote the formula. I'm very sorry about previous version.

- The term "net muscle volume" should be introduced at page 9, line 56.
- The number of scans performed for the prospective volumetry study should be mentioned as well as the mean time from one scan to the next.
-> We added to our article according to the reviewer's comment.

- The exact statistical calculations (e.g. spearman correlation coefficient?, Bland-Altman blots etc.) should be described
-> We added to our article according to the reviewer's comment.

Figure Legends:
- Page 18, line 9: The previous method to calculate muscle volume should be mentioned.
-> We added the reference according to the reviewer's comment.

- Figure 4: SD-lines should be included in the Bland-Altman Blot. In addition, the difference of scale between the axes should be emphasized (to highlight the excellent correlation).
-> We added SD-lines and Average-line to Figure 4 according to reviewer's comment.

Page2, line 34: attached software should be changed to "vendor provided software"
Page 6, line 46f: The meaning of this sentence is not clear, the sentence should therefore be rewritten.
Page 7, line 19: It is not clear, whether the umbilicus was included in the evaluation.
Page 7, Line 38: "Patients gave written informed consent".
Page 11, line 44: "In addition, we could demonstrate, that the decrease …."
-> We rewrote our article according to the reviewer's comment.

Page 18, line 13: It is not clear, what "to walk obviously" indicates in this sentence.
-> We rewrote our article according to the reviewer's comment.

Results:
- Page 11, line 11 ff: This section should be clarified. It appears, that muscle volume correlated to muscle cross sectional area at mid thigh, however it is difficult to extract this meaning from the text.
-> We rewrote method section and added the paragraph which mentioned about correlation between muscle cross sectional area and muscle volume.

- Page 11, line 31. This section should be expanded upon. How did the clinical

parameters change in these patients compared to the 5 patients without change in gait disturbance.
-> We added that “the patient’s functional classification was not changed”.

- Page 11, Line 33: This probably was meant to be:” At this rate, a reduction
of muscle volume of 41% would be expected over a 10 year period”
-> We rewrote our article according to reviewer’s comment.

Discussion
- Emphasis should be given to the fact, that MRI would be preferable in children due to radiation dose. However, in adults with muscular dystrophy and a low life expectancy due to the natural course of the disease, CT might be a valuable alternative.
- This method can be automated in a simple way and might therefore be superior
to MRI evaluations, where extensive manual segmentation is necessary. This should be emphasized in the text.
-> We added these points to discussion section. We were thankful for the reviewer’s comments.