Circulating Leptin Concentrations Can Be Used as a Surrogate Marker of Fat Mass in Acute Spinal Cord Injury Patients

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To determine the acute effect of neurological lesion on body composition, plasma leptin level, and the lipid profile, 7 male patients with acute and complete spinal cord injury (SCI) and 9 able-bodied (AB) males were investigated. At 16, 24, 36, and 48 weeks after injury, plasma leptin level and the lipid profile were analyzed, while whole body (WB) and regional fat mass (FM) and fat-free soft tissue (FFST) were measured by dual-energy x-ray absorptiometry (DXA). At all stages, despite no difference being found between both groups for body mass index (BMI), SCI patients had higher FM at WB ($P < .01$), lower ($P < .01$), and upper limbs ($P < .05$), while FFST was lower at WB ($P < .05$) and lower limbs ($P < .01$). The leptin level increased gradually from week 24 and was higher at weeks 16, 36, and 48 in SCI patients than in AB patients (7.0 ± 3.9; 9.7 ± 5.1; 10.6 ± 5.3, respectively, *v* 3.5 ± 2.5 ng · mL^{-1}). SCI patients had lower high-density lipoprotein-cholesterol (HDL-C) ($P < .05$) and apolipoprotein (apo) A1 ($P < .01$), while no difference was found for total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), or ApoB levels. At all stages, leptin was strongly and positively correlated with WB and regional FM % ($r > 0.75$; $P < .05$) and with TC, LDL-C, and ApoB levels ($r > 0.65$; $P < .05$). Leptin was negatively correlated with FFST and the ApoA1/ApoB ratio ($r > -0.75$; $P < .05$). In conclusion, neurological lesion induced an early and acute alteration in body composition and lipid profile. The strong relationship between serum leptin and FM suggests that this hormone can be used as a surrogate marker of FM in acute SCI patients and thus would serve as a good indicator for cardiovascular disease risk.
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SPINAL CORD INJURY (SCI) induces many types of psychological and pathological damage, including an increase in the bone resorption process,[1] variations in various hormonal levels,[2,3] and modifications in body composition.[4,5] After a stroke, the neurological lesion and subsequent immobilization lead to noticeable muscle atrophy and a gain in relative adiposity,[4-6] and these body composition changes generate metabolic disturbances. Duckworth et al[7] showed that one half of chronic patients developed diabetes mellitus, while Bauman et al[2] found that 22% of this population were diabetic compared with only 6% in a population of age-matched able-bodied (AB) controls. In addition, several abnormalities, such as peripheral insulin resistance associated with hyperinsulinemia and lipid abnormalities, have also been reported.[2] These metabolic responses to the neurological lesion could predispose patients to various diseases, especially coronary heart disease (CHD).[8] Potential markers to detect the body composition changes affecting SCI patients are thus needed.

Leptin, the product of the ob gene, is a hormone secreted by adipocytes[9] and involved in the regulation of body weight and energy expenditure.[10] The circulating concentration of leptin is closely and positively correlated with body fat in humans.[11] In male subjects with chronic SCI, plasma leptin levels were higher than in an AB group,[12,13] probably because of the relative increase in adipose tissue.[12] Moreover, a relationship between plasma leptin and body mass index (BMI)[12,13] and percent fat mass[12] has been demonstrated. No data, however, on the variation in plasma leptin level during the acute phase of SCI, corresponding in fact to a determinant period in the development of neurological lesion-related pathologies, are available.

The objective of this longitudinal study was to follow the effect of neurological lesion on body composition (fat mass [FM] and fat-free soft tissue [FFST]), plasma leptin level and the lipid profile in acute SCI patients for 48 weeks. Moreover, to determine whether leptin can be used to evaluate the acute changes in body composition during this period, we looked for relationships between plasma leptin level and BMI, FM, FFST, and the lipid profile parameters.

MATERIALS AND METHODS

Subjects

We longitudinally followed 7 male patients with SCI (mean, 31.3; range, 20 to 41 years) who had sustained the injury within approximately 3 months (range, 90 to 110 days), and we made various measurements at 16, 24, 36, and 48 weeks after the stroke. All patients had initially been recruited from the PROPARA Rehabilitation Center of Montpellier, France to participate in a previously published study.[1] All had traumatic and complete lesion of the spinal cord, and 4 were paraplegics (D4 to D10), and 3 were tetraplegics (C4 to C8). The control group comprised 9 male sedentary age-matched subjects (mean, 27.7; range, 22 to 35 years). For all subjects, exclusion criteria were diabetes mellitus, eating disorders, liver disease, renal disorders, smoking, and excessive alcohol intake. Each subject's stature was determined by self-report of the preinjury height or, in instances where a subject was not sure of his height, it was measured (in centimeters) using a scale to the nearest 0.1 cm. Body mass (in kilograms) was estimated using a medical scale to the nearest 0.5 kg and the BMI was calculated as weight divided by the square of the height (kg · m^{-2}). The

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Table 1. Body Composition in Patients With SCI During the First Year After Neurological Lesion

Parameters	Patients With SCI (n = 7)				Able-Bodied (n = 9)
	Duration Postinjury				
	16 Weeks	24 Weeks	36 Weeks	48 Weeks	
Weight (kg)	67.5 ± 6.1	67.2 ± 7	68.1 ± 7.8	70.0 ± 8.5	67.1 ± 4.1
BMI (kg · m^{-2})	21.5 ± 2.3	21.4 ± 2.4	21.7 ± 2.6	22.3 ± 2.9	22.2 ± 1.1
Fat mass (%)					
Whole body	23.7 ± 5.4†	23.3 ± 4.7†	23.8 ± 5.6†	24.9 ± 6.2†	17.3 ± 2.7
Lower limb	30.9 ± 6.20‡	31.4 ± 6.5‡	31.9 ± 64‡	32.6 ± 7.2‡	20.1 ± 3.0
Upper limb	24.0 ± 7.2†	21.4 ± 5.6*	22.1 ± 7.2*	22.1 ± 7.5*	17.3 ± 2.6
Trunk	19.2 ± 5.7	18.6 ± 4.5	19.3 ± 5.8	21.1 ± 6.6*	14.9 ± 2.8
Fat mass (kg)					
Whole body	16.0 ± 3.6†	15.6 ± 3.4†	16.4 ± 4.8†	17.7 ± 5.4†	11.6 ± 2.1
Lower limb	6.7 ± 1.3†	6.8 ± 1.5†	7.1 ± 1.9†	7.5 ± 2.2†	4.6 ± 0.8
Upper limb	2.2 ± 0.5†	2.0 ± 0.5*	2.1 ± 0.7*	2.2 ± 0.8†	1.4 ± 0.4
Trunk	6.0 ± 2.0	5.9 ± 1.7	6.3 ± 2.4	7.0 ± 2.6*	4.6 ± 1.0
Lean tissue mass (kg)					
Whole body	48.8 ± 5.7*	48.8 ± 5.7*	49.0 ± 5.0*	49.7 ± 5.6*	53.0 ± 3.2
Lower limb	14.1 ± 2.0†	13.9 ± 2.0†	13.9 ± 1.5†	14.1 ± 2.0†	17.4 ± 1.6
Upper limb	6.7 ± 1.3	6.9 ± 1.3	6.9 ± 1.0	7.4 ± 1.2	6.8 ± 0.6
Trunk	24.5 ± 2.9	24.6 ± 3.2	24.7 ± 3.2	24.6 ± 3.6	25.28 ± 1.42

NOTE. Data are presented as means ± SD.

*$P < .05$ SCI patient *v* able-bodied.

†$P < .01$ SCI patient *v* able-bodied.

‡$P < .001$ SCI patient *v* able-bodied.

anthropometric characteristics of the SCI and AB groups are shown in Table 1.

Experimental Protocol

For the patients, 4 investigations were performed at weeks 16 ± 2, 24 ± 2, 36 ± 3, 48 ± 4 after neurological lesion. The protocol was reviewed and approved by the Regional Research Ethics Committee (the University Hospital of Montpellier), and each subject gave informed consent before the study. For the AB group, only 1 investigation was performed at the start of the study, since either no variation or only very minor ones have been reported to occur over time for BMI, percent body fat, leptin level, and lipid profile parameters.[14]

After a 10-hour overnight fast, venous blood samples (20 mL) were taken between 8 AM and 9 AM and were then centrifuged at 3,000 rpm for 10 minutes at 4°C. Serum was stored at −80°C until analysis. All samples were run in duplicate and to eliminate interassay variation, all the serum samples were analyzed in a single session. Blood was collected for determination of leptin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), apolipoprotein-A1 (ApoA1), and apolipoprotein-B (ApoB) levels. Whole and regional body composition (FM and FFST) was determined by dual-energy x-ray absorptiometry (DXA).

Measurement of Body Composition

DXA (Hologic QDR-4500A; Hologic, Bedford, MA) was used to measure the soft tissue body composition: FM (kilogramsg), percent FM (%), and FFST (kilograms) were derived from the whole body (WB) scan. The WB scan was subdivided into regions according to standard procedures with the arm:torso boundary bisecting the glenohumeral head and the pelvis:leg boundary bisecting the femoral neck. All scanning and analyses were performed by the same operator to ensure consistency and followed standard quality control procedures. DXA measurements were based on the methods described by Mazees et al.[15] The procedure for scanning lasts approximately 10 minutes. Identical and accurate positioning of the region of interest was ensured by superimposing the image from the very first session on the image of the explored bone area; this initial image thus served as the visual reference. The coefficient of variation (CV) was <1% for FM and FFST.

Hormone Assessment

Leptin concentrations were measured by commercial immunoradiometric assay (IRMA) technique (ActiveTM human leptin IRMA DSL-23100; Diagnostic Systems Laboratories, Webster, TX). The intra- and interassay CVs were 4.9% and 6.6%, respectively, with a sensitivity of 0.1 ng · mL^{-1}.

Serum Lipid Parameters

TC, HDL-C, and TG were measured in serum by routine enzymatic methods (KonePro; Konelad, Cergy Pontoise, France). LDL-C was calculated by the equation:

LDL-C (g · L^{-1}) = TC−(TG/2,2)-HDL. ApoA1 and ApoB concentrations were determined by immunonephelometric assay using a Behring Nephelemeter 100 (Berhing Diagnostic, Marburg, Germany).

Statistical Analysis

The results are expressed as means ± SD. For continuous variables, the distribution was tested by the Shapiro-Wilk statistical method and a nonparametric test for the small sample was then used. For all the parameters, the baseline data were set at 16 weeks after injury because before this period, all the patients were in the intensive care unit. The significance of difference between baseline data and successive time points was determined by the Wilcoxon paired sample test. At all stages, Spearman correlations were used to determine the relationships between circulating leptin level and body composition or parameters of the lipid profile. A level of $P < .05$ was accepted as significant. As the population of patients was relatively small, no distinction according to lesion level or age at the time of SCI was taken into account. SAS

Table 2. Basal Leptin Levels and Lipid Profile in Patients With SCI During the First Year After Neurological Lesion

Parameters	Patients With SCI (n = 7)				Able-Bodied (n = 9)
	Duration Postinjury				
	16 Weeks	24 Weeks	36 Weeks	48 Weeks	
Leptin (ng · mL^{-1})	7.0 ± 3.9*	6.1 ± 3.5§	9.7 ± 5.1†‡	10.6 ± 5.3†§	3.5 ± 2.5
TC (g · L^{-1})	1.81 ± 0.34	1.66 ± 0.38	1.76 ± 0.15	1.65 ± 0.27	1.91 ± 0.24
TG (g · L^{-1})	1.17 ± 0.38†	0.96 ± 0.50‡	0.85 ± 0.28§	0.88 ± 0.23§	0.77 ± 0.38
HDL-C (g · L^{-1})	0.38 ± 0.05‖	0.39 ± 0.06‖	0.42 ± 0.09†	0.41 ± 0.06†	0.56 ± 0.11
LDL-C (g · L^{-1})	1.19 ± 0.31	1.08 ± 0.31	1.17 ± 0.45	1.06 ± 0.26	1.19 ± 0.23
ApoA1 (g · L^{-1})	1.13 ± 0.11‖	1.08 ± 0.10‖	1.15 ± 0.19†	1.16 ± 0.16†	1.51 ± 0.21
ApoB (g · L^{-1})	0.99 ± 0.25	0.87 ± 0.23	0.92 ± 0.36	0.85 ± 0.21	0.89 ± 0.14
ApoA1/ApoB	1.23 ± 0.44*	1.32 ± 0.39*	1.38 ± 0.44	1.43 ± 0.38	1.73 ± 0.36

NOTE. Data are presented as means ± SD.

Abbreviations: TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ApoA1, apolipoprotein-A1; ApoB, apolipoprotein-B.

*$P < .05$ SCI patient *v* able-bodied.

†$P < .01$ SCI patient *v* able-bodied.

Values significantly different from values at 16 weeks using the Wilcoxon paired sample test: ‡$P < .05$, §$P < .01$.

‖$P < .001$ SCI patient *v* able-bodied.

software, version 8.2 (SAS Institute, Cary, NC), was used for the statistical analysis.

RESULTS

Body Composition

The clinical data of the patients are summarized in Table 1. There was no statistical difference between the 2 groups with regard to age, height, or weight. Although no statistical difference was observed for BMI, patients with SCI had significantly higher FM (kilograms and %) at WB and lower and upper limbs ($P < .05$ or $P < .01$). These differences appeared from 16 weeks and remained significant at all stages, except for the trunk, where the difference was observed at week 48 only. The increase in FM (%) was principally localized in the lower limbs (53%; $P < .001$) and more moderately in the upper limbs (38%; $P < .01$). No statistical variation with time was observed for FM during the study at any body site. The SCI patients had significantly lower FFST than the AB group at WB (8%, $P < .05$) and at lower limbs (19%, $P < .01$). Upper limbs and trunk FFST were not significantly different between the 2 groups. No statistical variation was observed for FFST during the study.

Hormonal and Lipid Profiles

As shown in Table 2, plasma leptin was significantly higher in the group with SCI than in the AB group at 16 ($P < .05$), 36 ($P < .01$), and 48 weeks ($P < .01$). Compared with the values at 16 weeks, plasma leptin increased significantly and continuously with the duration of injury, except for the stage at 24 weeks where a substantial decrease was noted (14%; $P < .01$).

No difference was found between SCI patients and AB subjects for serum TC, LDL-C, or ApoB levels. The SCI patients had significantly lower mean HDL-C, ApoA1 (at all stages, $P < .001$ and $P < .01$), ApoA1/ApoB ratio (at 16 and 24 weeks, $P < .05$) and TG (at 16 weeks, $P < .05$) than the AB group. Of all the lipid profile parameters, only TG showed significant variation with time.

Relationship Between Leptin Levels and Parameters of Body Composition or Lipid Profile

Table 3 shows the Spearman correlations between basal leptin level and body composition or parameters of lipid profile in patients with SCI. At all stages, the plasma leptin level was strongly and positively correlated ($r = 0.71$ to 0.92; $P < .001$ to .05) with WB and regional FM (lower limbs, upper limbs, and trunk). Leptin was also slightly and positively correlated with TC, LDL, ApoB, and ApoA1/ApoB (see details in Table 3). The significance of the correlations varied over time, how-

Table 3. Association of Basal Leptin Levels With Fat Mass, Lean Tissue Mass, and Parameters of Lipid Profile in Patients With SCI During the First Year After Neurological Lesion

Parameters	Duration Postinjury			
	16 Weeks	24 Weeks	36 Weeks	48 Weeks
Fat mass (%)				
Whole body	0.89†	0.96‡	0.84†	0.64*
Lower limb	0.89†	0.89†	0.92†	0.75*
Upper limb	0.96‡	0.90†	0.92†	0.76*
Trunk	0.85†	0.85†	0.85†	0.71*
Lean mass (kg)				
Whole body	−0.64	−0.64	−0.21	−0.35
Lower limb	−0.46	−0.75*	−0.35	−0.57
Upper limb	−0.53	−0.76*	−0.75*	−0.51
Trunk	−0.54	−0.53	−0.43	−0.14
Biochemical parameters				
TC	0.82*	0.92†	0.65*	0.77*
LDL-C	0.82*	0.94†	0.65*	0.71*
ApoB	0.77*	0.84*	0.77*	0.77*
ApoA1/ApoB	−0.71	−0.77*	−0.65	−0.77*

NOTE. Data are presented as coefficients of correlation (*r*). No relationship was found between leptin level and TG, HDL, or Apo A1 (data not shown).

*$P < .05$.

†$P < .01$.

‡$P < .001$.

ever, and tended to decrease with time. Moreover, partial negative correlations were found between plasma leptin and FFST for the lower and upper limbs at 24 weeks ($r = 0.75$) and for the upper limbs only at 36 weeks ($r = 0.75$). No relationship was found between leptin level and TG, HDL, or ApoA1.

DISCUSSION

Body Composition Changes

Our data showed no difference in BMI between acute SCI patients and AB subjects, in line with previous reports regarding chronic SCI patients and controls.[2,4,5] Among the AB, individuals with similar age and BMI are expected to have approximately the same body composition. In this study, however, we confirmed that despite the same BMI, the composition and distribution of body FM and FFST were modified in the SCI patients in comparison with controls. The DXA technique was previously validated[16] and may be the most suitable and practical measuring tool for the direct determination of body composition in this population.[4]

In the present study, FFST was significantly reduced in the SCI patients at the WB and the lower limbs, but not at the upper limbs. Arms play a major role in the locomotion of paraplegic patients, and this new function likely contributes to the increase in muscle mass during the rehabilitation program[5,17] and its conservation in chronic paraplegic patients.[4,18] Earlier studies reported a similar profile concerning the loss of muscle mass in chronic SCI patients.[2,5,17] After 6 months of injury, Uebelhart et al[17] found muscle atrophy of 10.7% in the legs and 5% in the WB in 6 young male paraplegic patients, whereas muscle mass increased significantly by 19.6% in the arms. In addition to muscle fiber atrophy, SCI induces alterations in muscle composition in the paralyzed muscle areas, including fiber type changes[19] and reduced capillary numbers.[20]

At all stages and in most sites, body FM was significantly greater by an average of approximately 40% in the paralyzed patients. Our results confirmed some data,[4,17] but differed partially with other findings.[18] The value of WB FM found in the present work (24%), as well as the values reported by Bauman et al,[2] Spungen et al,[16] and Jones et al[4] (range, 26.5% to 31%), was near 25%, suggesting that these patients were overweight or obese.[21] However, the patients did not satisfy a second obesity index, which is a BMI >30,[4,11,18,22] presumably because the lost muscle mass had been replaced by extra fat.[4] It thus appears that the BMI and percentage of FM indices lack reliability and robustness for determining obesity in these patients, and new indicators are needed that take into account specific regional modifications.

The moderate changes in body composition seen in our longitudinal study suggest that the major modifications may have occurred during the acute phase of neurological lesion when the patient was strictly immobilized. Wilmet et al[5] reported a dramatic decrease in lean tissue mass in the legs during the first 15 weeks postinjury, while fat content tends to increase. Uebelhart et al[17] observed substantial muscle atrophy between the first and third month postinjury, with no further loss measured up to the sixth month. Spungen et al[18] however, demonstrated a linear loss of lean tissue mass with duration of injury in chronic paraplegics, although it is probable that after a period characterized by an intense catabolic state, this process slows down with time. This change in body composition is quite likely related in part to the physical inactivity that reduces energy expenditure[23] and/or depresses anabolic[24] and lipolytic[3] hormone levels.

In SCI patients, muscle atrophy and the gain in relative adiposity associated with neurological lesion and physical inactivity are not without risk and may be at the origin of metabolic disturbances, such as insulin resistance and hyperinsulinemia.[2] These abnormalities probably contribute to the high prevalence of CHD and diabetes mellitus in this population.[6-8] Epidemiologic studies suggest that fat distribution, especially visceral obesity, may be a more important determinant of diseases than generalized obesity.[25] In our study, the fat mass of the trunk was higher in the SCI patients than the AB subjects only after 48 weeks, which may indicate that this aggravating factor appears relatively later after injury. In addition, the risk of CHD is reflected by the lipid profile,[26] as confirmed in our study by the depressed HDL-C and ApoA1 levels. Indeed, decreased HDL-C is an independent cardiovascular risk factor.[27] Our results are in agreement with previous findings in early[28,29] and chronic SCI patients.[28,30-32] The increase in abdominal adiposity[31] and the extreme sedentary lifestyle imposed by paralysis[28] could be important determinants of the dyslipidemia seen in the SCI population. Although active or highly trained men with SCI have higher HDL-C values than sedentary SCI patients, they show values similar to those of AB controls.[28,32]

Leptin

Higher values of plasma leptin in chronic SCI patients than in AB subjects have been reported,[12,13] however, no data concerning variations during the acute phase of lesion are available. In the present study, plasma leptin level was also significantly higher in patients from 16 weeks and increased continuously after 24 weeks to 48 weeks. Our population was composed of paraplegic and tetraplegic patients, and it seems that serum leptin variation was not related to the level of the neurological lesion.[13] These preliminary observations suggest that modification of leptin synthesis and/or secretion took place early after neurological lesion and was amplified with time postinjury.

The increase of plasma leptin levels from 16 to 36 or 48 weeks postinjury was not associated with an apparent significant modification in total or regional measurement of body fat. This might be related in part to the difficulty of accurately determining the infiltration of muscle tissue by fat using DXA methodology.[33] Nevertheless, the correlation remained strongly significant at all time points (correlation coefficient >0.64), suggesting that the gain in adipose tissue may have been responsible for the increase of serum leptin levels. This hormone could thus constitute a robust circulating marker of the evolution of adipose tissue in SCI patients, especially in the acute postinjury phase. However, Jeon et al[34] showed that leptin levels adjusted to fat mass remained 45% higher in an SCI group compared with an AB group. These findings suggest that factors other than FM also contribute to serum leptin regulation. For example, an inhibitory effect of the adrenergic

system on leptin secretion has been reported.[35,36] As suggested by Jeon et al,[34] removal of this inhibition by postinjury sympathetic nervous system dysfunction, in addition to a reduced catecholamine level, would probably contribute to the increase in plasma leptin levels. In addition to the interest in using plasma leptin levels to follow the changes in body fat, higher plasma leptin levels may be considered as a surrogate measure of increased fat mass, which is a determinant of insulin resistance. This appreciation may make plasma leptin levels of some utility in clinical medicine because of the association of insulin resistance and cardiovascular disease, and thus heighten the need for appropriate intervention in this specific population. Moreover, in AB subjects, an increase in leptin concentration is an independent risk factor for CHD,[37] which is substantially more frequent in an SCI population.

Conclusion

In summary, our data confirm that SCI induced a profound alteration in body composition. In the SCI patients, skeletal muscle atrophy and adipose tissue gain occurred during the first months following injury. At all stages of this longitudinal study, our data clearly show that plasma leptin concentration was higher in the patients than in the controls and was highly correlated with measures of WB and regional FM. Because these modifications contribute to the development of diseases, such as diabetes mellitus and CHD, we thus propose that leptin concentration can be used as a surrogate-circulating marker of the evolution of adipose tissue in these patients. Based on endocrine and metabolic data, we suggest that this management begin as early as possible after the stroke.

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