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Ricard Navinés, Giovanni Oriolo, Igor Horrillo, Myriam Cavero, Bruno Aouizerate, Martin Schaefer, Lucile Capuron, J. Javier Meana, Rocio Martin-Santos

Department of Psychiatry and Psychology, Hospital Clinic, Instituto de Investigaciones Biomédicas August Pi i Sunyer (IDIBAPS), Barcelona; Centro de Investigación Biomédica en Red en Salud Mental (CIBERSAM), Barcelona, Spain (Drs Navinés, Oriolo, Cavero, and Martin-Santos); Hospital de día Córcega, Centre Psicoterapèutic Barcelona (CPB); and Department of Experimental and Health Sciences, Psychiatry Unit, Universitat Pompeu Fabra, Barcelona, Spain (Dr Oriolo); Department of Pharmacology, University of the Basque Country UPV/EHU, Leioa, Bizkaia, Spain; CIBERSAM, Leioa, Spain; Biocruces Bizkaia Health Research Institute, Barakaldo, Bizkaia, Spain (Drs Horrillo and Meana); University of Bordeaux, INRAE, Bordeaux INP, NutriNeuro, UMR 1286, Bordeaux, France (Drs Aouizerate and Capuron); CH Charles Perrens, Pole de Psychiatrie Générale et Universitaire, Centre de référence régional des pathologies anxieuses et de la dépression, Bordeaux, France (Dr Aouizerate); Department of Psychiatry and Psychotherapy, Charité-Universitâtsmedizin Berlin, Campus Charité Mitte, Berlin, Germany (Dr Schaefer); Department of Psychiatry, Psychotherapy, Psychosomatics and Addiction Medicine, Evang. Kliniken Es-sen-Mitte, Essen, Germany (Dr Schaefer); Department of Medicine, Functional Psychiatric Unit, Institute of Neuroscience, University of Barcelona, Barcelona, Spain (Dr Martin-Santos).

Correspondence: Rocio Martin-Santos, MD, PhD, Senior Consultant, Department of Psychiatry and Psychology, Hospital Clinic, IDIBAPS, CIBERSAM; and Department of Medicine, Institute of Neuroscience, University of Barcelona, 08036-Barcelona, Spain (rmsantos@clinic.cat).

Abstract

Background: The relationship between antidepressant response and glial, inflammatory, and metabolic markers is poorly understood in depression. This study assessed the ability of biological markers to predict antidepressant response in major depressive disorder (MDD).

Methods: We included 31 MDD outpatients treated with escitalopram or sertraline for 8 consecutive weeks. The Montgomery-Åsberg Depression Rating Scale (MADRS) was administered at baseline and at week 4 and 8 of treatment. Concomitantly, blood samples were collected for the determination of serum S100B, C-reactive protein (CRP), and high-density lipoprotein cholesterol (HDL)-C levels. Treatment response was defined as ≥50% improvement in the MADRS score from baseline to either week 4 or 8. Variables associated with treatment response were included in a linear regression model as predictors of treatment response.

Results: Twenty-seven patients (87%) completed 8 weeks of treatment; 74% and 63% were responders at week 4 and 8, respectively. High S100B and low HDL-C levels at baseline were associated with better treatment response at both time points. Low CRP levels were correlated with better response at week 4. Multivariate analysis showed that high baseline S100B levels

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Significance Statement

The glial-derived neurotrophic marker S100B is a calcium-binding protein involved in numerous regulatory and immune pathways. The aim of the present study was to study the association of the S100B protein levels with antidepressant treatment response considering inflammatory (C-reactive protein) and metabolic markers (high-density lipoprotein cholesterol [HDL-C]).

We included 31 outpatients with a major depressive disorder treated with antidepressants (escitalopram or sertraline) for 8 weeks. Treatment response was defined as ≥50% improvement in the Montgomery-Åsberg Depression Rating Scale score from baseline to either week 4 or 8. High-S100B levels and low HDL-C levels at baseline were good predictors of treatment response at 4 weeks, although this was only true for S100B at week 8. Serum S100B levels appear to be a useful biomarker of antidepressant response in major depression disorder even when considering inflammatory and metabolic markers.

and low baseline HDL-C levels were good predictors of treatment response at week 4 ($R^{2=}$0.457, P = .001), while S100B was at week 8 (R^2 = 0.239, P = .011). Importantly, baseline S100B and HDL-C levels were not associated with depression severity and did not change over time with clinical improvement.

Conclusions: Serum S100B levels appear to be a useful biomarker of antidepressant response in MDD even when considering inflammatory and metabolic markers.

Keywords: S100B protein, reactive-C protein, HDL-cholesterol, major depression, antidepressant

Introduction

Psychoimmunology has sought to elucidate how inflammatory and metabolic abnormalities are related to major depressive disorder (MDD) and treatment response (Ioannou et al., 2020). A recent approach to study the interplay between the immune system, brain function, and novel therapeutical strategies is focused on the regulatory action exerted by the immune system on neurotrophic factors, neural plasticity, and neurodegeneration (Shi et al., 2020; Branchi et al., 2021). In this sense, glial activation has come to the fore with the finding that glial-derived S100B seems to be involved both in depression and antidepressant response (Ponath et al., 2007; Bargerstock et al., 2014).

Glial-derived S100B is a calcium-binding protein linked to numerous regulatory and immune pathways. Produced and secreted by both intracerebral (e.g., astrocytes) and extracerebral (e.g., adipocytes) sources (Bargerstock et al., 2014), S100B has paracrine and autocrine effects on neurons and glia (Ponath et al., 2007). At low concentrations, S100B provides beneficial neurotrophic effects, limits stress-related neuronal injury, inhibits microglial tumor necrosis factor α (TNF-α) release, and increases astroglial glutamate reuptake (Steiner et al., 2011; Najjar et al., 2013). Thus, it contributes to neurite outgrowth, enhancing neuron survival and supporting serotonergic neuron development (Huttunen et al., 2000; Najjar et al., 2013). By contrast, higher extracellular S100B concentrations have harmful effects mediated by the receptor for advanced glycation end products. These effects include neuronal apoptosis, increased production of the pro-inflammatory prostaglandins such as cyclooxygenase-2-mediated prostaglandin E2, interleukin (IL)-1β, inducible nitric oxide species, and the upregulation of monocytic/microglial TNF-α secretion (Steiner et al., 2011, 2012; Najjar et al., 2013). Additionally, due to their predominantly glial origin, elevated serum S100B levels may also indicate reduced integrity of the brain blood barrier and less neural protection from peripheral inflammation or circulating toxins (Thelin et al., 2013; Koh and Lee, 2014; Wu et al., 2021).

Increased levels of S100B in the cerebrospinal fluid (CSF) and serum have been associated with various neuropathological conditions, such as acute brain injury, neurodegenerative disorders, and psychiatric disorders (Michetti et al., 2012, 2019). In mood disorders, S100B has been shown to be elevated in acute affective episodes, that is, major depressive episode in MDD or both manic and depressive episodes in bipolar disorders (Kroksmark and Vinberg, 2018). Nonetheless, there are several inconclusive reports whether S100B levels are elevated in MDD over time (Jang et al., 2008) or decline with successful antidepressant treatments (Schroeter et al., 2008). Another aspect of great interest is the potentiality of S100B in modulating the course of MDD and predicting antidepressant response. In patients with MDD who were followed naturalistically in a standard hospital setting, elevated S100B levels have been reported at the beginning of antidepressant treatment and correlate positively with subsequent treatment response (Arolt et al., 2003; Jang et al., 2008). Moreover, in a randomized double-blind trial, elevated S100B levels were shown to be related to a better antidepressant response in melancholic features of MDD (Ambrée et al., 2016).

Regarding the relationship between inflammation, immunity, and depression, elevated serum levels of inflammatory cytokines, including C-reactive protein (CRP), IL-6, IL-1β, and TNF-α, have been reported in patients with MDD (Capuron et al., 2017a; Poole and Steptoe, 2020). Consistent with this observation, low levels of CRP and pro-inflammatory cytokines have been associated with greater response to selective serotonin reuptake inhibitors (SSRIs) (Jha et al., 2018). However, not all patients with increased inflammatory marker levels develop MDD (Lotrich, 2015), nor do all patients with MDD have immune activation (Osimo et al., 2019). Inflammation could be considered a trigger for the further development of MDD when it interacts with other risk factors. In this sense, it seems that metabolic factors may play a crucial role in this relationship. Indeed, today it is clearly established that obesity, as defined by a body mass index (BMI) >30, and related abnormal eating habits activate inflammatory processes, thereby precipitating the occurrence of MDD (Capuron et al, 2017b; Delgado et al., 2018; Oriolo et al., 2019). Adipocytes secrete hormones that regulate energy homeostasis (e.g., leptin, ghrelin, adiponectin) and also produce pro-inflammatory cytokines. Interestingly, it has been shown that HDL-cholesterol (HDL-C) levels are typically low in inflammatory states (Feingold and Grunfeld, 2016), which is important when implicating inflammatory processes in MDD (Melin et al., 2019). Cholesterol is a key synapse-promoting signal released to neurons by the

astroglia (Mauch et al., 2001; Stenovec et al., 2020). It has been suggested that loss in glial cell numbers in patients with MDD (Rajkowska and Stockmeier, 2013; Sanacora and Banasr, 2013) is related to cholesterol imbalance (Stenovec et al., 2020). Not only has MDD been linked to lower levels of HDL-C (Lehto et al., 2008a; Penninx et al., 2013), but also low levels of HDL-C have been observed in people after attempting suicide (Zhang et al., 2005). Reciprocally, high psychological well-being also predicted high HDL-C levels in a longitudinal study (Radler et al., 2018).

To our knowledge, there is no study assessing the relationship of MDD with glial activation and injury, blood–brain barrier disruption, inflammation, and metabolic markers simultaneously in a prospective design. Moreover, the question of the predictive value of baseline serum S100B levels, together with inflammatory and metabolic markers, on antidepressant treatment response remains to be elucidated. Based on previous findings, we hypothesized that patients with high baseline S100B levels would respond better to antidepressant treatment. Since some studies have also reported an association between inflammatory markers (e.g., CRP) and metabolic markers (e.g., HDL-C) with treatment response, the influence of S100B levels was controlled for this association (Ioannou et al., 2020).

METHODS

Study Participants

We studied 31 adult patients fulfilling the DSM-IV-R criteria for current MDD. They were consecutively recruited at the outpatient unit of the Department of Psychiatry and Psychology, Hospital Clinic, University of Barcelona.

To be included in the study, patients could not be older than 70 years or currently suffer from bipolar disorder, schizophrenia, anxiety disorders (except for social anxiety and generalized anxiety disorders), alcohol or drug abuse/dependence (except for nicotine), and severe suicidal ideation. Patients were also excluded if they met any of the following criteria: had an acute or chronic inflammatory condition or a serious medical condition requiring steroids or non-steroidal anti-inflammatory drugs, immunosuppressive drugs, or chronic thyroid hormone replacement; received an antidepressant less than 3 days before starting the study (8 days for fluoxetine or 2 weeks for a non-selective and irreversible monoamine oxidase inhibitor); were previously treated unsuccessfully with venlafaxine; and were pregnant or breastfeeding women.

The ethics committee of our institution approved the study. The protocol was conducted in accordance with the ethical standards laid down in the Declaration of Helsinki (1964), as amended in Edinburgh (2000). All patients gave written informed consent after the study procedures had been explained in detail.

Sociodemographic and Clinical Assessments

At baseline, we gathered details about sociodemographic and clinical variables from all participants, including their medical and psychiatric histories, current pathologies and treatments, tobacco consumption, heart rate, blood pressure, body weight, and BMI (kg/m^2). At baseline, all patients underwent routine physical examination and laboratory screening (serum electrolytes; CRP; lipid profile; renal, liver, and thyroid function; standard ECG) and were evaluated by a trained psychiatrist. The MINI International Neuropsychiatric Interview (Sheehan et al., 1998) was used to explore current and past MDD and associated psychopathology. The Global Assessment of Functioning (GAF) scale (Endicott et al., 1976) was used to assess how well an individual was functioning in their daily lives (scored 0–100, with higher scores representing superior functioning). Depressive symptomatology was assessed using the Spanish validated version (Lobo et al., 2002) of the 10-item (apparent sadness, reported sadness inner depression, reduced sleep, reduced appetite, concentrations difficulties, lassitude, inability to feel, pessimistic and suicidal thoughts), clinician-administered, Montgomery and Åsberg Depression Rating Scale (MADRS) (Montgomery and Åsberg, 1979). This 10-item rating scale consists of items with a Likert scale ranging from 0 to 6. A total score between 34 and 60 indicates severe depression, 20–24 moderate depression, and 7–19 mild depression. MADRS and GAF scales were also administered after 4 and 8 weeks of treatment.

Antidepressant Treatment

After full evaluation and confirmation of the current diagnosis of MDD, one of the following standard antidepressant treatments was initiated: escitalopram 10 mg/d, increased up to 20 mg/d at week 4 depending on clinical efficacy and tolerance; sertraline 50 mg/d, increased up to 100 mg/d at the end of week 4, based on clinical efficacy and tolerance. The clinical status of depressed patients was evaluated every 4 weeks. Antidepressant response was considered if patients achieved a ≥50% reduction in their MADRS scores at weeks 4 or 8. If antidepressant response was achieved at week 4, medication was not increased.

S100B, CRP, and HDL-C Analysis

Sampling for serum S100B, CRP, and HDL-C levels took place at 8:00 AM. Blood samples were immediately centrifuged to remove plasma, which was stored at –80°C until all samples had been collected. These were transported on dry ice to the University of the Basque Country. S100B levels were measured using a specific sandwich enzyme-linked immunosorbent assay kit (ELISA Kit for S100 Calcium Binding Protein B, product n° SEA567Hu) according to the manufacturer's instructions (Cloud-Clone Corp, Wuhan, China). The concentration gradients of the kit standards or positive controls have a detection range from 0.156 to 10 ng/mL, with an estimated sensitivity of 0.056 ng/mL. The inter- and intra-assay coefficients of variation (CV) were <12% and 10%, respectively. CRP levels were analyzed using Atellica CH C-Reactive Protein_2 (CRP_2) (Siemens Healthcare Diagnostics, Erlanguen, Germany). It measures CRP by an inmunoturbidimetric assay potenciated with latex. It provides results in a range of values between 0.4 and 30.4 mg/dL. The reference interval of CRP for healthy adults was established at <1.0 mg/dL. Precision was calculated as intra- and inter-assay CV, where CV (%) = SD/mean × 100 (intra-assay: CV < 8%; inter-assay: CV < 9%). HDL cholesterol levels were analyzed using Atellica CH Direct HDL Cholesterol assay (Siemens Healthcare Diagnostics) based on the procedures developed by Izawa et al. (1997). It provides results in a range of values between 20 and 129 mg/dL. The reference intervals are <40.0 mg/dL for low HDL (high risk) and ≥60.0 mg/dL for high HDL (low risk). Precision was calculated as intra- and inter-assay CV with intra-assay CV < 8% and inter-assay CV < 8%).

Statistical Analysis

Histograms and the Shapiro–Wilk test were used to check the normality of continuous variables. S100B protein, CRP, HDL-C, MADRS, and GAF deviated from normal distribution (Shapiro–Wilks, >0.05). In the bivariate analysis, chi-square tests were used for qualitative analysis of 2 independent variables, with Student

t tests or Mann–Whitney *U* tests used when variables deviated from the normal distribution. Spearman's correlation was calculated to assess the association between 2 continuous variables, using the following cut-offs: 0 (absence), 0.1–0.3 (weak), 0.4–0.6 (moderate), 0.7–0.9 (strong), and 1 (perfect). To compare S100B, CRP, and HDL-C levels with the MADRS and GAF scores at the 3 time-points, we used the repeated-measures non-parametric Friedman test for non-normally distributed related samples.

Finally, linear regression analysis was done with the antidepressant response (≥50% reduction in the MADRS score) from baseline to week 4 and 8 as the dependent variable. Those variables significantly correlated with treatment response at any time in the bivariate analysis were included in the multivariant linear regression model. The results are expressed as adjusted R^2, F(df). Effects were considered significant when $P<.05$. All analyses were calculated using IBM SPSS Version 22 (IBM Corp., Armonk, NY, USA).

Sensitivity, specificity, positive and negative predictive values, and rates of false positive and negative were calculated for S100B levels as marker of treatment response using the median concentrations at baseline as cut-off value.

RESULTS

Characteristics of Cohort Participants

Table 1 summarizes the basal demographic and clinical variables of the 31 participating outpatients (58% female). Their mean age was 37.4±8.9 years. Nine (29%) met the diagnosis of recurrent MDD. All were candidates to receive standard antidepressant treatment.

Baseline Relationship Between Clinical and Biological Data

Analysis of baseline depression severity (MADRS) with baseline S100B ($r=-0.249$, $P=.177$), CRP ($r=-0.113$, $P=.545$), or HDL-C ($r=1.137$, $P=.461$) revealed no significant correlation between these variables. The only significant correlation between GAF scores and biological data was a moderate inverse association with CRP levels ($r=-0.487$, $P=.006$). Finally, we analyzed the association within biological markers showing a significant moderate inverse association between S100B and HDL-C levels at baseline ($r=-0.362$, $P=.046$). Table 2 shows baseline clinical and biological data.

Longitudinal Clinical and Biological Data of the Treated Sample

Table 2 shows the longitudinal clinical and biological data for the remaining 27 patients with MDD who received antidepressants and were followed over the next consecutive 8 weeks of treatment (i.e., baseline, weeks 4 and 8). Clinical variables (MADRS, GAF scores) showed a statistically significant clinical improvement (Friedman test) in response to the antidepressant treatment (weeks 4 and 8, $P<.001$). In addition, S100B, CRP, and HDL-C levels did not change over time with clinical improvement, as

Table 1. Sample Characteristics at Baseline (n=31)

Variables	N (%)/×(SD)	Range
Age	37.4 (8.9)	(20–59)
Gender		
Female	17 (54.8)	
Male	14 (45.2)	
Job status		
Student	1 (3.2)	
Employed	17 (54.8)	
Student and employed	4 (12.9)	
Employed but sick leave	4 (12.9)	
Unemployed	4 (12.9)	
Pensioner	1 (3.2)	
Marital status		
Unmarried	17 (54.8)	
Married/engaged	8 (25.8)	
Separate/divorced	4 (12.9)	
Widowed	2 (6.4)	
Ethnicity		
Caucasian	25 (80.6)	
Arab	1 (3.2)	
Hispanic American	5 (16.1)	
Weight (kg)	71.0 (13.0)	(47–98)
Height (cm)	171.0 (8.08)	(157–186)
Abdominal circumference (cm)	87.4 (10.5)	(71–111)
BMI	24.2 (3.9)	(18.4–33.4)
Psychiatric history		
Major depressive episode	4 (12.9)	
Depression, no specified	1 (3.2)	
General anxiety disorder	3 (9.7)	
Adjustment disorder with anxiety/depressive symptoms	3 (9.7)	
Any mental disorder	11 (35.5)	
Tobacco consumption	16 (51.6)	
Medical comorbidities (hypertension, dyslipidemia)	4 (13.0)	

Abbreviation: BMI, body mass index.

Table 2. Longitudinal Clinical and Biological Data of the Treated Cohort (n = 27)

	Baseline N (%)/×(SD)	4 wk N (%)/×(SD)	8 wk N (%)/×(SD)	Q[a]	*P*
Clinical variables					
MADRS total score	25.3 (3.5)	11.3 (4.1)	8.9 (6.1)	44.5	<.001
GAF total score	66.1 (1.5)	78.6 (1.8)	84.3 (2.3)	44.0	<.001
Biological variables					
S100B (ng/mL)	0.36 (0.44)	0.33 (0.74)	0.30 (0.47)	.651	.722
CRP (mg/dL)	0.27 (0.22)	0.36 (0.33)	0.41 (0.34)	2.46	.290
HDL cholesterol (mg/dL)	59.8 (17.6)	61.2 (21.1)	57.4 (14.4)	.081	.960
LDL cholesterol (mg/dL)	119.2(32.3)	112.9 (32.7)	116.8 (30.7)	1.43	.489
Triglycerides (mg/dL)	99.9 (57.3)	95.2 (54.5)	104.8 (84.1)	3.43	.180
Glycemia (mg/dL)	78.9 (9.3)	84.2 (21.9)	85.2 (24.7)	2.9	.236
Leukocytes (10^9/L)	6.2 (1.40)	5.69 (1.24)	6.48 (2.01)	9.12	.111

Abbreviations: CRP, C-reactive protein; GAF, General Assessment Functioning of DSM-IV-R; MADRS, Montgomery-Åsberg Depression Rating Scale; S100B, S100 calcium-binding protein B.
[a]Friedman non-parametric test for repeated measures.

indicated by the lack of a significant difference between S100B, CRP, and HDL-C levels from baseline ($P > .05$).

Treatment Response

Twenty-six participants (83.9%) were treated with escitalopram and 5 (16.1%) with sertraline. Four participants expressed personal reasons to withdraw from the study. The final sample at week 8 was 27 patients (87%). Escitalopram and sertraline were generally well-tolerated. Only 2 patients of those receiving escitalopram experienced dizziness within the first few days of therapy. Overall adherence was >80% at both assessment points: (1) at week 4, four patients had missed medication for 1 day, and 1 patient had missed it for 3 days; and, (2) at week 8, five patients had missed their medication for 1 day. At week 4 or 8, 25 (74%) and 21 (63%) patients had responded adequately to antidepressant treatment, respectively.

Differences in Baseline Clinical and Biological Variables Among Responders and Non-responders

The sample was stratified into responders and non-responders based on ≥50% reduction in MADRS scores. Twenty-five (74%) and 21 (63%) patients were responders at week 4 and 8, respectively.

Bivariate analysis showed no statistically significant gender difference in treatment response at either week 4 or week 8 ($x^2 = 0.306, P = .580$; $x^2 = 0.422, P = .516$), psychiatric history ($x^2 = 0.290$, $P = .590$); $x^2 = 0.337$, $P = .561$), tobacco use ($x^2 = 0.306$, $P = .580$; $x^2 = 0.022$, $P = .883$), medical comorbidities ($x^2 = 0.652$, $P = .419$; $x^2 = 3.672$, $P = .055$), or on SSRI treatment used ($x^{2=}0.633$, $P = .426$; $x^{2=}1.388$, $P = .239$). Moreover, no correlation was found at any assessment point between age and treatment response (week 4: $r = -0.177$, $P = .342$; week 8: $r = -0.162$, $P = .421$) or between baseline BMI and treatment response (week 4: $r = 0.014$, $P = .940$; week 8: $r = -0.006$, $P = .978$).

Figure 1 presents the significant correlations between baseline biological markers S100B, CRP, HDL-C, and treatment response (50% reduction in MDRS) at week 4 or week 8, respectively. This analysis revealed a significant association with a moderate effect size between baseline S100B levels and treatment response at week 4 ($r = 0.451$, $P = .011$) and week 8 ($r = 0.440$, $P = .022$). In addition, there was a significant inverse association of moderate effect size between baseline HDL-C levels and treatment response at week 4 ($r = -0.450$, $P = .013$) and week 8 ($r = -0.401$, $P = .042$). Although there was also an inverse significant association with a moderate effect size between baseline CRP levels and treatment response, this was observed only at week 4 ($r = -0.402$, $P = .025$).

Finally, to define groups with high and low baseline S100B levels, the median level dichotomized this variable. Patients with high baseline S100B levels (≥0.058 ng/mL) had a significantly larger improvement in MADRS scores than those with low S100B levels (<0.058 ng/mL) at both week 4 ($z = -2{,}329$, $P = .020$) and week 8 ($z = -2{,}761$, $P = .006$) (see Figure 2).

Multivariate Linear Regression Models of Treatment Response

Table 3 shows multivariate linear regression models and simple regression models of treatment response. Multivariate linear regression models showed that basal S100B (high/low) and HDL-C predicted 45.7% of the variation in treatment response at week 4 (adjusted $R^2 = 0.457$, $P = .001$). Baseline S100B levels alone accounted for a 23.9% of the variation at week 8 (adjusted $R^2 = 0.239$, $P = .011$), but baseline CRP levels were not entered in the final models.

Simple linear regression analysis showed that S100B as the only predictor had a modest predictive value of 29.1% at week 4 (adjusted $R^2 = 0.291$, $P = .004$) and that HDL-C alone was similar at 31.7% (adjusted $R^2 = 0.317$, $P = .003$). At week 8, simple linear regression with S100B alone predicted 25.9% of the variation in treatment response (adjusted $R^2 = 0.259$, $P = .007$) and that HDL-C predicted 16.1% (adjusted $R^2 = 0.171$, $P = .143$).

The analysis of the statistical quality of serum S100B as treatment predictor (Table 4) revealed moderate sensitivity (75%), good specificity (86%), positive predictive value (93.75%), and a false negative rate of 14.28%. On the other hand, at 8 weeks of treatment, the results of the analysis showed moderate sensitivity (76.5%) and specificity (70%), a positive predictive value of 81.3%, and a false positive value of 23.53%.

Discussion

In this study, we found that high S100B levels predicted antidepressant response in patients with MDD, even when considering inflammatory (CRP) and metabolic markers (HDL-C). Of note, high S100B levels (compared with a low level) and low HDL-C levels at baseline were good predictors of treatment response at week 4, although this was only true for S100B at week 8. Interestingly, S100B, CRP, and HDL-C levels were not associated with depression severity and did not change with clinical

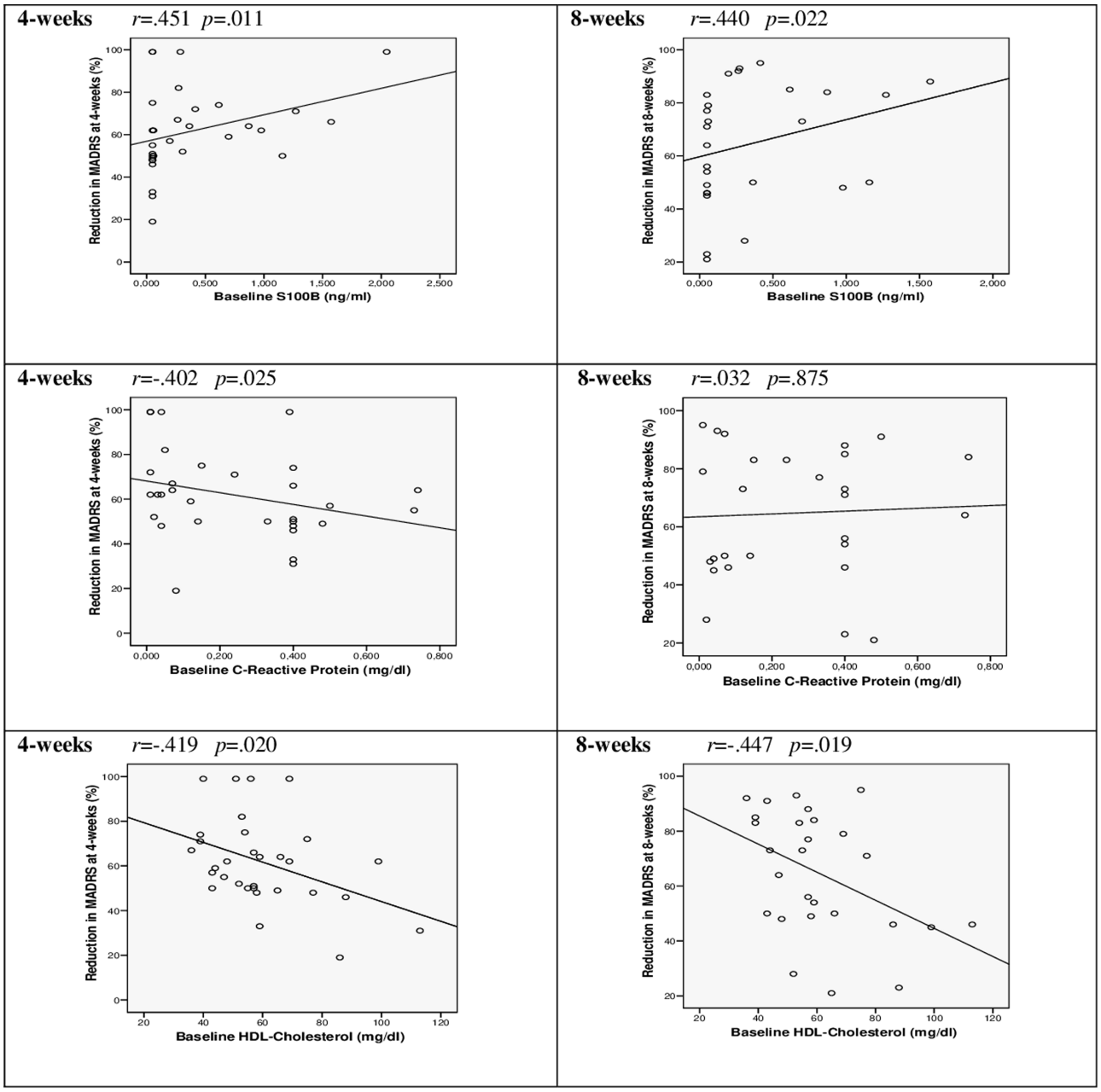

Figure 1. Correlation between baseline key variables and treatment response.

improvement. The results suggest that S100B protein could be a candidate as a potential biomarker of antidepressant responsiveness, which remains stable regardless of clinical changes in depressive mood.

The study of biological markers of antidepressant response still represents an unmet need that would help to predict the response and allow us to better personalize the treatments of depression in the future (Ambrée et al., 2016; Shi et al., 2020). A topic of great clinical relevance is whether levels of the glial protein S100B before starting an antidepressant treatment are associated with clinical outcome. Supporting our results, previous studies have reported that high baseline S100B levels predict treatment response. Using different patient groups (i.e., melancholic/non-melancholic MDD), type of antidepressant treatments (serotoninergic, noradrenergic, dopaminergic) and assessment instruments (i.e., Hamilton Depression rating Scale), and endpoints (from 4 weeks to 6 months), 3 of 4 studies plead for a predictive effect of baseline S100B for antidepressant response (Arolt et al., 2003; Jang et al., 2008; Ambrée et al., 2016; Jha et al., 2019). A recent meta-analysis of the 3 first studies that included 51 responders and 73 non-responders found that S100B levels at baseline were significantly elevated in responders (Shi et al., 2020). These findings were similar in patients treated with electroconvulsive therapy, where higher baseline S100B levels were associated with better clinical outcome at both 5 and 30 posttreatment days (Arts et al., 2006) and long-term remission time (Carlier et al., 2010; Maier et al., 2018), although no relationship with treatment response was reported (Kranaster et al., 2014). Our findings reinforce these previous data and might suggest that patients with high baseline S100B have an increase in this neurotrophic factor, which may promote the antidepressant response (Ambrée et al.,

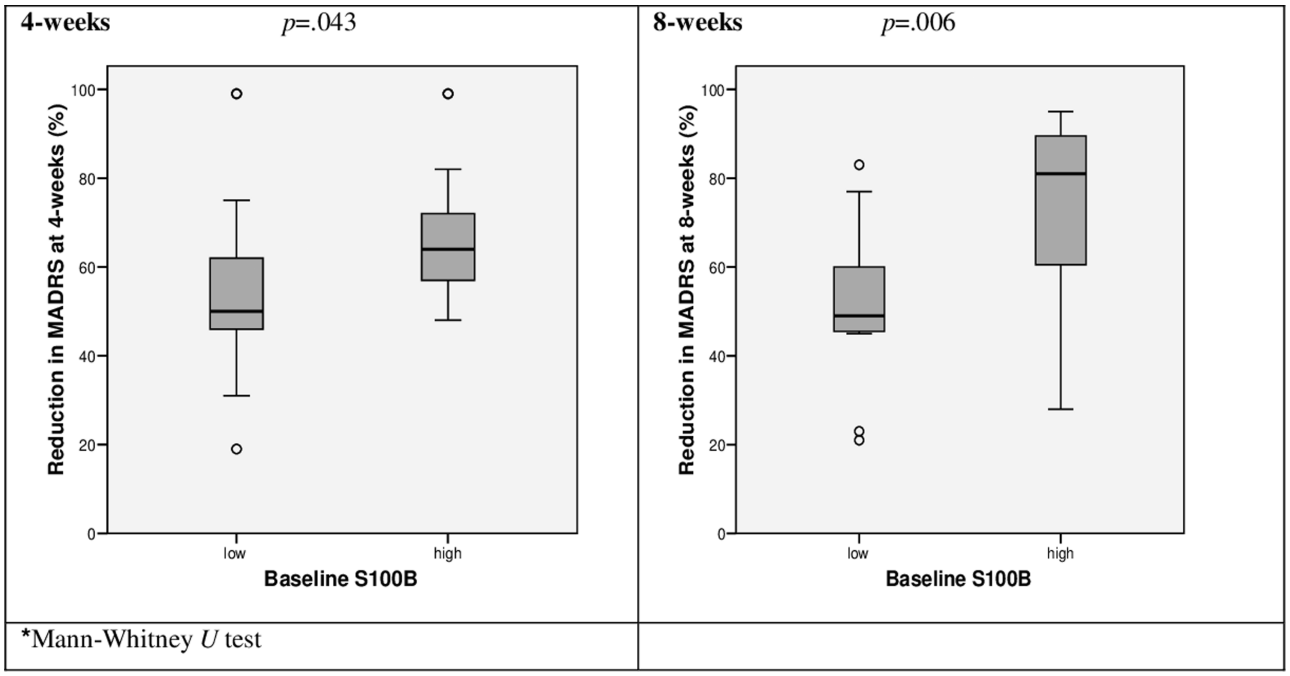

Figure 2. Comparison of high and low baseline S100B levels with treatment response. *Mann–Whitney *U* test

Table 3. Linear Regression Models for Percentage Reduction in MADRS Score at 4 and 8 Weeks

	Treatment response at 4 wk			Treatment response at 8 wk		
Multiple linear regression models	*B*	*SE*	*P*[a]	*B*	*SE*	*P*[b]
Baseline S100B (high/low)	12.017	4.940	.023	22.038	8.031	.011
Baseline HDL-C	−0.320	0.139	.031			
Adjusted R^2	0.457			0.239		
F (df)	9.664 (2, 27)		.001	7.530 (1, 24)		.011
Simple linear regression models	*B*	*SE*	*P*	*B*	*SE*	*P*
Baseline S100B (high/low)	15.318	4.783	.004	22.665	7.633	.007
Adjusted R^2	0.291			0.259		
F (df)	10.258 (1, 25)		.004	8.748 (1, 25)		.007
Baseline HDL-C	−0.463	0.139	.003	−0.511	0.238	.042
Adjusted R^2	0.317			0.161		
F (df)	11.130 (1, 24)		.003	4.609 (1, 24)		.042

Abbreviations: CRP, C-reactive protein; df, degrees of freedom; HDL-C, high-density lipoprotein cholesterol; MADRS, Montgomery-Åsberg Depression Rating Scale; S100B, S100 calcium-binding protein B; SE, standard error.
[a]Excluded variables from the model at 4 weeks: baseline CRP level.
[b]Excluded variables from the model at 8 weeks: baseline CRP level and baseline HDL-C levels.

2016). Regarding inflammatory markers and their association with the antidepressant response, we found an inverse significant correlation between basal CRP levels and treatment response at week 4 but not at week 8. This is consistent with reports suggesting that elevated inflammatory markers, such as CRP, IL-1β, IL-6, IL-17, and TNF-α, predict poor antidepressant outcomes (Baune et al., 2010; Jha et al., 2017, 2018; Miller et al., 2017; Benedetti et al., 2021). However, baseline CRP levels did not predict treatment response at either week 4 or 8 by simple or multiple linear regression analysis. It would be interesting to simultaneously evaluate other inflammatory markers and correlate them with a clinical response to understand better these interactions between them. Lastly, in our study, the inverse association between baseline HDL-C levels and treatment response at both assessment points was an unexpected finding (higher levels/less response). HDL-C and S100B levels contributed to the variation in antidepressant response in the multivariate linear regression models after 4 weeks of treatment but not at 8 weeks. Contrary to our results, 2 previous large cohort studies confirmed that low HDL-C levels predicted lower antidepressant response at 2- (Vogelzangs et al., 2014) and 5-year (Virtanen et al., 2017) follow-up, respectively. The metabolic and inflammatory alterations underlying chronic depression could have a less determining role in depressive episodes or in the acute antidepressant response (Lehto et al., 2010).

In relation to the association of protein S100B and depression, although some studies have reported a significant positive correlation between depressive severity scores and serum S100B levels in patients with MDD (Schroeter et al., 2002; Hetzel et al., 2005; Jang et al., 2008; Tsai and Huang, 2016), most have reported no association (Arolt et al., 2003; Schroeter et al., 2008;

Table 4. Quality of S100B as Antidepressant Response Predictive Marker

Responders	Sensibility	Specificity	Positive predictive value	Negative predictive value	Accuracy
At 4 wk	75% (50.90%–91.34%)	85.71% (42.13%–99.64%)	93.75% (70.60%–98.94%)	54.6% (34.64%–73.10%)	77.78% (57.74%–91.38%)
At 8 wk	76.5% (50.10%–93.19%)	70% (34.75%–93.33%)	81.3% (61.86%–92.05%)	63.6% (40.41%–81.87%)	74.07% (53.72%–88.89%)

Zhang et al., 2009; Schmidt et al., 2015; Ambrée et al., 2016), as confirmed in our study. Again, differences in the type or course of depression, antidepressant treatment history, and measures of depression severity may account for variations in outcomes across these studies. More specifically, heterogenous glial activity in patients suffering from depression could explain these differences. Increasing S100B protein levels has been proposed to be a mechanism by which the brain could compensate for impaired neuroplasticity in depression (Jang et al., 2008; Hidese et al., 2020). However, this compensatory mechanism will neither occur in the same way in all patients nor be related directly to the severity of depression, explaining the conflicting findings in these studies. Finally, some authors have shown that antidepressant treatment reduced S100B levels as depression alleviated (Schroeter et al., 2002). Although others have shown that S100B levels increased significantly after treatment with different antidepressants, the observed increase was more prominent in non-responders than in responders (Jang et al., 2008). However, consistent with our results, most studies have failed to show that medication significantly affects S100B levels during treatment (Rothermundt et al., 2001; Arolt et al., 2003; Hetzel et al., 2005; Ambrée et al., 2016; Fang et al., 2016; Tsai and Huang, 2016). In addition, an important number of patients with MDD exhibit evidence of increased inflammation, and S100B alterations could be related to the presence of a metabolic "low inflammation status" in MDD. Moreover, elevated circulating metabolic markers are often comorbid (Lamers et al., 2018; Osimo et al., 2019; Felger and Capuron, 2021). In the present study, it seems that depressed patients with higher CRP levels at baseline are associated with lower general functioning, whereas CRP concentrations do not correlate with depression score. It could be hypothesized that CRP levels are more associate with functional impairment than with current depressive symptoms. We did not find an association between HDL-C levels or other metabolic markers and MDD severity or with clinical improvement. Initial data from a previous case-control study found that persistent depression symptoms (>3 years) were associated with low HDL-C levels (Lehto et al., 2010). It is known that the duration of depressive symptoms may modify biological correlates over time (Lehto et al., 2008a, 2008b). In this sense, most depressed patients in our sample were recruited during their first depressive episode. Also, we excluded inflammatory medical comorbidity and obesity while HDL-C levels were in the normal range.

Limitations

There are several limitations to the present study. First, patients were recruited consecutively from a single center, thereby reducing the external validity. Although the sample was representative of outpatients with moderate-to-severe MDD without significant suicidal ideation, we cannot draw conclusions about patients with atypical, psychotic, melancholic type, or other forms of depression. Second, this was a naturalistic study using standard SSRI antidepressant treatment regimens without randomization or placebo control, and the sample size limited our ability to study other variables that could be of interest. Indeed, only serum S100B levels were measured and not CSF levels that more accurately reflect intracerebral concentrations (Uher and Bob, 2012). Nevertheless, serum S100B levels are indicative of CSF concentrations even though extracranial sources secreted S100B (e.g., adipocytes) might interfere with the accurate interpretation of serum levels (Reiber et al., 2001; Ambrée et al., 2016). As it was shown in a previous work, S100B levels displayed important value dispersion, generating a non-normal statistical distribution (Jha et al., 2019). Results from the present study are compatible with this previous observation, being in the same range of values although with less data dispersion. Also, we only measured the nonspecific inflammatory marker CRP using the standard, non-high sensitivity CRP method. Determining the levels of pro-inflammatory cytokine would have been interesting to draw conclusions about how inflammation and various biological and clinical parameters are inter-related. Nevertheless, CRP is considered a reliable marker of the inflammatory status, and HDL-C changes are an essential component of the metabolic syndrome (Virtanen et al., 2017; Jha et al., 2019). Moreover, we enrolled mostly young adults with no other medical comorbidities that could interfere with the interpretation of findings.

In conclusion, the results of our study suggest that S100B levels show promise as a biomarker of the antidepressant response. If confirmed, these findings would open new perspective in antidepressant treatment, advancing precision care to patients. Using more effective treatments based on biomarkers would optimize psychiatric patient care towards a more personalized medicine. However, the interaction of this marker with other biological biomarkers, together with its impact on depressive symptoms or disorders, requires further investigation.

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Interest Statement

The authors have declared they have no conflicts of interest to disclose. For the financial disclosures not directly related to the subjects of the paper, B.A. received speaker's honoraria and/or a travel allowance from Lundbeck, Janssen-Cilag, Sanofi, and Eli Lily. He has served on the advisory board of Janssen-Cilag.

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