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Muscle analysis using pQCT, DXA and MRI

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ABSTRACT

Skeletal muscle is one of the larger organs of the body and is integrally involved in metabolic processes in both health and disease. The ability to accurately and precisely measure skeletal muscle structure is essential for understanding the changes that occur naturally over the lifespan as well as those observed in chronic disease, and in response to targeted interventions. Musculoskeletal imaging allows for the quantification of skeletal muscle mass and select modalities are also able to determine muscle quality. The purpose of this paper is to review peripheral quantitative computed tomography (pQCT), dual X-ray energy absorptiometry (DXA) and magnetic resonance imaging (MRI) techniques used to assess skeletal muscle size and quality *in-vivo*. Each modality is briefly described and the strengths and limitations are provided. No single imaging technique will be able to best address every clinical and research question of interest. Selecting the most appropriate imaging device for measuring skeletal muscle depends on access to technology, availability of expertise required for image acquisition and analysis, characteristics of the population, anatomical site of interest, and the level of structural detail required.

1. Introduction

Skeletal muscle is one of the larger organs of the body and is the body's major protein reserve. In addition to a central role in mechanical function, skeletal muscle is integrally involved in metabolic processes in both health and disease [1]. Healthy skeletal muscle structure and function are critical for performing activities of daily living and maintaining independence with aging. With advancing age, all adults lose muscle mass [2]. Aging is also associated with less organized muscle fibers [3], a preferential decline in the size and proportion of high-tension type II muscle fibers [4], and greater muscular fat infiltration [5]. The ability to accurately and precisely assess skeletal muscle structure is essential for understanding the changes that occur naturally over the lifespan as well as those observed in chronic disease, and in response to targeted interventions.

In 1989, the term sarcopenia was coined to describe the age-related loss of skeletal muscle mass and function [6]. As the proportion of aging adults increases along with the expected prevalence of sarcopenia, scientific and clinical communities have begun to highlight the significant public health burden associated with low muscle mass and strength. Sarcopenia increases the risk for falls, fractures, hospitalizations, and mortality in older adults and chronic disease populations [7–10]. Despite the well-characterized consequences of diminishing musculoskeletal health, there is no widely accepted consensus definition or standardized assessment protocol for sarcopenia [11]. Given the potential for interventions (e.g., exercise, nutrition, pharmacological) to mitigate the onset of sarcopenia and its sequelae, there is a need to establish objective, valid, and reliable measures of skeletal muscle mass and muscle quality.

Medical imaging techniques facilitate the non-invasive evaluation of skeletal muscle size (thickness, cross-sectional area, mass or volume) and architecture (fiber length and pennation angle) [1]. As such, muscle imaging has the potential to improve our understanding of the etiology of age-related musculoskeletal conditions, such as sarcopenia, in addition to examining the efficacy of interventions aiming to improve or maintain musculoskeletal health. While sarcopenia is defined as the age-related loss of muscle mass, studies have shown that muscle quality, strength, and function are important components to consider in the assessment and treatment of sarcopenia and other musculoskeletal conditions [9,12]. Age-related loss of muscle mass and increasing accumulation of intramuscular fat is associated with lower muscle density and health-related consequences, such as worse physical function, hos-

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pitalizations, and fractures [13,14]. This infiltration of fat within the muscle is often referred to as decreasing the '*quality*' of the muscle. Intermuscular fat is an important modifiable characteristic of muscle structure. When intermuscular fat is reduced, muscle strength and physical function improve [15]. Therefore, muscle quality is an important determinant of a healthy musculoskeletal system.

Select imaging modalities are able to determine the quality of skeletal muscle as well as traditional measures of muscle mass (size). Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the gold standards and most accurate imaging methods to assess muscle mass, muscle cross-sectional area, and muscle quality as determined by muscle density and intramuscular adipose tissue (IMAT). However, due to their high cost and operational complexity, other imaging techniques as such dual energy X-ray absorptiometry (DXA) and peripheral quantitative computed tomography (pQCT) are more popular in clinical and research settings. The purpose of this paper is to review pQCT, DXA, and MRI techniques used to assess skeletal muscle size and quality *in-vivo*. Strengths and limitations of each modality are provided in Table 1.

2. Peripheral quantitative computed tomography (pQCT) assessment of skeletal muscle

Historically, computed tomography (CT) was the first available imaging method for body composition analysis [16]. Many studies have examined the validity of CT. Mitsiopoulous et al. [17] found CT-derived measures of muscle cross-sectional area of the arm and leg were highly correlated with corresponding cadaver values ($R^2 = 0.98$, SEE = 3.8 cm^2, $p < 0.001$). However, the high radiation dose, high cost, and operational complexity of CT scanners limit its availability and utility.

Peripheral QCT is a newer imaging tool that is designed and has been primarily used to determine volumetric bone mineral density, bone mineral content, and estimated bone strength. Similar to a standard CT scan, pQCT produces a cross-sectional image that permits quantification of three dimensional tissue structure properties of a limb segment (Fig. 1). Whilst pQCT is most commonly utilized to determine bone parameters, measures of muscle cross-sectional area (MCSA), muscle density, and IMAT area can be acquired from a single image [18–20]. Therefore, pQCT (Stratec, Medizintechnik GmbH, Germany) is increasingly used for assessing skeletal muscle in the limbs, particularly in the research setting. Peripheral QCT emits a significantly lower effective radiation dose per scan (<1 μSv), has a shorter scan time, and costs considerably less than a whole-body CT scanner [21–23]. Although pQCT is limited to scanning peripheral limbs, the most common sites being the tibia and radius, newer pQCT models with larger gantry diameters facilitate scanning of the femur and the humerus.

Peripheral QCT is proving to be a useful tool for the measurement of muscle and has been found to be highly correlated to MRI-derived measures of MCSA [24]. However, there are important limitations of the tool. Notably, standard image acquisition and analysis protocols have not been established. Studies of adults have predominantly examined skeletal muscle parameters from scans acquired at the 66% tibia and 65% radius sites; however, others have examined the 38% or 55% sites [18,19,25,26]. In studies of children, there is greater variation in scan acquisition site that arises from controversy regarding the placement of the reference line in relation to the growth plate [23]. The exact region to be scanned is calculated as a percentage of limb length from the reference line; therefore, the placement of the reference line will change the area of the limb being measured. In children, the reference line is placed at the distal growth plate or varying parts of the distal surface of the metaphysis [23]. These issues make comparisons between studies difficult. Despite the inconsistencies in pQCT scanning and analysis protocols, smaller MCSA and lower muscle density are associated with frailty and mortality in older adults [27]. There is limited information regarding the precision of pQCT-derived muscle and fat variables, particularly for the upper extremity. A recent study in postmenopausal women; however, suggested error (root mean squared coefficient of variation) of less than 5% for muscle area and density for the upper and lower extremity [28]. Additionally, studies have applied a variety of thresholds (used to define muscle and fat tissue borders based on their volumetric tissue density), software versions and analysis programs to analysis the soft tissue compartments [29]. To analyze soft tissue a software system (generally Stratec XCT; manufacturers software) is applied to a pQCT image and a threshold is chosen to define tissue borders of bone, skeletal muscle, and subcutaneous fat. Post-analysis calculations are then required to determine muscle and fat area and density. A recent study by Frank-Wilson et al. [29] compared pQCT image acquisition and analysis protocols reported in the literature and found that root mean square coefficients of variation ($CV\%_{RMS}$) for muscle area and density range between 2.1 to 3.7% and 0.7 to 1.9%, respectively. Precision for IMAT area varied, with values between 3% and 42% [29]. These findings suggest that pQCT may be a useful tool for examining MCSA and density, but the precision may be too low for the investigation IMAT.

High-resolution peripheral quantitative computed tomography (HR-pQCT) is another peripheral QCT modality that may be useful for measuring skeletal muscle parameters (Fig. 2). Similar to pQCT,

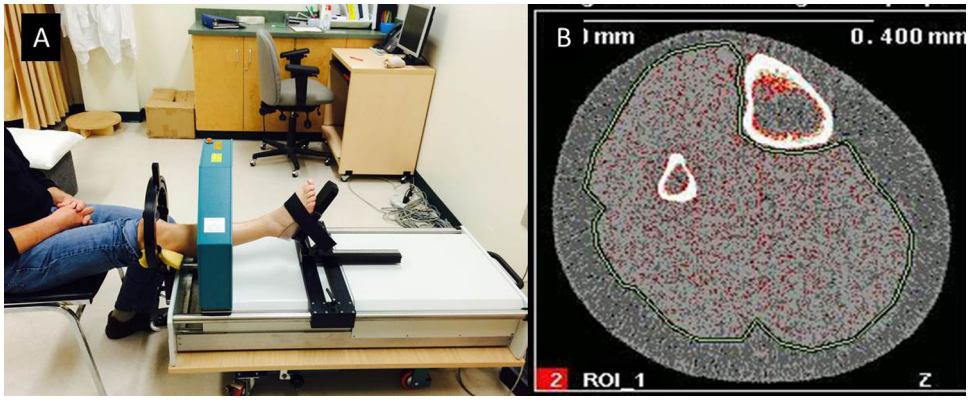

Fig. 1. Peripheral quantitative computed tomography (pQCT) scanner (XCT2000, Stratec) with a participant positioned for lower extremity scanning (A). A representativecross-sectional pQCT image (B) obtained at the 66% site of tibial length (large, white bone). The green outline between the light grey (muscle) and darker grey (subcutaneous fat) is the threshold defined border between tissues. Colours in the pQCT image (B) represent tissue densities, with dark grey (fat) being the lowest density and white (bone)being the highest density.

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