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Obesity worsens central inflammation and disability in multiple sclerosis

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Abstract

Background: Previous studies evidenced a link between metabolic dysregulation, inflammation, and neurodegeneration in multiple sclerosis (MS).

Objectives: To explore whether increased adipocyte mass expressed as body mass index (BMI) and increased serum lipids influence cerebrospinal fluid (CSF) inflammation and disease severity.

Methods: In this cross-sectional study, 140 consecutive relapsing-remitting (RR)-MS patients underwent clinical assessment, BMI evaluation, magnetic resonance imaging scan, and blood and CSF collection before any specific drug treatment. The CSF levels of the following cytokines, adipocytokines, and inflammatory factors were measured: interleukin (IL)-6, IL-13, granulocyte macrophage colony-stimulating factor, leptin, ghrelin, osteoprotegerin, osteopontin, plasminogen activator inhibitor-1, resistin, and Annexin A1. Serum levels of triglycerides, total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were assessed.

Results: A positive correlation emerged between BMI and Expanded Disability Status Scale score. Obese RR-MS patients showed higher clinical disability, increased CSF levels of the proinflammatory molecules IL-6 and leptin, and reduced concentrations of the anti-inflammatory cytokine IL-13. Moreover, both the serum levels of triglycerides and TC/HDL-C ratio showed a positive correlation with IL-6 CSF concentrations.

Conclusion: Obesity and altered lipid profile are associated with exacerbated central inflammation and higher clinical disability in RR-MS at the time of diagnosis. Increased adipocytokines and lipids can mediate the negative impact of high adiposity on RR-MS course.

Keywords: Obesity, adipocytokines, multiple sclerosis, inflammation, serum lipid profile, BMI

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Introduction

A growing body of evidence highlighted the link between metabolic pressure, autoimmunity, and neurodegeneration in different chronic inflammatory conditions.[1,2] Obesity represents a proinflammatory condition characterized by increased expression of inflammatory mediators, including interleukin (IL)-6 and leptin.[3,4] Leptin, the prototypic adipocytokine, supports proinflammatory immune responses against central nervous system (CNS).[5,6]

Obesity during childhood and adolescence represents a risk factor for multiple sclerosis (MS).[7,8] Altered lipid metabolism has been associated with worse disease course in MS patients.[9,10] In particular, higher levels of adiposity and altered serum lipid profile negatively influence disability progression,[11,12] and higher body mass index (BMI) has been associated with reduced response to interferon-β (IFN-β) therapy in MS patients.[10] However, how BMI and serum lipid–related variables may influence MS disability and risk of relapse is not yet established.

Neuroinflammation represents a key factor influencing MS progression and neurodegeneration. Experimental studies showed that specific inflammatory molecules

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promote excitotoxic neuronal damage in vitro[13] and are associated with disease exacerbations in MS patients.[14] Both in animal models (i.e. experimental autoimmune encephalomyelitis (EAE)) and in MS, elevated central levels of proinflammatory cytokines have been associated with worse disease course and increased measures of neuronal damage.[13–15] Conversely, anti-inflammatory cytokines and neurotrophic factors showed neuroprotective effects[16] and beneficially influenced the disease course of MS.[17]

It is important to clarify the relationship between altered lipid metabolism and disease course in MS, because interventions aimed at lowering abnormal serum lipid levels could reduce the accumulation of disability. We therefore explored in a group of relapsing-remitting (RR)-MS patients whether elevated BMI and altered serum lipid profile at the time of diagnosis can influence inflammatory molecule concentration in the cerebrospinal fluid (CSF) and clinical disability.

Methods

MS patients

A group of 140 consecutive patients admitted to the neurological clinic of the IRCCS Neuromed, Pozzilli (IS), between 2017 and 2018 and diagnosed as RR-MS participated in the study. According to the published criteria, the diagnosis of RR-MS was established based on clinical, laboratory, and magnetic resonance imaging (MRI) parameters.[18] The study was approved by the Ethics Committee of the IRCCS Neuromed. All patients gave a written informed consent.

Blood and CSF withdrawal, clinical examination, and MRI scan were performed during hospitalization. All patients were untreated before hospitalization, and corticosteroids or immunoactive therapies were initiated after lumbar puncture (LP).

Clinical evaluation

Disease duration was calculated as the time interval between disease onset, defined as the first episode of focal neurological dysfunction suggestive of MS, and the time of diagnosis. The number of clinical relapses that occurred before hospitalization was recorded. A relapse was defined as the appearance of new or recurrent neurological symptoms not associated with fever or infection, lasting at least 24 hours. Clinical activity at LP was defined as the presence of an ongoing relapse at the time of hospitalization. The Expanded Disability Status Scale (EDSS) was used to assess clinical disability, and single functional system involvement (vision, brainstem, pyramidal, cerebellar, sensory, bowel/bladder, cerebral, and ambulation) was also recorded.[19] Body height and weight were measured during hospitalization. BMI was calculated as weight (kg)/height (m^2). Information on smoking habit was collected from all patients, asking about current and previous smoking.

MRI

A 1.5- or 3.0-tesla MRI scan was performed, including dual-echo proton density sequences, fluid-attenuated inversion recovery, T1-weighted spin-echo (SE), T2-weighted fast SE, and contrast-enhanced T1-weighted SE after intravenous gadolinium (Gd) infusion (0.2 mL/kg). A Gd-enhancing (Gd+) lesion was defined as an area of hyperintense signaling on contrast-enhanced T1-weighted images. Radiological activity at LP was defined as the presence of a Gd+ lesion at brain, and spine MRI scan was performed during hospitalization.

Biochemical serum lipids

Blood sample of patients were collected after a 12-hour period of fasting using recommended procedures for collection of blood specimens by venipuncture. Samples were centrifuged at 3500*g* for 10 minutes at 4°C. In vitro enzymatic diagnostic tests on the DimensionR clinical chemistry system (Siemens) were used for total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglyceride serum determinations.

CSF collection and analysis

We assessed the CSF concentrations of a group of proinflammatory and anti-inflammatory molecules, including specific adipocytokines, which are known to be involved in MS pathogenesis and metabolic inflammation.[6,14,16] CSF was centrifuged and then stored at –80°C immediately after LP. The CSF levels of the following molecules were measured: interleukin (IL)-6, IL-13, granulocyte macrophage colony-stimulating factor (GM-CSF), leptin, ghrelin, osteoprotegerin (OPG), osteopontin, plasminogen activator inhibitor-1 (PAI-1), resistin, and Annexin A1 (ANXA1).

The ProcartaPlex Mix&Match Human 8-plex (Invitrogen by Thermo Fisher Scientific) was used for the quantitative detection of ghrelin, GM-CSF, IL-6, leptin, OPG, osteopontin, PAI-1, and resistin in CSF in accordance with manufacturer's instructions. Fluorescence intensity was measured using Luminex®

Table 1. Demographic and clinical characteristics of MS patients.

MS patients	*N*	140
Sex, F	*n* (%)	95 (68)
Age, years	Median (IQR)	36.97 (28.67–47.68)
Disease duration, months	Median (IQR)	12 (1.71–36.65)
Clinical activity at LP	*n* (%)	42 (30)
Radiological activity at LP	*n* (%)	56 (40)
EDSS at LP	Median (IQR)	2 (1–3)
BMI	Median (IQR)	23.9 (21.48–27.75)

MS: multiple sclerosis; IQR: interquartile range; LP: lumbar puncture; EDSS: expanded disability status scale; BMI: body mass index.

200™ system (Luminex, Austin, TX), and data were analyzed with xPONENT Software Version 3.1 (Luminex). ANXA1 and IL-13 levels were determined by enzyme-linked immunosorbent assay (ELISA). Briefly, samples were diluted 1:2 and used on a pre-coated ELISA plate per manufacturer's instructions. Absorbance was measured using a microplate reader (Model 500; Bio-Rad, Hercules, CA), and sample readings were extrapolated against a concurrently run standard curve.

Statistical analysis

Kolmogorov–Smirnov test was applied to verify the normality distribution of continuous variables.

Continuous data were presented as mean (standard deviation, SD) or, if they were not assumed as normally distributed, as median (interquartile range, IQR = 25th–75th percentile). Categorical or dichotomous variables were presented in terms of frequency (percentage, %). Logarithmic transformation was applied to reduce the variability of data distribution and to obtain a better approximation to the normal distribution. Correlations between continuous variables (cytokines, adipocytokines, disease duration, etc.) were evaluated by the Spearman's rho correlation coefficients. Partial correlation was also calculated while controlling for the effect of age. The relationship between two continuous variables was depicted by a scatter plot and, when specified, was described by the Passing–Bablok regression model; this regression model is a nonparametric procedure not sensitive to outliers and distribution of errors.[20] Differences in continuous variables among two groups were evaluated by parametric *t*-test or, if necessary, nonparametric Mann–Whitney test. Differences in continuous variables among more than two groups were evaluated by analysis of variance (ANOVA) or Kruskal–Wallis test. Analysis of covariance (ANCOVA) models were applied to evaluate differences in BMI classes in IL-6, leptin, and IL-13 (on logarithmic scale) adjusting for sex, age, disease duration, smoking, and the presence of radiological activity. Benjamini–Hochberg (B-H) procedure at an α of 0.05 was applied to control the false discovery rate both in post-ANCOVA and Kruskal–Wallis multiple comparisons between the three BMI groups (a total of three comparisons were performed: normal vs overweight, normal vs obese, obese vs overweight) and in multiple correlations. A value of $p < 0.05$ was regarded statistically significant. Cytokine or adipocytokine distribution in the three BMI groups was presented by boxplot; the box was drawn from the 25th percentile to the 75th percentile; the horizontal line in the box represents the median values. All statistical analyses were performed by SPSS 15 (IBM Corp., Armonk, NY).

Results

A high BMI associates with an increased EDSS in RR-MS patients

The clinical and demographic characteristics of MS patients are shown in Table 1. No significant correlations emerged between serum lipid profile (TC, triglycerides, TC/HDL-C) and clinical characteristics at the time of diagnosis. Significant correlations were observed between BMI and both EDSS and age at LP (Spearman's rho = 0.242, $p = 0.008$ and Spearman's rho = 0.309, $p < 0.001$, respectively). In particular, the positive correlation with EDSS remained significant after controlling for sex, age, disease duration, smoking, and the presence of radiological activity (partial Spearman's rho = 0.248, $p = 0.014$). No significant correlations emerged between BMI and other clinical or demographic parameters (all $p > 0.2$).

To better explain the impact of BMI values on clinical parameters, patients were divided according to BMI

Table 2. Demographic and clinical characteristics according to BMI group.

MS patients		Normal weight	Overweight	Obese	*p*
	N	83	33	24	
Age, years	Median (IQR)	33.3 (24.3–45.4)	40.3 (31.4–50.4)	42.1 (35.5–47.9)	0.017
Sex, F	*n* (%)	62 (75)	15 (46)	18 (75)	0.007
Disease duration, months	Median (IQR)	9.1 (1.6–35.4)	17.9 (3.2–49.1)	12.1 (1.5–40.5)	0.772
Number of previous clinical relapses	Median (IQR)	1 (1–2)	1 (1–2)	1 (1–2)	0.496
Clinical activity at LP	*n* (%)	29 (35)	7 (21)	6 (25)	0.373
Radiological activity at LP	*n* (%)	36 (43)	10 (30)	10 (42)	0.376
Patients assuming lipid-lowering medications	*n* (%)	1 (1)	2 (6)	2 (8)	0.2
Smokers	*n* (%)	32 (39)	17 (52)	12 (50)	0.856

BMI: body mass index; MS: multiple sclerosis; IQR: interquartile range; LP: lumbar puncture.

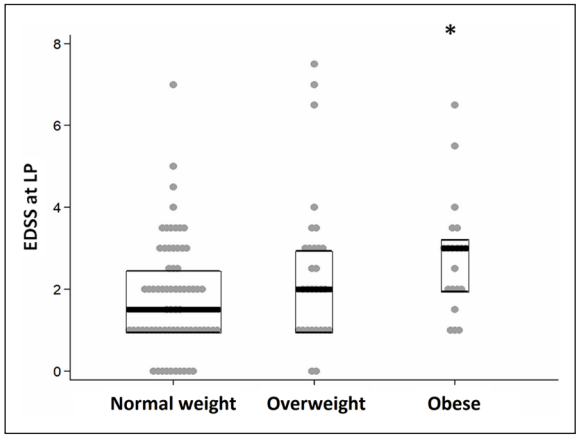

Figure 1. EDSS score according to BMI group.
*Mann–Whitney comparison: obese vs normal; B-H adjusted $p < 0.05$.

score into three groups: "normal" (BMI 18.5–24.9), "overweight" (BMI 25–29.9), and "obese" (BMI >30).[21] The BMI median was 24.1 (IQR = 21.8–28.6); the percentage of patients who belonged to the "normal" category was 58% ($n = 83$); "overweight," 24% ($n = 33$); and "obese," 18% ($n = 24$). The clinical and demographic characteristics of MS patients according to the BMI group are shown in Table 2. Results confirmed a significant association with EDSS (Kruskal–Wallis test $p = 0.013$); in particular, EDSS was significantly higher in the "obese" MS group (median = 3, IQR = 2–3.4) than in the "normal" group (median = 1.5, IQR = 1–2.75; B-H adjusted $p = 0.015$; Figure 1). Higher EDSS in obese MS patients was driven by increased likelihood of pyramidal system involvement in these patients (normal weight = 29%; overweight = 42%; obese = 54%; $p = 0.02$). No significant associations emerged between other functional systems and BMI (all $p > 0.2$).

Finally, although BMI showed some correlation with serum lipids (triglycerides: Spearman's rho = 0.299, $p < 0.001$, B-H adjusted $p = 0.001$; HDL-C: Spearman's rho = –0.231, $p = 0.007$, B-H adjusted $p = 0.014$; TC/HDL-C: Spearman's rho = 0.322, $p < 0.001$, B-H adjusted $p = 0.0008$), these correlations were not significant after controlling for all other clinical variables (age, sex, disease duration, smoking, and the presence of radiological activity; all $p > 0.05$).

A high BMI associates with increased proinflammatory leptin and IL-6 and reduced anti-inflammatory IL-13 in CSF

We first examined whether disease activity at the time of LP influences the CSF levels of the cytokines and adipocytokines analyzed. Radiological activity at the time of LP was associated with increased leptin CSF levels (Gd+ patients: median = 461 pg/mL, IQR = 284.75–682.48 pg/mL; median = 310.42, IQR = 192–532 pg/mL; $p = 0.030$). Conversely, no statistically significant differences emerged in all CSF molecules examined according to the presence of clinical disease activity at the time of LP (all $p > 0.2$).

To explore the impact of BMI on CSF cytokine levels, BMI groups were considered (Table 3). A significant association emerged between BMI group and leptin CSF levels (on logarithmic scale) adjusting for sex, age, disease duration, smoking, and the presence of radiological activity (ANCOVA main effect: $F(2, 132) = 9.69$; $p < 0.001$). Post hoc comparisons showed that the "obese" MS groups presented higher leptin CSF concentrations than normal-weight MS patients (B-H adjusted $p < 0.001$; Figure 2(a)). Figure 2(b) depicts the association between BMI and leptin in

Table 3. CSF molecules in the three BMI groups.

MS patients		Normal weight	Overweight	Obese	ANOVA *p*
	N	83	33	24	
Leptin	Median (IQR)	311 (187.4–465)	337.9 (206–495)	662 (434.5–812.5)	<0.001
IL-6	Median (IQR)	4 (0.92–7.48)	6.5 (2.94–21)	10 (6–22.95)	0.007
IL-13	Median (IQR)	1.46 (1.05 - 2.87)	1.04 (0.63–1.83)	1.14 (0.78–1.41)	0.004
Ghrelin	Median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.898
	Min–max	0–1340.55	0–569.09	0–1276	
GM-CSF	median (IQR)	17 (15–22)	17.5 (13.23–23)	24 (18.26–30)	0.124
OPG	Median (IQR)	61.7 (52–73.9)	62.2 (49–67.38)	57 (47.5–70.83)	0.53
Osteopontin	Median (IQR)	43,956 (23,463–62,456)	32,439 (6100–55,237.44)	36,389 (12,993.49–58,525.77)	0.143[a]
PAI-1	Median (IQR)	363 (288.09–483.84)	413 (299.90–549.69)	384 (235–452)	0.895
Resistin	Median (IQR)	0 (0–13.16)	0 (0–16.05)	10 (0–14.95)	0.448
ANXA1	Median (IQR)	0 (0–0)	0 (0–0)	0 (0–1)	0.461
	Min–max	0–12	0–5	0–6	

Data are presented as median (IQR = 25th–75th percentile). All analyses were performed on logarithmic transformation of data. CSF cytokine concentrations are expressed in picogram per milliliter; ANXA1 CSF concentration is expressed in nanogram per milliliter.
CSF: cerebrospinal fluid; BMI: body mass index; ANOVA: analysis of variance; MS: multiple sclerosis; IQR: interquartile range; IL: interleukin; GM-CSF: granulocyte macrophage colony-stimulating factor; OPG: osteoprotegerin, PAI-1: plasminogen activator inhibitor-1; ANXA1: Annexin A1.
[a]Nonparametric Kruskal–Wallis test

each patient in the three BMI groups. Moreover, the CSF levels of IL-6 (on logarithmic scale) were significantly different among the three BMI groups adjusting for sex, age, disease duration, smoking, and the presence of radiological activity (ANCOVA main effect: $F(2, 132) = 3.84$; $p = 0.024$). Post hoc comparisons showed that the "obese" MS groups presented higher IL-6 CSF concentrations than normal-weight MS patients (B-H adjusted $p = 0.029$; Figure 3(a)). Finally, the CSF levels of IL-13 (on logarithmic scale) were significantly different among the three BMI groups adjusting for sex, age, disease duration, smoking, and the presence of radiological activity (ANCOVA main effect: $F(2, 132) = 5.21$; $p = 0.007$). Post hoc comparisons showed that the "obese" MS groups presented lower IL-13 CSF concentrations than normal-weight MS patients (B-H adjusted $p = 0.021$; Figure 3(c)). The associations between IL-6 and BMI, and between IL-13 and BMI in each patient in the three BMI groups are shown in Figure 3(b) and (d).

Sensitivity analyses were performed excluding the outliers shown in Figures 2 and 3. The ANCOVA model adjusting for sex, age, disease duration, smoking, and the presence of radiological activity showed a significant difference between the BMI groups for leptin (ANCOVA main effect: $F(2,130) = 11.19$; $p = 0.001$), IL-13 (ANCOVA main effect: $F(2, 129) = 8.68$; $p < 0.001$), and IL-6 (ANCOVA main effect: $F(2, 130) = 3.47$; $p = 0.034$).

No statistically significant associations emerged between BMI groups and the other CSF molecules examined (Table 3).

Serum lipids show a direct correlation with increased IL-6 in CSF of MS patients

We explored the correlation between serum lipid profile parameters (triglycerides, TC, TC/HDL-C) and CSF cytokine composition. A significant positive correlation emerged between serum triglyceride levels and the CSF levels of IL-6 (Spearman's rho = 0.273, $p = 0.003$; B-H adjusted $p = 0.017$). Moreover, also the TC/HDL-C ratio was positively correlated with IL-6 CSF levels (Spearman's rho = 0.258, $p = 0.005$; B-H adjusted $p = 0.017$). After controlling for all other clinical variables (sex, age, disease duration, smoking, and the presence of radiological activity), these correlations remained significant ($p = 0.013$ and $p = 0.030$, respectively) (Figure 4). No significant correlations emerged between serum lipids and the other CSF molecules examined.

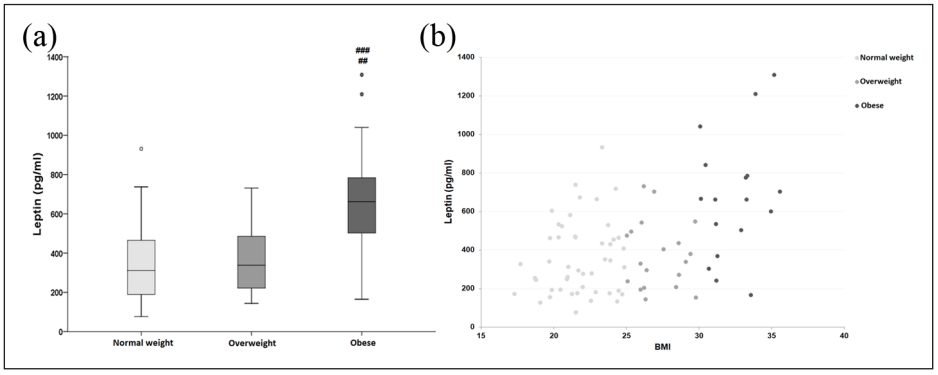

Figure 2. Leptin CSF concentration and BMI: (a) boxplot of leptin CSF median concentration according to BMI group. The circles represent outlier patients. ##Post-ANOVA comparison: obese vs overweight; B-H adjusted $p \leqslant 0.01$. ###Post-ANOVA comparison: obese vs normal; B-H adjusted $p < 0.001$. (b) Correlation between leptin CSF concentration and BMI.

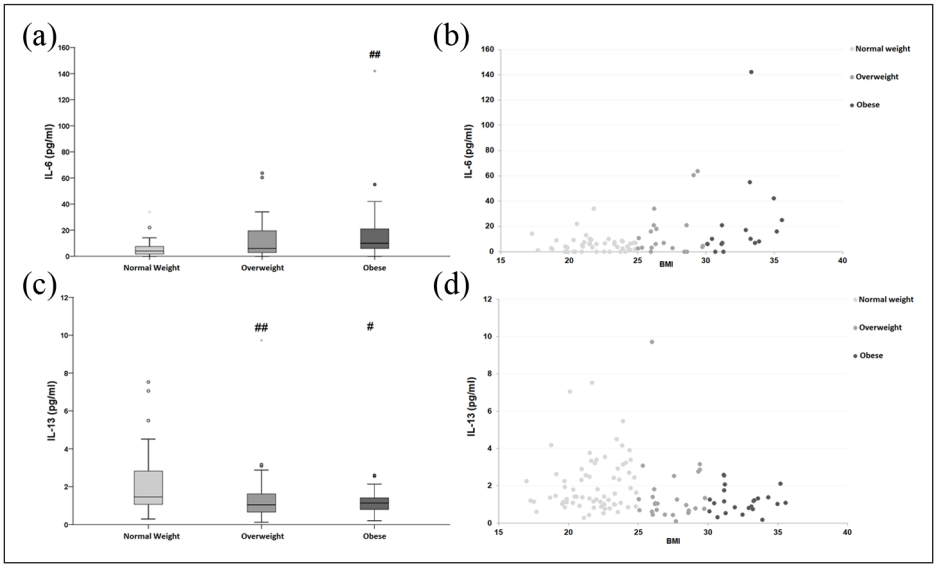

Figure 3. CSF levels of IL-6 and IL-13 and BMI: (a) boxplot of CSF concentration of IL-6 in the three BMI groups. (b) Correlation between IL-6 CSF concentration and BMI. (c) IL-13 CSF median concentration in the three BMI groups. (d) Correlation between IL-13 CSF concentration and BMI.
The circles represent outlier patients. The star marks the extreme values. #Post-ANOVA comparison: overweight vs normal; B-H adjusted $p < 0.05$. ##Post-ANOVA comparison: obese vs normal; B-H adjusted $p \leqslant 0.01$.

Discussion

Emerging evidence suggests that metabolism controls immune responses in different chronic autoinflammatory conditions. Indeed, adipocytes release a number of molecules with pleiotropic functions, able to influence the immune response.[1,2] Obesity represents a chronic low-grade inflammatory condition and is characterized by increased release of proinflammatory cytokines, including leptin, tumor necrosis factor (TNF), and IL-6, while anti-inflammatory molecules are downregulated.[22] A relationship between disrupted metabolic balance and increased neuroinflammation and neurodegeneration has been proposed in different neurological conditions.[1] Obesity has been associated with increased risk of mild cognitive impairment and Alzheimer's disease.[23] In MS, dyslipidemia and altered serum lipid profile (low HDL-C/high low-density lipoprotein) have been associated with increased disability progression[9] and enhanced disease activity.[24,25] High BMI during childhood and adolescence has been associated with increased risk of developing MS.[7,26] Moreover, although with some difference among studies, some correlations between BMI and measures of clinical progression have been previously reported in MS patients.[9–12,27]

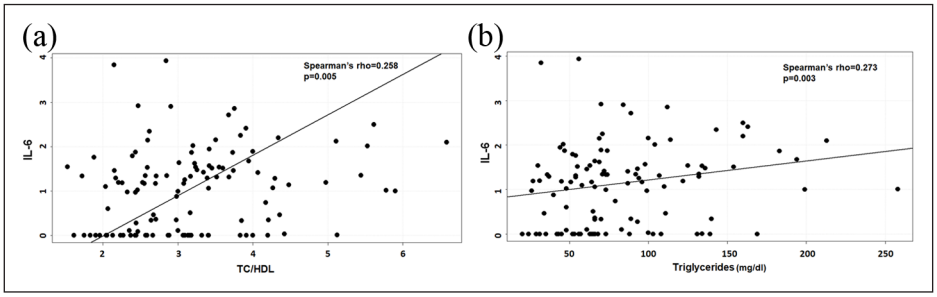

Figure 4. Serum lipids and IL-6: (a) correlation between IL-6 CSF levels (logarithmic scale) and serum triglycerides; (b) correlation between IL-6 CSF levels (logarithmic scale) and TC/HDL-C ratio. The relation between the two variables is depicted by a scatter plot and is described by the Passing–Bablok regression model.

In our study, we confirmed that obesity is associated with worse disability and demonstrated that this association is likely mediated by exacerbated central inflammatory reaction. In particular, in the CSF of obese MS patients, we found higher levels of the proinflammatory molecules IL-6 and leptin and reduced levels of the anti-inflammatory cytokine IL-13. In addition, altered serum lipid profiles were associated with enhanced CSF inflammation, as both increased serum triglyceride levels, and TC/HDL-C ratio positively correlated with the CSF levels of IL-6.

IL-6 is a major proinflammatory cytokine released by a number of immune cells and is involved in the pathogenesis of different neurological diseases.[28] It has been previously reported that IL-6 concentrations are elevated in the CSF of MS patients and may negatively impact the disease course.[14,28,29] It has been shown that monocytes from RR-MS patients produce more IL-6 compared to normal subjects,[30] and elevated IL-6 expression and glial cell activation have been described in ongoing human demyelinating lesions.[31]

Enhanced CSF levels of proinflammatory molecules could promote disease reactivations and neurodegeneration in MS and may represent the pathophysiological mechanism underlying the worse disease course observed in obese MS patients. In addition, we found reduced expression of the anti-inflammatory molecule IL-13 in the "obese" MS group. It has been previously shown that IL-13 may exert neuroprotective effects in MS, reducing glutamate-mediated excitotoxicity.[16] These results suggest that increased neuronal damage and reduced neuroprotection may exacerbate disease severity in obese MS patients. A recent study evidenced that in MS higher BMI was associated with increased measures of gray matter atrophy,[32] and some correlation has been evidenced between obesity and the risk of developing secondary progressive MS phenotype.[33]

In our MS cohort, increased levels of leptin have been detected in the CSF of obese MS patients, suggesting that this molecule may represent the link between altered lipid metabolism and central inflammation in MS. Leptin is released by the adipose tissue according to the body fat mass and mediates a wide range of physiological functions.[34] Preclinical studies evidenced that in the CNS leptin interacts with specific hypothalamic and brainstem neurons,[35] regulating food intake, autonomic nervous system function, and the hypothalamic–pituitary–adrenal axis.[34] Importantly, in animal models it has been extensively demonstrated that leptin modulates both the innate and adaptive immune responses,[36] regulating the production of proinflammatory cytokines, including TNF and IL-6, by different immune cells.[37] Our findings are in line with previous data showing that leptin is critically involved in the pathogenesis of EAE and MS. Accordingly, leptin neutralization in EAE mice reduced disease manifestations.[38] Leptin-deficient mice are resistant to the induction of EAE showing reduced CNS inflammation, and leptin replacement is able to restore EAE susceptibility.[5,39] Notably, leptin concentrations are increased in the CSF of treatment-naïve RR-MS patients and are associated with increased central inflammation.[6] In our study, increased CSF leptin concentrations in patients with radiological disease activity are in line with previous findings. In particular, elevated serum leptin levels have been reported in MS patients treated with IFN-β before disease reactivations,[40] and increased leptin has been detected in active MS lesions.[41] It has been reported that higher blood levels of both leptin and IL-6 could be associated with enhanced prospective disease activity.[42] The positive correlation that emerged between BMI score and clinical disability at the time of diagnosis suggests that obesity and the ensuing enhanced central inflammation could negatively influence the disease characteristics already in the early phases of MS. This

finding is in line with previous studies showing that higher BMI and adverse lipid profile are associated with increased disability in MS patients.[9] In addition, caloric restriction in EAE was associated with increased survival, reduced IL-6 levels, and increased neuroprotection through reduced leptin concentrations.[5,43] Limitations of this study include the lack of prospective measures of clinical disability and neuronal damage. Moreover, this was a single-center cross-sectional study, and further confirmation is required.

The relationship between altered lipid metabolism and inflammation highlights the key role of adipocytokines in the cross talk between metabolism, immunity, and neurodegeneration.[44] Overall, these findings could provide new therapeutic opportunities aimed at limiting the negative impact of altered lipid metabolism on inflammatory response in MS, representing useful adjunctive strategies to modify the course of this potentially devastating disease.

Declaration of Conflicting Interests

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