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Association of markers of inflammation and intestinal permeability in suicidal patients with major mood disorders

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ABSTRACT

Background: Patients with major mood disorders are at high risk of suicidal behavior compared to the general population. Suicide is a public health concern, accounting for around 1.2% of deaths worldwide. Understanding its underlying mechanisms may help identify predictive biomarkers and design novel targeted treatments. Immune dysfunctions, in particular affecting the gut-brain axis, are of interest given their dual involvement in mood disorders and suicidal behavior. We thus explored the possible relationships between suicide attempt (SA) and circulating biomarkers of intestinal permeability and systemic inflammation in patients with major depressive disorder (MDD) or bipolar disorder (BD) with and without a history of SA.

Method: 137 patients with BD and 168 with MDD were included, and among them, 133 had a history of SA and 172 did not. Among them, 104 were males (34%) and 201 females (66%). Depressive symptoms were evaluated using the Inventory of Depressive Symptomatology clinical scale (IDS-C30). Circulating levels of intestinal fatty acid binding protein (IFABP), calprotectin, apolipoprotein E (ApoE), lipopolysaccharides binding protein (LBP), lipopolysaccharides (LPS), soluble beta-2-microglobulin (B2m), and C-reactive protein (CRP), were determined. Multivariate linear regressions were performed according to the gender status given the proportion of the herein studied male and female individuals and the higher propensity of females to experience SA as compared to males.

Results: After adjusting for confounding variables, patients in the SA group had significantly higher CRP, and lower IFABP levels in comparison to the NSA group.

Limitations: The unavailability of confounding variables such as dietary habits, should be noted. In addition, the cross-sectional nature of the study hampers the identification of causative effects.

Conclusion: Although preliminary, our observations revealed associations between markers of inflammation and intestinal permeability in patients with suicidal behavior warranting further confirmation in larger cohorts.

1. Introduction

Suicide is a worldwide public health concern. According to the latest World Health Organization report, more than 700 000 individuals committed suicide in 2019, accounting for around 1.2% of deaths (World Health Organization, 2019). While more males than females die from suicide, females exhibit a higher rate of suicide attempts (SA) (Schrijvers et al., 2012). Even if not fatal in all cases (Owens et al.,

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2002), a prior suicide attempt is consistently one of the strongest predictors of death by suicide (Bostwick et al., 2016). SA is defined as a self-directed potentially injurious behavior associated with at least some intent to die (American Psychiatric Association, 2013). Psychiatric illness and suicidal ideation are the most commonly cited risk factors for SA, even if they do not exclusively predict suicidal behavior (Klonsky and May, 2014). Several studies report a strong association between SA and mood disorders, especially major depressive disorder (MDD) and bipolar disorder (BD) (Monson et al., 2021). BD exhibits the highest rate of suicide attempts (30-50%) which is nearly twice greater than the rate observed in MDD (Miller and Black, 2020).

Along with the long-standing stress-diathesis model of suicide, the nascent field of immunopsychiatry has repeatedly provided evidence of pro-inflammatory processes in the development of both MDD and BD (Benedetti et al., 2020; Köhler et al., 2017). This is reflected by increased circulating levels of potent inflammatory mediators including, amongst others, interleukin 1 (IL-1), IL-6, and tumor necrosis factor-alpha (TNF-α), together with elevated levels of chemokines and adhesion molecules (Lengvenyte et al., 2021), even if inconsistencies are observed (Kim et al., 2007). We have also contributed studies addressing inflammatory underpinnings of BD. We showed that low levels of oxidative stress/inflammatory-related mitochondrial DNA copy numbers characterized "inflamed" manic BD patients (Angrand et al., 2021), while heightened levels of the pro-inflammatory soluble isoforms of non-classical HLA-E molecules are observed in patients with BD who are experiencing depressive episodes (Boukouaci et al., 2021). More recently, we have shown that kynurenine metabolites allowed us to distinguish acutely ill patients from those in a stable phase of their disease, both in patients with a diagnosis of SZ or BD (Skorobogatov et al., 2023). Taken together, these observations reinforce the well-known intertwining between pro-inflammatory processes and BD with possible consequences of increased impulsivity and/or suicidal behavior. Multiple studies have previously implicated inflammatory processes in the pathogenesis of suicidality (Janelidze et al., 2011; Keaton et al., 2019; Vasupanrajit et al., 2022) with association of elevated levels of IL-6, TNF-α, and C-reactive protein (CRP) (Courtet et al., 2015; Dolsen et al., 2021). Other biomarkers, reflecting more specific pathways, such as intestinal dysbiosis, have been reported (Brundin et al., 2017; Ohlsson et al., 2018).

Accordingly, compelling evidence suggests that exaggerated pro-inflammatory processes and systemic low-grade inflammation, repeatedly demonstrated in psychiatric disorders, may be viewed under the prism of the so-called "leaky gut" pathway which likely results from a pro-inflammatory weakening of the intestinal epithelium (Cryan et al., 2019; Obrenovich, 2018). Consequently, lipopolysaccharides (LPS) and other immunogenic bacterial components can leak from the gut lumen into the bloodstream with possible further activation of immune cells and deleterious effects on the central nervous system (Obrenovich, 2018; Ohlsson et al., 2018). Gut microbiota is an integral component of the gut-brain axis therefore any alteration of its functioning can have an effect on the central nervous system and display an inflammatory component (Bravo et al., 2012; Obrenovich et al., 2017). Of note, such processes can initiate a vicious circle of inflammation. Yet, very few studies have investigated gut permeability biomarkers in the context of suicidal behavior, bipolar disorder and/or a major depressive episode (Fasano, 2020; Niculescu et al., 2015; Ohlsson et al., 2018).

To fill this gap, we explored markers of intestinal permeability and inflammation including lipopolysaccharides (LPS), its binding protein (LBP), intestinal fatty acid binding protein (IFABP), and calprotectin, all linked to gut dysbiosis. We also evaluated circulating levels of apolipoprotein E (ApoE), belonging to the cholesterol cycle, and required for blood brain barrier integrity. Furthermore, we measured the soluble isoform of beta-2-microglobulin (B2m) and high sensitivity CRP (*hs*CRP) levels, respectively reflecting T-lymphocyte activation and peripheral inflammation, both involved in various disorders, including psychiatric disorders and suicide (Courtet et al., 2015; Dargél et al., 2015; Leboyer et al., 2021; Luan and Yao, 2018). In the present study we evaluated patients with MDD or BD, with and without a history of suicide attempt.

2. Material and methods

2.1. Participants

Study participants were recruited in the University affiliated psychiatric department of Montpellier following a consultation for a major depressive episode or a suicidal crisis (suicide attempt or suicidal ideation). All included subjects gave written informed consent to participate, and the study protocol was approved by the Montpellier University Hospital ethics committee (CPP Sud Mediterranée IV). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline (Von Elm et al., 2007) was followed. To be included, patients had to fulfil the following inclusion criteria: i) age between 18 and 79 years; ii) presence of a current major depressive episode during a unipolar or bipolar disorder according to the Diagnostic and Statistical Manual IV (DSM-IV) criteria; iii) ability to understand the study design. Exclusion criteria were as follows: i) presence of any acute inflammatory condition; ii) currently undergoing treatment with antibiotic or anti-inflammatory medications; iii) pregnant or breastfeeding women; iv) limited capacity to understand study aims and to sign the informed consent. At the time of inclusion, patients were receiving psychotropic medication treatment including antidepressants, antiepileptic drugs, antipsychotics, lithium, benzodiazepine drugs, and psychostimulants.

2.2. Bipolar disorder and major depressive disorder diagnoses

Diagnoses of BD or MDD and psychiatric comorbidities were established by a psychiatrist or psychologist using the French version of the Structured Clinical Interview for DSM-IV (American Psychiatric Association, 1994). Information about sociodemographic data, consumption of alcohol, tobacco or other substances, and somatic comorbidities were recorded using a pre-designed questionnaire. Current and lifetime psychiatric comorbidities were screened with the Mini-International Neuropsychiatric Interview (M.I.N.I.) for DSM-5.

The severity of depressive symptoms was assessed with the French version of the clinician-rated 30-item version of the Inventory of Depressive Symptomatology (IDS-C30) (Corruble et al., 1999). With a Cronbach's alpha reported as 0.94 and its established psychometric features, the IDS-C30 is useful to detect depressive symptoms and their change over time in patients with mood disorders (Rush et al., 2000, 1996). The patients were considered according to the sex status.

2.3. Measurement of serum and plasma protein levels

Morning fasting peripheral blood samples were collected into the EDTA-treated tubes from all individuals within 24 hours of the clinical evaluation. Serum and plasma samples were stored at -80°C. Immunoassays were in all cases performed on the first thawing of samples.

Circulating levels of lipopolysaccharides (LPS, antibodies-online), and intestinal fatty acid binding protein (IFABP, R&D Systems) were quantified in plasma using commercially available ELISA kits, while lipopolysaccharides binding protein (LBP, MSD V-PLEX) and calprotectin (MSD R-PLEX) were quantified in plasma using electrochemiluminescence assays (MesoScale Discovery, Rockville, Maryland, USA), according to the manufacturer's recommendations. Circulating levels of beta-2-microglobulin (B2m, BioVendor) and apolipoprotein E (ApoE, Abcam) were quantified in serum using commercially available ELISA kits, and C-reactive protein (CRP, MSD V-PLEX) was quantified in serum using the aforementioned electrochemiluminescence and ELISA assays, according to the manufacturer's recommendations. For MSD kits, plates were analyzed using MSD's Workbench plate reader and software package according to the manufacturer's recommendations.

For ELISA assays, plates were read with a spectrophotometer at λ=450 nm and 570 nm, according to the manufacturer's instructions. Detection ranges were as follows: ApoE 0.06-0.25 μg/mL, B2m 0.2-10 μg/L, calprotectin 273-200000 pg/mL, CRP 1.33-49 600 pg/mL, IFABP 2.12-6.21 pg/mL, LBP from 0.038 ng/mL, and LPS 3.12-200 ng/mL.

2.4. Statistical analyses

Quantitative data were expressed as Mean ± Standard Deviation. Chi-square or Fisher's exact tests for comparisons of categorical variables, and the Wilcoxon signed-rank, or Spearman's ρ correlations for continuous variables were used for univariate analysis. Multivariate linear regression, controlling for the covariates of age, smoking, body mass index (BMI), principal diagnosis (BD and MDD), alcohol, substance, and pharmacological treatment. As biomarker scores did not follow a normal distribution (as shown by Shapiro tests with a *p*-value and graphical methods), a Box-Cox, log and Inverse square root transformation of all continuous variables (Biomarker scores) was performed to fulfil the normality assumption required by the parametric procedure. Finally, a cross-sectional model was conducted by multiple linear regressions with a stepwise backward variable selection method to remove variables with highest p-values from the models step by step, until all the remaining variables had a statistical contribution. Significance was based on a two-sided *p*-value $\leq$0.05 throughout. Analyses were performed using R software version 4.1.3. Analyses were considered to be exploratory and thus were not further adjusted for multiple testing. This statistical pipeline was used after sex-based stratification.

3. Results

3.1. Sample characteristics

Demographic and clinical characteristics of the study participants according to the sex status that distinguish female and male participants are shown in Tables 1A and 1B. The whole sample was composed of 305 patients including 137 with BD and 168 with MDD. Among them, 133 presented a history of suicide attempt (SA, 44%) while the remaining 172 did not (NSA, 56%). 104 were males (34%) and 201 were females (66%). The mean ages were 41.6 years ± 13.4 and 41.7 years ± 14.1, respectively, for the SA and the NSA groups of patients. We did not observe any difference in sex, age or body mass index (BMI) distribution between NSA and SA patients. In terms of IDS-C30 total score, the SA group scored higher than the NSA group (SA 29.7 ± 13.8 and NSA 24.0 ± 15.2, $p = 0.003$. We found that patients with SA had a higher proportion of alcohol dependence (34.9% vs 20.2%, $p = 0.005$) and were more often treated with psychotropic medications (94.7% *vs* 87.8%, $p = 0.035$).

3.2. Distribution of systemic inflammation and gut-related biomarkers

The SA group had significantly higher levels of calprotectin (272.8 ng/L ± 177.4 vs 247.1 ng/L ± 194.0; $p = 0.044$, respectively, in SA and NSA), CRP (4685.3 ng/L ± 6419.8 vs NSA 3396.9 ng/L ± 4835.1; $p = 0.013$ respectively in SA and NSA), and LBP (5037.3 μg/L ± 3299.8 vs 4364.2 μg/L ± 3265.4; $p = 0.003$, respectively, in SA and NSA). We also observed a statistically significant decrease in IFABP (1388.3 pg/mL ± 720.3 vs 1537.5 pg/mL ± 780.2; $p = 0.044$, respectively, in SA and NSA) and LPS (272.8 ng/L ± 177.4 and 247.1 ± 194.0; $p = 0.002$, respectively, in SA and NSA) levels between SA and NSA. No differences were observed in terms of ApoE and B2M levels. Between-groups comparisons according to the patient's gender are summarized in Tables 1A and 1B.

3.3. Correlation analysis

All the studied biomarkers correlated positively with age (rho (ρ) between 0.18 and 0.30), but calprotectin and the IDS-C30 scores did not. All of them also correlated positively with BMI (ρ between 0.18 and 0.49) except for IFABP and LPS, BMI and IDS-C30 did not correlate either. Only IFABP correlated with IDS-C30, negatively (ρ = -0.22; $p < 0.001$). CRP correlated positively with ApoE ($\rho = 0.26$; $p < 0.001$), B2m ($\rho = 0.36$; $p < 0.001$), calprotectin ($\rho = 0.47$; $p < 0.001$), and LBP ($\rho = 0.36$; $p < 0.001$). Calprotectin also correlated positively with ApoE ($\rho = 0.38$; $p < 0.001$), B2m ($\rho = 0.14$; $p < 0.05$), and LBP ($\rho = 0.12$; $p < 0.05$). And IFABP correlated positively with B2m ($\rho = 0.26$; $p < 0.001$) and LBP ($\rho = 0.20$; $p < 0.001$). Correlation analyses are summarized in Tables 2A and 2B.

3.4. Higher CRP and lower IFABP levels characterize patients with suicidal behavior

Cross-sectional models for each biomarker were created to adjust for confounding variables that can have an impact on the associations between suicidal behavior and the studied biomarkers. To this end, stepwise backward multiple linear regressions were performed for each protein adjusting for age, sex, BMI, tobacco use, substance and alcohol use disorders, principal psychiatric diagnosis (MDD or BD), and psychotropic treatment. We observed that only elevated levels of CRP ($p = 0.016$) and decreased levels of IFABP ($p = 0.048$) remained statistically significant in female patients with SA as compared to female patients without. None of the other markers reached statistical significance. Concerning the associations between biomarkers and the principal psychiatric diagnosis (MDD or BD), our cross-sectional model revealed elevated levels of calprotectin ($p = 0.005$) in females with MDD compared to those with BD; whereas in males we found higher levels of CRP ($p = 0.016$) and LBP ($p = 0.010$) in MDD patients compared to BD patients. Elevated levels of B2m ($p < 0.001$) were found in male patients with BD compared to those with MDD. More details on the multivariable analysis are summarized in Tables 3A and 3B.

4. Discussion

Pro-inflammatory processes at a systemic level and/or reflecting dysregulations of the gut-brain axis have been previously reported as possible underlying factors in major mood disorders and in suicide (Bergmans et al., 2019; Margolis et al., 2021; Melhem et al., 2017; Ohlsson et al., 2018). Associations with these markers were also found in non-psychiatric settings where patients suffering from intestinal disorders, such as irritable bowel syndrome/disease (IBS/D), exhibit psychological distress (Gracie et al., 2019). Accordingly, we herein retrospectively evaluated the potential influence of circulating levels of systemic and gastro-intestinal tract-related (GI-tract) inflammatory markers in patients with BD or MDD with and without a history of suicide attempt.

We first found that high levels of C-reactive protein are observed in female patients having experienced SA. In addition, further stepwise regression analysis demonstrated that such increase constitutes the best predictor of suicide behavior accounting for 35% of the CRP variance. Our observation not only replicates previous finding in suicidal patients (Courtet et al., 2015), but also highlights the involvement of the associated markers independently of a major mood disorder diagnosis and of the severity of depressive symptoms.

The second main observation concerns the statistically significant relationship between low circulating levels of IFABP and SA, especially in females. IFABP is an intracellular protein expressed in enterocytes and released into the blood circulation upon damage to the intestinal mucosa (Lau et al., 2016). Although it has also been demonstrated to be involved in the pathophysiology of mood disorders (Iordache et al., 2022), its implication in the context of suicide has scarcely been studied. To the best of our knowledge, only one study evaluated its role in suicide and showed, contrary to our finding, high circulating levels of IFABP in patients with suicidal behavior (Ohlsson et al., 2018). Given the relatively small sample size of Ohlsson's study (54 suicide attempters), and

Table 1
Sample characteristics according to sex.

A. Males Mean(SD) or N(%)	NSA (N=64)	SA (N=40)	Chi^2 or Wlicoxon *p*-value
ApoE			0.973
NA	0	1	
Mean (SD)	134.5 (66.8)	139.3 (76.7)	
Range	39.1 - 358.9	57.0 - 359.4	
B2m			0.862
Mean (SD)	2.1 (0.6)	2.1 (0.6)	
Range	1.2 - 4.8	1.4 - 4.9	
Calprotectin			0.995
Mean (SD)	287.6 (224.5)	318.9 (429.4)	
Range	55.6 - 1297.8	33.6 - 2778.0	
CRP			0.738
Mean (SD)	5948.3 (18387.5)	4146.3 (4874.5)	
Range	56.0 - 145123.0	181.3 - 19381.0	
IFABP			0.057
NA	1	0	
Mean (SD)	1551.4 (659.5)	1356.9 (647.2)	
Range	442.7 - 3486.0	609.6 - 3479.6	
LBP			**0.027**
Mean (SD)	4247.4 (3153.9)	4984.9 (2389.4)	
Range	1249.9 - 23453.5	1460.2 - 12314.3	
LPS			**0.007**
NA	1	1	
Mean (SD)	79.8 (36.9)	59.7 (30.6)	
Range	9.2 - 181.2	6.7 - 128.9	
Age			0.635
Mean (SD)	44.4 (13.8)	45.1 (14.1)	
Range	22.0 - 79.0	19.0 - 73.0	
Diagnostic			0.336
MDD	35 (54.7%)	18 (45.0%)	
BD	29 (45.3%)	22 (55.0%)	
Alcohol abuse			0.103
NA	1	1	
No	44 (69.8%)	21 (53.8%)	
Yes	19 (30.2%)	18 (46.2%)	
Substance abuse			0.572
NA	0	1	
0	46 (71.9%)	30 (76.9%)	
1	18 (28.1%)	9 (23.1%)	
BMI			**0.044**
NA	15	19	
Mean (SD)	25.0 (4.0)	27.8 (5.8)	
Range	16.3 - 36.0	18.3 - 41.8	
Smoker			0.150
NA	8	10	
No	25 (44.6%)	7 (23.3%)	
Current	19 (33.9%)	14 (46.7%)	
Past	12 (21.4%)	9 (30.0%)	
IDS-C30 score			0.496
NA	10	12	
Mean (SD)	22.7 (14.3)	24.9 (13.4)	
Range	0.0 - 55.0	3.0 - 58.0	
Psychotropic medication			0.144
None	9 (14.1%)	2 (5.0%)	
At least one	55 (85.9%)	38 (95.0%)	
B. Females Mean (SD) or N(%)	NSA (N=108)	SA (N=93)	Chi^2 or Wlicoxon *p*-value
ApoE			0.665
Mean (SD)	105.2 (58.1)	105.4 (50.7)	
Range	23.0 - 348.0	33.5 - 345.8	
B2m			**0.020**
Mean (SD)	2.0 (0.6)	2.1 (0.5)	
Range	0.8 - 4.8	0.6 - 3.3	
Calprotectin			**0.004**
Mean (SD)	223.1 (170.1)	393.2 (1106.9)	
Range	21.5 - 1202.8	50.8 - 10807.6	
CRP			**0.008**
NA	1	0	
Mean (SD)	3195.4 (4674.3)	4917.2 (6991.4)	
Range	54.9 - 29259.2	129.1 - 34540.8	

(*continued on next page*)

Table 1 (*continued*)

B. Females Mean (SD) or N(%)	NSA (N=108)	SA (N=93)	Chi^2 or Wlicoxon *p*-value
IFABP			0.220
NA	0	3	
Mean (SD)	1529.3 (845.6)	1402.3 (753.5)	
Range	372.4 - 4852.9	336.8 - 3826.7	
LBP			**0.038**
Mean (SD)	4433.4 (3342.3)	5059.8 (3633.3)	
Range	1000.0 - 26107.2	1120.3 - 27578.0	
LPS			0.056
NA	1	2	
Mean (SD)	81.3 (33.6)	70.9 (33.7)	
Range	8.1 - 174.1	7.1 - 142.7	
Age			0.879
Mean (SD)	40.1 (14.1)	40.1 (12.8)	
Range	18.0 - 70.0	18.0 - 65.0	
Diagnostic			0.278
MDD	58 (53.7%)	57 (61.3%)	
BD	50 (46.3%)	36 (38.7%)	
Alcohol abuse			**0.008**
NA	3	3	
No	90 (85.7%)	63 (70.0%)	
Yes	15 (14.3%)	27 (30.0%)	
Substance abuse			0.746
NA	5	4	
0	79 (76.7%)	70 (78.7%)	
1	24 (23.3%)	19 (21.3%)	
BMI			0.219
NA	23	18	
Mean (SD)	23.8 (6.3)	24.3 (5.3)	
Range	14.8 - 53.6	12.9 - 41.7	
Smoker			0.291
NA	9	10	
No	41 (41.4%)	29 (34.9%)	
Current	40 (40.4%)	43 (51.8%)	
Past	18 (18.2%)	11 (13.3%)	
IDS-C30 score			**0.004**
NA	13	23	
Mean (SD)	24.7 (15.7)	31.7 (13.5)	
Range	0.0 - 61.0	0.0 - 60.0	
Psychotropic medication			0.145
None	12 (11.1%)	5 (5.4%)	
At least one	96 (88.9%)	88 (94.6%)	

Table 2
Correlation analysis.

A. Spearman's correlation matrix in males	ApoE	B2m	Calprotectin	CRP	IFABP	LBP	LPS	Age	BMI	IDS-C30 score
ApoE	1.00									
B2m	0.04	1.00								
Calprotectin	0.17	0.01	1.00							
CRP	-0.03	0.11	0.14	1.00						
IFABP	0.02	0.24*	-0.06	-0.03	1.00					
LBP	-0.12	0.30**	0.15	0.75***	0.07	1.00				
LPS	-0.13	0.04	0.08	0.08	0.03	0.03	1.00			
Age	0.14	0.50***	0.00	0.05	0.27**	0.20*	0.15	1.00		
BMI	0.24	-0.02	0.28*	0.13	0.05	0.22	-0.06	0.25*	1.00	
IDS-C30 score	-0.11	-0.14	0.12	-0.02	-0.20	-0.05	-0.22*	-0.35**	-0.05	1.00
B. Spearman's correlation matrix in females	ApoE	B2m	Calprotectin	CRP	IFABP	LBP	LPS	Age	BMI	IDS-C30 score
ApoE	1.00									
B2m	-0.01	1.00								
Calprotectin	0.39***	0.11	1.00							
CRP	0.26***	0.26***	0.41***	1.00						
IFABP	-0.07	0.32***	-0.08	-0.06	1.00					
LBP	-0.13	0.29***	0.02	0.32***	0.14*	1.00				
LPS	0.09	0.07	0.14	-0.05	0.07	-0.04	1.00			
Age	0.24***	0.24***	0.09	0.07	0.23**	0.09	0.25***	1.00		
IMC	0.07	0.14	0.08	0.56***	-0.03	0.36***	0.03	0.07	1.00	
IDS-C30 score	0.17*	-0.04	0.12	0.10	-0.12	-0.09	-0.07	-0.13	-0.04	1.00

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

Table 3
Stepwise multivariate linear regression models for each biomarker.

A. In females																				
	CRP			**Calprotectin**			**B2m**			**ApoE**			**IFABP**			**LBP**			**LPS**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	2.92	1.85 – 3.98	**<0.001**	4.39	3.80 – 4.98	**<0.001**	0.90	0.81 – 0.99	**<0.001**	4.20	3.91 – 4.48	**<0.001**	6.95	6.45 – 7.45	**<0.001**	7.50	7.10 – 7.90	**<0.001**	34.26	13.20 – 55.33	**0.002**
SA [Yes vs No]	0.52	0.11 – 0.93	**0.014**	0.16	-0.05 – 0.37	0.143	-0.02	-0.05 – 0.01	0.154				-0.18	-0.35 – -0.00	**0.049**				-9.94	-21.58 – 1.70	0.094
Age	0.02	0.00 – 0.03	**0.036**	0.01	0.00 – 0.02	**0.019**	-0.00	-0.00 – -0.00	**0.019**	0.01	0.01 – 0.02	**<0.001**	0.01	0.00 – 0.01	**0.046**				0.82	0.37 – 1.27	**<0.001**
BMI	0.15	0.11 – 0.19	**<0.001**	0.02	0.00 – 0.04	**0.026**	-0.00	-0.01 – 0.00	0.084				0.01	-0.00 – 0.03	0.134	0.03	0.01 – 0.05	**<0.001**			
Tobacco [Current vs No smoker]				0.16	-0.09 – 0.42	0.208				-0.04	-0.22 – 0.13	0.622							19.80	6.67 – 32.94	**0.003**
Tobacco [Past vs No smoker]				0.34	0.03 – 0.65	**0.034**				-0.28	-0.51 – -0.05	**0.019**							7.95	-8.90 – 24.80	0.352
Diagnosis [BD vs MDD]				-0.32	-0.54 – -0.10	**0.005**													9.72	-2.36 – 21.80	0.114
Alcohol [Yes vs No]				-0.21	-0.50 – 0.07	0.144															
Psy.medication [[≥1vs No]							-0.06	-0.12 – 0.00	**0.044**				-0.34	-0.67 – -0.01	**0.043**						
Observations	121			120			120			121			117			119			121		
R^2 / R^2 adjusted	0.406 / 0.391			0.242 / 0.195			0.145 / 0.115			0.139 / 0.117			0.130 / 0.099			0.105 / 0.097			0.217 / 0.183		
B. In males	**CRP**			**Calprotectin**			**B2m**			**ApoE**			**IFABP**			**LBP**			**LPS**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	3.93	1.94 – 5.92	**<0.001**	5.43	5.23 – 5.63	**<0.001**	0.85	0.79 – 0.92	**<0.001**	4.15	3.39 – 4.91	**<0.001**	6.68	6.26 – 7.10	**<0.001**	7.30	6.91 – 7.70	**<0.001**	12.54	11.42 – 13.66	**<0.001**
SA [Yes vs No]													-0.20	-0.48 – 0.08	0.155						
Age	0.05	0.02 – 0.07	**<0.001**				-0.00	-0.01 – -0.00	**<0.001**				0.01	0.01 – 0.02	**0.002**	0.02	0.01 – 0.03	**<0.001**			
BMI	0.06	-0.02 – 0.15	0.123							0.03	-0.00 – 0.06	0.068									
Tobacco [Current vs No smoker]	0.34	-0.32 – 1.00	0.306																2.05	0.14 – 3.96	**0.036**
Tobacco [Past vs No smoker]	-0.65	-1.43 – 0.14	0.103																1.26	-0.79 – 3.30	0.223
Diagnosis [BD vs MDD]	-0.78	-1.41 – -0.15	**0.016**				0.07	0.04 – 0.11	**<0.001**							-0.31	-0.54 – -0.08	**0.010**			
Psy.medication [≥1vs No]													-0.17	-0.42 – 0.08	0.177						
Alcohol [Yes vs No]																0.16	-0.07 – 0.39	0.170	-1.87	-3.63 – -0.10	**0.038**
Observations	50			50			50			50			50			50			50		
R^2 / R^2 adjusted	0.369 / 0.297			0.000 / 0.000			0.458 / 0.435			0.068 / 0.048			0.299 / 0.253			0.348 / 0.306			0.121 / 0.064		

the fact that their result has not been replicated, we are confident that our finding deserves to be considered as valid, especially as studies involving knock out mice for IFABP have demonstrated its pivotal role in efficient uptake and trafficking of dietary fatty acids, and that the reduction/absence of IFABP induces alterations in intestinal morphology and secretory cell abundance (Lackey et al., 2020). Along this line, it is worth mentioning that patients with septic shock, or having experienced a trauma with intestinal injury as well as COVID 19 with gastrointestinal manifestations (Tyszko et al., 2022), displayed low circulating levels of IFABP. Finally, given the aforementioned role of IFABP in the processing of fatty acids, we cannot exclude that the observed dysregulated expression of IFABP may underpin the development of the metabolic syndrome (MetS), a well-known deleterious comorbidity of mood disorders, as suggested by studies showing that genetic variation in the IFABP encoding gene is associated with MetS (Turkovic et al., 2012), and that conformational changes of the IFABP molecules can interfere with their function (Storch and McDermott, 2009).

Concerning the other studied biomarkers, we did not observe any statistically significant association with SA although strong trends yielded by univariate analysis were observed. Indeed, both elevated levels of calprotectin and LBP as well as a decrease in LPS were observed in the SA group compared to the NSA group.

The calprotectin molecular complex is pivotal in the generation of inflammatory processes and is mainly produced by the innate immune neutrophil cell subset (Pathirana et al., 2018). Elevated levels of calprotectin reflect heightened rate of inflammation in various pathological settings including chronic inflammatory/autoimmune diseases. High levels of the circulating isoform have been found, for example, in the context of rheumatic diseases (Romand et al., 2020), while in the gut, inflammatory processes are observed in fecal material (Romero-Mascarell et al., 2022; Sarikaya et al., 2015; Turvill, 2014). Such observation can explain, at least in part, the failure to detect an association with the circulating levels in our study. Nevertheless, we found that calprotectin was the only studied biomarker to be statistically different between BD and MDD patients, with elevated levels found in female patients with MDD, suggesting a potential disease-specific role (Table 2B).

Lipopolysaccharides (LPS) are gram-negative bacterial outer cell wall components sensing the TLR4 pathogen-associated molecular pattern (PAMP) receptor. Upon binding to the lipopolysaccharide binding protein, LPS interact with TLR4 initiating a pro-inflammatory signaling cascade with consequent production of pro-inflammatory cytokines. Besides merely reflecting bacterial infection, LPS and LBP, together with IFABP, are markers of gut epithelium integrity (Lau et al., 2016). Moreover, LPS directly binds to apolipoprotein E (ApoE) (Brown, 2019), a well-known protein of the cholesterol metabolism pathway playing a pivotal role in blood brain barrier (BBB) integrity (Montagne et al., 2020) and implicated in the development of neurological disorders including Alzheimer's disease (Yamazaki et al., 2019). The trend towards high levels of LBP may hence be related to a potential intestinal dysbiosis. Concerning the low levels of LPS, we cannot exclude that this compound was not measured immediately after blood clotting which may have altered the structure of the molecules given their very short half-life.

From a clinical perspective, the SA group exhibited a more severe depressive symptomatology measured with the IDS-C30, although failing to reach statistical significance after adjusting for confounding variables. Nevertheless, such observations are in agreement with previous studies postulating that depression does appear to increase suicide risk, even if its effect might be weaker than expected (Holma et al., 2014; Ribeiro et al., 2018). The significant positive correlation between advanced age and levels of inflammatory biomarkers found here is in agreement with the concept of "inflammaging" that conceptualizes natural ageing processes as a strong provider of inflammation (Minciullo et al., 2016; Watson et al., 2017). Only calprotectin did not correlate significantly with age, which makes it a reliable biomarker. Indeed, its levels were significantly reduced in our patients with BD, after adjusting for many confounding factors. Accordingly, previously described trait markers of suicidal vulnerability (Courtet et al., 2015) should be investigated in longitudinal studies to determine time-related level changes of such biomarkers and their role in the pathophysiology of suicidal behavior. In this context, the involvement of CRP in suicidality deserves to be highlighted. CRP is one of the most used inflammatory makers in psychiatric settings (Baysak et al., 2022) especially in association with major mood disorders (Fernandes et al, 2016). Synthesized in the liver under the control of IL-1beta and IL-6, two major pro-inflammatory cytokines, CRP is an acute phase reactant and established marker of inflammation whose concentration increases in circulation during acute inflammatory events but can also be a marker of chronic inflammation as observed in psychiatric disorders (Edberg et al, 2018). In the present study, we found that elevated levels of CRP constitute the best predictor of suicidality which may reflect a peak of inflammation at the time of patient engagement in a suicide act.

Strengths of our study reside mainly in the concomitant evaluation of circulating levels of both systemic and intestinal inflammatory molecules, and in the way we have carefully managed our findings by a statistical approach taking into account confounding factors known to be implicated in inflammatory processes or suicidality, such as BMI and tobacco consumption (Galan et al., 2022; Harrison et al., 2020).

4.1. Limitations

The following limitations should be mentioned: (i) the exploratory nature of the study with a rather small sample size and missing data for some patients, such as the precise date of SA according to the time of evaluation of the studied biomarkers and clinical items, (ii) the lack of a healthy control group and the absence of access to fecal samples which would have allowed to compare fecal with circulating levels of intestinal markers of interest such as calprotectin, (iii) since it was a cross-sectional study, we cannot infer any causal relationship between biomarkers, psychiatric symptoms and suicidal behavior, (iv) although we adjusted for many potential confounding variables, other such as dietary habits, cognitive function, and personality traits (e.g., impulsivity) (Harrison et al., 2020), were not measured and (v) the possible influence of medications on the circulating levels of the studied biomarkers.

4.2. Future directions

Identifying measurable predictive risk factors for SA is of utmost importance, since clinical predictors have poor effectiveness and the current therapeutic strategies for depression (e.g., antidepressants) are not sufficiently protective against suicidal events (Brent, 2016; Van Heeringen and Mann, 2014). Biomarkers can be used not only as independent diagnostic markers for suicidal behaviors in mood disorders, but also to increase the diagnostic accuracy of such disorders when they are used in combination with clinical tools. These findings contribute to expanding and utilizing our understanding of the pathophysiology of intestinal and blood-brain barrier injury involved in suicidal behaviors, and further support the pivotal role of gut-brain interactions in the symptomatology of mood disorders and in suicidal behavior in particular.

From this perspective, future extensive and longitudinal evaluation of inflammation biomarkers might be helpful not only to understand the underlying mechanisms of suicidal behavior, but also to design personalized predictive strategies against suicide attempts in patients with psychiatric diseases, and ultimately to facilitate the development of novel psychopharmacological compounds that might reduce vulnerability to suicide.

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Contributors

JZB performed immunoenzymatic measurements. JZB and MB drafted this article. JZB, MB and MLa performed data analysis. AL, RS, SG, MS and EO were in charge of patients' inclusions and data and sample collection. JRR was in charge of the database management. MC, CLW, WB, JB and SS participated in the experiment design and its execution. RT, MLe and PC conceived and supervised the project and contributed to the writing of the manuscript. RT and MLe finalized the manuscript.

All authors read and approved the final version.

Credit author statement

The present work has not been published previously and is not under consideration for publication elsewhere. Its publication is approved by all authors and tacitly or explicitly by the responsible authorities where the work was carried out, and that, if accepted, it will not be published elsewhere in the same form, in English or in any other language, including electronically without the written consent of the copyright-holder.

Declaration of Competing Interest

All authors declare that they have no conflicts of interest relative to this study.

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