




The relation between mortality, intramuscular adipose tissue and sarcopenia in hospitalized geriatric patients

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Abstract

Introduction One of the biggest healthcare challenges that arises with increasing age expectations is sarcopenia. However, as a multi-dimensional construct with both neurological and musculoskeletal factors involved, the exact contribution of these different components of sarcopenia to mortality outcomes is not clear. Therefore, in mortality assessment, it is advisable to use subitems of sarcopenia such as the intramuscular adipose tissue (IMAT), instead of using sarcopenia as a construct itself. IMAT is negatively correlated with strength and performance, and positively correlated with mortality, both all-cause and cardiovascular. In this study, IMAT and its relation to long-term mortality, muscle strength and function is studied.

Materials and methods Patients admitted to the University Geriatrics Department during 6 months were screened for muscle mass, strength and function through computed tomography (upper leg), Jamar dynamometer and short physical performance battery, respectively. After 4 years, health status (mortality) was obtained by telephone.

Results Three hundred and two patients were included (69.6% female). Mean IMAT was $29.3 \pm 12.3\%$. There was a positive correlation between IMAT and mortality in the male 70–79-year-old age group ($n = 20$), but not in the whole cohort. IMAT was negatively correlated with muscle strength and function.

Conclusion IMAT is negatively correlated with muscle strength and muscle function. IMAT is correlated with mortality in a specific subgroup of this cohort. This data adds to the discussion of the value of IMAT in the construct of sarcopenia. More studies need to be done regarding the evolution of IMAT in function of time and functional decline.

Keywords Sarcopenia · Myosteatorsis · Intramuscular adipose tissue · Assessment · Mortality

Introduction

One of the biggest healthcare challenges that arises together with increasing age expectations is sarcopenia [1]. As the age-related decline of muscle mass, strength and function [2], it is associated with mortality and increased healthcare costs because of—among others—functional decline,

progressive disability, a higher rate of falls, a higher incidence of hospitalizations, and a lower quality of life [3]. Regarding sarcopenia, much work has been done in the field of prevention, which mostly consists of physical exercise and nutritional support [4]. However, as a multi-dimensional construct with many factors involved [5], the exact contribution of the different components of sarcopenia to mortality and other negative health outcomes is not clear. Therefore, measuring subitems of sarcopenia in mortality assessment is recommended. In this study, the focus was put on myosteatorsis.

Myosteatorsis is the process of increased uptake of lipids in muscle adipocytes, which are located in the deep fascia of the muscle [6]. There are some hypotheses that provide a possible explanation into the evolution of myosteatorsis inadequate function and capacity of subcutaneous depots to store excess fat, increased fatty acid transport, uptake and storage, reduced fatty acid oxidation, increased macrophage

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infiltration that inhibits adipocyte differentiation, disuse, altered leptin signaling, sex steroid deficiency and an age-related altered differentiation of muscle stem cells (satellite cells) into adipocytes rather than into myocytes [7–10]. There are three types of myosteatosis that could be distinguished: lipid depositions between muscle groups (intermuscular lipids), lipid depositions between the myocytes (intramuscular lipids) and lipid depositions within the myocytes (intramyocellular lipids) [11, 12]. In this study, the second kind was evaluated. This intramuscular adipose tissue (IMAT) can be measured both by computed tomography (CT) or magnetic resonance imaging (MRI), but not with either dual-energy X-ray absorptiometry (DEXA) or bio-impedance absorptiometry (BIA). The latter two tend to overestimate the total muscle mass [13–15]. Intramuscular adipose tissue thus mistakenly considered as muscle mass can represent an important bias in the evaluation of the muscle mass component in sarcopenia [16].

IMAT is correlated with decreased muscle function, decreased muscle strength, decreased mobility and physical performance, impaired longevity, increased insulin resistance and type 2 diabetes, increased risk of osteoporotic fractures and increased mortality, both all-cause and cardiovascular [6, 17–21]. However, there is hardly no evidence regarding the relation between IMAT and long-term mortality. In this study, therefore, the relation between IMAT and mortality was investigated in this cohort of hospitalized geriatric patients. As a secondary objective, the relation between IMAT and muscle mass, strength, function and nutritional status was investigated.

Materials and methods

Design

This retrospective cohort study was conducted with the primary objective of determining the relation between intramuscular adipose tissue and mortality in hospitalized geriatric patients. As a secondary objective, the relation of intramuscular adipose tissue and muscle mass, strength, function and nutritional status was investigated.

Patients

All patients admitted to the University Geriatrics Department from the 1st of August 2012 until the 31st of January 2013 were screened for nutritional status, muscle mass, muscle strength and functional capacity. Inclusion criterion was admittance to the ward in this period. Exclusion criteria were: refusal to undergo the screenings tests or refusal to undergo the CT scan. Patients with long-stemmed hip

implants were excluded from the CT scan, since the implant interferes with the measurement.

After 4 years, patients or their relatives were contacted by telephone to obtain the current health status (mortality). If it was not possible to contact either the patient or their relatives, the general practitioner of the patient was contacted. Alternatively, the Civil Affairs Office was contacted to check if the patient was already deceased.

Measurements

The following determinants were used: IMAT, muscle mass, muscle strength and physical performance.

Muscle mass was measured by CT scan (Siemens Somatom Balance, Siemens, Erlangen, Germany) of both upper legs. The mid thigh was set by a cranial–caudal scan of the femur, where the middle was located half way between the most proximal part of the femur head and the intercondylar region of the distal femur. Five CT-slices, each 1 cm apart, were taken above and five slices below this midpoint. The difference between fat, bone, muscle and other tissue was made by measuring the difference in Hounsfield units (HU). In computed tomography, attenuation values in Hounsfield units are standardized, where water has a value of 0 HU, fat a value of -100 HU, muscle a value of 50 HU, and bone a value of >1000 HU [22]. The measuring and interpretation of the CT images were done by an experienced radiologist. The muscle volume was measured in cubic millimeters (mm^3) by integration between the slices.

Muscle strength was obtained by measuring the handgrip strength with a Jamar dynamometer (Lafayette Instrument, Lafayette, IN, USA). Handgrip measurements were done according to the protocol described by Roberts et al. [23]. Cut-off points were set on 30 kg for men and 20 kg for women, as proposed by the European working group on sarcopenia in older people [2].

The functional capacity was measured by performing the short physical performance battery (SPPB). The SPPB consists of three timed tests: a balance test, a repeated chair stand test and a walking speed test. Each subtest can yield a maximum score of four, with the maximum total score being 12. Three different groups were considered: those with low (0–4), middle (5–7) and high (8–12) scores, as used by Ostir et al. [24]. Patients who were not able to perform the functional tests because of reasons unchanged since before hospitalization, e.g., post-stroke paralysis, were scored accordingly (score = 0). Patients who were not able to perform the functional tests because of acute problems leading to hospitalization, e.g., temporarily bedbound due to pneumonia, were tested as soon as possible.

The nutritional status was screened for using the standardized Mini-Nutritional Assessment-Short Form (MNA-SF) [25], which was taken on either the day of admission

or the day thereafter. The standardized cut-off points were used to divide the included patients in three groups: ‘Normal nutritional status’ (scores 12–14), ‘At Risk of Malnutrition’ (scores 8–11) and ‘Malnourished’ (scores 0–7).

Statistics

Statistical analysis was done with SPSS 24 (SPSS Inc., Chicago, IL, USA). The determinants were subdivided into categories for all the statistical analyses, as described in the previous section. Descriptive statistics were used to describe demographic and key clinical characteristics of the study population. Multiple cox proportional hazard regressions were used to determine hazard ratios (HR), each time adjusted for the confounding variables age and gender. A Kolmogorov–Smirnov test and Shapiro–Wilk test were used to verify the normal distribution of the different variables. Unpaired *t* tests were used to test for differences in the distribution of continuous variables. A Chi square test was used for significance of associations with categorical variables. *p* values < 0.05 were considered statistically significant. *p* values were adjusted for multiple comparisons using the Bonferroni method. Correlations were measured by Pearson’s correlation coefficient (PCC). If variables were not normally distributed, a logarithmic transformation was done before performing the PCC.

Results

In total, 302 patients were included. Baseline characteristics (gender, age, height, weight, BMI) and follow-up time are summarized in Table 1. After 4 years, follow-up data were gathered on all 302 patients (100% follow-up was obtained).

During the period of follow-up, 162 patients died (53.6%). Of these 162 patients, 102 (63.0%) was female. When excluding the deceased persons, mean follow-up time after admittance was 1412 ± 46 days (range 1340–1494 days).

Data about IMAT are summarized in Table 2. The difference in mean IMAT between men and women was significant ($p = 0.023$).

CT data on muscle mass were not collected in the whole group, but only 199 of the 302 patients (65.9%). Of these, 140 (70.4%) were women. There were two reasons for not performing a CT to collect muscle mass data: on one hand the fact that some hip implants (long-stemmed) give too much distortion for correct measurements ($n = 43$), on the other hand patients that did not give their consent for performing the CT scan ($n = 60$).

In the following paragraphs, all data is arranged according to parameter. Both significant and non-significant results are shown in the text. For an overview of significant

Table 1 Baseline characteristics and follow-up time of study group ($n = 302$)

Parameters	<i>n</i> (% total)	Mean \pm SD	Median	Range
Gender (female)	211 (70)	NA	NA	NA
Age (years)	NA	83 ± 6	83	64–101
Height (cm)	NA	163 ± 8	163	142–186
Weight (kg)	NA	66 ± 15	64	33–155
BMI (kg/m^2)	NA	25 ± 5	24	14–47
Follow-up time (days)	NA	949 ± 533	1261	2–1494
Handgrip strength (men, kg)	83 (28)	17 ± 9	16	0–43
Handgrip strength (women, kg)	189 (63)	14.4 ± 8.8	14	0–52
SPPB	276 (91)	4 ± 3	3	0–12

n number, *SD* standard deviation, *NA* not applicable, *cm* centimeter, *kg* kilogram, *m* meter, *BMI* body mass index, *SPPB* short physical performance battery

Table 2 Muscle mass (gr) and intramuscular adipose tissue (IMAT, %) values in men and women from both left and right leg

Parameters	Mean		<i>p</i> value	Median		Range	
	Left	Right		Left	Right	Left	Right
Thigh muscle mass	522 ± 15	533 ± 16	0.080	484	518	114–1244	60–1325
Men	549 ± 215	565 ± 226	0.213	548	545	123–1197	97–1169
Women	511 ± 209	518 ± 216	0.213	470	472	114–1244	60–1325
Thigh IMAT (%)	29.3 ± 13.4	29.1 ± 12.5	0.751	25.8	25.6	3.2–82.7	8.5–86.2
Men	27.2 ± 11.0	26.9 ± 11.9	0.731	23.8	22.9	13.5–56.7	14.0–63.0
Women	30.2 ± 14.3	30.0 ± 12.6	0.860	26.9	26.6	3.2–82.7	8.5–86.2

Table 3 Significant correlations of handgrip strength and short physical performance battery with intramuscular adipose tissue

Parameters	<i>n</i>	<i>p</i> value	PCC
Handgrip strength	272	<0.001	-0.305
Handgrip strength (men)	83	0.003	-0.375
Handgrip strength (women)	189	0.032	-0.192
Handgrip strength (men, 79–79 years age group)	13	0.025	-0.615
SPPB	276	<0.001	-0.455
SPPB (men)	86	<0.001	-0.440
SPPB (women)	190	<0.001	-0.460
SPPB (men, 80–89 years age group)	48	0.011	-0.432
SPPB (women, 80–89 years age group)	108	<0.001	-0.488
SPPB (men, 90–99 years age group)	17	0.043	-0.617
SPPB (women, 90–99 years age group)	52	0.001	-0.566

Correlations were screened for three times, once in the whole group, once divided per gender, and once divided per gender and age group. Only significant results are shown

n number of patients per group, *PCC* Pearson's correlation coefficient, *SPPB* short physical performance battery

results regarding correlations with IMAT, see Table 3. For an overview of significant results regarding correlations with mortality, see Table 4.

Mortality and IMAT

In univariate analysis in the whole group, IMAT was not significant for 4-year mortality ($p=0.279$, PCC 0.077). IMAT was also not significant for 4-year mortality for either men alone ($p=0.246$, PCC 0.148), or women alone ($p=0.287$, PCC 0.092).

Patients were then divided by gender and age group: 60–69 years, 70–79 years, 80–89 years, 90–99 years and 100–109 years. In this configuration, a significant positive correlation was found in the male 70–79 year-old-age group ($n=20$, $p=0.046$, PCC 0.540).

In multivariate analysis, IMAT was assessed together in a model with age, gender, MNA-SF, handgrip strength and SPPB. In this model, only MNA-SF ($p<0.001$, hazard ratio 0.864, 95% CI 0.811–0.921), gender ($p=0.001$, hazard ratio 2.018, 95% CI 1.325–3.075) and SPPB ($p=0.002$, hazard ratio 0.896, 95% CI 0.834–0.962) were significant. IMAT had no significant correlation with mortality after multivariate analysis.

Muscle mass and IMAT

In the whole group, muscle mass was negatively correlated with mortality ($p=0.022$, PCC -0.160). When divided by gender, muscle mass was negatively correlated with mortality in women ($p<0.001$, PCC -0.304), but not in men

Table 4 Significant correlations of intramuscular adipose tissue, muscle mass, handgrip strength and short physical performance battery with mortality

Parameters	<i>n</i>	<i>p</i> value	PCC
IMAT in male 70–79 age group	20	0.046	0.540
Muscle mass	203	0.022	-0.160
Muscle mass in women	193	<0.001	-0.304
Muscle mass in male 70–79 years age group	20	0.001	-0.795
Muscle mass in female 80–89 years age group	116	0.003	-0.330
Muscle mass in female 90–99 years age group	60	0.024	-0.371
Handgrip strength	272	0.018	-0.144
Handgrip strength (men)	83	<0.001	-0.403
Handgrip strength (women)	189	0.005	-0.206
Handgrip strength (men, 70–79 years group)	17	<0.001	-0.767
Handgrip strength (men, 80–89 years group)	47	0.002	-0.438
Handgrip strength (women, 80–89 years group)	106	0.021	-0.224
SPPB	276	<0.001	-0.243
SPPB (men)	86	0.001	-0.344
SPPB (women)	190	0.004	-0.207
SPPB (men, 70–79 years group)	20	0.001	-0.697
SPPB (women, 70–79 years group)	23	0.007	-0.548

Correlations were screened for three times, once in the whole group, once divided per gender, and once divided per gender and age group. Only significant results are shown

n number of patients per group, *PCC* Pearson's correlation coefficient, *IMAT* intramuscular adipose tissue, *SPPB* short physical performance battery

($p=0.057$, PCC -0.239). When divided by gender and age group (decade), muscle mass was negatively correlated with mortality for men in the age group 70–79 years ($n=20$, $p=0.001$, PCC -0.795) and for women in the age groups 80–89 years ($n=116$, $p=0.003$, PCC -0.330) and 90–99 years ($n=60$, $p=0.024$, PCC -0.371).

Data on IMAT and muscle mass can be found in Table 2. The difference between left and right side were not significant for both IMAT and muscle mass. In comparison to women, higher muscle mass values ($p<0.001$) and lower IMAT ($p<0.001$) values were seen in men. In both genders, a relative high mean percentage of IMAT was seen.

Handgrip strength and IMAT

Data on handgrip strength can be found in Table 1. Men had a significant higher mean handgrip strength in comparison to women ($p<0.001$).

In the whole group, handgrip strength was negatively correlated with mortality ($p=0.018$, PCC -0.144). When divided by gender, handgrip strength was negatively correlated with mortality for both men ($p<0.001$, PCC -0.403)

and women ($p=0.005$, $PCC -0.206$). When divided by gender and age group (decade), handgrip strength was negatively correlated with mortality for men in the age group 70–79 years ($p<0.001$, $PCC -0.767$), 80–89 years ($p=0.002$, $PCC -0.438$) and in women for the age group 80–89 years ($p=0.021$, $PCC -0.224$).

In the whole group, IMAT was negatively correlated with handgrip strength ($p<0.001$, $PCC -0.305$). When divided for gender, IMAT in men was slightly better negatively correlated with handgrip strength ($p=0.003$, $PCC -0.375$), in women the negative correlation was less ($p=0.032$, $PCC -0.192$). When divided for gender and age group (decade), IMAT was only negatively correlated with men in the age group 70–79 years ($n=13$, $p=0.025$, $PCC -0.615$).

SPPB and IMAT

For data about SPPB, see Table 1. SPPB-scores were positively correlated with both handgrip strength ($p<0.001$, $PCC 0.311$) and muscle mass ($p<0.001$, $PCC 0.406$). In the whole group, SPPB had a negative correlation with mortality ($p<0.001$, $PCC -0.243$). When divided by gender, SPPB had a negative correlation with mortality for both men ($p=0.001$, $PCC -0.344$) and women ($p=0.004$, $PCC -0.207$). When divided by gender and age group, SPPB was negatively correlated with mortality in the age group 70–79 years for both men ($n=20$, $p=0.001$, $PCC -0.697$) and women ($n=23$, $p=0.007$, $PCC -0.548$).

In the whole group, there was a negative correlation between SPPB-scores and IMAT ($p<0.001$, $PCC -0.455$). When divided by gender, SPPB was negatively correlated with both men ($p<0.001$, $PCC -0.440$) and women ($p<0.001$, $PCC -0.460$). When divided by gender and age group, SPPB was negatively correlated with both men and women in the age groups 80–89 years (men: $p=0.011$, $PCC -0.432$; women: $p<0.001$, $PCC -0.488$) and 90–99 years (men: $p=0.043$, $PCC -0.617$; women: $p=0.001$, $PCC -0.566$).

Discussion

There is enough evidence in the literature to confirm a correlation between IMAT and mortality in community-dwelling patients, as is stated in the introduction. However, the evidence in this specific cohort does not confirm these data completely. This study aimed to investigate the relation between IMAT, parameters of sarcopenia, nutrition and four-year mortality in a cohort of acutely hospitalized geriatric patients.

In this cohort, there was no clear correlation between IMAT and mortality for the whole group. However, if subanalyses were done, a strong positive correlation was

found for males in the age group 70–79 years old. This is an interesting finding. Although there have been many advances into the insight of the pathophysiological process of sarcopenia, little is known about the exact timing and order of onset of deviations. It is not clear at which age or at which percentage IMAT starts to become relevant. Therefore, differentiation by age (decade) could help unravel this sequence. In addition, it is unclear to what extent the (small) sizes of the subgroups have influenced the results. Larger subgroups could potentially give a more clear picture of the relation between IMAT and mortality. More studies are needed to clarify this hypothesis.

As a percentage of total volume measured, IMAT in this population was high with a large range. This is much higher than in community-dwelling persons in the literature [27, 28]. It is not clear whether this is due to acute illness, or due to other reasons. As a note of interest, in a review by Aubrey et al. [29], it is clear that there is probably a very large range in which the attenuation ranges of different tissues should be found. Muscle is described to possibly have an attenuation range of 0–200 HU. Possible reasons for variation in attenuation are age, obesity and training status, pointing towards an influence of depositions of fat in muscle. More research is needed in this specific field to create more detailed cut-off points.

In this cohort, muscle mass, strength and function were all negatively correlated with mortality. This is in line with the current literature [30–35], and strengthens the evidence also in a cohort of acutely hospitalized geriatric patients. The link between IMAT, strength and function status is less well described in this specific cohort.

There was a clear negative correlation between IMAT and grip strength, most pronounced in men in the age group 70–79 years. There was also a negative correlation between IMAT and muscle function—the strongest correlations here were found in the age groups 80–89 years old and 90–99 years old. These data could perhaps be interpreted as fitting the cascade deterioration in sarcopenia [36], i.e., the sequence of muscle architectural changes, decline of muscle mass, loss of strength and worsening muscle function. Therefore, it is important to screen for IMAT as an architectural change in an early stage, before strength or function abnormalities occur, to start treatment and (secondary) prevention as soon as possible.

The strengths of this study are the long follow-up period and the absence of missing data in the follow-up. Limitations are not registering all comorbidities to further refine the model used for mortality prediction. Unfortunately, it was not possible to use ‘sarcopenia’ as a construct to correlate with mortality, because of the absence of reference values for the specific muscle mass measurement that was taken in this study.

The use of CT could be considered both as a strength and a limitation. CT has a high accuracy and reproducibility when used in human body composition, but is an expensive technique that exposes patients to radiation [37]. It is also not feasible in every situation because it is a non-transportable machine, that needs an experienced technician. In comparison to other techniques, such as BIA, this could be seen as a disadvantage. As a note of interest, other techniques are emerging in the field of muscle mass assessment. Ultrasound could be a very interesting alternative to both CT and BIA, because it can give detailed anatomical information, is portable, easy, cheap and reproducible [38]. However, much like CT, no clear cut-off point for the diagnosis of sarcopenia are as of yet available for ultrasound. Additionally, clear guidelines need to be set up to standardize the ultrasound measurement technique.

This study raises some important issues in the investigation of the importance of early architectural changes in the muscle, in this case the IMAT. More studies have to be done to clear out the exact timing and order of onset of architectural changes in the ageing muscle, and the influence of comorbidities on this evolution. This study adds to the evidence of the link between IMAT and the other components of sarcopenia.

Conclusions

In conclusion, this study strengthens the evidence for the relevance of measuring the IMAT and need of early detection hereof, to intervene in the process of sarcopenia in an as early stage as possible. More studies are needed to unravel the exact timing and evolution of IMAT in an ageing muscle.

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Author contributions SP and MV conceived and designed the study; SP, SL, and RD collected the data; SP, SL, RD and EVM analyzed the data; SP wrote the paper; SP, SL, RD, EVM, MV, AMDC and VV revised the manuscript.

Compliance with ethical standards

Conflict of interest The authors confirm that there are no conflict of interests

Ethical approval This research was done in accordance with the Helsinki Declaration on ethical principles for medical research involving human subjects [26]. As all investigations used (blood analyses, handgrip measurement, SPPB, nutritional screening and muscle mass measurements with CT scan) were part of the routine investigations

performed on the geriatric ward, explained to all patients orally and through a standardized information leaflet (admittance brochure).

Informed consent In every patient, oral consent was obtained before performing the analyses and this consent was noted down in the electronic patient file. Because this study is to be regarded as an analysis of anonymously registered routine-based data, no new explicit question was addressed to the local ethics committee.

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