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Comment on: "Pitfalls in the measurement of muscle mass: a need for a reference standard" by Buckinx et al.

Keywords standard; methods; measurement; dual-energy x-ray absorptiometry; sarcopenia; muscle

We read with interest the article by Buckinx *et al*.[1] titled 'Pitfalls in the measurement of muscle mass: a need for a reference standard', which sought to review the methods to assess muscle mass and to reach consensus on the development of a 'reference standard'. This work was carried out by members of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis working group on frailty and sarcopenia. Their final conclusion was to adopt dual-energy X-ray absorptiometry (DXA) as a reference standard to (i) make studies comparable, (ii) improve diagnosis and treatment of sarcopenia, and (iii) monitor the development of muscle mass in healthy, athletic, and sick subjects, and state that '… DXA is the gold standard for the measurement of muscle mass'.

DXA has several advantages as a tool to quantify appendicular lean soft tissue mass (LSTM). These advantages are namely related to feasibility and cost, which make it more clinically viable than several other competing technologies, such as magnetic resonance imaging (MRI) or computed tomography (CT). However, a word of caution is necessary, given the word *standard* is 'authoritative or recognized exemplar of quality or correctness', which is generally interpreted to denote the best tool available at a given time to compare different measures.[2] We don't believe DXA should be considered the *standard* by which all other techniques should be judged. The most accurate methods of quantifying skeletal muscle size *in vivo* are, arguably, MRI and CT, as these technologies are near perfectly correlated with cadaveric values (r = 0.99) of full-length limb scans.[3,4] Accuracy of MRI single-slice anatomical cross sectional area has also been demonstrated in the quadriceps,[5] and in response to exercise in the triceps brachii,[6] with accuracy improving as the number of analysed slices increases.[5] These methods are ideal in terms of accuracy and fit the terminology of a 'reference standard', but the high cost of instrumentation, lack of equipment availability, radiation (for CT), contraindications for scanning (namely for MRI), and the expertise required to operate the equipment and analyse the data often preclude the use of these devices in many settings. As such, DXA has gained popularity over the years through its ease of use, reduced cost, low radiation, and accessibility. While MRI and CT measures are estimates of appendicular muscle volume or cross sectional area (CSA), DXA is a measure of appendicular lean soft tissue mass,[7] a substitute for muscle mass consisting of skeletal muscle (~75%) and skin and connective tissue (~25%).[1,7]

Buckinx *et al*. correctly pointed out that appendicular LSTM measures by DXA are highly correlated with both MRI (r = 0.88) and CT (r = 0.77–0.95) measures of skeletal muscle volume.[7–16] However, while this may be used to identify individuals with low muscle mass, there is evidence that repeated scans increase measurement error. DXA reliability studies have demonstrated good repeatability (less than 2% coefficient of variation)[14,15]; however, least significant change (LSC) values (percent change in LSTM required to be accurately detected by DXA) have been reported in the range of 3.85–19.4% for individual extremities.[14,15] In these studies, scans were performed serially with a 5-min rest and subsequent repositioning prior to the second scan, indicating measurement differences can be attributed almost exclusively to machine and rater error. As such, tracking changes over time becomes problematic if at least a 4% increase/decrease in LSTM must occur for DXA to detect a change, which is made worse by the fact that other variables may increase measurement error (e.g. hydration status, the possibility that changes in tissue properties may occur in response to an exercise intervention).[17,18] Additionally, there is evidence that DXA-derived measures of change in mass correlate poorly with MRI- or CT-derived changes in mass/volume.

While longitudinal comparison studies are few,[18–23] several have reported poor to moderate agreement between DXA- and MRI- or CT-derived measures of percent change in size [explained variances (R^2-values) on the order of 4–33%].[19–22] For instance, Delmonico *et al*.[20] compared changes in muscle

size in older adults in response to a 3-month resistance exercise training programme and only found a moderate association (r = 0.53) between DXA and full-thigh multi-slice CT-derived measures of change in muscle size. In support, Hansen *et al*.[19] also found a moderate association between mid-thigh CT single-slice CSA and DXA LSTM from a comparable region of interest (r = 0.51) in older adults after surgical repair of the femoral neck. The above-mentioned studies are not without limitations, and expressing changes in size is likely to magnify the differences that were observed. However, these studies highlight the probability that the measurement error of repeated DXA scans is magnified by increased time between scans and by interventions that may affect muscle and connective tissue morphology. At the very least, more carefully controlled studies tracking changes in LSTM over time should be performed. Data of this nature raise concern about the working group's recommendation that DXA be considered the *standard* for assessing muscle mass, particularly when one considers that their recommendation was within the broader context of monitoring the change in muscle mass in healthy adults, athletes, and in those managing chronic diseases.

Ethical Guidelines

All authors certify that they comply with the ethical guidelines for authorship and publishing in the Journal of Cachexia, Sarcopenia, and Muscle.[24]

Conflict of Interest

B.C.C. has received research funding from Regeneron Pharmaceuticals, Astellas Pharma Global Development, Inc., and RTI Health Solutions. In the past 5 years, B.C. has received consulting fees from Regeneron Pharmaceuticals, Abbott Laboratories, and the Gerson Lehrman Group. Additionally, B.C. is co-founder with equity and scientific director of AEIOU Scientific, LLC. P.M.C. has received an in-kind grant from GlaxoSmithKline PLC. (doses and assays for D3Cr dilution test). The other authors declare no conflict of interest.

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