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Original article

Circulating myostatin as a biomarker of muscle mass and strength in individuals with cancer or obesity

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SUMMARY

Background & aims: Our study aims to determine whether myostatin (MSTN) is associated with muscle mass and strength in individuals with cancer or obesity, as well as with cancer cachexia (CC) or sarcopenic obesity (SO).

Methods: The ACTICA study included individuals with CC (n = 70) or without CC (NC, n = 73). The MYDIASECRET study included individuals with obesity evaluated before (T0) and 3 months (T3) after bariatric surgery (n = 62). Body composition was assessed using bioelectrical impedance analysis (BIA). Skeletal muscle mass (SMM) and appendicular SMM (ASMM) were calculated from Janssen's and Sergi's equations, respectively, and expressed as indexes (SMMI and ASMMI). Handgrip strength (HGS) was assessed using a Jamar hand-held dynamometer. MSTN plasma levels were measured using ELISA. Spearman's coefficient was used to correlate MSTN with muscle mass and strength. Receiver operating characteristic (ROC) curve analysis was performed to identify an optimal MSTN cutoff level for the prediction of CC or SO.

Results: In the ACTICA study, muscle mass and strength were lower in CC individuals than in NC individuals (SMMI: 8.0 kg/m^2 *vs* 9.0 kg/m^2, $p = 0.004$; ASMMI: 6.2 kg/m^2 *vs* 7.2 kg/m^2, $p < 0.001$; HGS: 28 kg *vs* 38 kg, $p < 0.001$). MSTN was also lower in CC individuals than in NC individuals (1434 pg/mL *vs* 2149 pg/mL, $p < 0.001$). Muscle mass and strength were positively correlated with MSTN (SMMI: R = 0.500, $p < 0.001$; ASMMI: R = 0.479, $p < 0.001$; HGS: R = 0.495, $p < 0.001$). ROC curve analysis showed a MSTN cutoff level of 1548 pg/mL (AUC 0.684, sensitivity 57%, specificity 75%, $p < 0.001$) for the prediction of CC. In the MYDIASECRET study, muscle mass and strength were reduced at T3 (SMMI: −8%, $p < 0.001$; ASMMI: −12%, $p < 0.001$; HGS: −6%, $p = 0.005$). MSTN was also reduced at T3 (1773 pg/mL *vs* 2582 pg/mL, $p < 0.001$). Muscle mass and strength were positively correlated with MSTN at T0 and T3 (SMMI-T0: R = 0.388, $p = 0.002$; SMMI-T3: R = 0.435, $p < 0.001$; HGS-T0: R = 0.337, $p = 0.007$; HGS-T3: R = 0.313, $p = 0.013$). ROC curve analysis showed a MSTN cutoff level of 4225 pg/mL (AUC 0.835, sensitivity 98%, specificity 100%, $p = 0.014$) for the prediction of SO at T3.

Conclusions: MSTN is positively correlated with muscle mass and strength in individuals with cancer or obesity, suggesting its potential use as a biomarker of muscle mass and strength. The ROC curve analysis suggests the potential use of MSTN as a screening tool for CC and SO.

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1. Introduction

Skeletal muscle, the largest tissue in the human body, is a dynamic metabolic tissue essential for vital functions such as posture, locomotion, and breathing [1]. Muscle wasting is therefore associated with poor outcomes such as functional impairment and increased mortality [2–4]. Measurement of muscle mass is required to identify individuals with sarcopenia, a muscle disease that can be primary (e.g., age-related) or secondary (e.g., cancer- or obesity-related) [4,5]. Direct measurement of muscle mass is based on one of several imaging modalities, including dual-energy x-ray absorptiometry (DXA), computed tomography (CT), or magnetic resonance imaging (MRI) [6,7]. However, these imaging modalities are impractical and expensive for routine clinical use, whereas bioimpedance analysis (BIA) can easily provide an indirect estimation of muscle mass as long as validated equations are used [8,9]. In this context, the identification of biomarkers of muscle mass, easily obtained from a single blood sample, would facilitate the screening of sarcopenia [10–13].

Myostatin (MSTN), also referred to as growth-differentiation factor 8 (GDF-8), is a member of the transforming-growth factor beta (TGF-Beta) superfamily, mainly expressed in and secreted from skeletal muscle [14]. This myokine acts as a direct negative regulator of muscle growth through activin type II receptors and SMAD2-3 transcription factors [14]. MSTN gene knock-out in mice leads to muscle hypertrophy whereas transgenic mice that overexpress MSTN in skeletal muscle have muscle atrophy [14]. In line with these data, several studies have suggested that MSTN could contribute to muscle wasting in humans [15–18]. However, recent studies have found a positive correlation between circulating MSTN and muscle mass, suggesting that this myokine could be used as a biomarker of muscle mass [10,11].

Cancer and obesity are growing public health issues that adversely affect quality of life and life expectancy [19–22]. Both conditions can be associated with muscle wasting. Cancer cachexia (CC) is a multifactorial syndrome defined by an ongoing loss of muscle mass, with or without fat mass loss, that cannot be fully reversed by conventional nutritional support [23]. Sarcopenic obesity (SO) is characterized by the coexistence of excess fat mass and a relative reduction of muscle mass adjusted to body weight [5,24]. In both conditions, muscle wasting results from a combination of decreased food intake, physical inactivity, hormonal changes, protein catabolism, inflammation, anabolic resistance, and mitochondrial dysfunction [1,5,25–28]. In addition, bariatric surgery, which remains the most effective intervention for achieving long-term weight-loss [29], inevitably leads to muscle wasting [30,31]. This unintended muscle wasting is suggested to counteract the long-term benefits of bariatric surgery, due to the potential occurrence of sarcopenia [31]. To the best of our knowledge, it has not been investigated whether MSTN could be a biomarker of muscle mass in individuals with CC or SO, before or after bariatric surgery.

In this study, we first investigated the association of circulating MSTN with muscle mass and strength in two independent cohorts, one of individuals with cancer and another of individuals with obesity undergoing bariatric surgery. We then investigated whether MSTN was associated with CC or SO.

2. Materials & methods

2.1. Study designs

The ACTICA study is a prospective observational study investigating the role of activin A in CC (NCT2011/19AVR/157) [32]. Briefly, individuals with colorectal or lung cancer were enrolled at diagnosis or relapse before any therapeutic intervention. Individuals with cachexia (CC individuals) were compared to those without cachexia (NC individuals).

The MYDIASECRET study is a prospective, longitudinal, and interventional study investigating the potential role of myokines in glucose homeostasis after bariatric surgery (NCT03341793) [33]. Briefly, individuals with obesity were evaluated before (T0) and 3 months (T3) after bariatric surgery which consisted of either a sleeve gastrectomy or a Roux-en-Y gastric bypass.

Both studies were approved by the institutional review board and conducted in accordance with the principles of the Declaration of Helsinki. Patients were enrolled after obtaining written informed consent.

2.2. Muscle mass assessment using CT

In the ACTICA study, muscle mass was assessed at inclusion using CT imaging performed for standard cancer care. Briefly, skeletal muscle area was quantified on a transverse CT image taken at the level of the third lumbar vertebrae using the Slice-O-Matic software, version 4.3 (Tomovision) [32]. Hounsfield unit thresholds ranged from −29 to 150 units for skeletal muscle. Cross-sectional area was normalized for the height and expressed as skeletal muscle mass index (SMMI-CT, cm^2/m^2).

2.3. Muscle mass assessment using BIA

In both studies, body composition was assessed using BIA (BIA101 device, Akern®, Pisa, Italy). Whole body resistance and reactance were measured with the subject in a supine position, with arms and legs slightly separated. Surface electrodes were placed on the right side of the body on the dorsal surface of the hand and foot. Fat mass (FM) was estimated using Bodygram® software and proprietary manufacturer algorithms (Akern®, Pisa, Italy). Skeletal muscle mass (SMM) was calculated using Janssen's equation which is based on MRI as reference method [8]. Appendicular SMM (ASMM) was calculated using Sergi's equation which is based on DXA as reference method [9]. FM, SMM, and ASMM were expressed as absolute values (kg), percentage values (percentage of body weight, %BW), and indexes (I, kg/m^2). In the MYDIASECRET study, longitudinal changes from baseline (T0) were expressed as absolute changes (kg or kg/m^2) or percentage changes (percentage change from T0, %T0). Individuals from the original ACTICA study in whom BIA data were not available were not included in the present study (n = 9/152) [32].

2.4. Muscle strength assessment

In both studies, handgrip strength (HGS) was assessed using a Jamar hand-held dynamometer. Three measures were made on the nondominant side in a time interval of 30 seconds. The highest value (kg) was used.

2.5. Definition of CC and SO

In the ACTICA study, CC was defined as either involuntary weight loss >5% over the past 6 months or weight loss >2% with body mass index (BMI) < 20 kg/m^2 or weight loss >2% with low muscle mass, as previously reported [32,34]. Low muscle mass was defined as SMMI-CT < 55 cm^2/m in men and 39 cm^2/m^2 in women.

In the MYDIASECRET study, SO was considered in individuals with obesity (BMI ≥30 kg/m^2 and/or percentage FM ≥ 25% in men and ≥35% in women) and low muscle mass. Low muscle mass was defined as SMM adjusted for body weight (SMM/BW, %) <37.7% in men and <26.7% in women [5]. Class I and class II SO were defined

as SMM/BW between 31.5 and 37.7% in men and 22.1–27.6% in women, and <31.5% in men and <22.1% in women, respectively [5].

2.6. Plasma MSTN measurement

In both studies, blood samples (EDTA) were taken in standardized conditions and centrifuged for 10 min at 4 °C, 2.000g. Plasma was transferred to microtubes and stored at −80 °C. Mature MSTN levels were measured using quantitative sandwich ELISA (DGDF80, R&D Systems, Minneapolis, USA) according to the manufacturer's recommendations, as previously reported [32,33]. Plasma levels were expressed as absolute values (pg/mL). In the MYDIASECRET study, longitudinal changes from baseline (T0) were expressed as absolute changes (pg/mL) or percentage changes (percentage change from T0, %T0).

2.7. Statistical analysis

Continuous and discrete variables are reported as medians with 95% confidence interval (95%CI) and numbers with frequencies, respectively. Cross-sectional and longitudinal differences in continuous variables were assessed using the non-parametric Mann–Whitney U or the Wilcoxon signed rank test, respectively. Cross-sectional and longitudinal differences in discrete variables were assessed using the Chi–Carré test and McNemar test, respectively. Correlations were estimated using Spearman's Rank correlation coefficient. Associations between MSTN, muscle mass, and muscle strength were assessed using uni- and multivariate linear regression. Multivariate analysis was adjusted for age and sex (Model 1), and for age, sex, and BMI (Model 2). Results were expressed as estimates with 95%CI. Associations between MSTN and CC or SO were assessed using uni- and multivariate logistic regression. Multivariate analysis was adjusted using Model 1 and Model 2, unless there was a collinearity issue. Results were expressed as odds ratio (OR) with 95%CI. Receiver operating characteristic (ROC) curve analysis was performed to identify an optimal MSTN cutoff level for the prediction of CC or SO. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS Statistics software (IBM SPSS Statistics, Version 27.0. Armonk, NY, USA) and SAS software (version 9.4; SAS Institute Inc, Cary, NC, USA). Graphs were made with GraphPad Prism (version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com).

3. Results

3.1. Patients' characteristics

The ACTICA study included 143 individuals of whom 70 (49%) had CC and 87 (61%) had colorectal cancer (Table 1). The median age was 66 (39–84) years. Most were men (57%). Age and sex ratio were comparable between CC and NC individuals. As expected, body weight and BMI were lower in CC individuals than in NC individuals (for both, $p < 0.001$). CC was unrelated to cancer site, tumor staging, or presence of metastases [32].

The MYDIASECRET study included 62 individuals of whom 26 (42%) were males and 39 (63%) underwent a sleeve gastrectomy (Table 2). The median age was 44 (25–62) years. BW and BMI were reduced after bariatric surgery (−18% and −17%, respectively, $p < 0.001$), as reported in detail earlier [33].

3.2. Muscle mass assessment

In the ACTICA study, muscle mass was lower in CC individuals than in NC individuals, whatever the technique used to estimate it, when expressed as absolute values and indexes (Table 1). In contrast, percentage muscle mass (%BW) was similar in CC and NC individuals, suggesting muscle and fat mass loss of similar amplitude during CC. CT, considered as the reference method, was available in 130 individuals. SMMI-CT was 6% lower in CC individuals than in NC individuals ($p = 0.004$). SMMI-CT was positively and strongly correlated with SMMI (R 0.635, $p < 0.001$), and ASMMI (R 0.702, $p < 0.001$).

In the MYDIASECRET study, SMM and ASMM were reduced after surgery, when expressed as absolute values and indexes (Table 2). Specifically, SMMI and ASMMI were reduced by 8% and 12%, respectively (for both, $p < 0.001$). However, percentage muscle mass (%BW) was increased after bariatric surgery, suggesting a predominant loss of FM.

3.3. Muscle strength assessment

In the ACTICA study, HGS was lower in CC individuals than in NC individuals (Table 1). HGS was positively and strongly correlated with SMMI-CT (0.623, $p < 0.001$), SMMI (R 0.718, $p < 0.001$), and ASMMI (R 0.670, $p < 0.001$).

In the MYDIASECRET study, HGS was significantly reduced after bariatric surgery ($p = 0.005$) (Table 2). However, HGS adjusted for BMI (HGS/BMI) or muscle mass (HGS/ASMMI) was increased, suggesting improved muscle performance after bariatric surgery, despite muscle mass loss. HGS was positively and well correlated with SMMI (T0: R 0.623, $p < 0.001$ and T3: R 0.627, $p < 0.001$) and ASMMI (T0: R 0.521, $p < 0.001$ and T3: R 0.450, $p < 0.001$). In contrast, no significant correlation was found between muscle mass and HGS changes after bariatric surgery (not shown).

3.4. MSTN plasma levels

In the ACTICA study, MSTN was lower in CC individuals than in NC individuals (−33%, $p < 0.001$) (Table 1). MSTN was positively correlated with muscle mass (Fig. 1A), whatever the technique used to estimate it, as well as with HGS, in CC and NC individuals (Table 3).

In the MYDIASECRET study, MSTN was reduced after bariatric surgery (−32%, $p < 0.001$) (Table 2), as previously reported [33]. MSTN was positively correlated with SMMI at both timepoints (Fig. 1B). A positive correlation was also found between MSTN and muscle mass changes (Table 3). In addition, MSTN was positively correlated with HGS at both timepoints, whereas no significant correlation was found between MSTN and HGS changes. MSTN was also correlated with SMM/BW (Table 3). Interestingly, MSTN adjusted for FM (MSTN/FM) was more strongly correlated with SMM/BW than MSTN alone. Therefore, MSTN adjusted for adiposity correlated well with muscle mass adjusted for body mass, the parameter defining SO.

3.5. Associations of MSTN with muscle mass and CC

Using linear regression analysis, MSTN was positively associated with SMMI and ASMMI, in both models (Table 4). In addition, an inverse association was found between MSTN and CC using univariate logistic regression. The association remained significant in both models. ROC curve analysis of the relationship between MSTN and CC showed an AUC of 0.684 ($p < 0.001$) (Fig. 2A). The MSTN threshold with the best sensitivity (57%) and specificity (75%) was 1548 pg/mL.

3.6. Associations of MSTN with muscle mass and SO

Using linear regression analysis, MSTN was positively associated with SMMI at both timepoints (Table 5), but not with ASMMI (not

Table 1
Clinical characteristics and body composition in NC and CC individuals (ACTICA).

	Study population (n = 143)	NC (n = 73)	CC (n = 70)	*p* value (CC vs NC)
General characteristics				
Male sex (n, %)	81 (57)	45 (62)	36 (51)	0.218
Age (years)	66 [39–84]	64 [38–82]	68 [40–86]	0.458
Colon cancer (n, %)	87 (61)	47 (64)	40 (57)	0.375
Anthropometry				
Body weight (kg)	72.0 [49.2–102.4]	75.7 [52.7–103.9]	64.2 [48.1–99.5]	<0.001
BMI (kg/m^2)	24.9 [19.1–34.5]	26.6 [20.7–34.7]	23.5 [18.4–34.1]	<0.001
CT scan				
SMMI-CT (cm^2/m^2)	48.6 [35.2–69.1]	50.5 [37.9–69.1]	47.3 [33.0–67.6]	0.004
BIA				
SMM (kg)	25.2 [14.5–35.2]	25.8 [16.7–35.8]	22.8 [14.2–35.2]	0.018
SMM, percentage (%BW)	33.0 [24.4–44.7]	33.0 [23.1–43.3]	33.4 [26.1–45.3]	0.541
SMMI (kg/m^2)	8.6 [5.8–11.2]	9.0 [6.3–12.0]	8.0 [5.5–10.9]	0.004
ASMM (kg)	19.3 [13.1–27.1]	20.4 [14.1–28.1]	18.0 [12.5–26.2]	0.002
ASMM, percentage (%BW)	26.6 [22.0–31.9]	26.6 [31.3–31.5]	26.5 [23.4–32.0]	0.663
ASMMI (kg/m^2)	6.9 [5.1–8.8]	7.2 [5.6–9.5]	6.2 [5.0–8.6]	<0.001
FM (kg)	18.5 [10.1–30.1]	20.8 [12.3–31.0]	16.8 [8.9–27.3]	0.001
FM, percentage (%BW)	26.5 [15.7–36.1]	27.6 [18.4–38.7]	26.3 [14.5–33.8]	0.117
FMI (kg/m^2)	6.6 [3.3–10.6]	7.4 [4.4–11.0]	6.1 [3.2–9.7]	0.001
Muscle strength				
HGS (kg)	30 [18–52]	38 [20–52]	28 [14–45]	<0.001
MSTN plasma levels				
MSTN (pg/mL)	1811 [718–4144]	2149 [829–4165]	1434 [594–4070]	<0.001

Data expressed as medians [95%CI] or numbers (frequencies). Abbreviations: ASMM: appendicular skeletal muscle mass; ASMMI: appendicular skeletal muscle mass index; BIA: bioelectrical impedance analysis; BMI: body mass index; BW: body weight; CC: with cancer cachexia; FM: fat mass; FMI: fat mass index; HGS: handgrip strength; MSTN: myostatin; NC: without cancer cachexia; SMMI-CT: skeletal muscle mass index using CT-scan; SMM: skeletal muscle mass; SMMI: skeletal muscle mass index; %BW: percentage of body weight. Differences assessed using the Mann–Whitney U test, Chi-carré test. *p* statistically significant <0.05.

Table 2
Clinical characteristics and body composition before (T0) and 3 months (T3) after bariatric surgery (MYDIASECRET).

Study population (n = 62)	T0	T3	*p* value
General characteristics			
Male sex (n, %)	26 (42)	–	–
Age (years)	44 [25–62]	–	–
Sleeve gastrectomy (n, %)	39 (63)	–	–
Anthropometry			
Body weight (kg)	124.8 [96.6–168.2]	103.4 [75.8–141.1]	<0.001
BMI (kg/m^2)	43 [40–55]	35 [29–47]	<0.001
BIA			
SMM (kg)	28.1 [20.4–46.6]	26.0 [19.2–42.6]	<0.001
SMM, percentage (%BW)	22.9 [18.6–32.7]	25.9 [20.8–37.5]	<0.001
SMMI (kg/m^2)	10.3 [8.1–14.0]	9.5 [7.6–12.5]	<0.001
ASMM (kg)	25.9 [19.1–37.9]	22.8 [16.7–33.5]	<0.001
ASMM, percentage (%BW)	20.8 [18.8–25.2]	21.9 [19.7–27.5]	<0.001
ASMMI (kg/m^2)	8.9 [7.8–11.3]	7.9 [6.7–9.7]	<0.001
FM (kg)	56.2 [42.2–78.2]	41.6 [27.4–62.2]	<0.001
FM, percentage (%BW)	48.4 [34.8–53.8]	42.1 [27.3–49.6]	<0.001
FMI (kg/m^2)	20.5 [13.4–26.3]	14.9 [8.2–20.1]	<0.001
Muscle strength			
HGS (kg)	34 [20–56]	32 [18–56]	0.005
HGS (kg) adjusted to BMI (kg/m^2)	79 [46–133]	90 [51–173]	<0.001
HGS (kg) adjusted to ASMMI (kg/m^2)	367 [241–579]	404 [231–647]	<0.001
MSTN plasma levels			
MSTN (pg/mL)	2582 [1209–5311]	1773 [896–3424]	<0.001

Data expressed as medians [95%CI] or numbers (frequencies). Abbreviations: ASMM: appendicular skeletal muscle mass; ASMMI: appendicular skeletal muscle mass index; BIA: bioelectrical impedance; BMI: body mass index; BW: body weight; FM: fat mass; FM: fat mass; FMI: fat mass index; SMM: skeletal muscle mass; HGS: handgrip strength; MSTN: myostatin; SMMI: skeletal muscle mass index; %BW: percentage of body weight. Differences assessed using the Wilcoxon signed-rank test. *p* statistically significant <0.05.

shown). However, the association was no longer significant in Models 1 and 2. Changes in MSTN were positively associated with changes in ASMMI, but not with changes in SMMI (not shown). Here, the association remained significant in both models. In addition, MSTN/FM was positively associated with SMM/BW (Table 5). This association was observed in uni- and multivariate analysis at both timepoints. The prevalence of SO was significantly decreased after bariatric surgery, particularly with fewer individuals having class II SO (26% *vs* 79%, $p < 0.001$) (Supplementary Table 1). Using logistic regression analysis, we found an inverse association between MSTN and SO at T3 (Table 5), but not at T0 (not shown). The association was no longer significant in Model 1. We also found an inverse association between MSTN/FM and SO at T3 (Table 5) which remained significant in Model 1. ROC curve analysis of the relationship

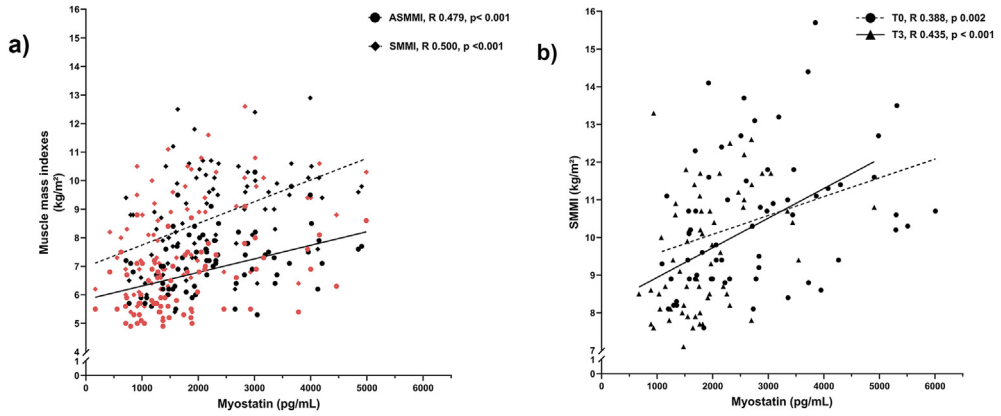

Fig. 1. Relationships between MSTN and muscle mass. A. ACTICA study: correlation between MSTN and muscle mass indexes, ASMMI: circles and plain line, SMMI: squares and dotted line, NC individuals: black, CC individuals: red, n = 143, Spearman's correlation. **B.** MYDIASECRET study: correlation between MSTN and SMMI, T0: black circles and dotted line, T3: black triangles and plain line, n = 62, Spearman's correlation. ASMMI: appendicular skeletal muscle mass index, MSTN: myostatin; CC: with cancer cachexia; NC: without cancer cachexia; SMMI: skeletal muscle mass index, T0: before bariatric surgery, T3: after bariatric surgery.

Table 3
Correlations estimate with myostatin plasma levels (Spearman's Rank correlation coefficient).

		SMMI-CT (cm^2/m^2)	SMMI (kg/m^2)	ASMMI (kg/m^2)	HGS (kg)	SMM/BW (kg/kg)
ACTICA study						
MSTN (pg/mL), study population (n = 143)	r Spearman	0.391	0.500	0.479	0.495	–
	p value	<0.001	<0.001	<0.001	<0.001	–
MSTN (pg/mL), CC patients (n = 70)	r Spearman	0.247	0.468	0.383	0.330	–
	p value	0.046	<0.001	0.001	0.005	–
MSTN (pg/mL), NC patients (n = 73)	r Spearman	0.336	0.398	0.406	0.478	–
	p value	0.007	<0.001	<0.001	<0.001	–
MYDIASECRET study (n = 62)						
MSTN-T0 (pg/mL)	r Spearman	–	0.388[a]	0.282[a]	0.337[a]	0.428[a]
	p value	–	0.002	0.026	0.007	<0.001
MSTN-T3 (pg/mL)	r Spearman	–	0.435[a]	0.238[a]	0.313[a]	0.455[a]
	p value	–	<0.001	0.062	0.013	<0.001
MSTN, T0-T3 (pg/mL)	r Spearman	–	0.309[b]	0.295[b]	−0.016[b]	–
	p value	–	0.014	0.020	0.905	–
MSTN, T0-T3 (%T0)	r Spearman	–	0.340[b]	0.169[b]	−0.016[b]	–
	p value	–	0.007	0.189	0.904	–
MSTN/FM-T0 (pg/mL)	r Spearman	–	–	–	–	0.610[a]
	p value	–	–	–	–	<0.001
MSTN/FM-T3 (pg/mL)	r Spearman	–	–	–	–	0.726[a]
	p value	–	–	–	–	<0.001

Abbreviations: ASMMI: appendicular skeletal muscle mass index; BW: body weight; CC: with cancer cachexia; HGS: handgrip strength; NC: without cancer cachexia; SMM: skeletal muscle mass; SMMI: skeletal muscle mass index. Correlations assessed using Spearman's Rank correlation. T0 and T3 refer to before and after surgery, respectively.
[a] T0 or T3, as appropriate in the MYDIASECRET study.
[b] Muscle indexes or HGS expressed as absolute changes (T0-T3, pg/mL) and percentage changes from baseline (%T0), as appropriate.

Table 4
Associations between myostatin, muscle mass indexes, and cancer cachexia (ACTICA, uni- and multivariate analysis).

Dependent variable	Independent variables	Unadjusted OR/estimate (95%CI)	Unadjusted *p* value	Model 1 Adjusted OR/estimate (95%CI)	Adjusted *p* value	Model 2 Adjusted OR/estimate (95%CI)	Adjusted *p* value
Linear regression analysis							
SMMI	MSTN	7.59.10E-4 (5.11.10E-4 −10.06.10E-4)	<0.001	3.25.10E-4 (1.55.10E-4 −4.96.10E-4)	<0.001	1.60.10E-4 (0.27.10E-4 −2.93.10E-4)	0.019
ASMMI	MSTN	4.75.10E-4 (3.12.10E-4 −6.38.10E-4)	<0.001	2.66.10E-4 (1.26.10E-4 −4.06.10E-4)	<0.001	0.83.10E-4 (0.18.10E-4 −1.49.10E-4)	0.013
Logistic regression analysis							
CC	MSTN	0.999443 (0.999089 −0.999797)	0.002	0.999464 (0.999089 −0.999840)	0.005	0.999577 (0.999182 −0.999972)	0.036

Abbreviations: 95CI, 95% confidence interval; ASMMI: appendicular skeletal muscle mass index; BMI: body mass index; CC: cancer cachexia; MSTN: myostatin plasma levels; OR: odds ratio; SMMI: skeletal muscle mass index. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, and BMI.

between MSTN and SO at T3 showed an AUC of 0.835 (*p* 0.014) (Fig. 2B). The MSTN threshold with the best sensitivity (98%) and specificity (100%) was 4225 pg/mL. ROC curve analysis of the relationship between MSTN/FM and SO at T3 showed an AUC of 0.971 (p < 0.001) (Fig .2C). The MSTN/FM threshold with the best sensitivity (94%) and specificity (100%) was 8374 pg/mL/kg.

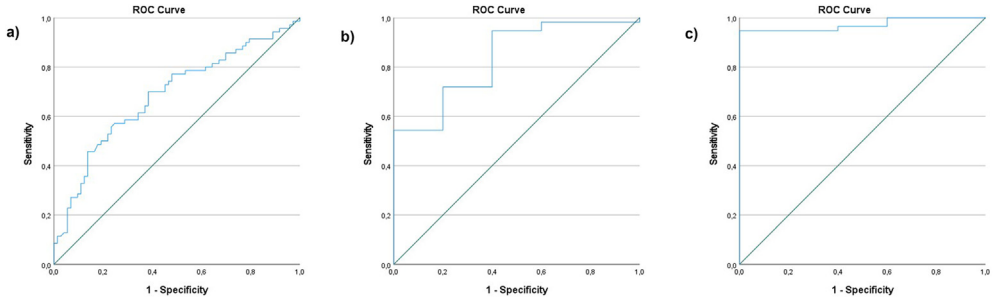

Fig. 2. ROC curve analysis. A. ACTICA study: relationship between MSTN and CC. **B.** MYDIASECRET study: relationship between MSTN and SO after bariatric surgery (T3). **C.** MYDIASECRET study: relationship between MSTN/FM and SO after bariatric surgery (T3). MSTN: myostatin; CC: cancer cachexia; FM: fat mass; SO: sarcopenic obesity.

4. Discussion

Our study shows that circulating MSTN is positively correlated with muscle mass and strength in individuals with cancer or obesity. In addition, MSTN was inversely associated with CC or SO. Taken together, our data suggest the potential use of MSTN as a biomarker of muscle mass and strength in individuals with cancer or obesity, as well as a screening tool for CC and SO.

4.1. MSTN as a biomarker of muscle mass

Our data reinforce previous observations of positive associations between MSTN and muscle mass in humans [10,11,35]. In addition, our study extends this observation to individuals with CC or individuals with obesity undergoing bariatric surgery. Indeed, among these, we also found a positive correlation between MSTN and muscle mass changes. In addition, MSTN was interestingly positively correlated with muscle strength in the two cohorts, which is relevant for clinical practice since low muscle strength is overtaking the role of low muscle mass as a principal determinant of sarcopenia [4,5]. However, the positive association of MSTN with muscle mass and strength seems at first counter-intuitive given that MSTN is an established negative regulator of muscle mass [14]. MSTN indeed induces myotubes atrophy *in vitro* [36]. Similarly, muscle overexpression or systemic administration of MSTN induce muscle atrophy in rodents whereas MSTN inhibition induce muscle hypertrophy [37–39]. However, the role of MSTN in muscle wasting in humans in unclear. As ours, other studies reported positive associations between MSTN and muscle mass in various muscle wasting conditions that differ in their mechanisms, including liver cirrhosis [10], chronic kidney disease [40], peritoneal dialysis or hemodialysis [41,42], older age [12], genetic muscle diseases [43], and bedrest due to hospitalization [44]. In addition, this positive association between MSTN and muscle mass seems independent of age, sex, and sarcopenia [45]. Taken together, these data suggest the potential use of circulating MSTN as a biomarker of muscle mass and strength in humans.

4.2. MSTN as a biomarker of CC

In our study, an inverse association between circulating MSTN and CC was observed even after adjustment for co-factors. The ROC curve analysis suggests that a MSTN cutoff value could be established for the prediction of CC in clinical practice. The association of MSTN, as a surrogate of muscle mass, with clinical variables such as involuntary weight loss [34], could facilitate the screening of CC. A timely diagnosis of CC is critical since this syndrome is associated with poorer outcomes [25]. However, measuring muscle mass in individuals with cancer remain challenging owing to limited accessibility and repeatability of imaging modalities or limited availability of simpler but indirect methods [46]. Therefore, identification of biomarkers of muscle mass would facilitate the screening of CC [46]. Our results suggest that MSTN could be one of these biomarkers and support the need for validation studies in larger cohorts.

4.3. MSTN as a biomarker of SO

To the best of our knowledge, our study investigated for the first time the association between circulating MSTN and SO in individuals undergoing bariatric surgery. We found that the prevalence of SO was reduced after bariatric surgery, despite muscle mass loss. In fact, bariatric surgery was associated with increased percentage muscle mass, that is an improved muscle mass to body mass ratio. Thus, the predominant loss of FM could explain the reduction in SO after bariatric surgery since SO is defined as a relative reduction of muscle mass in combination with excess adiposity [47]. In addition, muscle strength adjusted for muscle mass was also improved after bariatric surgery. Taken together, these findings suggest an improved body composition (i.e., increased muscle to fat ratio), improved muscle function (i.e., strength to muscle mass ratio), and, overall, improved muscle health after bariatric surgery despite muscle mass loss. The ROC curve analysis suggests that a MSTN cutoff value could be established for the prediction of SO in clinical practice. In addition, the observation that the correlations between MSTN and muscle mass were stronger after adjusting MSTN for adiposity suggests that the MSTN/FM ratio could be used as a marker of SO. Taken together, our results suggest that MSTN, alone or adjusted for adiposity, could be useful to monitor changes in muscle mass and screen for SO after bariatric surgery.

4.4. Rationale for decreased MSTN in muscle wasting conditions

Several hypotheses can be put forward to explain the decreased circulating MSTN in muscle wasting conditions. On the one hand, decreased MSTN could merely reflects decreased muscle mass since MSTN is mainly secreted by skeletal muscle [14], as observed for leptin and adipose tissue [48]. On the other hand, decreased circulating MSTN could result from decreased muscle MSTN expression, as we previously reported after bariatric surgery [33]. In this case, decreased MSTN expression and circulating levels could represent a counter-regulatory mechanism to preserve muscle mass during acute caloric restriction [33,49]. However, this hypothesis could extend to other muscle wasting conditions. In neuromuscular diseases, MSTN receptor and signaling pathway are, counter-intuitively, downregulated and preclude good clinical efficacy of anti-myostatin approaches [50]. In various types of cancers, decreased circulating MSTN or MSTN pro-peptide levels which reflect decreased MSTN production were reported in individuals

Table 5
Associations between myostatin, muscle mass indexes, and sarcopenic obesity (MYDIASECRET, uni- and multivariate analysis).

Dependent variable	Independent variables	Unadjusted OR/estimate (95%CI)	*p* value	Model 1 Adjusted OR/estimate (95%CI)	*p* value	Model 2 Adjusted OR/estimate (95%CI)	*p* value
Linear regression analysis							
SMMI-T0	MSTN-T0	5.04.10E-4 (1.58.10E−8.50.10E-4)	0.005	1.14.10E-4 (−1.92.10E−4−4.21.10E-4)	0.459	1.58.10E-4 (−1.24.10E−4−4.40.10E-4)	0.267
SMMI-T3	MSTN-T3	7.87.10E-4 (3.00.10E−4−12.74.10E-4)	0.002	1.39.10E-4 (−2.05.10E−4−4.84.10E-4)	0.421	1.96.10E-4 (−0.99.10E−4−4.91.10E-4)	0.189
ASMMI, T0-T3	MSTN, T0-T3	1.74.10E-4 (0.00.10E−4−3.48.10E-4)	0.040	1.87.10E-4 (0.04.10E−4−3.70.10E-4)	0.046	1.90.10E-4 (0.07.10E−4−3.73.10E-4)	0.043
ASMMI, %T0	MSTN, T0-T3	1.74.10E-4 (0.00.E−4−3.48.10E-4)	0.040	1.87.10E-4 (0.04.10E−4−3.70.10E-4)	0.046	1.90.10E-4 (0.07.10E−4−3.73.10E-4)	0.043
SMM/BW-T0	MSTN/FM-T0	9.61.10E-4 (6.15.10E−4−13.07.10E-4)	<0.001	4.23.10E-4 (1.35.10E−4−7.10.10E-4)	0.005	–	–
SMM/BW-T3	MSTN/FM-T3	14.55.10E-4 (11.1.10E−4−17.9.10E-4)	<0.001	8.34.10E-4 (5.64.10E−4−11.0.10E-4)	<0.001	–	–
Logistic regression analysis							
SO-T3	MSTN	0.999776 (0.997680−0.999874)	0.029	0.998997 (0.997830−1.000165)	0.092	–	–
SO-T3	MSTN/FM-T3	0.998768 (0.997677−0.999860)	0.027	0.998417 (0.996971−0.999864)	0.032	–	–
SO-T3, class 2	MSTN/FM-T3	0.999704 (0.999411−0.999997)	0.003	0.999479 (0.999114−0.999845)	0.005	–	–

Abbreviations: 95CI, 95% confidence interval; ASMMI: appendicular skeletal muscle mass index; BMI: body mass index; BW: body weight; MSTN: myostatin plasma levels; OR: odds ratio; SMMI: skeletal muscle mass index; SO: sarcopenic obesity. Model 1 adjusted for age and sex. Model 2 adjusted for age, sex, and BMI.

with low muscle mass [32,51]. These data together with ours suggest that circulating MSTN does not play a major pathogenic role in muscle wasting during CC or after bariatric surgery. On the contrary, decreased MSTN could even be interpreted as a protective down-regulatory mechanism to counteract muscle wasting.

4.5. Preanalytics and other factors influencing MSTN determination and interpretation

Several pre-analytical factors need to be taken into account when considering circulating MSTN levels for clinical decision-making. These factors can include age, gender, several common diseases, smoking, physical exercise, and fasting [52]. Contradictory results have been reported concerning the effect of age and gender on circulating MSTN levels. Earlier studies have reported an increase in circulating MSTN levels with age [53,54], whereas recent studies have shown no correlation between MSTN and age [55]. Similarly, some studies have reported higher circulating MSTN levels in men, while others have found higher levels in women, or no difference between genders [55]. Common diseases such as type 2 diabetes and insulin-resistance are associated with higher circulating MSTN levels [55]. In addition, active smoking [54] and exercise training decrease circulating MSTN levels [56]. Although overnight fasting is routinely recommended to minimize variability in laboratory tests [52], short-term fasting does not affect circulating MSTN [57]. As with many laboratory tests, these factors should be managed by appropriate reference limits for each population and standardized preparation of individuals before sampling [52,58]. Finally, circulating MSTN levels could differ between immunoassays that detect either mature MSTN only, or different forms of MSTN or cross-react with other TGF-Beta members (e.g., GDF-11) [46,55]. The immunoassay must therefore be carefully selected according to the specific use clinicians intend to make of it.

4.6. Limitations

Our study has several limitations. In both cohorts, we used an immunoassay that measures only mature MSTN levels. Our result could therefore differ from studies using other immunoassays [46]. In the ACTICA study, CT was available only at inclusion, precluding longitudinal muscle mass assessment using this gold standard method. However, muscle mass indexes determined using BIA and CT correlated well. In the MYDIASECRET study, BIA could have overestimated muscle mass since obesity violates the constant hydration assumption [5,31]. In addition, the equations used to estimate muscle mass were not originally designed for individuals with cancer or obesity. However, they were established from data of individuals from both sexes, with a wide range of age and BMI [8,9]. In addition, our multivariate analyses were adjusted for age, gender and BMI (where applicable), factors likely to influence circulating MSTN levels and muscle mass. In this study, SO was defined using muscle mass alone while adding muscle strength is currently suggested [5]. However, none of the individuals of the MYDIASECRET study reached the cutoff values suggested for low muscle strength [5]. Indeed, individuals with obesity commonly have comparable or even higher absolute muscle mass and strength compared to lean individuals [4,5]. The strengths of our study include consistent findings in two very different populations, relatively large population of individuals with cancer, and longitudinal assessment in those with obesity undergoing bariatric surgery.

5. Conclusion

Our study shows that circulating MSTN mirrors muscle mass and strength in individuals with cancer or obesity. In individuals

with obesity undergoing bariatric surgery, MSTN changes also mirror those of muscle mass. In addition, MSTN is inversely associated with CC and SO, especially after adjustment for fat mass in the latter case. Taken together, our data suggest the potential use of MSTN as a biomarker of muscle mass and strength in individuals with cancer or obesity, as well as a screening tool for CC and SO.

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Authors contribution

Laura Orioli: Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Writing, Visualization, Funding acquisition. **Sofia Samaras:** Methodology, Software, Formal analysis, Investigation. **Kiswendsida Sawadogo:** Formal analysis. **Pascale Lause:** Resources. **Marie de Barsy:** Investigation. **Yannick Deswysen:** resources. **Benoit Navez:** resources. **Jean-Paul Thissen:** Conceptualization, Methodology, Resources, Writing, Visualization, Supervision, Project administration, Funding acquisition. **Audrey Loumaye:** Conceptualization, Methodology, Investigation, Writing, Visualization, Supervision, Project administration.

Data availability statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Conflict of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.05.046.

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