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Review Article

The assessment of sarcopenia using magnetic resonance imaging

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Abstract

Sarcopenia is a quantitative and qualitative muscle disorder with multifactorial pathogenesis intertwining with aging. The negative consequences on everyday life and functional ability are significant and have as final result the reduction of overall survival. Various and advanced magnetic resonance imaging techniques make prompt detection and disease characterization feasible, thus contribute to the modification of coexistent diseases prognosis.

Keywords: Fat, Magnetic Resonance Imaging, Muscle, Proton density fat fraction, Sarcopenia

Introduction

According to the recent definition by the European Working Group on Sarcopenia in Older People (EWGSOP), sarcopenia is considered highly likely if low muscle strength is present, while the decrease of muscle quality or quantity establishes the diagnosis. The condition is considered severe when both aforementioned criterions are combined with low physical performance. It may be exclusively age-related (primary sarcopenia) when no other specific cause is evident[1]. In the secondary form, sarcopenia may be related to activity (e.g., bed rest or zero gravity conditions), disease (e.g., advanced organ failure, malignancy) or inadequate nutrition[2]. The term "sarcopenic obesity" has been proposed to identify obesity with low skeletal muscle function and mass[3].

The overall prevalence of sarcopenia is estimated at 10% in men and women aged over 60. The loss of muscle fibers is gradual so that almost 50% of them is lost by the age of 80. Low physical activity is the main risk factor. Other contributing conditions seem to be the reduction in food quality and quantity, low vitamin D levels, hormonal decline and an increase in inflammatory age-related indices. Myostatin constitutes a probable mediator, whilst there are indications of potential genetic predisposition and connection to circadian rhythm[4].

Sarcopenia appertains to main causes of morbidity and mortality among elderly people. It interconnects with frailty, cardiac and pulmonary disease, mental decline, increased risk for falls, fractures and hospitalization. Even though recognizing sarcopenia can be done through a special questionnaire filling in and clinical test performance, imaging plays a determinant role in sarcopenia's diagnosis confirmation by estimating the muscle quality and quantity. There are various imaging methods that can be used for this purpose, such us ultrasonography, dual energy-ray absorptiometry, computed tomography and Magnetic Resonance Imaging (MRI)[5].

The aim of this review is to present the applications of MRI in sarcopenia assessment, by giving prominence to the advantages of this imaging modality, the specific MRI-derived surrogate parameters/biomarkers of sarcopenia and the MRI techniques serving that scope.

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MRI characteristics and capabilities contributing to high diagnostic value in sarcopenia assessment

MRI allows the quantification of muscular and adipose tissue. MRI renders the estimation of muscle quality by giving the ability to detect intramuscular edema and fibrous tissue, as well as the fiber contraction ability and elasticity. MRI seems to be a good prospect for sarcopenia assessment, since it does not expose the patient to radiation. Also, MRI has enough space to become more precise and dependable[6].

Dixon methods rely on the phase shifts created by fat–water resonance frequency differences to separate water from fat[7], allowing for precise measurements of muscle volume and the degree of fat infiltration[8]. Fatty infiltration is usually seen in association with muscle atrophy[9]. Nevertheless, the cross- sectional area (CSA) of the muscle could be preserved due to intramuscular accumulation of fat. The capacity of MRI to highlight the intramuscular fat accumulation justifies the fact that it is currently the radiological method of choice[10]. One of the results of Dixon technique modifications is Iterative decomposition of water and fat with echo asymmetry and least-squares estimation (IDEAL), a method that provides uniform and reliable fat suppression throughout the body. It is compatible with essentially any pulse sequence[11].

Diffusion- weighted imaging (DWI) reflects the level of water molecules motility in tissues which is associated with their cross-reaction with cell membranes and macromolecules. DWI is a reliable technique for assessing muscle and bones' pathological entities, such as sarcopenia. Diffusion Tensor Imaging (DTI) permits vicarious evaluation of tissues' anisotropy as well as their architectural orientation. These characteristics can be revealed by measurable values, such as fractional anisotropy (FA), mean (MD), radial and axial diffusivity. Recently DTI has been successfully applied to sarcopenia[12]. T1 and T2 mapping sequences provide useful data in respect of alterations that take place to the whole muscle extent, beyond the focused portions of the muscle. muscle and not just in targeted areas. T1 measurements are an index of fatty infiltration. Also, they are strongly related with the fat fraction derived from the application of Dixon. T2 mapping sequences provide hopeful outcomes on the evaluation of muscle changes due to aging. Water T2 rise could be the result of fiber type alteration. In addition, T2 eterogeneity could be linked to muscle derangement, owing to, for example, in case of fibrous changes[12].

Magnetic resonance spectroscopy (MRS) is routinely used to detect and quantify ectopic fat deposition in skeletal muscle[13]. MRS can be used to specifically quantify intramyocellular lipid, which cannot be accompliced with other MRI techniques[14]. Volume estimation with the use of MRI can be completely calibrated. This leads to low possibility of miscalculation, which in this case originates distinctly from tissue allocation and composition, and finally results in statistically robust measurements with small atomic fluctuations for a given sample size[15]. In fact, muscular CSA, as well as fat (subcutaneous, intramuscular) evaluation with the use of MRI is in concordance with cadaveric studies, since it has been shown that they have a strong correlation[16].

MRI is an excellent tool for longitudinal studies of body composition, which can be also used in susceptible populations due to the inherent absence of radiation[17].

Clinical and experimental data supporting MRI usefulness on sarcopenia assessment

MRI capabilities have been deployed for sarcopenia assessment in various regions of human and animals' body, both in defined clinical contexts and in distinctly experimental studies.

There is an increased interest in paraspinal muscles composition as a marker of spinal health. The structural solidarity, the architecture, as well as the functional ability of the paraspinal musculature are negatively affected in sarcopenia. Erector spinal muscles and psoas muscle were evaluated in correspondence with the last four lumbar vertebrae. Muscle cross- sectional area (CSA) was determined and with the use of multi-echo m DIXON algorithm. It was possible to radiologically calculate proton density fat fraction (PDFF), by diving the fat signal by the total of fat and water signals. Imaging findings were combined with isometric muscle strength measurements. Paraspinal muscle PDFF was shown to be a parameter significantly correlating with relatively paraspinal musculature power more than muscular CSA. These results corroborate the hypothesis according to which muscle fat infiltration has a direct influence on muscle functionality. Assessment of paraspinal muscle fat infiltration could be of great value in the detection of intramuscular alterations in the initial stage of the sarcopenia, providing the chance of prompt therapeutic intervention[18].

It appears that there is purposefulness in the use of fat deposition of lumbar extensor muscle in order to detect sarcopenia in subjects suffering from osteoporotic vertebral injuries, a combination related to poor outcome. On T2-weighted images and with the help of a specialized program it is possible to calculate the paraspinal muscle mass at the level of L3, the percentage of fat mass and fat degeneration. The analysis between sarcopenia delineation criterions and fat deposition in the aforementioned muscle showed an unfavorable correlation with walking velocity, hand grip power. Also, fatty infiltration of the specific muscle demonstrates a strong correlation with osteoporotic vertebral fractures[19]. Similarly, through MRI morphometrical analysis of superficial and deep paravertebral muscles of the cervical spine, it has been demonstrated that deep flexor sarcopenia is a negative prognostic factor in terms of amelioration following anterior cervical diskectomy for single-level cervical disc disease[20].

Paraspinal muscles CSA and PDFF have been also estimated at the level of superior mesenteric artery included

in MRI and computer tomography, performed within the same day in the context of lung cancer screening program. The specific anatomical landmark was proposed because it is routinely imaged during the commonest radiological studies for body assessment, it shows high demarcation and it is simple to delineate on transverse images[21].

The superior mesenteric artery level can be used for sarcopenia assessment in subjects suffering from long-term hepatic illness undergoing liver MRI, by evaluating T2 images of erector spinae. The muscle CSA measurements are related with follistatin levels, a myokine that reflects quality or activity of the muscle and is involved in muscle hemostasis and sarcopenia. Fat free muscle area (FFMA) reflects metabolically active muscle[22]. Similarly, FFMA calculated on T2 images of the erector spinae muscles and total muscle area at the same level can be used as an easy-to -apply MRI index of sarcopenia and facilitate prognostication for overall survival in patients undergoing radioembolization in order to treat liver predominant metastatic colorectal cancer[23]. Based on the same methology, Faron et al suggested that FFMA could serve as an unbiased radiological index of sarcopenia and an independent prognostic factor of survival, which can be calculated without any difficulty on routinely performed liver MRI before treatment for hepatocellular carcinomas[24].

Transverse psoas muscle thickness has been evaluated on axial T1 and T2 weighted MRI images of patients with chronic liver disease at the level of L3 vertebra. It was concluded that this technique is a reproducible and robust method. The measurement is quick and does not require the administration of paramagnetic agent, thus providing an easy but conformed method for sarcopenia evaluation in clinical practice, while giving prognostic information for subjects suffering from late-stage liver disease, since sarcopenia increases their mortality[25]. Psoas muscle and skeletal muscle area could be estimated with the use of T2 weighted images at the level of L4 on MR enterography as surrogate indices of sarcopenia with good interobserver concordance. Also, the psoas muscle intensity to cerebrospinal fluid ratio was evaluated, which is a valid representative measure of myosteatosis[26].

Fitzpatrick et al. (2020) found that there is an accelerated muscle volume decline in aging males[27]. They created a strong as well as dependable model with the use of Dixon sequence and a convolutional neural network to automatically segment iliopsoas muscles. They proved that the specific method can be applied in a large cohort, a fact that gives the ability to conduct future population-wide studies on the usefulness of iliopsoas muscle as a prognostic factor regarding the course of health problems[27].

MRI segmentation of abdominal skeletal muscle area has been evaluated at mid L3 lumbar level on an axial T2-weighted image with the use of T2 histogram. In the latter, different peaks correspond to muscular and adipose tissue. There is strong correlation with computer tomography measurements. With the absence of radiation exposure, the usefulness of MRI in locoregional staging and detection of liver metastasis in colorectal cancer and its high ability to provide soft tissue contrast resolution in renal cell carcinoma, the results given by the study seem to be especially relevant to these specific groups of patients[28].

Total abdominal muscle area (i.e., psoas, paraspinals, transversus abdominus, rectus abdominus, quadratus lumborum and internal and external obliques) was demarcated using the signal intensity on T1-weighted MRI before contrast administration at the level of L3 endplate, during MRI-magnetic cholangiopancreatography of patients post pancreaticoduodenectomy. The method allows sarcopenia assessment and through simultaneous measurement of visceral fat area, using the adipose tissue thresholds, assessment of sarcopenic obesity, both of which have an impact on surgical outcome[29]. Kim et al. (2020) developed a semi-automatic quantification software on 3D THRIVE images at the L3 level that demonstrates good discrimination in diagnosing sarcopenic obesity patients in clinical abdominal MR images[30]. Also, with the use of a semi-automatic method on skeletal muscles at the L3 level on MR enterography images, it was found that measurement of body composition parameters is feasible, reproducible and reliable. Sarcopenia was significantly associated with severe Crohn's disease[31].

In another study, analysis of body components was achieved with the use of full body MRI in T1 sequence and skeletal muscle volume, subcutaneous and visceral adipose tissue volumes were calculated. Results where compared to those of a single slice. The data suggested that for both sexes a single slice at L3 level is the best tradeoff to assess whole body adipose tissue and skeletal muscle volume[32]. A novel method that accurately, reproducibly and automatically quantifies total muscle volume and individual muscle groups based rapid whole-body Dixon MRI was presented by Karlsson et al. (2015)[33]. Utilization of whole-body MRI has been supported by laboratories as the modality of choice on the evaluation as well as follow up of the gradual alterations in total and segmental body synthesis[34].

Lately, there is an abundance of scientific research about detecting alterations in skeletal muscle mass with the use of MRI. Ageing in both women and men is accompanied by a reduction in muscular quantity, which is prominent to the legs compared to the loss to the upper extremities. Additionally, it has been ascertained by a large number of studies that there is structural divergence of lower limb musculature in elderly in comparison with young people[35]. From that point of view, abnormal edema as well as gradual aggregation of fat and fibrous connective tissue (with no ability of contraction) within muscles conduce to the decline of muscle strength and quality, which is identified to an increasing extent as a crucial feature of aging and sarcopenia. A decrease in CSA and volume in lower limb muscles is attributed in a great extent to a decrease in type II muscle fiber size, and a concurrent propensity for lesser type I muscle fibers[36]. MRI is capable

of muscle fiber type characterization, as it was ascertained by the results of vastus lateralis MRI examinations two weeks post biopsy. There is high correlation between T1 and T2 relaxation times and the percentage of fast twitch fibers in muscle[37]. High resolution fast T1 mapping of thigh muscles demonstrated that mean T1 values are decreased in dystrophic muscles and are linearly correlated with intramuscular fat fraction, as it is measured with DIXON sequence[36].

With the application of a 6-minutes dual-echo DIXON VIBE protocol and advanced image analysis lean muscle tissue (with fat fraction less than 50%- viable muscle tissue) and fat infiltration of anterior thigh muscles were calculated. The combination of the two parameters appeared to be related with muscular and motor function, such us hand grip strength and falls, making detection of sarcopenia feasible with the use of quantitative imaging biomarkers[38].

Thigh muscles of sarcopenic patients have been evaluated to their whole extent by a combination of MRI parameters. T1 sequence allows the determination of total amount of muscle mass, the ratio with fat and bone as well as macroscopical evaluation of fat infiltration. Multi-echo sequence with chemical shift permits the calculation of PDFF (microscopic fat infiltration) and T2* relaxation time, which is correlated with muscle hydration. The latter is also estimated with DWI. A strong correlation exists between cineanthropometric variables and imaging biomarkers[39]. In addition, a recent study of multiparametric MRI evaluation of thigh muscles has demonstrated that muscle T2, fat fraction and MD increase with age, they correlate (along with muscle volume) with muscle power and strength and their measurement could be used in the management of sarcopenia and frailty[40].

Values obtained at the 50% femur length from a single MRI section and the use of modified GRE DIXON sequence are able to stand for the total thigh for volume evaluation of muscle, subcutaneous as well as intermuscular fat. Moreover, that corresponds very well to the clinical criterions of sarcopenia[41].

During the lockdown period in Italy, muscles CSA at the level of the central third of the thigh was estimated by T1 and Dixon sequences in a randomized controlled trial on patients between 60 and 80 years old. It was concluded that it is necessary of the elderly to follow resistance exercise program indoors, particularly when they are limited to their residence, in order to prevent muscle tissue loss as well to protect their ability to function[42].

With the use of 3-point Dixon at the mid-thigh area of older adults, Marcus et al estimated total fat and lean tissue CSA. The measurements were combined with muscle strength and mobility function evaluation. They concluded that intramuscular adipose tissue adversely affects motor ability, a factor of great importance in sarcopenia of the aged population[43]. Animals muscle evaluation has proved that quantification of muscle/fat fractions based on Dixon is reliable and valid with no statistically significant differences across field strength and with no significant differences with histological measures[44]. Volume and PDFF Dixon MRI are accurately reproducible, thus could be utilized to prognosticate motor disfunction and measure therapeutic response in sarcopenia[45].

Quantitative parameters derived from MRI scans (Short Tau Inversion Recovery - STIR and T1 - weighted sequences) have been applied in extremity muscles of both affected and contralateral limb of patients suffering from juvenile localized scleroderma. All parameters where lower at the affected side. It was demonstrated that the disease affects the muscles mainly causing low grade edema and significant sarcopenia, which can be reliably and easily estimated in the clinical routine practice[46].

In another exploratory study, T1 axial MRI images of quadriceps muscle were evaluated and the results were used for cluster analysis using the k-means algorithm. It was shown that fat deposition is significantly higher in women with body mass decrease and upper gastrointestinal malignancy, even if age is taken into consideration. Non-invasive objective separation of contractile and non-contractile volume compartments can be achieved by the use of MRI[47].

After studying the thigh muscles of patients suffering from Charcot - Marie - Tooth disease, Kim et al suggested that 3D multiple gradient echo Dixon - based MRI may have the sensitivity to detect fatty degeneration in initial stages, the recognition of which could be challenging during the visual evaluation of T1 weighted image. In such a way, incorporation of the specific sequence as part of the usually performed MRI for the evaluation of patients with neuromuscular disease could be clinically significant[48].

DIXON MRI at mid-thigh has been compared with HISTO MRS of semitendinosus muscle in young healthy and sarcopenic subjects with high PDFF. It was shown that both methods have comparable accuracy for PDFF measurements in the thigh. MRS is a local measurement, whereas DIXON sequences provide map of the PDFF distribution, which is important in case of inhomogeneous fat infiltration in muscle that characterizes sarcopenia[49].

Quadriceps musculature, which is affected more often by ageing compared with the rest of thigh muscles, was studied at the mid-thigh of patients with clinical frailty syndrome. It was shown that clinical frailty syndrome and the related sarcopenia led to an augmentation of fractional anisotropy, thus establishing DTI as a possible helpful implement in the research about the assessment of skeletal muscles concerning the elderly. An increase in T2 time and MRI-derived intramuscular fat content was noted, reflecting a well-recognized relationship between fat accumulation and the process of growing old[50]. These results are in good concordance with previous animal experimental study which combined MRI and histological examination[51] and another animal study that correlated these features with aging and high fat diet[52].

A feature of MRI is its highest capacity to distinguish

muscles from the adjacent tissues. Also, MRI is able to detect little differences in muscle volume. These characteristics have been used to calculate quadriceps femoris muscle volume with the application of T1-weighted MRI, to evaluate therapeutic effect of anti-TNF agent therapy on inflammatory sarcopenia in Crohn's disease, a condition found in 60% of the patients[53].

A structural MRI explorative study evaluated muscle thigh- rectus femoris area (T1 MRI) and grey matter volume (voxel base morphometry at the native 3D brain MRI) in older people with type 2 diabetes melitus. It was proven that sarcopenia characteristics were present with greater frequency in frail compared to prefrail patients. In addition, a correlation was noted between these characteristics and a reduction in grey matter volumes linked with motor control[54].

Wang et al. (2019) showed that the signal intensity of IDEAL sequence fat fraction map is almost equivalent to that of muscles, thus it provides the ability of early sarcopenia detection, as it was demonstrated by the evaluation of psoas and thigh muscles on patients with Parkinson Disease[55].

Another study showed that lower magnetization transfer ratio (MTR) indicates impaired muscle quality as it was demonstrated during MTR evaluation of the entire musculature of the calf. In this study, MRI was combined with muscle strength measurements and electrophysiological studies. Lower MTR is related with decreased amount of protein and therefor aging is connected to a deprivation in viable tissue with the ability to contract in proportion to CSA. As a probable consequence, there are fewer actin myosin crossbridge interactions, contributing to impaired force reduction[56].

Results from a study about detection of alterations in muscles caused by aging with the use of DTI, have demonstrated that the acquired parameters correlate strongly with age. When fibers are smaller, there is a restriction in space for a given molecule and therefor a reduction in diffusion coefficient, i.e., eigenvalues, which could partially explain the decrease in that parameter in older plantar flexors[57].

Ex vivo measurements conducted with Diffusion-weighted MRS on samples from pig lower hindlimbs have shown that intramyocellular fat exhibits substantially lower apparent diffusion coefficient in comparison with extramyocellular fat[58]. MRI of the gastrocnemius muscle of female mice showed a definite relationship between aging and CSA reduction in the calf area. Spectroscopy (PRESS) revealed that aging arbitrates to a decrease in the amount of the produced lactate. The results were combined with locomotor activity and evaluation and histological examination. It was found that melatonin administration had a positive result on the muscle fibers. The researchers concluded that melatonin is a significant tool in the protection from aging-induced sarcopenia[59]. Except from extremities and trunk muscles, MRI assessment of sarcopenia is feasible in various other sights. Depending on the pre-existing pathology, muscle groups that are evaluated for sarcopenia assessment can be adjusted to the clinical MRI studies.

Recent study has shown that temporal muscle thickness has a strong correlation with grip strength and is a novel surrogate parameter of sarcopenia. The measurement can be done simply, fast, and reliably on T1weghted images of routinely performed MRI of neurological patients[60]. Results from another study have shown that the temporal muscle thickness, as it can be estimated on cranial MRI images in patients with progressive glioblastoma, may serve as an objectively assessable parameter of sarcopenia[61]. In patients with head and neck cancer undergoing neck MRI scans, muscle CSA was measured at the level of C3 vertebra in T1-weighted and T2 TSF DIXON images. The authors discovered a significant correlation for total CSA in the neck scans, regardless of the sequence and the power of the field. Nevertheless, the use of T2 sequence may be preferred. The results support the constitution of clinically helpful imaging index on sarcopenia evaluation in head and neck cancer patients[62].

Fatty infiltration of tongue muscles induces sarcopenic dysphagia. It has been appreciated with the use of Dixon MRI. It was found that age significantly affected tongue fat mass[63]. Sarcopenia is considered as a contributing factor in presbyphagic alterations of the shallowing process. Pixel-based measures at the level of C2, C3 and the vallecula demonstrated that aging is accompanied by a reduction in the wall thickness combined with an increase in lumen area of the pharynx[64].

Sarcopenia is an autonomous negative predictive factor in respect to the outcome in breast cancer patients. Rossi et al came to the conclusion that pectoralis major area (calculated on T1-weighted images) on breast MRI can be implemented for the direct evaluation of a female's musculature on breast MRI[65].

In the year we are going through, Birkbeck et al. (2021) published data that pertain to an innovative diffusion weighted MRI technique called Motor unit magnetic resonance imaging (MUMRI) and its combination with a phase-contrast MRI (PC MRI) sequence, conventionally used to look at blood flow. With the use of MUMRI, the authors discovered discrepancies in size, physical form and arrangement of single human motor units between healthy young and older subjects and PC MRI allows to demonstrate if there are inactive fibers (66).

Conclusions

MRI has the potential of playing a pivotal role in sarcopenia assessment, with the use of simple, classical sequences as well as with the implementation of novel and advanced techniques. MRI allows non-invasive skeletal muscle mass quantification and the estimation of muscle quality with high reproducibility and reliability. MRI is able to depict changes occurring at intracellular environment in sarcopenia and provides robust imaging biomarkers for sarcopenia assessment. MRI is a field with continuing development.

Data over the years suggest that MRI could significantly contribute to sarcopenia assessment at every day clinical practice in future.

Authors' contributions

KM: Drafted the manuscript, reviewed literature. GIL: Proof-edited the manuscript and gave final permission for publication.

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