ORIGINAL ARTICLE

Evaluation of serum myostatin and sclerostin levels in chronic spinal cord injured patients

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Study design: Case–control study.

Objectives: To assess serum myostatin levels, bone mineral density (BMD), appendicular skeletal muscle mass (ASMM) and serum sclerostin levels in chronic spinal cord injured (SCI) patients and healthy controls.

Setting: SCI centre in Italy.

Methods: Blood samples, whole-body bioelectrical impedance analysis and BMD measurement with the ultrasound technique at the calcaneus level were taken from patients suffering from chronic SCI (both motor complete and incomplete) and healthy control subjects.

Results: A total of 28 SCI patients and 15 healthy controls were enrolled. Serum myostatin levels were statistically higher ($P < 0.01$) in SCI patients compared with healthy controls. Similar results were found comparing both the motor complete and the motor incomplete SCI subgroups to healthy controls. Serum sclerostin was significantly higher in patients with SCI compared with healthy controls ($P < 0.01$). BMD, stiffness and mean T-score values in SCI patients were significantly lower than those in healthy controls. Serum myostatin concentrations in the motor complete SCI subgroups correlated only with serum sclerostin levels ($r^2 = 0.42$; $P = 0.001$) and ASMM ($r^2 = 0.70$; $P = 0.002$) but not in healthy controls.

Discussion: Serum myostatin and serum sclerostin are significantly higher in chronic SCI patients compared with healthy controls. They are potential biomarkers of muscle and bone modifications after SCI. This is the first study reporting an increase in serum myostatin in patients suffering from chronic SCI and a correlation with ASMM.

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INTRODUCTION

Both animal and human models show that unloading is the main determinant of osteoporosis after spinal cord injury (SCI), a condition known to increase the risk of fractures, mainly at distal femur and proximal tibia.¹ The Wntless and Int signaling pathway has been identified as one of the key regulators of mechanical load responses^{2–5} that is involved in osteoporosis after SCI. Moreover, sclerostin, a powerful selective inhibitor of Wntless and Int signaling produced by osteocytes, is able to induce a reduction in osteoblast activity and proliferation ultimately resulting in the loss of bone mass.⁶ Recently, Morse *et al.*^{6,7} found a strong correlation between bone mineral density (BMD) and serum sclerostin in patients with SCI, suggesting its possible use as a biomarker complementary or in alternative to dual X-ray absorptiometry (DXA), to assess osteoporosis and to monitor its treatment in patients with chronic SCI.

Pathological muscle modifications after SCI can be as severe as those observed at the bone level, with a relevant impact on disability and comorbidities.⁸ However, research about muscle modifications after SCI is still at its beginnings, and the pathophysiology, diagnosis and treatment of these changes are still unclear.⁹ Recently, the evidence of a biochemical cross-talk between the muscle and bone

has been postulated, overtaking the previous hypothesis of a simple mechanical correlation between these two tissues.^{10,11} *In vitro* studies suggest the possible existence of a biunivocal cross-talk between the bone and muscle, indicating that factors produced by osteocytes could target muscle and that muscle-derived soluble factors could target bone.¹² It is likely that, although osteocytes and sclerostin are responsible for cross-talk between bone and muscle, satellite cells (at skeletal muscle level) could have a role in the opposite way.^{12–15} Myostatin is a powerful inhibitor of overall muscle differentiation and growth both *in vivo* and *in vitro*.¹⁶ As the inhibition of myostatin pathway facilitates muscle growth, myostatin could be used as a possible biomarker to monitor the evolution of muscular modifications in SCI patients and could also represent a potential therapeutical target.^{14,17} However, to date, possible modifications of serum myostatin levels in SCI patients have not been described yet.

In light of these considerations, the aim of our work is to assess, in a population of chronic SCI patients, the serum myostatin concentration. Secondarily, assuming the previously described biochemical cross-talk between the bone and muscle tissue and the key role of osteocytes, we investigated a possible correlation between serum

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myostatin levels, serum sclerostin levels, appendicular skeletal muscle mass (ASMM) and BMD in this population.

MATERIALS AND METHODS

Subjects

Twenty-eight patients suffering from chronic SCI were consecutively enrolled from the Physical and Rehabilitation Unit of the AOU 'Maggiore della Carità' in Novara (Italy).

Demographical data are summarized in Table 1. Inclusion criteria were the following: (1) SCI; (2) a grade from A to C on the American Spinal Injury Association (AIS) Impairment Scale¹⁸; (3) neurological level of lesion from C5 to T12; (4) age > 18; and (5) time from lesion > 2 years (24 months). The exclusion criteria were as follows: concomitant diabetes; oral anticoagulation; other concomitant chronic neurological pathologies (of central and/or peripheral nervous system and/or neuromuscular diseases), use of drugs acting on the bone (bisphosphonates, corticosteroids, lithium, anticonvulsant drugs, parathyroid hormone analogs, estrogens, calcium and vitamin D) and muscle (statins) metabolism. Moreover, 15 healthy controls were enrolled and the inclusion criteria were the following: absence of SCI and/or any other neurological pathologies; absence of musculoskeletal pathologies; absence of functional limitations (such as gait limitation); age > 18; control subjects should not have any intense physical activity at least in the 24 h before serum sample collection. The exclusion criteria were the same as those of patients suffering from SCI. All study participants signed informed consent forms and the Institutional Review Board approved the study, which was conducted in accordance with the Declaration of Helsinki guidelines.

Study procedure

All patients at baseline underwent a physical examination by a trained physician and sensory-motor impairment was determined using the AIS impairment scale.^{19,20} According to the AIS score, patients were divided in two groups: complete motor (AIS A, B) and incomplete motor (AIS C).

For patients with SCI, the level of disability was measured with the SCIM-III scale.²¹ After enrollment, all patients underwent blood sample and BMD measurement in the same morning.

Table 1 Patient characteristics at enrollment

<i>Patients characteristics</i>	<i>SCI (n = 28)</i>	<i>CT (n = 15)</i>
Age (years)*	40.5 ± 7.1 41 (18-64)	28.4 ± 4.1 28 (23-36)
Age at injury (years)	34.8 ± 14.7 36 (20-57)	—
Sex (F/M)	5/23	10/5
Body mass index (BMI)	24.7 ± 3.4	22.8 ± 2.1
Smoke (Y/N)*	10/18	0/15
Injury severity—ASIA score	A 18 B 4 C 6	—
Complete/incomplete	78.6/21.4 (22/6)	—
Wheelchair use	78.6 (22)	—
Time since injury (months)	90.8 ± 53.1 57 (29-384)	—
Lesion level	Paraplegia 85.7 (24) D1-D12 75.0 (18) D12-L5 25.0 (6) Tetraplegia 14.3 (4)	—
SCIM-III score	72.8 ± 10.3	—
Fractures (any site)*	11	0

Abbreviations: CT, healthy control group; F, female; IQR, interquartile range; M, male; N, no; SCI, spinal cord injury group; SCIM-III: spinal cord independence measure III version; Y, yes. Data are presented as mean ± s.d. or median and IQR (only age, age at injury and time since injury). * $P < 0.017$.

Biochemical markers, appendicular muscle and bone mass

Blood samples were collected at the same hour in the morning in fasting conditions. Samples were centrifuged for 15 min at 3000 r.p.m. at 4 °C and stored at -80 °C until final analysis.

Serum plasma iodized calcium, phosphate, creatinine, 1-84 parathyroid hormone (PTH), 25(OH) Vitamin D (25(OH)D), insulin-like growth factor I, C reactive protein, osteocalcin and Beta-Crosslaps (CTX) were measured in the laboratory analysis of our Hospital.

Myostatin was quantified by the Elisa assay (MyBioSource, San Diego, CA, USA, MBS703668; normal range: 0.625–20 ng ml⁻¹; minimum detectable dose 0.312 ng ml⁻¹). Serum sclerostin was measured using the SOST Elisa Kit (Biomedica Gruppe, Vienna, Austria; normal range: 0–240 pmol l⁻¹; detection limit: 2.6 pmol l⁻¹ and a unit conversion of 1 pg ml⁻¹ = 0.044 pmol l⁻¹).

Whole-body tetrapolar bioelectrical impedance analysis (BIA) was performed using an alternating sinusoidal electric current of 400 mA at a single operating frequency of 50 kHz (BIA 101 Anniversary Sport Edition—ASE—Akern Srl; Florence, Italy). The device's precision was 1% for resistance (Rz) and 5% for reactance (Xc). BIA was performed with subjects supine with their limbs slightly away from their body, after an overnight fast, and bladder voiding. To avoid inter-observer errors, all BIA measurements were taken by the same investigator (MI). Active electrodes (BIATRODES Akern Srl; Florence, Italy) were placed on the right side on conventional metacarpal and metatarsal lines, recording electrodes in standard positions at the right wrist and ankle.²² All resistance measurements were normalized for stature (height in centimeters squared/Rz) to obtain the resistive index (RI).

Appendicular muscle mass (ASMM) was obtained using a validated equation.²³ Then, the ASMM index (ASMMI) value was obtained using the following calculation: ASMM/height^{2.24}

BMD of patients and healthy controls was measured with calcaneus ultrasonography (Achilles Express 2001 GE Medical System, Lunar Corporation—Madison, WI, USA), obtaining data about T-score and stiffness.

Statistical analysis

Statistical analyses were performed using the GraphPad 4 package, version 4.0 (GraphPad Software, Inc., San Diego, CA, USA). Because of the small sample size, we assumed a non-gaussian distribution of the considered variables. After enrollment, patients were divided into two subgroups, depending on motor completeness of the lesion (complete and incomplete). Differences between single variables in different groups were evaluated with the Mann-Whitney *U*-test. A type I error level of 0.05 was chosen. The Bonferroni correction for multiple comparisons was applied considering three variables, which resulted in a new alpha-error level of 0.017. Relationships between serum myostatin values and the other variables were analyzed with linear regression using Pearson's correlation coefficients. Regression lines were compared using confidence intervals. A $P < 0.017$ was considered statistically significant.

RESULTS

Demographic characteristics of SCI patients with SCI and healthy controls are resumed in Table 1. Patients with SCI showed statistically significant differences regarding smoke, age and history of previous fractures at any site compared with healthy controls, whereas all the other demographical variables showed no statistical difference.

Serum myostatin levels were statistically higher ($P < 0.01$) in patients suffering from SCI compared with healthy controls (Figure 1a). Similar results were found comparing both patients with motor complete and motor incomplete SCI to healthy controls (Figure 1a).

Serum sclerostin was significantly higher in SCI patients compared with healthy controls ($P < 0.01$) as shown in Figure 1b.

Regarding other biochemical variables, parathyroid hormone and C reactive protein serum values showed statistically significant differences between the two groups (Table 2). However, the mean values in both groups were in the normality range. 25(OH)D serum levels were significantly higher in healthy controls compared with patients with

Figure 1 Differences between serum myostatin (a) and sclerostin (b) in all groups. Data are presented as mean $\pm$ s.d. * $P < 0.017$ SCI Tot vs CT; ** $P < 0.017$ SCI complete vs CT; *** $P < 0.017$ SCI incomplete vs CT; # $P < 0.017$ SCI complete vs SCI incomplete. SCI, spinal cord injured; CT, healthy controls.

SCI. However, the mean value in the control group was far from the normality level and only 20% of healthy controls showed values of 25(OH)D higher than 30 ng mL^{-1} . On the contrary, 50% of SCI patients showed 25(OH)D values $< 10 \text{ ng mL}^{-1}$.

BMD, stiffness and mean T-score values in SCI patients were significantly lower than those in healthy controls. Interestingly, we also observed a statistically significant difference between the motor complete and incomplete subgroups regarding these variables.

Serum myostatin concentrations in the motor complete SCI subgroup ($n = 22$) correlated only with serum sclerostin levels ($r^2 = 0.42$; $P = 0.001$; Figure 2a). None of the other instrumental, biochemical or demographical variables considered showed any correlation with serum myostatin concentrations.

Thus, unlike previous studies on bone biomarkers like sclerostin in SCI patients,⁷ any correction of serum myostatin for any variable considered in this study was needed.

Moreover, 10 patients with motor complete SCI (AIS A and B) and seven healthy controls performed whole-body BIA evaluation. Mean ASSMI in patients with SCI was inferior to those of healthy subjects (7.29 ± 1.97 vs $8.01 \pm 0.95 \text{ Kg m}^{-2}$). This difference was not statically significant, but the sample size of this subgroup was extremely small. We found a strong correlation between serum myostatin concentrations and ASSMI in patients with complete SCI ($r^2 = 0.70$; $P = 0.002$) but not in healthy controls, as shown in Figure 2b.

DISCUSSION

Our data point out a statistically significant difference in serum myostatin concentration in SCI patients compared with healthy controls; thus, SCI patients, considering both motor complete and incomplete subgroups, showed higher serum values of myostatin compared with healthy controls. To our knowledge, this is the first study investigating serum myostatin levels in SCI patients.

Similarly, we observed a significant increase in serum sclerostin levels in chronic SCI patients compared with healthy subjects, confirming findings described in a previous study.⁷ Moreover, the differences at the bone tissue level between SCI patients and healthy controls were confirmed also by a huge statistically significant reduction in BMD measured at the calcaneus level between these two groups. Finally, serum myostatin correlated only with serum sclerostin ($r^2 = 0.42$) and ASSMI ($r^2 = 0.70$) in SCI but not in healthy controls. Circulating biomarkers have been advocated as a useful surrogate measure for diagnosis, therapeutic monitoring and research purposes, considering that they can be easily and noninvasively obtained and that they have a low economic cost.²⁵ This is the case of BMD measured with the DXA technique, which is the gold standard for osteoporosis, but in a condition like SCI, as we will discuss later, can present some important technical and accuracy issues.^{1,2}

Myostatin and muscular modifications

In patients suffering from SCI, the main feature of underlesional muscle tissue is the atrophy of muscle fibers, in conjunction with a transformation of their fiber type, leading to a reduction in slow-twitch fibers (type I) and an increase in fast-twitch fibers (type IIA and IIX).²⁶ Mohr *et al.*²⁷ showed that conversion of quadriceps myosin to myosin heavy chain IIA was almost complete by 3 years in SCI patients. These modifications, and particularly the severe muscle atrophy in chronic complete SCI, are a major contributor to comorbidity risk factors such as diabetes, obesity, lipid disorders and cardiovascular diseases.⁸

Myostatin is a member of the transforming growth factor superfamily, mainly expressed in satellite cells and is a powerful inhibitor of muscular regulating factors and overall muscle differentiation and growth both *in vivo* and *in vitro*.¹⁶ Our findings suggest that, in SCI patients, independently from the level and completeness of the lesion, myostatin serum levels are significantly higher than those in healthy controls; this could partially explain the severe pathological muscular modifications observed.

Being SCI the extreme pathological unloading condition in humans, our results are intriguing as myostatin, a factor selectively produced by satellite cells in the muscle microenvironment, is an attractive candidate biomarker to monitor the muscular modifications in these patients as well as a possible pharmacological target to prevent muscle loss not only after SCI but also in other pathological conditions (that is, prolonged bed immobilization or absence of gravity). To date, bimagrumab, a selective anti-type II activin receptor monoclonal antibody preventing myostatin activity, has shown to be effective in humans with inclusion body myositis²⁸, possibly becoming in the near future a therapeutic option to prevent muscular modifications in SCI and other pathological conditions.

Previous studies showed a strong relation existing between unloading and muscle cross-sectional area reduction in both the acute²⁹ and sub-acute³⁰ phases of SCI. Moreover, myostatin messenger RNA expression has been investigated in different conditions like HIV and chronic stroke, showing a significant increase compared with healthy subjects. At present time, serum myostatin concentrations

Table 2 Biochemical and BMD variables between groups

Serum and clinical variables	SCI Tot (n = 28)	SCI complete (n = 22)	SCI incomplete (n = 6)	CT (n = 15)
25(OH)D serum levels (ng ml ⁻¹)	12.3 ± 6.6	12.6 ± 7.0	11.2 ± 5.3	20.5 ± 7.1 ^{#,**,††}
Normal (> 30 ng ml ⁻¹) %	0	0	0	20% (3)
Low (< 30 ng ml ⁻¹) %	50% (14)	50% (11)	50% (3)	80% (12)
Very Low (< 10 ng ml ⁻¹) %	50% (14)	50% (11)	50% (3)	0%
Phosphate (mg dl ⁻¹)	3.0 ± 0.4	3.1 ± 0.4	2.8 ± 0.3	3.1 ± 0.5
Serum creatinine (mg dl ⁻¹)	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.1	0.9 ± 0.2
eGFR (ml min ⁻¹ per 1.73 m ²)	86 ± 7.8	84 ± 8.1	87 ± 6.9	81 ± 5.4
CTX (pg ml ⁻¹)	461.7 ± 215.5	479.4 ± 215.8	396.9 ± 220.6	399.2 ± 223.9
PTH (pg ml ⁻¹)	43.9 ± 13.8	43.4 ± 13.9	45.8 ± 14.6	29.7 ± 6.9
IGF-I (ng ml ⁻¹)	177.6 ± 47.7	181.2 ± 49.7	164.2 ± 40.2	241.1 ± 92.8
CRP (mg dl ⁻¹)	0.77 ± 0.44	0.79 ± 0.69	0.67 ± 0.59	0.05 ± 0.04 ^{#,**,††}
iCa (mg dl ⁻¹)	4.9 ± 0.2	4.9 ± 0.3	4.9 ± 0.2	5.0 ± 0.2
BALP (mcg l ⁻¹)	12.6 ± 4.0	12.6 ± 4.3	12.5 ± 2.9	11.6 ± 6.0
Stiffness	36.8 ± 20.0	28.6 ± 12.0	66.8 ± 13.0 §	117.8 ± 19.0 ^{#,**,††}
T-score	-4.8 ± 1.6	-5.4 ± 0.9	-2.9 ± 1.1	1.4 ± 1.3
		SCI complete (n = 10)		CT (n = 7)
ASMMI (kg m ⁻²)		7.29 ± 1.97		8.01 ± 0.95

Abbreviations: ASMMI, appendicular skeletal muscle mass divided per height²; BALP, bone alkaline phosphatase; BMD, bone mineral density; CRP, C reactive protein; CT, controls; CTX, serum Beta-Crosslaps; 25(OH)D, 25 hydroxy vitamin D; eGFR, estimated glomerular filtration rate; iCa, ionized calcium; IGF-I, insulin growth factor I; PTH, parathyroid hormone; SCI, spinal cord injury. Data are presented as mean ± s.d.

**P* < 0.017; Mann-Whitney *U*-test SCI Tot vs SCI complete.

†*P* < 0.017; Mann-Whitney *U*-test SCI Tot vs SCI incomplete.

‡*P* < 0.017; Mann-Whitney *U*-test SCI Tot vs CT.

§*P* < 0.017; Mann-Whitney *U*-test SCI complete vs SCI incomplete.

***P* < 0.017; Mann-Whitney *U*-test SCI complete vs CT.

††*P* < 0.017; Mann-Whitney *U*-test SCI incomplete vs CT.

Figure 2 (a) Correlation between serum myostatin and serum sclerostin levels in motor complete SCI subgroup (*n* = 22)—*r*² = 0.42; *P* = 0.0012. (b) Correlation between serum myostatin and ASMMI in motor complete SCI subgroup (*n* = 10)—*r*² = 0.70; *P* = 0.002. SCI, spinal cord injured; ASMMI, appendicular skeletal muscle mass index.^{23,24}

after SCI in humans have not been published, and only few studies, with contrasting results, investigated this issue on animal models.^{31,32} To date, only one study investigated myostatin messenger RNA expression in muscular biopsies in patients with chronic SCI, finding a reduction of 46% compared with healthy subjects. However, the authors did not find a statistical difference regarding myostatin concentration measured by western blotting.³³ The main difference with our work is that, in previous studies, the authors measured myostatin expression and concentration at the muscular microenvironment level, without evaluating serum myostatin concentrations. Thus, the differences found by Léger *et al.* regarding myostatin concentration and expression at the local level could not reflect those at the circulating level. Our results integrate these molecular data, showing that myostatin concentration is increased in SCI patients even at the systemic level if compared with healthy controls, and this difference is similar in both motor complete and incomplete patients. Moreover, Léger *et al.* had a smaller sample size than ours, and, the time from lesion ranged from 3 months to 30 years, whereas in our study we only enrolled patients 24 months from SCI. This could have determined an enrollment bias, putting on the same level acute and chronic patients, considering that Castro *et al.* previously observed a peak of skeletal muscle mass reduction only 6 months after SCI.³⁰

As the inhibition of the myostatin pathway could be a key target to facilitate muscle growth, our data support the hypothesis that myostatin could be a possible biomarker to monitor the evolution of muscular modifications in SCI patients and a potential target for therapeutic purposes.

Sclerostin

In our study, both motor complete and incomplete SCI patients showed statistically significant higher values of serum sclerostin

compared with healthy subjects. Our results are somehow conflicting with those obtained by Morse *et al.*,⁶ which is the only study in literature investigating serum sclerostin levels in patients suffering from SCI. They proposed a model in which serum sclerostin is increased in the acute and sub-acute phase (up to 6 months) after SCI and even reduced in the chronic phase compared with healthy controls.⁶ Morse *et al.* enrolled a larger population than ours; however, considering the complete SCI subgroup only, the sample size was similar. Moreover, in our opinion, the two study populations show some differences regarding both age (40.5 years vs 55.8 years) and time from lesion (8 years vs 22 years). Furthermore, the age of control group was different in the two studies (28.4 years vs 61.7 years). These could be, in our opinion, relevant differences between our study and that by Morse *et al.*⁶ considering that sclerostin has been demonstrated to increase with age³⁴ and that the way authors performed age correction has not been clearly explained. However, even though the differences found in our study could lie in the younger age of patients enrolled (both SCI and healthy controls), the results showed no correlation between serum sclerostin and age. Nevertheless, our data could have important therapeutic implications, suggesting that anti-sclerostin antibodies^{35–37} could be a valid option even in chronic phase after SCI, as serum sclerostin levels are still elevated during this phase.

BMD

Patients with SCI enrolled in our study showed statistically significant lower BMD values than healthy controls. This difference was present in both complete and incomplete patients, with a lesser magnitude in the second subgroup. Our data are similar to those previously obtained by Warden *et al.*³⁸ with ultrasound technique and Jiang *et al.*³⁹

DXA measurement of BMD is the gold standard for the diagnosis of osteoporosis.⁴⁰ However, this technique could not be so easy to perform in SCI patients because of several factors limiting correct scan positioning (paresis, contractures, spasms and amputation) or the presence of scan artifacts due to heterotopic ossifications, joint replacement or metal rods.² Moreover, fracture risk prediction by bone density category after SCI has not well been defined yet, and fractures are most common at distal sites (knee and tibia), which are not routinely included in standard clinical DXA scans.

For these reasons, we choose to measure BMD with the heel quantitative ultrasound technique, being easier (patients can sit on their wheelchair during measurement) and faster compared with DXA. Finally, the quantitative ultrasound technique has shown an excellent reproducibility and a strong correlation with osteoporotic fracture risk at both vertebral and femoral site.^{2,41–43}

Correlations

As emerges in Figures 2a and b, serum myostatin positively correlated with serum sclerostin and ASMMI. Regarding serum myostatin and sclerostin we choose to perform the correlation only in the subgroup of patients suffering from motor complete SCI because of the low number of patients in the motor incomplete group, finding a good correlation between these two variables ($r^2 = 0.42$; $P = 0.001$). Our data about the supposed correlation between sclerostin and myostatin should be taken cautiously, considering the small sample size. However, assuming the hypothesis of a biochemical cross-talk between the bone and muscle tissue,¹² which could partially explain the mechanisms underlying the observed modifications in these two tissues after SCI, myostatin could be one of the responsible of this cross-talk by the muscle side. However, this is just an hypothesis, and

further studies are needed to deeply investigate this possible cross-talk in which other mediators could be involved.

Interestingly, serum myostatin concentrations correlated also with ASMMI. Considering the low number of patients performing this evaluation ($n = 10$), the correlation found was strong ($r^2 = 0.70$; $P = 0.002$), and this correlation was absent in healthy controls. As previously noted, this finding should be taken cautiously, considering the small sample size; however, it shows that serum myostatin could be a useful marker to monitor skeletal muscle modifications in SCI patients. This consideration is also supported by the fact that, similarly to bone tissue, other muscular imaging techniques to quantify muscle mass like DXA may have underestimated in the past the degree of muscle atrophy associated with SCI.^{44,45} However, previous studies showed that skeletal fat-free muscle mass from magnetic resonance imaging and from DXA were very strongly related and can accurately predict thigh skeletal muscle mass in men with long-term, complete SCI but only if appropriate regression equations are developed.⁴⁵ However, at present time, equations specific to patients suffering from SCI have not been developed yet.

Study limitations

This study has some limitations. First, the population sample size was relatively small, mainly for the motor incomplete group. Another limit of this study is that we do not have data about the muscle microenvironment to correlate with those obtained at the circulating level.

CONCLUSIONS

Muscular modifications in chronic SCI patients are a growing issue, considering their impact on vascular risk factors (that is, diabetes, obesity, lipid disorders and cardiovascular disease) in these patients and the overall disability and health-care costs.⁹ It should be remembered that cardiovascular diseases are becoming the primary cause of death among SCI patients.⁴⁶ Moreover, in light of all the research to improve neural repair after SCI, it is imperative that we understand whether deleterious musculoskeletal adaptations after chronic SCI can be reversed.⁴⁷ Then, in contrast with bone tissue modifications after SCI, those at the muscle level, and the underlying pathological mechanisms, have been little analyzed.

In this study, according to the previous hypothesis of a biochemical more than functional relation between the bone and muscle, we showed that serum myostatin, a powerful inhibitor of muscle proliferation selectively produced by satellite cells, is significantly higher in patients suffering from chronic SCI compared with healthy controls, finding also a strong correlation between serum myostatin concentrations and ASMMI in SCI patients but not in healthy controls. Moreover, we confirmed previously published data about serum sclerostin in SCI patients, and, we also found out a correlation between serum sclerostin and myostatin, giving some evidence about a possible biochemical cross-talk involving osteocytes and sclerostin from the bone side and satellite cells and myostatin on the muscle side.

In conclusion, our results are encouraging, suggesting myostatin as a potential biomarker of muscular modifications and a potential therapeutic target to prevent these pathological modifications not only in SCI patients but also in other pathological unloading conditions.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest

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