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## FGF19 and muscle architecture in older patients

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### ABSTRACT

**Background:** Sarcopenia has a significant medical and economic impact. Serum fibroblast growth factor 19 (FGF19) has recently been described as promoting muscle mass and strength, and could be an interesting marker for early diagnosis of sarcopenia and prevention of its consequences. Ultrasound is a robust non-invasive technique used to measure muscle parameters, which cannot be evaluated by usual body composition measures, but are known to be associated with muscle function. In this cross-sectional cohort study, we aimed to determine whether FGF19 levels were correlated with functional muscle tests and muscle ultrasound parameters.

**Methods:** Patients over 70 years old with a mobility disability risk were recruited from the cohort of the “well on your feet” mobility loss prevention program. Sarcopenia was diagnosed according to the European Working Group on Sarcopenia in Older Patients 2 (EWGSOP2) criteria. We have performed functional battery tests, muscle ultrasound measures and bioimpedance spectroscopy. FGF19 levels were measured by the ELISA method.

**Results:** Out of 52 patients involved (34 women, mean age 81.3 years), 30 patients were sarcopenic (15 patients with probable sarcopenia and 15 with certain sarcopenia). Sarcopenic patients were older (mean 82.8 versus 79.6 years,  $P = 0.033$ ), with higher frailty Fried score ( $P = 0.006$ ), lower IADL score ( $P = 0.008$ ), had lower daily protein intakes ( $P = 0.023$ ) and were less performant to muscle functional tests than non-sarcopenic patients. Serum FGF19 levels were negatively correlated with the SPPB score ( $r_s = 0.28$ ;  $P = 0.045$ ). FGF19 levels were correlated positively with the pennation angle ( $r_s = 0.31$ ;  $P = 0.024$ ), but negatively with muscle fiber length ( $r_s = -0.44$ ;  $P = 0.001$ ). We found no association between FGF19 and muscle thickness ( $P = 0.243$ ).

**Conclusion:** We highlighted in older patients significant correlations between FGF19 levels, pennation angle and muscle fiber length, suggesting that FGF19 could provide an enabling environment for the development of large muscle fibers, as previously suggested in histological studies in mice. However, high FGF-19 levels were unexpectedly associated with a low SPPB score. Further studies are needed to validate and further elucidate these exploratory findings.

### 1. Introduction

Sarcopenia, a geriatric syndrome, corresponds to low skeletal muscle mass associated with low muscle strength which increase functional impairments. Its definition is now more consensual according to the European Working Group on Sarcopenia in the Elderly 2 (EWGSOP2) criteria (Cruz-Jentoft et al., 2019). Sarcopenia is related to aging and is increasingly prevalent in our societies. It is linked with number of

chronic diseases and pathological conditions, and augments the global disease burden (Shafiee et al., 2017). Sarcopenia is associated with progressive functional limitations which increase the mobility disability risk (Janssen, 2006). Sarcopenia, especially in the older adult population, threatens the patient's prognosis (Xu et al., 2021) and quality of life (Tsekoura et al., 2017; Oh et al., 2014) with increased morbidity and mortality (Volaklis et al., 2015).

Ultrasound appears to be a robust tool for the assessment of muscle

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mass compared with dual-emission X-ray absorptiometry (DEXA), which is the gold standard (Neira Álvarez et al., 2021). Ultrasound is a non-invasive technique, which allows accurate measurement of muscle parameters, related to muscle architecture, such as muscle thickness (which typically represents the muscle mass), pennation angle, and muscle fiber length (Ticinesi et al., 2018; Perikis et al., 2018). In the literature, numerous studies showed a significant correlation between muscle parameters in ultrasound imaging and muscle functional tests (Neira Álvarez et al., 2021; Aubertin-Leheudre et al., 2019; Leigheb et al., 2021). Nevertheless, ultrasound remains not ubiquitously available in all centres due to lack of equipment and skills.

In this context, a simple indicator in routine practice for early detection of a muscular disorder would be valuable, in order to prevent the aggravation of sarcopenia and its bad consequences, to develop screening and preventive actions and to promote long-term physical autonomy.

Endocrine fibroblast growth factors (FGF) regulate numerous metabolic signaling pathways and are involved in maintaining whole-body homeostasis (Degirolamo et al., 2016; Beenken and Mohammadi, 2012). Fibroblast growth factor 19 (FGF19) is part of the endocrine FGFs family, with FGF21 and FGF23. FGF19 is an ileal hormone secreted by the gut epithelium, particularly in the post-prandial period in response to secondary bile acid stimulation. Recent evidence has shown that gut microbiota is involved in skeletal muscle metabolism by regulating several molecular pathways, especially by FGF19 metabolism. Microbiota can influence muscle function and also muscle quality (Li et al., 2022). It has been highlighted that skeletal muscle atrophy was provoked in mice in whom dysbiosis and bile acid dysmetabolism were induced (Qiu et al., 2021). Many molecular pathways leading to sarcopenia have been described, and numerous studies explore the impact of the modulation of gut microbiota to reduce the risk of sarcopenia (De Spiegeleer et al., 2022; Lee et al., 2021). Benoit et al. recently described the significant positive effect of FGF19 treatment on muscle mass and strength in a mouse model (Benoit et al., 2017). Up to today, very scarce data are available in humans about FGF19 and its potential benefit on muscle parameters. Bag Soytaş et al. highlighted an interesting positive association between FGF19 concentrations and sarcopenic status in a cohort of older patients (Bag Soytaş et al., 2021).

FGF19 levels appear as a promising marker to detect and monitor sarcopenia in humans. In this cross-sectional open cohort study, we wanted to explore in older adults the correlation between serum FGF19 levels and muscle functional tests and, whether FGF19 concentrations were correlated with muscle architecture parameters assessed with ultrasound.

## 2. Materials and methods

### 2.1. Study design and population

The study protocol was approved by the local ethics committee on December 15, 2017 (NCT03667664) and was conducted in accordance with the ethical standards and the principles of the second Declaration of Helsinki.

Older community-dwelling patients who were evaluated at a single geriatric department in Lyon (France), according to the preventive program “Well on your feet” between July 2018, and February 2022, were asked to participate. All participants involved in the study signed written informed consent forms before enrollment.

Inclusion criteria were subjects aged  $\geq 70$  years old and diagnosed with mobility disability risk at the initial assessment of the program. The assessment of risk of mobility disability to include patients has been described previously by Delaire et al. (2021). It consisted in the report of at least one fall within the last 12 months prior to the initial assessment, usual gait speed  $\leq 0.8$  m/s, or score  $< 6$  on the RAPA questionnaire.

Exclusion criteria were patients without available serum FGF-19 result and those for whom the muscle ultrasound was not performed

or was not useable.

Demographic factors, anthropometric measurements and relevant medical history were collected at enrolment. Frailty was assessed using the Fried score (Fried et al., 2001). Comorbidity was assessed by the Charlson comorbidity index (Charlson et al., 1987).

### 2.2. Muscle functional tests

During the day-hospital session that is a part of the program, several functional tests to evaluate muscle performances were performed. The short physical performance battery (SPPB) score tested the physical function of the lower limbs. It consists in a static balance test, a 6-meter gait speed test, and the 5-repetition chair stand test (Guralnik et al., 1995). The SPPB score was calculated and compared to a scale from 0 to 12 and a score  $\leq 8$  was considered as a high risk of mobility disability and as a factor of severe sarcopenia according to the EWGSOP2 criteria. A gait speed  $\leq 0.8$  m/s was considered as a factor of severe sarcopenia. The chair stand test was used to evaluate the strength of the lower limbs. For women and men, a score  $> 15$  s was considered as low strength of the lower limb and as a criterion of probable sarcopenia. The handgrip test, on the dominant side, using a hydraulic hand dynamometer (model SH5001, SAEHAN Corporation, South Korea) was used to estimate the strength of the upper limbs. The thresholds used for reduced muscle strength in women and men were a score  $< 16$  kg and  $< 27$  kg, respectively, and were also considered as a probable sarcopenia criterion. We also used the Timed-up-and-Go (TUG) test to evaluate the global functional capacity. A time  $\geq 20$  s was considered as a factor of severe sarcopenia.

To quickly evaluate usual daily physical activities and self-assessment of quality of life, we also reported the result of the Rapid Assessment of Physical Activity (RAPA, score  $< 6$  was insufficient) questionnaire, the Sarcopenia & Quality of Life (SarQoL) questionnaire and the Falls Efficacy Scale International (FES-I) concerning the fear of falling.

The diagnosis of sarcopenia was made according the EWGSOP2 criteria (Cruz-Jentoft et al., 2019). Probable sarcopenia was defined by a low muscle strength with conserved muscle mass. Confirmed sarcopenia was defined by a probable sarcopenia associated with low muscle quantity. The term severe sarcopenia applies to patient with confirmed sarcopenia who also present low physical performances (gait speed, SPPB test, TUG test). If the handgrip strength test and 5-chair stand test were discordant (only one of the two tests with insufficient results below the standard), patients were considered with probable sarcopenia.

### 2.3. Muscle architecture

We performed ultrasound measurements according to the Ticinesi et al. protocol (Ticinesi et al., 2018; Aubertin-Leheudre et al., 2019), on the *vastus lateralis* on the dominant side, around the distal third of the femur, with using a SonoSite Edge II Ultrasound system (M Turbo Ultrasound system, SonoSite, USA) and a 15–6 MHz transducer probe (HFL 50 $\times$ , SonoSite, USA). Patients were seated with relaxed limb muscles, with the hip and knee angles at 90°. The ultrasound transducer was placed parallel to the muscle major axis.

Muscle thickness corresponds to the distance from superior and deep aponeuroses. Pennation angle is the insertion angle of the muscle fiber into the deep aponeurosis. Muscle fiber length was estimated by using muscle thickness and pennation angle according to the following equation (Abe et al., 2000, 1998):

$$\text{Fiber length} = \text{muscle thickness} \cdot \sin \alpha - 1$$

with  $\alpha$  = pennation angle (in radians)

Images were treated using the ImageJ software © (National Institute of Health, USA).

## 2.4. Nutritional status and body composition

Dietary protein and caloric intakes were assessed by a trained dietician evaluation, using a 3-day food log. Body mass index (BMI) was defined as the weight (in kilograms) divided by height squared (in meters squared). The mini nutritional assessment (MNA) was used for nutritional screening (Cereda, 2012).

Whole-body bioimpedance spectroscopy (BIS) measurement was performed using a body composition monitor (Bodystat®, QuadScan 4000, Isle of Man, British Isles). Electrodes were attached to the hand and foot on the nondominant side of the body, after the patient had been in a reclining position for at least 10 min. BIS was performed in the morning or in the early afternoon. Due to feasibility reasons, all patients were not strictly fasting, but we aimed to respect 6 h of fasting for the majority of them. Subjects should have voided before measurement. BIS was not performed in patients with a pacemaker or another electronic intra-cardiac device. This method provides lean tissue mass (kg) and fat tissue mass (kg). Muscle mass estimation was defined using the skeletal muscle index (SMI; using Janssen equation, dividing the adjusted appendicular muscle mass by the height squared) (Janssen et al., 2000) with usual cut-off points (estimated SMI  $\leq 6.42$  kg/m<sup>2</sup> for women and  $\leq 8.87$  kg/m<sup>2</sup> for men). (Cruz-Jentoft et al., 2019)

## 2.5. Laboratory measurements

Blood samples were obtained at the beginning of the day hospital. Standard methods in the routine clinical laboratory were used to measure biological parameters. Albumin, prealbumin and CRP were measured in plasma on an Architect C8000 (Abbott®) by immunoturbidimetry with Diagam® and Abbott reagents® respectively.

The serum FGF-19 level was measured using a BioVendor® ELISA kit (Human FGF-19 catalog no. RD191107200R; Czech Republic) according to the manufacturer's instructions. Limit of detection (LOD) (defined as concentration of analyte giving absorbance higher than mean absorbance of blank plus three standard deviations of the absorbance of blank:  $\text{Ablank} + 3 \times \text{SDblank}$ ) is calculated from the real human FGF-19 values in wells and is: 4.8 pg/mL. The values considered as normal for FGF19 level in our laboratory are 31–554 pg/mL. Results exceeding human FGF-19 level of 800 pg/mL should be repeated with more diluted samples. The antibodies used in this ELISA are specific for human FGF-19. No cross reactivity with recombinant human FGF-21 and recombinant human FGF-23 has been observed.

## 2.6. Statistical analysis

Data distributions were tested for normality using the D'Agostino-Pearson test. FGF-19 appeared non-normally distributed ( $P < 0.001$ ) and was log-transformed prior to analyses. Data were expressed as mean  $\pm$  standard deviation if normally distributed or median and interquartile range, otherwise. Simple comparisons between the two groups were made using the Mann-Whitney *U* test or *t*-test as appropriate. The Chi-square test or the Fisher's test was used to compare categorical variables. Univariate analysis was performed using the Spearman rank correlation method. Regression analysis was performed only if the Spearman correlation analysis results was significant enough with a correlation coefficient  $r_s > 0.5$  or  $< -0.5$  for the main data. In the context of an exploratory study, no multiple test corrections were conducted in the analyses. Data were analyzed using GraphPad Prism 8.0 (GraphPad Software, La Jolla, CA) and R software version 4.0.3 (<https://www.r-project.org/>). *P*-value  $< 0.05$  was considered statistically significant in all analyses.

## 3. Results

### 3.1. Baseline characteristics

We screened a total of 476 patients which had been included in the prevention program. 279 patients were not included and 145 were excluded. Finally, 52 patients were included (Supplementary Fig. 1). Baseline characteristics of the cohort and of the sarcopenic and the non-sarcopenic groups are summarized in Table 1. The mean age was  $81.3 \pm 5.4$  years. 65.4 % were females ( $n = 34$ ). Thirty patients (57.7 %) were diagnosed with sarcopenia (probable  $n = 15$ , certain  $n = 5$  or severe  $n = 10$  sarcopenia). Sarcopenic patients were significantly older than non-sarcopenic patients ( $P = 0.033$ ), had also a higher Fried score ( $P = 0.006$ ) and a lower IADL score ( $P = 0.008$ ). Eleven patients had obesity (BMI  $> 30$  kg/m<sup>2</sup>), similarly distributed between the two groups (5 patients in the sarcopenic group and 6 patients in the non-sarcopenic group). Their daily protein intakes were lower than those of non-sarcopenic patients ( $P = 0.023$ ) and there was a non-significant trend towards an association between MNA score and daily caloric intakes ( $P = 0.072$  and  $P = 0.062$ , respectively). There were 22 (42.3 %) fallers with a median number of one fall per faller the last year before evaluation (IQR 1–5.3).

The median serum FGF19 level was 139 pg/mL (IQR 75.8–234.5 pg/mL) and was not significantly different between the two groups ( $P = 0.794$ ).

As expected, sarcopenic patients were less performant than non-sarcopenic patients in the following muscle functional tests: SPPB score, handgrip strength test, chair stand test, gait speed and TUG test.

The skeletal muscle index (SMI) was similar between groups ( $P = 0.754$ ) as well as the body composition assessed by bioimpedance spectroscopy (lean tissue mass and fat tissue mass). Concerning the three ultrasound parameters measured, pennation angle, muscle thickness and fiber length, there was no difference between the two groups of sarcopenic and non-sarcopenic patients.

Sarcopenic patients expressed fear of falling more frequently than non-sarcopenic patients, estimated by the FES-I score ( $P < 0.001$ ). The overall population had little physical activity regarding to the RAPA questionnaire (3, 2.25–4).

### 3.2. Serum FGF19 level correlation with muscle architecture

Confronting FGF19 concentrations and muscle ultrasound parameters, we highlighted a positive correlation with the pennation angle ( $r_s = 0.31$ ;  $P = 0.024$ ) (Table 2). In contrast, there was a negative correlation with fiber length ( $r_s = -0.44$ ;  $P = 0.001$ ).

We did not show significant correlation between FGF19 levels and muscle thickness measured in ultrasound ( $P = 0.243$ ).

### 3.3. Serum FGF19 level correlation with general, nutritional and muscle functional parameters

FGF19 levels were not correlated with age, BMI, or nutritional parameters such as MNA, daily caloric or protein intakes (Table 2).

There was no correlation between FGF19 concentrations and SMI, lean or fat tissue mass.

We highlighted here a significant negative correlation between FGF19 levels and SPPB score ( $r_s = 0.28$ ;  $P = 0.045$ ) and also with the balance sub-score of the SPPB ( $P = 0.039$ ). There was no association with other functional tests. There was a statistical negative trend between FGF19 levels and SarQoL score, but not reaching the threshold of statistical significance ( $P = 0.05$ ).

## 4. Discussion

To our knowledge, this is the first study exploring the association between FGF19 levels and muscle architecture parameters. We observed

**Table 1**  
Baseline characteristics of the cohort according to sarcopenic status.

	Total	Sarcopenic patients	Non-sarcopenic patients	p-Value
No. of patients	52	30	22	
<b>Clinical characteristics</b>				
Age (years)	81.3 ± 5.4	82.8 ± 5.7	79.6 ± 4.3	0.033
Sex % female (n)	65.4 (34)	63.3 (19)	68.2 (15)	0.717
BMI (kg/m <sup>2</sup> )	25.1 (22.5–28.6)	25.1 (22.4–28.4)	24.8 (22.8–33.8)	0.499
MNA	26.3 (24.5–28)	25.3 (23.5–27.6)	27 (25.4–28)	0.072
Daily caloric intakes (kcal)	1569 (1258–1795)	1470 (1253–1685)	1691 (1508–3300)	0.062
Daily protein intakes (g)	60.9 ± 15.3	56.8 ± 12.3	66.4 ± 17.3	0.023
Diabetes % (n)	11.5 (6)	16.7 (5)	4.5 (1)	0.226
Obesity % (n)	21.2 (11)	16.7 (5)	27.3 (6)	0.355
Cholecystectomy history % (n)	11.5 (6)	6.7 (2)	7.1 (4)	0.382
Number of falls last year	1 (1–5,3)	2 (1–7)	1 (1–4)	0.458
ADL/6	6 (6–6)	6 (6–6)	6 (6–6)	0.896
IADL/8	8 (7–8)	8 (4.4–8)	8 (8–8)	0.008
Fried score	2 (1–3)	3 (1.75–3)	1 (0–2)	0.006
Charlson Comorbidity Index	4 (4–6)	4 (4–6)	4 (4–6)	0.811
<b>Bioimpedance spectroscopy parameters</b>				
SMI (kg/m <sup>2</sup> )	7 (6.2–8.7)	7.2 (6.3–8.9)	6.7 (6–8.7)	0.754
Lean tissue mass (kg)	38.8 (33.8–49.4)	38.1 (32.9–46.6)	39.4 (34.6–53.6)	0.339
Fat tissue mass (kg)	26.5 (22–30.6)	26.2 (21.6–30.2)	27 (22.5–32.3)	0.509
<b>Muscle ultrasound parameters</b>				
Pennation angle (degree)	10.9 ± 2.9	10.8 ± 2.7	11 ± 3.3	0.837
Muscle thickness (cm)	1.57 ± 0.34	1.55 ± 0.28	1.60 ± 0.42	0.611
Muscle fiber length (cm)	7.9 (6.9–10.2)	7.84 (6.79–10.2)	7.95 (6.98–9.52)	0.947
<b>Functional testing - Questionnaires</b>				
SPPB score	9.5 (8–11)	8.5 (7.75–10)	11 (9–11.25)	<0.001
Balance sub-score of SPPB	3 (3–4)	3 (3–4)	4 (3–4)	0.355
Handgrip strength (kg)	18.4 (15.6–24)	16.2 (14–21.2)	22.6 (18.1–31.5)	<0.001
Chair stand test (s)	12.5 (10.8–15.8)	15.4 (12.2–18.2)	11.4 (10.4–12.4)	<0.001
Walking speed (m/s)	0.85 ± 0.22	0.79 ± 0.20	0.92 ± 0.22	0.029
Time Up and Go test (s)	12.3 (10.1–15.3)	14 (11.5–17.4)	10.9 (9.2–12.7)	<0.001
FES-I	25 (21–30)	28 (23.3–33.3)	23 (18.5–25.5)	<0.001
RAPA	3 (2.25–4)	3 (2–3)	3 (3–4)	0.103
SarQoL score	59.1 ± 50.5–67.9)	55.6 ± 10.2	65.8 ± 10.7	0.001
<b>Biological analysis</b>				
FGF-19 (pg/mL)	139 (75.8–234.5)	131.5 (63.8–253.5)	147.5 (98.3–220)	0.794
log-transformed FGF-19	2.14 (1.88–2.37)	2.12 (1.81–2.40)	2.17 (1.99–2.35)	
Serum albumin (g/L)	40.7 ± 3.2	40.7 ± 2.5	40.6 ± 4	0.902
Serum prealbumin (g/L)	0.26 ± 0.06	0.27 ± 0.06	0.26 ± 0.06	0.807
CRP (mg/L)	1.6 (0.7–3)	1.6 (0.7–2.6)	1.9 (0.7–5.8)	0.298

Data are mean ± standard deviation if the variable distribution is normal and expressed as median (interquartile range) otherwise; categorical data are presented as % (n). Differences between groups were tested using Student *t*-test, Mann-Whitney *U* test, Fisher's test or chi-square test, as appropriate. Number of falls was only described for faller patients. Significant *p*-value <0.05 are highlighted in bold.

Abbreviations: ADL, Daily life activities; BMI, body mass index; CRP, C-reactive protein; FES—I, Falls Efficacy Scale International; FGF19, Fibroblast growth factor 19; IADL, Instrumental daily life activities; MNA, Mini nutritional assessment; RAPA, Rapid Assessment of Physical Activity; SarQoL, Sarcopenia & Quality of Life; SMI, Skeletal mass index; SPPB, Short Physical Performance Battery.

**Table 2**  
Unadjusted Spearman correlation coefficients ( $r_s$ ) of FGF-19 and other relevant covariates.

Variable	$r_s$	95 % CI	<i>p</i> -Value
<b>General parameters</b>			
Age (years)	0.0813	–0.2039 to 0.3538	0.567
BMI (kg/m <sup>2</sup> )	0.0291	–0.2535 to 0.3071	0.838
MNA	–0.1632	–0.4243 to 0.1230	0.248
Daily caloric intakes (kcal)	–0.0861	–0.3580 to 0.1993	0.544
Daily protein intakes (g)	0.1394	–0.1469 to 0.4042	0.324
ADL/6	–0.126	–0.3927 to 0.1602	0.373
IADL/8	0.1659	–0.1203 to 0.4266	0.239
Fried score	0.1756	–0.1103 to 0.4348	0.213
Charlson Comorbidity Index	–0.0792	–0.3519 to 0.2059	0.577
<b>Bioimpedance spectroscopy parameters</b>			
SMI (kg/m <sup>2</sup> )	–0.0233	–0.3045 to 0.2618	0.871
Lean tissue mass (kg)	–0.0618	–0.3392 to 0.2254	0.667
Fat tissue mass (kg)	0.0804	–0.2077 to 0.3556	0.575
<b>Muscle ultrasound parameters</b>			
Pennation angle (°)	0.3126	0.0351 to 0.5453	0.024
Muscle thickness (cm)	–0.1648	–0.4257 to 0.1214	0.243
Muscle fiber length (mm)	–0.4423	–0.6448 to –0.1818	0.001
<b>Functional testing - Questionnaires</b>			
SPPB score	–0.2789	–0.5188 to 0.0018	0.045
Balance sub-score of SPPB	–0.2872	–0.5254 to –0.0072	0.039
Handgrip strength (kg)	–0.2255	–0.4759 to 0.0588	0.108
Chair stand test (s)	0.1183	–0.1707 to 0.3886	0.408
Walking speed (m/s)	–0.1812	–0.4394 to 0.1047	0.199
Time Up and Go test (s)	0.0133	–0.2683 to 0.2927	0.926
FES-I	0.0554	–0.2315 to 0.3334	0.699
RAPA	–0.1651	–0.4259 to 0.1210	0.242
SarQoL score	–0.2755	–0.5184 to 0.0084	0.050
<b>Biological analysis</b>			
Serum albumin (g/L)	–0.1569	–0.4214 to 0.1323	0.272
Serum prealbumin (g/L)	0.1464	–0.1428 to 0.4126	0.305
CRP (mg/L)	0.1143	–0.1777 to 0.3877	0.429

$r_s$ : Spearman correlation coefficient; 95 % CI, 95 % confidence interval. Significant *p*-value <0.05 are highlighted in bold.

Abbreviations: ADL, Daily life activities; BMI, body mass index; CRP, C-reactive protein; FES—I, Falls Efficacy Scale International; FGF19, Fibroblast growth factor 19; IADL, Instrumental daily life activities; MNA, Mini nutritional assessment; RAPA, Rapid Assessment of Physical Activity; SarQoL, Sarcopenia & Quality of Life; SMI, Skeletal mass index; SPPB, Short Physical Performance Battery.

a positive correlation with the pennation angle. It is now established that with training, the pennation angle increases with the fiber diameter growth. This modification enables to achieve greater physical power (Kawakami, 2005). The association between FGF19 and the pennation angle might be reflected as an indirect link between FGF19 and fiber diameter. It may be suggested that a high FGF19 concentration environment promotes the development of fast twitch muscle fibers in the muscle, with fast fibers being larger than the slow fibers (Karp, 2001).



This corroborates in the human population the results shown by Benoit et al., who described a shift towards large muscle fibers in mice and the increasing proportion of type II fibers in soleus muscle after FGF19 treatment (Benoit et al., 2017). The impact of FGF19 appears very interesting because sarcopenia in older patients affects particularly the type II muscle fibers with reduced size and atrophy while the size of type I fibers is less affected (Nilwik et al., 2013; Lexell, 1995).

FGF19 levels were negatively correlated with fiber length in our cohort. Muscle fiber strength is partly determined by its length (Gans, 1982). A high muscle fiber length is correlated with higher performances, as described in sprinters, but in the *vastus lateralis*, it was described as an inverse parabolic relation between muscle force and fiber length (Abe et al., 2001; Bohm et al., 2018). This is consistent in our study with the positive correlation between muscle fiber length and lean tissue mass. Although, there is no previous literature data on the relationship between FGF19 and fiber length, these results might suggest that FGF19 levels influence the diameter and also the length of the muscle fibers. The increased diameter of fiber might compensate the fiber shortening in order to modulate muscle strength. FGF19 has been described as a hypertrophic factor on myocytes and on muscles in mice (Benoit et al., 2017). However, we could not confirm a significant relation between FGF19 concentrations and muscle thickness.

The long-term objectives for pathways to prevent loss of mobility will be to develop personalized care programs. FGF19 may appear as an interesting indicator to orient the exercise program. The level of FGF19 could guide exercise program towards more resistance training with increasing exercise intensity adapted to slow twitch muscle fibers or towards power training adapted to fast twitch fibers. Targeted exercises according to FGF19 levels may thus contribute to obtain better response to exercise programs.

In our study, we performed a complete functional evaluation of muscle status in older patients and correlated it with FGF19 levels. Sarcopenia diagnosis was established according to the EWGSOP2 criteria, now recognized as global reference. Various muscle morphological and architectural parameters of patients were well characterized with bioimpedance spectroscopy and muscle ultrasound imaging, in parallel with performing FGF19 measurement. Nevertheless, FGF19 levels appeared significantly negatively correlated with the SPPB score and its specific balance sub-score, independently of nutritional and inflammatory parameters. The SPPB is a major criteria of sarcopenia diagnosis, and a low score is also accepted as a robust indicator of fall risk (Lauretani et al., 2019), loss of mobility, as well as mortality (Pavasini et al., 2016). This negative correlation was unexpected. It may suggest that FGF19 levels are more a reflection of a dynamic compensatory mechanism in patients with low overall functional capacity than a simple indicator of muscle status. We have noted a trend towards negative correlation between the SarQoL score and FGF19 level but not reaching statistical significance. A higher SarQoL score means a better quality of life. As discussed above, it may also be explained by a compensatory phenomenon: people who have the lower SPPB score have also a poorer quality of life, and these people might have higher FGF19 concentration to try to correct this phenotype.

In contrast to Bag Soytaş et al., we have highlighted a trend towards a negative correlation between FGF19 level and handgrip strength (HGS) test, even if it was not statistically significant. It may be explained by the determinants of HGS test and muscle fiber types in hand and arm. HGS test is mainly related to age and sedentarity. It is also positively associated with the adductor pollicis thickness, the most powerful of the intrinsic muscles of the hand (Budziarek et al., 2008). Hand intrinsic muscles are known to be composed mainly of fast fibers (Hwang et al., 2013). Consistently, since the FGF19 seems to be related to type II fibers, the HGS test would be positively correlated to FGF19 level. Our study was probably not powerful enough to demonstrate this positive association.

In the same way, there was a non-statistically significant negative correlation between FGF19 level and walking speed. Likewise, Bag

Soytaş et al. also found no relation between walking speed and FGF19, and the correlation coefficient was close to zero in their study (Bag Soytaş et al., 2021).

Until now, studies on FGF19 focused primarily on the effect of exogenous FGF19 treatment, usually resulting in supra-physiological concentrations of FGF19 (Benoit et al., 2017). This might raise the question of the impact of endogenous FGF19 levels on muscle mass and strength. Our results seem to show a significant effect of endogenous FGF19 secretion on muscle morphological parameters, as evaluated by ultrasound imaging. It encourages further research about stimulating endogenous FGF19 production, especially by gut microbiota and bile acid regulation (Wang et al., 2022) and open the path to future research regarding the potential clinical impact of endogenous FGF19 in physiological condition.

The program “well on your feet” will enable us to collect longitudinal data, especially pre- and post-training, and allowing cross evaluations of matched data of muscle architecture, functional tests and FGF19 dosages.

There are however some limitations in our study that should be noted. The main weakness is the sample size with only 52 patients enrolled in a monocentric centre. These patients were well phenotyped. They were mostly Caucasians, which may impact generalizability, as it is known, for instance, that patients with an African phenotype have increased lean tissue mass compared to other ethnic groups (Araujo et al., 2010). The small sample size might reduce the statistical power of analysis and underestimate associations. It was also a limit to proceed to relevant regression or multivariate analysis. We found in our cohort a similar SMI between the sarcopenic and the non-sarcopenic groups. Similarly, there was no difference between the two groups for the other body composition parameters, although they were well discriminated by the functional tests. With regard to muscle ultrasound parameters, there was no difference between the two groups for the three parameters studied. In our sarcopenic group, 15 patients (50 %) were diagnosed with probable sarcopenia, with decreased muscle strength but not with decreased muscle mass. The size of the sample and the low statistical power of analysis did not allow to separate the sample into 3 groups of non-sarcopenic, probable sarcopenic and confirmed sarcopenic patients. The significant number of probable sarcopenic patients may have influenced our results, particularly given the fact that FGF19 is known to be associated with muscle mass. In the same way, our patients, sarcopenic or non-sarcopenic, were considered as sedentary according to the RAPA questionnaire. It would be pertinent to compare our results to a physically active group. We may also mention the possible influence of sarcopenic obesity. Yet, obese patients were similarly distributed between groups. The blood sampling was obtained at the beginning of the day-hospital. FGF19 is a hormone regulated by bile acid secretion, thus especially in the post-prandial state. Due to the nature of the study, in real life, it was not possible to ensure that all patients were strictly fasting (6 h of fasting for many of them), which implies potential variability in FGF19 concentrations. Several studies explored FGF-19 secretion after a standardized meal. Results are consistent regarding the global kinetics of FGF19 secretion with a peak concentration around 2 h after ingestion (Wang et al., 2015; Matsyik et al., 2011). Studies on the effect of the meal composition on FGF19 level are somewhat discordant. Schmid et al. did not highlight any modification of FGF19 after glucose ingestion whereas others showed a significant increase of FGF19 concentration. For lipids, Schmid et al. measured an increase of 35 % of FGF19 concentration while Morton et al. did not show any change. Protein induced a significant but delayed peak of FGF19 levels, after around 6 h. Therefore, FGF19 secretion is very difficult to predict with a high variability of change percentage before and after a meal, ranging from 0 % to 125 %, especially according to the composition of the meals (Wang et al., 2015; Morton et al., 2014; Schmid et al., 2015). However, this may reflect that regardless of the basal FGF19 concentration, the most important marker of muscle status would be the FGF19 secretory capacity. Further studies are necessary to explore this research pathway.

In conclusion, FGF19 levels were positively associated with the pennation angle and negatively associated with muscle fiber length measured using ultrasound imaging in community-dwelling older patients, suggesting a significant impact of endogen FGF19 on muscle fibers length and diameter. However, this study also revealed an unexpected negative association between FGF19 concentrations and the SPPB score. This pilot study may serve as a proof of concept on the impact of FGF19 on muscle function and architecture in older patients. Considering its limitations, additional studies are needed to explore these relations in a larger population, and to elucidate, with longitudinal and dynamic data, the underlying mechanisms that could explain these exploratory findings.

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### Credit authorship contribution statement

EB and JB performed the study, researched data, analyzed the results, and wrote the manuscript. AC, LD, JH, ST researched data and analyzed the results. CC performed the laboratory analysis. EB and MF performed the statistical analysis. TG analyzed the results and reviewed the manuscript. MB conceived the study, analyzed the results, and reviewed the manuscript. EB is the guarantor of this work and, as such, take full responsibility for it. All authors read and approved the manuscript.

### Ethical standards

The study was conducted in accordance with the ethical standards and the principles of the second Declaration of Helsinki and its later amendments. The authors certify that the experiments comply with the current laws of the country in which they were performed.

### Declaration of competing interest

None. The results presented in this paper have not been published previously in whole or part except in abstract format. This work is not under consideration for publication elsewhere.

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