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UNIVERSITÉ NICE CÔTE D'AZUR

DOCTORAT EN MÉDECINE

THÈSE D'EXERCICE DE MÉDECINE

JANCZYK Ewa Magdalena

Née le 08/01/1993

**SONOELASTOGRAPHY TO ASSESS MUSCULAR STIFFNESS AMONG
OLDER ADULTS AND ITS USE FOR THE DIAGNOSIS OF
SARCOPENIA: A SYSTEMATIC REVIEW**

Thèse dirigée par le Dr CHAMPIGNY Noémie

Soutenue publiquement le 09/07/2020

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RÉSUMÉ

Les modifications structurelles apparaissant avec la sarcopénie sont susceptibles de modifier la qualité contractile du muscle. La sonoélastographie est une méthode accessible et non-irradiante permettant de quantifier les propriétés élastiques du tissu musculaire. Nous avons réalisé une revue systématique de la littérature afin de déterminer si la sonoélastographie peut être une méthode fiable pour évaluer l'importance de la sarcopénie chez les sujets âgés.

Nous avons cherché les articles publiés sur 5 bases des données : Medline, Google Scholar, Scopus, SpringerLink and Science direct du 1^{er} Janvier au 1^{er} Avril 2020. Trois investigateurs indépendants ont évalué l'éligibilité des études, réalisé l'extraction des données et l'évaluation du risque de biais. Nous voulions connaître quels types d'élastographie ont été réalisés, si la répétabilité des mesures a été vérifiée et si la sonoélastographie a été comparé avec les autres méthodes diagnostiques.

Dix études remplissaient les critères d'inclusion. La majorité des études étaient des études transversales avec des sous-groupes de personnes jeunes et âgées. Le muscle gastrocnémien, le muscle quadriceps fémoral et le muscle vaste intermédiaire étaient les muscles les plus évalués. Neuf études utilisaient l'élastographie par ondes de cisaillement et une étude utilisait l'étude du *strain* (déformation du tissu sous une contrainte). La constante élastique passive « k » été plus élevée chez les patients atteints de sarcopénie (124.98 ± 60.82 vs. 46.35 ± 15.85 , $p = 0.004$). Cependant, même chez les sujets âgés non-sarcopéniques l'âge était responsable de 45.5% de la variance de la vitesse des ondes de cisaillement. Parmi les dix articles inclus, quatre ont démontré l'augmentation de la rigidité musculaire avec l'âge, deux, au contraire, la diminution et quatre n'ont pas retrouvé de différence significative.

En définitive, au vu de l'importante hétérogénéité des données actuelles, nous n'avons pas pu conclure sur l'utilisation de l'élastographie dans l'évaluation de la sarcopénie. D'autres études

sont nécessaires, avec un protocole standardisé et reproductible sur un échantillon plus important de personnes âgées.

Mots clés : sarcopénie, personnes âgées, élastographie, atrophie musculaire, technique d'imagerie

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Sonoelastography to assess muscular stiffness among older adults and its use for the diagnosis of sarcopenia: a systematic review.

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Running title: sonoelastography and sarcopenia among older adults

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ABSTRACT

Background. Structural changes susceptible to modify its stiffness have been reported in sarcopenic muscle. Sonoelastography is an accessible and non-radiating imaging technic allowing quantification of elastic properties of the tissue. We performed a systematic review of the literature to investigate whether sonoelastography can be a reliable method to assess sarcopenia in older patients.

Methods. We search Medline, Google Scholar, Scopus, SpringerLink and Science direct from January 1st, 1990 up to April 1st, 2020. Three independent review authors assessed trial eligibility, extracted the data and assessed risk of bias. We intended to learn which types of elastography have been tested, the repeatability of such measures and if they have been compared to the currently accepted diagnostic method

Results. Ten studies met the inclusion criteria. Most followed a cross-sectional design with young and older adults' subgroups. Gastrocnemius, rectus femoris and vastus intermedius appeared the most. Nine of included studies used shear wave elastography and one-strain elastography. Passive elastic constant(k) was significantly greater in sarcopenic versus healthy subjects after passive stretching (124.98 ± 60.82 vs. 46.35 ± 15.85 , $p=0.004$), but even in non-sarcopenic patients age was responsible for about 45.5% of variance in SWV. Amongst ten included articles, four reported higher stiffness in older adults' muscles, two in contrary- lower, and four found no significant difference.

Conclusions. Due to the substantial heterogenicity of actual data, we could not conclude on the potential usefulness of elastography to assess sarcopenia. Further studies are needed, including larger sample of older patients, and using standardized and reproducible protocol.

KEYWORDS: sarcopenia, muscle atrophy, elderly, older adults, elastography, elasticity imaging technics, sonoelastography

INTRODUCTION

The European Working Group On Sarcopenia in Older People (EWGSOP) [1] recently updated recommendations on definition and diagnosis of sarcopenia, a progressive and generalized alteration of skeletal muscle structure and function exerting a negative impact on one's health, quality of life and entailing increased costs on the public health system [2]. Indeed, there is a proven correlation of sarcopenia with an increased risk of adverse outcomes such as falls [3], fractures [4], dependence [5], neurocognitive impairment [6] and death [7]. Sarcopenia is mainly caused by structural changes such as loss of muscle fibers, reduction in their size, the lower ratio of fast (type II) to slow (type I) muscle fibers, adipose and fibrotic tissue infiltrations [8-10] and muscular mass loss that occur with aging. The process may be accelerated and worsened by sedentary lifestyle, poor nutritional status [11] and chronic diseases, that cause inflammation [12] along with hormonal and metabolic dysregulations [13].

Currently the diagnosis of sarcopenia may be confirmed by one of the 4 imaging technics: computed tomography (CT), magnetic resonance (MR), dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA). In clinical practice all the above-mentioned methods have their limitations. CT and MR are both too expensive to be used for screening. It is particularly difficult for geriatric patients to hold a steady position, due to cognitive impairment and frequent arthropathic pains. Thus, they are currently only used in research protocols. Bioelectrical impedance analysis (BIA) is susceptible to underestimate lean muscle mass in case of fluid overload, often present in hospitalized, elderly patients. Moreover, its degree of concordance varies, depending on the type of equation used. They require validation for use in elderly population [14]. DXA seems to be the most appropriate option in terms of cost-accuracy balance, but lean body mass estimation may vary depending on the device manufacturer [15] and its availability in clinical practice remains heterogenous. Sonoelastography could be an interesting alternative to these imaging techniques. To simplify,

we can refer to sonoelastography as an ultrasonographic palpation of an organ or lesion of interest. We can distinguish acoustic radiation force (ARFI) imaging, strain elastography (SE), transient elastography (TE), pSWE (point shear wave elastography) and shear wave elastography (SWE). The difference between them is the type of force applied and the way of displaying the tissue's response.

Thus, we performed a systematic review of the literature aiming to investigate the use of sonoelastography in the assessment of muscular stiffness in elderly and its potential use in a diagnosis of sarcopenia. We intended to learn which types of elastography have been tested, whether the reproducibility and repeatability of such measures have been evaluated and if they have been compared to the currently accepted diagnostic methods (CT, MRI, DXA, BIA).

METHODS

Protocol and registration

The study protocol has been admitted to PROSPERO and is currently awaiting registration.

The review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA).

Eligibility criteria

The aim of this review was to identify studies that aim to evaluate structural changes in aging muscles and that include different kinds of sonoelastography, such as ARFI imaging, strain elastography, transient elastography and shear wave elastography. The conditions of eligibility were specified before the onset of screening. We took under consideration only human studies, in which patients over 70 years old were a part of a study sample. For our purpose, no comparators and/or controls were required. However, if the studies included other validated

imagery techniques, they were included and used to answer the sub-question of this review (whether sonoelastography was compared with other validated diagnostic methods).

The following study designs were accepted: randomized trials, diagnostic case-controlled studies, diagnostic cohort studies, prospective, retrospective, or non-reported cohort studies, cross-sectional studies, observational studies, and case series. Data could be collected from the diagnostic settings across all stages of the continuum of care including inpatient, outpatient or other. The studies had to be published since 1990 up to 01/04/2020. This year has been chosen due to the history of elastography, which started in the early 80s, by data used from the M-mode to track movement, then in the late 80s by modified color Doppler and finally led to the invention of strain elastography in 1991 by Cespedes and Ophir [16]. Only studies written in English, French, Italian, Spanish, Russian, Polish, or German were accepted, because of the author's limited linguistic skills. All the studies not available in full-text version were excluded.

The inclusion criteria were as follows: i) the ultrasound equipment operator or technician is definable (physician, radiologist, clinician, researcher, etc.), ii) the evaluation of muscle stiffness using ultrasound elastography is either the primary or secondary diagnostic objective or intervention.

Information sources and search

We performed the screening of 5 medical databases: MEDLINE (Pubmed), Google Scholar (Google), Scopus, SpringerLink and ScienceDirect. The search strategy used for MEDLINE database was as follows:

((((((((sarcopenia[MeSH Terms]) OR muscle atrophy[MeSH Terms]) AND elastography[MeSH Terms]) OR elasticity imaging techniques[MeSH Terms]) OR Vibro-Acoustography[MeSH Terms]) OR sonoelastography[MeSH Terms]) OR acoustic radiation

force impulse imaging[MeSH Terms]) OR arfi imaging[MeSH Terms]) OR elastogram*[MeSH Terms])

Study selection

All abstracts retrieved during the search were uploaded to Rayyan [17], a web-based abstract selection program. The duplicates were eliminated from search results. EJ searched through all the abstracts, and two other members (EM and GS) divided the same abstracts in two parts, so that each abstract was judged for eligibility by two team members independently. The abstracts were divided into one of 3 groups “excluded”, “included” and “maybe”. When the screening was finished, during a meeting of all researchers the inclusion/exclusion of the contentious abstracts were discussed, and the discrepancies resolved. The reference lists of the original research articles were then screened for any further relevant materials. The full texts of chosen abstracts were obtained, and the suitability of each study judged considering the PICO characteristics, as well as inclusion and exclusion criteria. Reasons for exclusion were documented at each stage.

Data collection process and items

Extracted data was documented on pre-defined form and comprised of the title, author’s information, year of publication, study design, subjects demographics and baseline characteristics, equipment used (type of transducer and ultrasound machine), details about the taken measures (type of muscle, number of repetition, axis), repeatability, type of elastography, results, comparison (if present) and missing data.

Risk of bias

The assessment of bias was conducted separately for each study included. EJ and NC evaluated independently all the articles using the QUADAS-2 checklist for the diagnostic test accuracy studies [18]. All the discrepancies including the risk of bias level were resolved by a consensus

between the two researchers and if necessary, the opinion of the third member of the review team (GS) was taken.

RESULTS

From the initial 8477 abstracts screened, 463 were identified as duplicates and 7926 were excluded. The reasons were: not matching the inclusion criteria or PICO characteristics, full text unavailable, foreign language. The remaining 88 articles were then accepted for the full-text assessment and 78 of them revealed discrepancies with the review criteria. Ten articles were included in the systemic review (Fig1).

As the presence of reference standard was not obligatory for this systemic review, nine out of ten articles did not include any of the four imaging technics (BIA, DXA, CT, MRI) as comparison. In Sun et al., 2020 [19] BIA of the lower right limb was performed at the inclusion stage among the patients of rehabilitation ward to confirm sarcopenia (using the criteria of Asian Working Group for Sarcopenia [20]). The elastic parameters tested in this study: “E₀” (slack elastic modulus) and “k” (passive elastic constant) had shown moderate to high sensitivity and specificity in sarcopenia diagnosis when compared with BIA. Respectively for E₀: sensitivity in women (83.3%), in men (50%); specificity in women (75%), in men (87.5%) and for k: sensitivity in women (83.3%), in men (66.7%); specificity in women (87.5%), in men (93.8%).

In Alfuraih et al., 2019 [21] participants underwent a bioelectrical impedance analysis by Tanita DC-430 MA system. However, the measurements were performed at the stage of inclusion, to ensure that none of the participants were sarcopenic. Nevertheless, age was a significant predictor of shear wave velocity (SWV) in the regression model [R^2 VL=0.455, RF=0.314, VM=0.587, VI=0.205, BB=0.191, BF=0.547, ST=0.600, SM=0.671] showing that even in non-sarcopenic patients age is responsible for about 45.5% of variance in SWV.

Nine out of ten articles were prospective, except for Baumer et al., 2017 [22], which was a retrospective study. The most repetitive scheme was a cross sectional study design with participants divided into young and older adults' groups or eventually young, middle-aged, and older adults' groups (eight out of 11 articles). Two studies were an exception. Baumer et al., 2017 [22] was a case-control study with 30 participants, amongst which 19 were asymptomatic control subjects and 11 were patients, diagnosed with a full-thickness rotator cuff tear of the supraspinatus tendon. In Sun et al., 2019 [19], 16 healthy volunteers were compared with 12 patients with lower leg weakness treated in a rehabilitation ward.

Elastography was performed on different striated muscles (Fig2.), both in the upper and lower limb, such as vastus lateralis [21], vastus intermedius [21,23,24], vastus medialis [21], rectus femoris [21,25,26] medial [25,19,27] and lateral gastrocnemius [26, 19, 27], soleus [26], the hamstrings [21], biceps brachii [28] and supraspinatus [22]. One study evaluated postural muscles: trapezius and erector spinae [29]. Most frequently appearing were lateral and medial gastrocnemius (four studies) and the quadriceps muscles: vastus intermedius and rectus femoris (both evaluated in three studies).

Most muscle measurements were taken in the longitudinal axis, except from two studies. The first one used transversal axis for the evaluation of rectus femoris and the medial head of the gastrocnemius (Saito et al., 2018 [25]) and the second one used transversal axis for erector spinae and transversal, but longitudinal to the fascicles, placement for trapezius muscle (Heizelmann et al., 2017 [29]).

In all studies a linear probe was used. The complete list of the commercial ultrasound machines and transducers is listed in the Table 1.

Wang et al. constructed and used in their studies from 2014 and 2017 [24,23] a vibro-ultrasound system consisted of a mechanical vibrator, a programmable ultrasound scanner and a custom-

made program for radio-frequency data acquisition, based on a commercial ultrasound scanner SonixRP. Its measurement accuracy has been tested in the first study on a set of silicon phantoms of known shear moduli.

All studies used shear wave elastography to evaluate muscle stiffness, except from Saito et al., 2018 [25] which used strain elastography performed with an acoustic coupler. Strain ratio (strain of the muscle to that of the acoustic coupler) was significantly higher in the older adults than in the young (RF in young: 0.31 ± 0.08 vs. older adults: 0.53 ± 0.17 , $p < 0.001$; MG in young: 0.28 ± 0.07 vs. older adults: 0.45 ± 0.14 , $p < 0.001$), signifying harder tissue.

Similar results can be seen in Eby et al., 2014 [28]: the biceps brachii muscle showed increased stiffness with advanced age in full elbow extension ($p=0.03$). In Heizelmann et al., 2017 [29] the shear wave velocity (m/s) was significantly higher in the older adults (> 60 years old) versus young group (< 60 years old) in right erector spinae (2.84 ± 0.58 vs. 3.07 ± 0.49 , $z=1.9641$, $p=0.02$), left erector spinae (2.85 ± 0.52 vs. 3.11 ± 0.75 , $z=1.7048$, $p=0.04$) and right trapezius (2.74 ± 0.41 vs. 2.91 ± 0.23 , $z=2.05613$, $p=0.005$) but not left trapezius (2.78 ± 0.38 vs. 2.81 ± 0.38 , $z= 0.3953$, $p= 0.35$). In Baumer et al., 2017 [22] for the control group mean SWV was significantly associated with age both in active muscle ($p=0.049$, $R^2= 0.24$) and passive muscle ($p=0.039$, $R^2=0.23$).

On the other hand, in Alfuraih et al., 2019 [21] the SWV were significantly lower between the young and middle-aged adults, and the older adults in all the tested muscles (quadriceps, the hamstrings and biceps brachii). The mean difference between older adults and middle-aged group was -12.9% (ranging from -6.5% to -18.8%) and the difference between the young and the older adults was the highest -16.5% (ranging from -11% to -23.3%). It is important to note that older participants in this study were non-sarcopenic, which may explain the discordance with the results of previously described studies.

Nevertheless, similar outcomes were reported by Akagi et al., 2015 [26] which revealed that RF and LG shear moduli are significantly higher in young vs. older adults group (RF $\eta^2=0.201$, $p < 0.001$, LG $\eta^2 =0.055$, $p=0.039$) except for soleus muscle, which did not show significant difference.

Four out of ten articles reported no significant difference between young and older participants.

Wang et al. 2017 [23] presented results that were already partially released in their 2014 study [24]. They tested shear moduli of vastus intermedius in all levels of mean voluntary contraction (MVC), starting with a relax state and ranging from 0° to 100° , increasing by 10° at each step and at two different knee joint angles (60° and 90°). There was no significant difference in VI shear modulus in a relaxed state ($p=0.221$), but the shear moduli increased faster in young subjects with the degree of MVC, especially for the higher isometric contraction levels.

In Nakamura et al. 2017 [27] the shear moduli of lateral and medial heads of the gastrocnemius muscle were tested at 3 ankle joint positions before and after 5 minutes of static stretching. There were no significant differences in shear moduli between young and older adults before the stretching ($p=0.92$ for LG at 30° plantar flexion, $p=0.14$ for MG at 30° PF, $p=0.62$ for LG at 0° PF, $p=0.24$ for MG at 0° PF, $p=0.21$ for LG at 20° PF, $p=0.72$ for MG at 20° PF).

Sun et al. 2019 [19] performed experimental measures of elastic modulus as a function of length (displacement of distal muscle-tendon junction of gastrocnemius muscle during passive stretching). The use of both, elastography and B mode evaluation, enabled them to define E° (slack elastic modulus), l° (slack length) and k (passive elastic constant). There was no significant difference between sarcopenic patients and healthy controls in E° and l° , but k was significantly greater in sarcopenic versus healthy subjects after passive stretching (46.35 ± 15.85 vs. 124.98 ± 60.82 , $p=0.004$).

In three of included articles repeatability was tested [24-26] and one reported result from their previous work [22]. The intraclass correlation coefficients were high ranging from 0.87 to 0.978 when performed by the same operator. Day-to-day repeatability was measured in Akagi et al., 2015 [26] on 4 young participants [RF= $8.1 \pm 7.0\%$, LG: $4.5 \pm 4.2\%$, SOL: $4.4 \pm 2.8\%$]. None of the articles tested the interobserver relation.

Regarding bias, the quality of included studies evaluated by QUADAS-2 checklist was moderate. Detailed results of bias evaluation are presented in Fig3. Concerns were mainly raised about the patient selection, either because the included sample was not random or because the case-control design was adopted. The applicability of certain studies was also put into question, because of the mean age of participants. Even though all studies included patients over 70 years old, the mean age of elderly subgroup in some of them was too low.

DISCUSSION

Our systemic review revealed that currently there is a lack of consensus in the literature on whether muscle stiffness increases, decreases or remains constant with age. Amongst ten included articles, four reported higher stiffness in elderly muscles, two in contrary- lower and four found that there is no significant difference.

There may be many reasons for these discrepancies. First, muscles are anisotropic tissues and the propagation of shear waves may differ depending on direction. Therefore, taken measures may be highly influenced by position of the probe (longitudinal or transversal axis) [30] and muscle architecture (parallel, unipennate, bipennate).

Secondly, muscles are viscoelastic and dynamic tissues. Their stiffness may depend on their recent history of movement or on their current state: relaxed, passively stretched or actively contracted. Different flexion angle of adjacent joints may be responsible for fascicule extension

and altered results. For example, elastic measures of biceps brachii taken on patients with flexed elbow should not be compared with those obtained in full extension. Furthermore, SWV may also differ depending on the external source of pressure, for example the compression applied by a transducer. Certain studies reported that the operator paid attention to put a minimal pressure while performing an examination [29] and others used rigid holders to eliminate the involuntary compression [19].

Moreover, the results may be affected by ultrasound parameters such as depth and size of the region of interest [31,32]. Lower SWV have been reported with increasing depth, so the position of muscle must be considered a variable. For example, SWV of vastus intermedius, which is located underneath rectus femoris or soleus lying underneath gastrocnemius muscle may be difficult to compare with more superficially placed muscles, such as trapezius. The included studies had shown substantial differences on the data acquisition. The ROI size differed from one to another, SWV were either measured as the mean from the whole ROI or by circles drawn in the ROI box (one or many). Young modulus was calculated using different values of muscle density (either 1000 kg/m³ [24] as it is a presumed density of soft tissues or 1084 kg/m³ [26], which was the value chosen by the authors, based on previous studies).

The above-mentioned dissimilarities did not allow us to complete the review with a meta-analysis.

Ultrasonographic settings and measurements may not be the only ones to be held responsible for the differences. It was reported that the muscle mass loss in sarcopenia is not progressing at the same pace, with lower limb exceeding upper limb. The later may explain the discrepancies between the shear modulus of shoulder rim muscles (biceps brachii, supraspinatus), the back muscles (trapezius, erector spinae) [33] and the lower limb muscles, such as quadriceps or the hamstrings.

Amongst four studies that had shown increased stiffness with age, three were performed on the upper limb or dorsal muscles: Eby et al., 2015 on biceps brachii; Baumer et al., 2017 on supraspinatus and Sun et al., 2020 on trapezius and erector spinae. It may constitute a pattern with stiffness increasing with age in the muscles of the upper parts of the body and decreasing in limb muscles, but further studies are needed to confirm or disprove this hypothesis.

A weakness of this systematic review was that a majority of included articles was based on a cross-sectional design, comparing young to elderly subjects. Only in the study of Sun et al., 2020 the sample of elderly patients had sarcopenia, confirmed following the recommendations on Asian Group for Sarcopenia [20]. Thus, their results do not allow us to draw a conclusion whether sonoelastography can differentiate a healthy muscle from sarcopenic one. Interesting insight was brought by Alfuraih et al., 2019 [21]. In this study the elderly non-sarcopenic participants (confirmed by BIA) were compared with young participants and it has been shown that age was responsible for 45.5% of the variance in SWV. If the impact is this important even in absence of sarcopenia, it is possible that the differences in SWV may be too small to differ significantly between a healthy elderly subject and an elderly with sarcopenia.

We pondered which types of elastography and what kind of measurements were used to assess muscle changes in sarcopenia. As we already mentioned in nine out of ten articles shear wave elastography has been used. This method seems to be more suitable for becoming a screening test, as it is less operator dependent and provides quantitative results. In Saito et al. 2018 [25] strain elastography was used. It is a valuable imagery technique, but in the hands of experienced ultrasonographer, as many artefacts produced by this method may either provide guidance or constitute an obstacle. The out-of-plane structures may exercise strain influencing in-plane measures, fluid displacement may entrain time-dependent reduction in strain (which is important in case of fluid overload), soft tissue in the close proximity of hard tissue strains more, the boundaries are enhanced by slippery borders and many more [34].

To become a reliable diagnostic method, a test needs to show high intra- and interobserver correlation. The intraclass correlation coefficients were high when performed by the same operator, both on young and elderly participants. The evaluation of interobserver variability is however lacking and should be explored in further studies.

CONCLUSION

Due to the substantial heterogeneity of actual data, we could not conclude on the potential usefulness of elastography to assess sarcopenia. Further studies are needed, including larger sample of older patients, and using standardized and reproducible protocol.

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All authors of this manuscript comply with the guidelines of ethical authorship and publishing in the Journal of Cachexia, Sarcopenia and Muscle [35]

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Ethics approval

Ethical approval was not required for this research.

Contributions of Authors

GS has full access to all of the data in the study, takes responsibility for the data, the analyses and interpretation and has the right to publish any and all data, separate and apart from the attitudes of the sponsors. All authors have read and approved the manuscript.

Study concept and design: EJ, CR and GS

Acquisition of data: EJ, NC, EM and GS

Analysis and interpretation of data: EJ, NC, EM and GS

Drafting of the manuscript: EJ, NC and GS

Critical revision of the manuscript for important intellectual content: CR, RZ, CA and OG

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Administrative, technical, or material support: CR and OG

Study supervision: GS

Declaration of interests

All authors state that they have no conflicts of interest with this paper. The authors have no relevant personal financial interest in this manuscript.

Availability of data and materials

There are no linked research data sets for this paper

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TABLES

Table 1. Characteristics of studies included in qualitative synthesis.

Study	Type	Inclusion / exclusion criteria	n/N	Women (n, %)	Age* (mean±sd, range)
Alfuraih et al., 2019	Cross-sectional	Healthy / Musculoskeletal or neurological disorder, corticosteroid or statin treatment, sarcopenia, fragility	30/77	41 (53)	81.7±4.1, 77–94
Saito et al., 2018	Cross-sectional	Healthy / Trunk or lower extremity surgery; Parkinson's disease; dementia; assisting devices	221/323	323 (100)	73.4±6.0
Wang et al., 2017	Cross-sectional	Healthy/ ND	20/40	20 (50)	Men 60.6±7.6 / Women 56.7±4.9
Akagi et al., 2015	Cross-sectional	ND / ND	49/118	38 (32)	Men 73±5 / Women 69±5
Eby et al., 2014	Cross-sectional	Healthy/ Neuromuscular or musculoskeletal disease; upper extremity injury or surgery	32/133	86 (65)	60-94
Sun et al., 2020	Cross-sectional	Sarcopenic/ Normal US** appearance of GM*** in B-mode US; muscle rigidity; peripheral palsy	44/44	22 (50)	Patients 61.7±12, 43-89 Controls 59.6±15.5, 41-88

Heizelmann et al., 2017	Cross-sectional	ND/ Surgery, fractures or injuries of the spinal region or shoulder joint; intervertebral disc prolapse; anabolic agents; pregnancy; diabetes, osteoporosis; rheumatic disorders; inadequate depiction of muscles in B-mode imaging; poor quality of elastic measures	24/278	168 (61)	ND
Wang et al. 2014	Cross-sectional	Healthy/ ND	10/20	20 (100)	56.7 ± 4.9
Baumer et al., 2017	Retrospective	Full-thickness rotator cuff tear of supraspinatus tendon/ ND	11/30	21 (70)	60.0 ± 6.1, 53-73
Nakamura et al., 2017	Cross-sectional	Healthy; no assisting devices/ Dementia; trauma; surgery; neuromuscular disorders; metabolic disorders; diseases impairing muscle function	15/30	30 (100)	75.9 ± 2.8

n: number of older adults; N: whole sample; ND: not defined; *: age of the subgroup of older adults; **: ultrasound; ***: gastrocnemius muscle

Table 2. Technical characteristics of included studies.

Study	Operators (n, experience in years)	Measurements per muscle	Ultrasound machine	Probe	Muscle	Axis
Alfuraih et al., 2019	NA, NA	3	Aixplorer (Supersonic Imagine, Aix-en-Provence, France)	SuperLinear™ SL10–2 MHz probe	quadriceps (VL, VI, VM, RF) , hamstrings (BF, SM, ST), biceps brachii	longitudinal
Saito et al., 2018	1, 7	3	Noblus (Hitachi, Tokyo, Japan)	linear, L64, 10 MHz (Hitachi)	rectus femoris, medial head of the gastrocnemius	transversal

Wang et al., 2017	1, NA	3	Custom-made vibro-ultrasound system incorporating SonixRP, Ultrasonix Medical Corp., Vancouver, Canada	linear, 5–14MHz	vastus intermedius	longitudinal
Akagi et al., 2015	NA, NA	5	Acuson S2000 (Siemens Medical Solutions, USA)	linear, 9L4, 4-9 MHz (Siemens Medical Solutions, USA)	rectus femoris, lateral head of gastrocnemius, soleus	longitudinal
Eby et al., 2014	NA, NA	2	Aixplorer (Supersonic Imagine, Aix-en-Provence, France)	linear, SL15-4	biceps brachii in flexed and extended elbow positions	NA

Sun et al., 2020	2, 6–10	NA	Aixplorer (SuperSonic Imagine, Aix-en- Provence, France)	linear, 4–15 MHz	gastrocnemius muscle	longitudinal
Heizelman n et al., 2017	10, NA	1	The Siemens Acuson S3000 + VTIQ (Siemens Healthcare, Erlagen, Germany)	NA in the text, linear 9L4 visible on Fig.1	trapezius muscle, erector spinae muscle	transversal for erector spinae, transversal (but longitudinal to the fascicles) in trapezius
Wang et al. 2014	1, NA	3	Custom-made vibro- ultrasound system incorporating SonixRP, Ultrasonix Medical	linear, 5-14 MHz	vastus intermedius	longitudinal

			Corp., Vancouver, Canada			
Baumer et al., 2017	NA, NA	5	Siemens Acuson S3000	9L4 Transducer, Erlangen, Germany	supraspinatus muscle	longitudinal
Nakamura et al., 2017	NA, NA	2	Aixplorer (SuperSonic Imagine, Aix-en- Provence, France)	linear, SL-15-4	medial and lateral gastrocnemius	longitudinal

NA: Not available; VL: vastus lateralis; VI: vastus intermedius; VM: vastus medialis; RF: rectus femoris; BF: biceps femoris, SM: semimembranosus, ST: semitendinosus; VTIQ: virtual touch tissue imaging and quantification

FIGURES

Figure 1. Prisma flow diagram

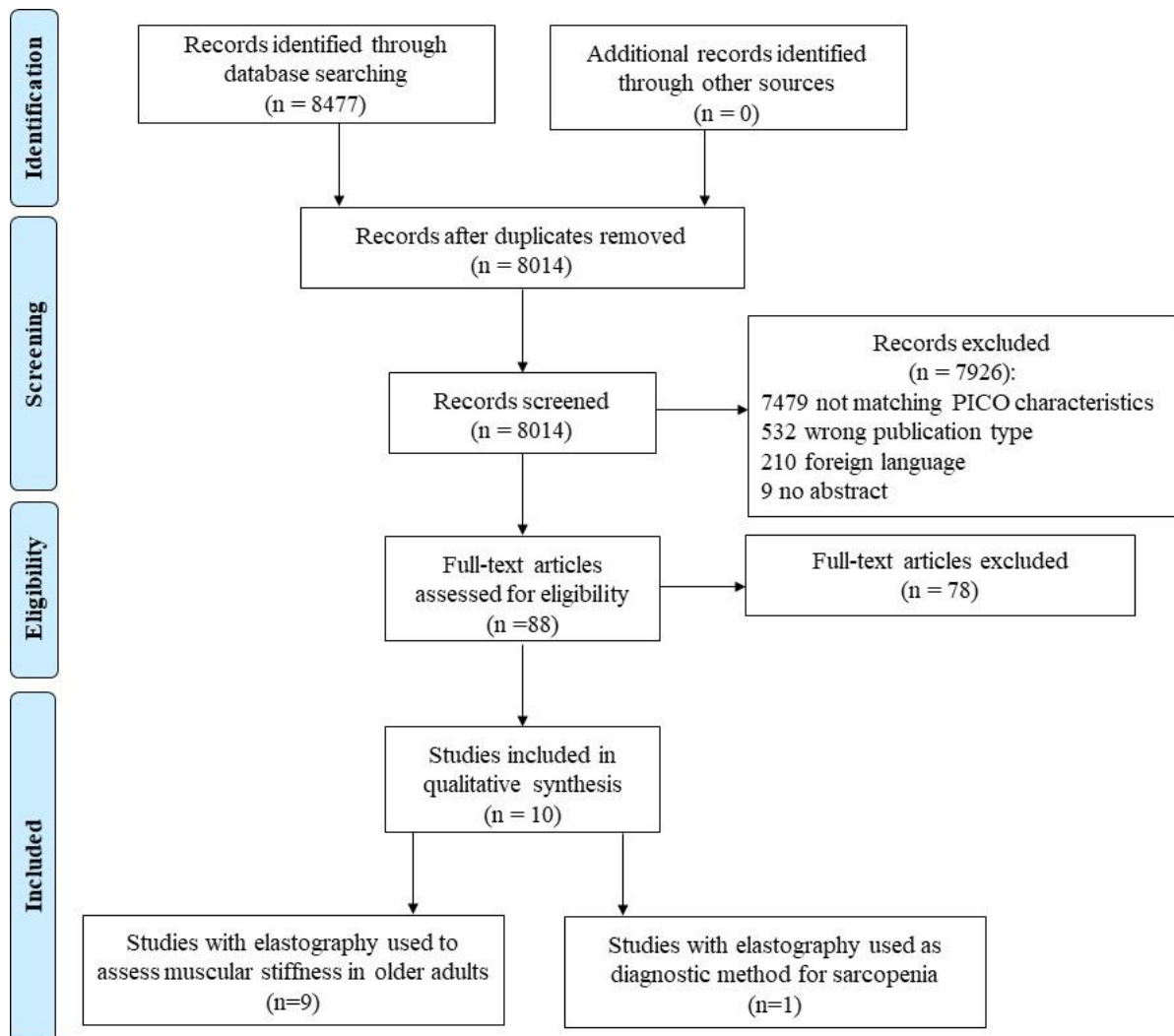
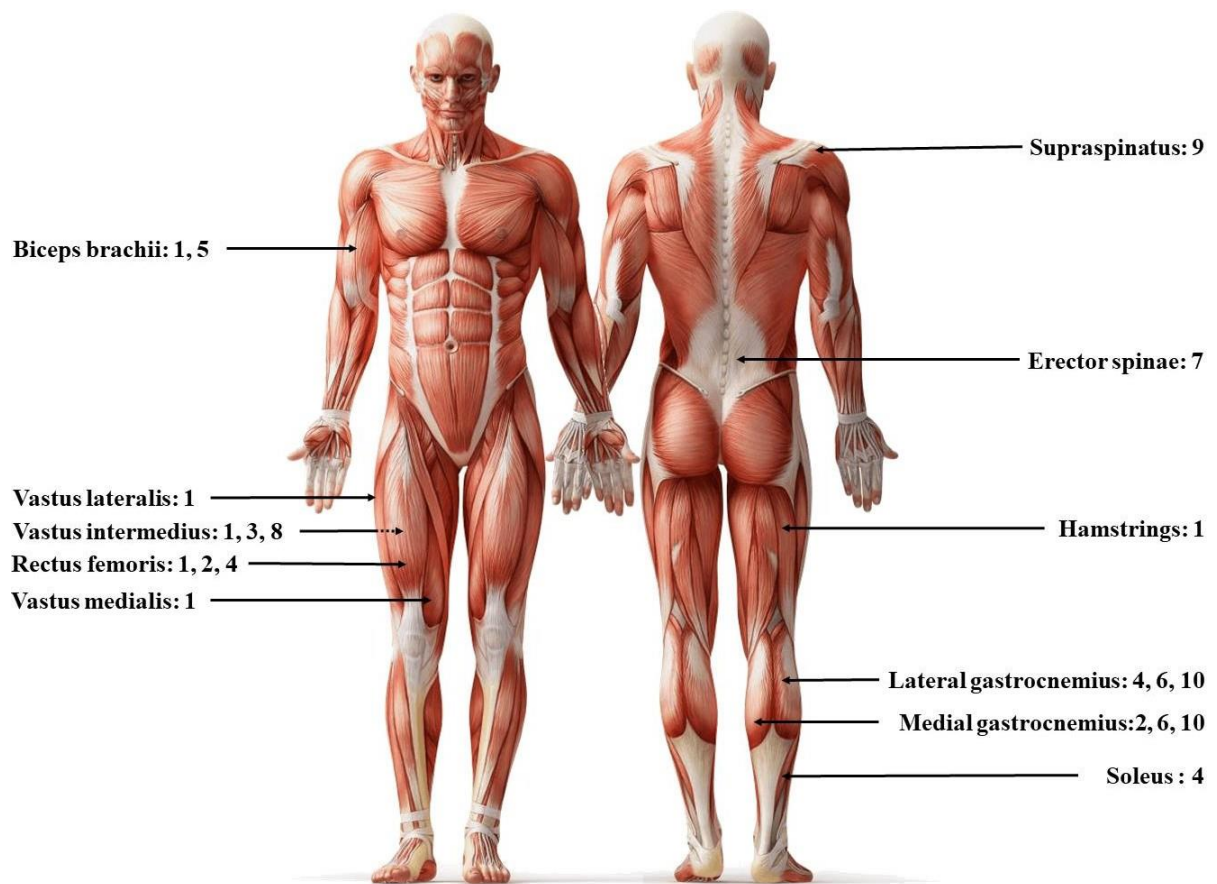
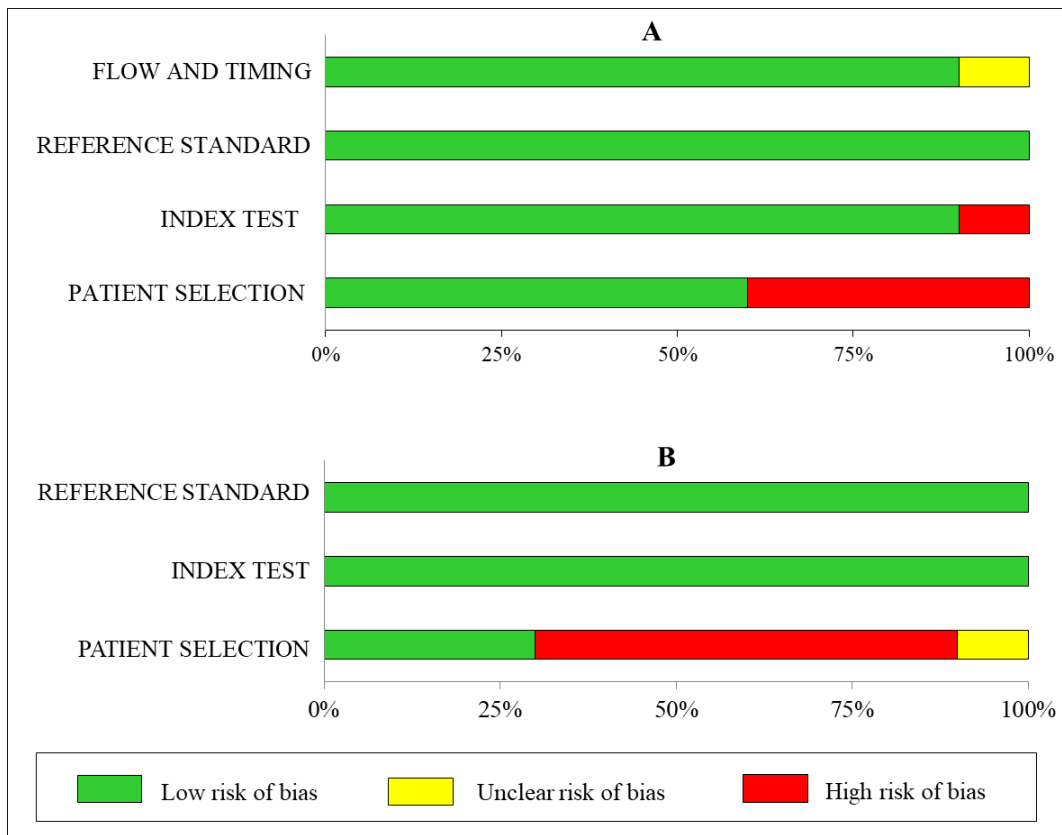


Figure 2. Muscles assessed in included studies



1: Alfuraih et al., 2019; 2: Saito et al., 2018; 3: Wang et al., 2017; 4: Akagi et al., 2015; 5: Eby et al., 2014; 6: Sun et al., 2020; 7: Heizelmann et al., 2017; 8: Wang et al. 2014; 9: Baumer et al., 2017; 10: Nakamura et al., 2017.

Figure 3. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included trials.



A : Risk of bias assessment ; B : Applicability assessment

Figure 4. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included trial

Study	Risk of bias				Applicability		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Akagi,2015							
Alfuraih,2019							
Baumer,2017							
Eby,2015							
Heizelmann,2017							
Nakamura,2017							
Saito,2018							
Sun,2020							
Wang,2014							
Wang,2017							