Association Between Enhanced Soluble CD40 Ligand and Proinflammatory and Prothrombotic States in Major Depressive Disorder: Pilot Observations on the Effects of Selective Serotonin Reuptake Inhibitor Therapy

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Objective: Major depressive disorder (MDD) is associated with low-grade inflammation, and it is considered a risk factor for coronary artery disease (CAD). CD40 ligand (CD40L) plays an important role in inflammation, platelet activation, and clotting system activation. We investigated soluble CD40L (sCD40L) expression in MDD and assessed whether it may represent a molecular mechanism that links inflammation and a prothrombotic state and whether this condition may be modified by selective serotonin reuptake inhibitor (SSRI) therapy.

Method: Levels of sCD40L, interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), soluble P-selectin (sP-selectin), activated factor VII (FVIIa), and prothrombin fragment 1+2 (F1+2) were measured in 46 drug-naïve, first-episode MDD patients without conventional CAD risk factors and in 46 matched healthy controls. Participants were screened between March 2002 and November 2005. Twenty of the 46 MDD patients were then randomly assigned to either sertraline 100 mg/day (N = 10) or citalopram 20 mg/day (N = 10); the aforementioned variables were measured at baseline and after 6 weeks of treatment.

Results: Compared with control subjects, MDD patients had higher baseline levels of sCD40L, IL-1β, IL-6, TNF-α, sP-selectin, FVIIa, and F1+2. In the clinical group, sCD40L levels, HAM-D total scores, and proinflammatory markers were strongly intercorrelated. In contrast, there were no significant correlations in the control group. Mood improvement achieved with SSRI therapy was associated with significant reduction in sCD40L, proinflammatory markers, and prothrombotic markers expression. (All p values < .0001.)

Conclusions: This pilot study shows that CD40/CD40L pathway up-regulation in MDD patients relates increased levels of sCD40L to a prothrombotic state and, preliminarily, indicates that SSRI therapy may significantly reduce sCD40L and CD40L levels associated with proinflammatory and prothrombotic states.

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Major depressive disorder (MDD) is one of the most prevalent diseases in the world and is associated with significant morbidity and mortality.[1] MDD and coronary artery disease (CAD) frequently co-occur[2] in primary[3–7] and secondary prevention settings.[8,9] The pathophysiological pathways explaining this relationship,[10] including poor compliance with medication and lifestyle changes,[11] autonomic dysregulation with lower heart rate variability,[12] hypothalamic-pituitary-adrenal axis overactivity,[10] greater platelet activation,[13] enhanced blood coagulation,[14] and endothelial dysfunction,[15] are largely unexplored. Recently, interest has arisen about the role of chronic inflammation in MDD and its association with atherosclerosis.[16–21] CD40 ligand (CD40L) is a transmembrane protein found on immune system, endothelial, and smooth muscle cells and platelets.[22] On interaction with its receptor CD40, CD40L elicits proinflammatory and prothrombotic activity[22] favoring and accelerating the progression of atherosclerosis.[23] Normally absent on the surface of resting platelets, CD40L is rapidly expressed after stimulation of common agonists; it is then cleaved, generating a soluble form (sCD40L) that retains much of its biological activities.[24] More than 95% of sCD40L originates from platelets,[23] and this substance maximally reflects in vivo platelet activation.[25] In the present study, conducted on drug-naive, first-episode MDD patients without conventional CAD risk factors, we investigated the relation between sCD40L and other proinflammatory

Table 1. Characteristics of Study Participants at Baseline

Characteristic	MDD Patients (N = 46)	Controls (N = 46)
Age, mean ± SD, y	34.85 ± 5.88	34.11 ± 5.22
Sex, male/female	20/26	19/27
BMI, mean ± SD, kg/m^2	27.70 ± 1.99	28.29 ± 2.06
Total cholesterol, mean ± SD, mg/dL	174.11 ± 18.67	169.51 ± 19.28
LDL cholesterol, mean ± SD, mg/dL	112.45 ± 13.73	102.54 ± 18.39
Triglycerides, mean ± SD, mg/dL	98.93 ± 16.89	94.37 ± 18.52
HAM-D score, mean ± SD*	22.63 ± 5.14	7.30 ± 1.81

*$p < .0001$.
Abbreviations: BMI = body mass index, HAM-D = Hamilton Rating Scale for Depression, LDL = low-density lipoprotein, MDD = major depressive disorder.

cytokines and depression symptom severity. To assess whether sCD40L represents a molecular mechanism that links low-grade inflammation and an ongoing prothrombotic state, sCD40L expression was further analyzed in association with soluble P-selectin (sP-selectin) levels, which are another platelet activation index[26]; activated factor VII (FVIIa) levels as a marker of extrinsic pathway activation[27]; and prothrombin fragment 1+2 (F1+2) levels as a marker of thrombin generation.[28] Finally, we examined whether sCD40L-associated proinflammatory and prothrombotic states may be normalized by selective serotonin reuptake inhibitor (SSRI) therapy.

METHOD

Study Participants

Between March 2002 and November 2005, we screened 845 subjects with mood disorders referred to the Department of Psychiatry, University of Rome Tor Vergata School of Medicine and 46 patients (26 women and 20 men [mean ± SD age = 34.85 ± 5.88 years]) with first-episode MDD (10 [22%] in a day hospital program and 36 [78%] outpatients) met inclusion criteria to enter the study. At the same time, 46 gender- and age-matched healthy subjects (27 women and 19 men [mean ± SD age = 34.11 ± 5.22 years]), recruited among hospital staff, with no past or current diagnosis of psychiatric disorder, were enrolled into the study as controls. Controls underwent the same diagnostic procedures as MDD patients to rule out any exclusion criteria mentioned below. All subjects were interviewed using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, (DSM-IV-TR) Axis I Disorders (SCID-I), Italian Clinician Version.[29,30] Each subject meeting all DSM-IV-TR criteria for a current diagnosis of MDD was enrolled. Depression symptom severity was measured by the Hamilton Rating Scale for Depression, 21-item version (HAM-D)[31] at admission and after 6 weeks of treatment. None of the patients had received psychotropic medication before entering the study. Medical or neurologic diseases were ruled out by clinical examination and medical history, laboratory blood analysis, electrocardiogram, and electroencephalogram. Exclusion criteria were comorbidity with other psychiatric disorders and conventional risk factors for CAD, including hypertension, hyperlipidemia, obesity, diabetes, family history, and smoking. None of the participants had taken steroid treatment, nonsteroidal anti-inflammatory drugs, or antibiotics during the 2 weeks preceding blood sampling. Participants were also instructed to abstain from caffeine-containing beverages on sampling day. After the sampling, weight and height were measured in all patients and control subjects in order to obtain the body mass index (BMI). The 2 groups were relatively well-matched for dietary intake and physical activity, and women in both groups were at the same menstrual cycle phase (as assessed by a questionnaire). Women on hormonal contraceptive therapy were specifically excluded. The baseline characteristics of MDD patients and controls are summarized in Table 1. Informed consent was obtained from all participants and volunteers after the approval of the Intramural Ethical Committee.

Study Design

First, we compared the baseline levels of sCD40L, interleukin-Iβ (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), sP-selectin, FVIIa, and F1+2 in MDD patients and controls. Then, we investigated the effects of 2 different SSRIs (sertraline and citalopram) on sCD40L levels to test our hypothesis concerning the influence of SSRI therapy on these levels. Thus, 20 of the 46 MDD patients were randomly assigned to either sertraline 100 mg/day (N = 10; 4 men, 6 women) or citalopram 20 mg/day (N = 10; 5 men, 5 women). sCD40L, IL-1β, IL-6, TNF-α, sP-selectin, FVIIa, and F1+2 levels and HAM-D scores were assessed at baseline and after 6 weeks' treatment.

Sample Collection and Immunoassays

Overnight fasting antecubital vein blood samples were taken from each consenting patient and control subject, between 8 a.m. and 9 a.m., after a 30-minute semirecumbent position rest, without stasis, using the Vacutainer technique, and anticoagulated in 0.13 mol/L sodium citrate test tubes (ratio 9:1, vol/vol). Samples were immediately centrifuged at 2000 r.p.m. for 20 minutes at 4°C; then supernatant was collected and stored at –80°C until the end of the study. To minimize random measurement error, all subjects returned for a follow-up session 1 week later, during which time study variables (other than depression status) were reassessed in an identical fashion. sCD40L and sP-selectin plasma levels were measured by commercially available enzyme immunoassays (Quantikine, R&D Systems, Minneapolis, Minn.).

Table 2. Plasma Levels of Proinflammatory and Prothrombotic Markers in MDD Patients and Controls at Baseline

Marker	MDD Patients (N = 46), Mean ± SD	Controls (N = 46), Mean ± SD
sCD40L, ng/mL	2.51 ± 1.28	1.49 ± 0.45
IL-1β, pg/mL	1.58 ± 1.23	0.67 ± 0.44
IL-6, pg/mL	2.59 ± 1.45	1.26 ± 0.63
TNF-α, pg/mL	3.37 ± 1.87	1.44 ± 0.83
sP-selectin, ng/mL	79.85 ± 26.66	35.76 ± 12.94
FVIIa, mU/mL	34.82 ± 13.64	24.03 ± 4.38
F1+2, nmol/L	1.32 ± 0.66	0.88 ± 0.42

Abbreviations: FVIIa = activated factor VII, F1+2 = prothrombin fragment 1+2, IL-1β = interleukin-1β, IL-6 = interleukin-6, MDD = major depressive disorder, sCD40L = soluble CD40 ligand, sP-selectin = soluble P-selectin, TNF-α = tumor necrosis factor-α.

Lowest detection limit of this assay was 0.170 ng/mL for sCD40L and 0.5 ng/mL for sP-selectin. Intra-assay and interassay coefficients of variation (CVs) were 7% and 9% for sCD40L and 5% and 8% for sP-selectin, respectively. IL-1β, IL-6, and TNF-α levels were assessed by specific high-sensitivity, commercially available quantitative enzyme immunoassays (Quantikine HS, R&D Systems, Minneapolis, Minn.). The lowest detection limits were 0.015 pg/mL for IL-1β, 0.094 pg/mL for IL-6, and 0.1 pg/mL for TNF-α. Intra-assay and interassay CVs were 7% and 9% for IL-1β, 5% and 8% for IL-6, and 6% and 8% for TNF-α, respectively. Plasma FVIIa was analyzed with a commercial kit (STAclot VIIa-rTF, Diagnostica Stago, Asnieres-sur-Seine, France). Values were expressed in mU/mL, 30 mU being equivalent to 1 ng of FVIIa. Lowest detection limit was 9.40 mU/mL. Intra-assay and interassay CVs for this method were 7% and 4%, respectively. Human prothrombin fragment F1+2 plasma levels were assayed by an enzyme immunoassay based on the sandwich principle (Enzygnost F1+2, Data Behring, Deerfield, Ill.). Lowest detection limit was 0.10 nmol/L. Intra-assay and interassay CVs for this method were 5% and 7%, respectively. All measurements were done blinded. All samples were performed in duplicate, and mean values were used for statistical analyses. To evaluate the markers' temporal stability in the absence of treatment, Spearman rank-order correlations were computed between values from the 2 baseline blood draws. Markers were stable over time, with Spearman ρ values ranging from 0.70 to 0.88 for all markers.

Statistical Analysis

Preliminary descriptive analysis revealed that evaluated indices showed a nonnormal distribution. In order to achieve a better approximation to a normal distribution, marker values were logarithmically transformed for analysis. Bivariate comparisons were performed using the χ^2 test and Student t test. The effects of gender (male vs. female) and diagnostic status on markers (sCD40L, IL-1β, IL-6, TNF-α, sP-selectin, FVIIa, F1+2) were assessed using a multivariate analysis of variance (MANOVA), followed by a univariate analysis of variance (ANOVA). To analyze the treatment effect of SSRIs on patients' and control subjects' markers, we used repeated-measures MANOVA (between-group factor: sertraline vs. citalopram; within-subjects factor: baseline vs. posttreatment), followed by repeated ANOVAs. Univariate results were examined only if Wilks Λ multivariate significance criterion was achieved. Statistical significance was defined at $p < .05$. Spearman rank correlation test was carried out to calculate bivariate correlations between markers and HAM-D scores in MDD and control groups. To deal with the problem of α inflation (type I error), the α level Bonferroni correction was used. Bivariate correlations were considered significant at $p < .006$ ($p < .05/8 = 0.00625$). All data are presented as mean ± SD. Statistical analysis was performed using SPSS 11.0.1 software package (SPSS, Inc., Chicago, Ill.).

RESULTS

The control group did not differ from the MDD group in terms of age ($t = –0.637$, $p = .526$) and sex ratio ($\chi^2 = 0.045$, $p = .833$). There were no significant differences between the 2 groups in terms of BMI and total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels. As expected, MDD patients had significantly higher HAM-D scores than controls ($t = 37.355$, $p < .0001$) (Table 1).

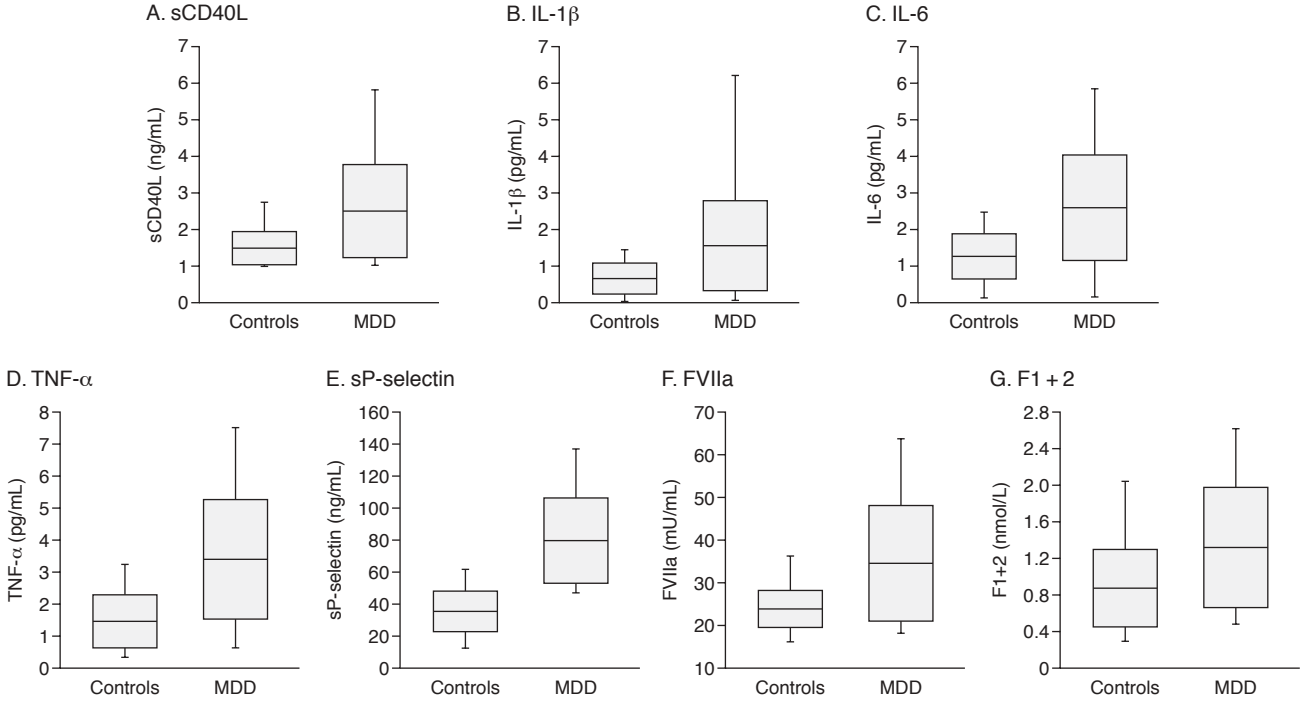
Proinflammatory and Prothrombotic Markers

Plasma sCD40L, IL-1β, IL-6, TNF-α, sP-selectin, FVIIa, and F1+2 levels of 92 subjects (46 MDD patients and 46 controls) are represented in Table 2. According to MANOVA analysis, a strong group effect was found (Wilks $\Lambda = 0.372$, $F = 19.778$, $df = 7,82$; $p < .0001$). There was neither a gender effect (Wilks $\Lambda = 0.934$, $F = 0.831$, $df = 7,82$; $p = .564$), nor an interaction gender × group effect (Wilks $\Lambda = 0.910$, $F = 1.164$, $df = 7,82$; $p = .332$). The sCD40L levels were significantly increased in MDD patients versus controls ($F = 29.933$, $p < .0001$; Figure 1A). Consistent with previous reports, we found that, compared with healthy subjects, MDD patients had significantly higher IL-1β ($F = 18.169$, $p < .0001$; Figure 1B), IL-6 ($F = 25.987$, $p < .0001$; Figure 1C), and TNF-α levels ($F = 43.659$, $p < .0001$; Figure 1D). MDD patients also had increased sP-selectin ($F = 114.431$, $p < .0001$; Figure 1E), FVIIa ($F = 27.029$, $p < .0001$; Figure 1F), and F1+2 ($F = 15.701$, $p < .0001$; Figure 1G) levels compared with controls.

Markers and Depression Severity

In the clinical sample, the severity of depressive symptoms (as measured by the total HAM-D score)

Figure 1. Circulating Levels of sCD40L, IL-1β, IL-6, TNF-α, sP-selectin, FVIIa, and F1+2 in MDD Patients and Controls[a,b]



[a]According to univariate analysis, all comparisons were significant at $p < .0001$. Data entered into statistical analysis were log-transformed.
[b]Bars are minimum and maximum values. Boxes are means ± SD. Middle lines in the boxes are mean values.
Abbreviations: FVIIa = activated factor VII, F1+2 = prothrombin fragment 1+2, IL-1β = interleukin-1β, IL-6 = interleukin-6, MDD = major depressive disorder, sCD40L = soluble CD40 ligand, sP-selectin = soluble P-selectin, TNF-α = tumor necrosis factor-α.

was significantly correlated with sCD40L and proinflammatory (IL-1β, IL-6, and TNF-α) and prothrombotic (sP-selectin, FVIIa, and F1+2) markers. In addition, there were strong positive correlations between sCD40L levels and proinflammatory and prothrombotic markers. In contrast, in the control group, we found no significant correlations between HAM-D score, sCD40L, and proinflammatory and prothrombotic markers (Table 3).

SSRI Therapy Effects

SSRI therapy was associated with a significant reduction in HAM-D score (treatment effect: $F = 85.478$, $df = 1.18$, $p < .0001$). Depression symptom improvement was independent of the drug used (drug effect: $F = 0.002$, $df = 1.18$, $p = .968$; treatment × drug effect: $F = 0.006$, $df = 1.18$, $p = .941$). According to repeated MANOVA measurements (Wilks $\Lambda = 0.001$, $F = 1641.727$, $df = 7,12$; $p < .0001$), after SSRI treatment, patients showed a significant reduction in sCD40L levels, proinflammatory marker levels, and prothrombotic marker levels, independently of the molecule used (Wilks $\Lambda = 0.701$, $F = 0.732$, $df = 7,12$; $p = .650$) and from the interaction "treatment × SSRI" (Wilks $\Lambda = 0.842$, $F = 0.322$, $df = 7,12$; $p = .929$) (Table 4). All univariate results of "baseline vs. posttreatment" indexes pairwise comparisons were highly significant. ($p < .0001$; see Table 4 for F values of single repeated-measures univariate ANOVAs.)

DISCUSSION

The present study, conducted on young adult, drug-naïve, first-episode MDD patients without conventional CAD risk factors, is the first (1) showing an up-regulation of the CD40/CD40L pathway in this clinical condition, (2) relating increased sCD40L levels to the prothrombotic state, and (3) providing preliminary evidence that SSRI therapy may significantly reduce sCD40L levels and the CD40L-associated proinflammatory and prothrombotic states.

sCD40L and Low-Grade Inflammation

A number of studies have demonstrated that patients with MDD have a chronic elevation of inflammatory cytokines[32–34] as a primary manifestation, representing risk markers for cardiac morbidity and mortality.[33–35] Recent evidence supporting low-grade inflammation involved in CAD progression makes this research line relevant to clarify the physiopathology of atherosclerosis and cardiovascular disease.[36,37] Although these findings are promis-

Table 3. Correlation Matrix Among Markers in MDD Patients (top line) and Controls (bottom line)[a]

	HAM-D	sCD40L	IL-1β	IL-6	TNF-α	sP-selectin	FVIIa
sCD40L	ρ = .83, p < .0001						
	ρ = –.16, p = .299						
IL-1β	ρ = .93, p < .0001	ρ = .80, p < .0001					
	ρ = .12, p = .417	ρ = –.01, p = .926					
IL-6	ρ = .89, p < .0001	ρ = .79, p < .0001	ρ = .87, p < .0001				
	ρ = –.03, p = .836	ρ = .07, p = .665	ρ = .35, p = .017				
TNF-α	ρ = .90, p < .0001	ρ = .72, p < .0001	ρ = .87, p < .0001	ρ = .87, p < .0001			
	ρ = –.05, p = .749	ρ = –.11, p = .460	ρ = –.09, p = .547	ρ = –.10, p = .512			
sP-selectin	ρ = .92, p < .0001	ρ = .80, p < .0001	ρ = .90, p < .0001	ρ = .86, p < .0001	ρ = .92, p < .0001		
	ρ = –.04, p = .795	ρ = .17, p = .269	ρ = –.08, p = .583	ρ = –.11, p = .476	ρ = –.08, p = .601		
FVIIa	ρ = .84, p < .0001	ρ = .72, p < .0001	ρ = .86, p < .0001	ρ = .84, p < .0001	ρ = .77, p < .0001	ρ = .78, p < .0001	
	ρ = –.04, p = .791	ρ = –.22, p = .139	ρ = .20, p = .186	ρ = –.14, p = .349	ρ = .23, p = .128	ρ = –.35, p = .016	
F1+2	ρ = .92, p < .0001	ρ = .79, p < .0001	ρ = .91, p < .0001	ρ = .87, p < .0001	ρ = .94, p < .0001	ρ = .95, p < .0001	ρ = .80, p < .0001
	ρ = –.10, p = .518	ρ = .21, p = .155	ρ = –.21, p = .163	ρ = .06, p = .708	ρ = –.15, p = .325	ρ = .38, p = .009	ρ = –.28, p = .061

[a]Significance level was set at p < .006.
Abbreviations: FVIIa = activated factor VII, F1+2 = prothrombin fragment 1+2, HAM-D = Hamilton Rating Scale for Depression, IL-1β = interleukin-1β, IL-6 = interleukin-6, MDD = major depressive disorder, sCD40L = soluble CD40 ligand, sP-selectin = soluble P-selectin, TNF-α = tumor necrosis factor-α.

ing, their interpretation is complicated by the failure of these studies to account for potential confounders such as the presence of conventional CAD risk factors and comorbidities.[13,38] The possibility that different psychotropic drugs or statins may affect the analysis must be considered as well.[23,26,38] This is why we studied a simple model of young adult, drug-naive MDD patients without conventional risk factors for CAD. These population characteristics may justify the low plasma levels of proinflammatory and prothrombotic markers found in our subjects.

CD40-CD40L interactions represent a main molecular mechanism linking inflammation and thrombosis,[39] and the association between sCD40L levels, inflammation, and ongoing prothrombotic states has never been investigated in MDD patients. Consistent with previous reports, we confirmed the presence of low-grade inflammation in MDD subjects free from confounding factors. sCD40L levels showed a positive correlation with proinflammatory cytokines expression, and it is noteworthy that CD40L elicits inflammatory responses on interaction with its receptor, CD40, including increased expression of IL-1β, IL-6, and TNF-α.[40]

sCD40L and Prothrombotic States

Abnormal platelet activation has been postulated as one of the mechanisms underlying the association between MDD and CAD.[13,41] Both sCD40L[23,25] and sP-selectin[26] are considered platelet activation markers. Research on platelet activation in MDD patients with or without CAD has been performed by measuring platelet-specific–released products (i.e., β-thromboglobulin and platelet factor 4), molecules exposed on and shed from platelet surfaces (i.e., CD40L and sP-selectin), and agonist-induced platelet aggregation.[14,42,43] None of these methods is perfect, but they give information about platelet activation states,[44] although data on platelet activity in MDD subjects are still inconclusive.[13] Laghrissi-Thode et al.[45] demonstrated dramatic differences among platelet activation markers in patients with depression and CAD. Schins et al.[42] did not find significant differences in sCD40L levels between post–myocardial infarction patients with and without depression. Pasic et al.[46] did not demonstrate significant differences in sP-selectin levels between chronic heart failure patients with or without depression. All these studies, however, had some limitations: nonhomogeneity and the presence of comorbidities and polytherapies that could affect results.[13] Our findings of enhanced sCD40L levels in MDD patients and the strong association between sCD40L and sP-selectin further support the evidence of increased platelet activation in this clinical condition.[13] It is commonly recognized that inflammation directly affects thrombosis, and this tight link is partly attributable to P-selectin, which is functional not only when expressed on the surfaces of activated platelets but also when shed, generating its soluble form, sP-selectin.[39]

Moreover, our study assessed the relation between sCD40L and coagulative activation. Factor VII is the first enzyme in the extrinsic pathway of the blood coagulation system. Although most factor VII circulates in plasma in the zymogen form, small but significant amounts of FVIIa also are present and appear to serve as a primer for triggering the extrinsic cascade.[27] Several studies have linked elevated concentrations of FVIIa in plasma to CAD. Thus, FVIIa has become recognized as a hemostatic coronary risk marker.[27] F1+2 is a polypeptide released by prothrombin during its activation to thrombin.[28] Circulating levels of F1+2 have been considered a specific marker of thrombin generation in vivo. Elevated F1+2 levels have been found in patients with peripheral arterial disease and CAD and in relation to the presence of conventional CAD risk factors.[28] In addition to its association with platelet

Table 4. Effects of SSRI Therapy on Depressive Symptoms, Proinflammatory Markers, and Prothrombotic Markers

	Sertraline[a] (N = 10), Mean ± SD		Citalopram[a] (N = 10), Mean ± SD		
Measure	Baseline	Posttreatment	Baseline	Posttreatment	F[b]
HAM-D score	23.50 ± 3.21	14.40 ± 2.07	23.50 ± 4.55	14.30 ± 2.21	195,722*
sCD40L, ng/mL	2.22 ± 0.72	1.66 ± 0.40	2.74 ± 1.32	1.84 ± 0.64	78,947*
IL-1β, pg/mL	1.53 ± 0.67	0.88 ± 0.35	1.84 ± 1.10	1.04 ± 0.61	402,599*
IL-6, pg/mL	2.74 ± 1.35	1.57 ± 0.59	3.08 ± 1.69	1.75 ± 0.90	950,765*
TNF-α, pg/mL	3.60 ± 1.63	2.05 ± 0.88	3.81 ± 1.86	2.26 ± 1.13	705,512*
sP-selectin, ng/mL	77.14 ± 24.98	42.17 ± 14.66	88.49 ± 24.19	48.31 ± 13.97	10,687;543*
FVIIa, mU/mL	37.80 ± 11.71	22.17 ± 6.00	37.22 ± 14.51	21.41 ± 7.70	1390,033*
F1+2, nmol/L	1.37 ± 0.65	0.84 ± 0.42	1.50 ± 0.61	0.90 ± 0.37	615,566*

[a]In each treatment group, all differences in baseline vs. posttreatment marker values were highly significant ($p < .00001$), and the results were independent of the drug used.
[b]F values of single repeated-measures univariate ANOVAs.
*$p < .0001$.
Abbreviations: ANOVA = analysis of variance, FVIIa = activated factor VII, F1+2 = prothrombin fragment 1+2, HAM-D = Hamilton Rating Scale for Depression, IL-1β = interleukin-1β, IL-6 = interleukin-6, sCD40L = soluble CD40 ligand, sP-selectin = soluble P-selectin, SSRI = selective serotonin reuptake inhibitor, TNF-α = tumor necrosis factor-α.

activation, sCD40L expression has shown a positive correlation with both FVIIa and F1+2,[27,28] indicating an ongoing prothrombotic state in MDD subjects. These findings could suggest that sCD40L release from activated platelets may subsequently induce a procoagulant response in endothelial and mononuclear cells through interaction with CD40.[25,47]

SSRIs and sCD40L-Associated Proinflammatory and Prothrombotic States

In the present study, sCD40L levels showed significant association with MDD severity as assessed by the HAM-D, and data indicating a strong correlation between the HAM-D, proinflammatory cytokines, and prothrombotic states are worthy of interest. MDD is woefully undertreated in medical populations overall and certainly within the cardiovascular population.[2] To date, SSRI antidepressants represent first-line treatment in MDD, particularly when comorbidity with CAD is present, because of their low cardiotoxicity; furthermore, knowledge of the anti-inflammatory and antithrombotic properties of these drugs is emerging.[21,47–51] Interestingly, all the cardiovascular benefits of these drugs are still considered side effects of their antidepressant activity.[52] The preliminary results of this study did not allow us to clarify if the reduction of proinflammatory and prothrombotic states was a specific effect of SSRI therapy or if, alternatively, it could be achieved with any antidepressant treatment associated with mood improvement (e.g., noradrenergic drugs, psychotherapy).

Study Limitations

In our study, we did not provide a detailed phenotypic characterization in terms of the absence of other inflammatory and platelet activation markers (i.e., C-reactive protein, β-thromboglobulin, platelet factor 4). In regard to the effects of SSRI therapy, our results must be considered preliminary observations due to the small size of the treatment arms and to the absence of a placebo-controlled group. Moreover, the study does not clarify if improvement in marker levels is due to symptom reduction or to selective drug effects, because of the lack of different kinds of treatment (i.e., psychotherapy, psychotherapy plus antidepressant) as comparators.

CONCLUSIONS

Our findings indicate that CD40L could represent a molecular mechanism linking low-grade inflammation, platelet activation, and coagulation activation in MDD patients with no conventional CAD risk factors and no other confounding factors. Moreover, our study provides preliminary evidence that sCD40L suppression by SSRI antidepressants is associated with proinflammatory and prothrombotic state reduction. Whether MDD treatment may reduce cardiovascular risk remains an unresolved question.

Drug names: citalopram (Celexa and others), sertraline (Zoloft and others).

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