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Brief Report

High hs-CRP levels after an attempted suicide: A matched case-control study

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ABSTRACT

We found significantly higher levels of hs-CRP in 27 subjects who had recently attempted suicide compared to 27 age- and sex-matched healthy subjects. Moreover, the levels of hs-CRP in suicide attempters were not related to background or psychopathological characteristics, nor to the methods of suicide attempt. Our matched case-control study confirms previous observations of high levels of the inflammation marker hs-CRP in patients who have attempted suicide, irrespective of their underlying type and levels of psychopathology.

1. Introduction

Suicidal behavior is a serious public health problem. In particular, the number of suicide attempts is estimated to be over twenty times higher than completed suicides worldwide (WHO, 2017).

Being young, widowed or divorced, and suffering from a psychiatric disorder depict overall risk factors for suicide attempts (Bernal et al., 2007); moreover, a long life history of suicide attempts is linked to a 42-fold increased risk for suicide, indicating that the suicide attempter group needs to be considered at highest risk to complete suicide (Finkelstein et al., 2015).

However, a clear understanding of suicidality pathophysiology is currently lacking. Several models have been proposed in the past decades, the most of which consider both population-level risk factors, such as socio-economical and cultural ones, and individual (heritable, psychosocial and biological) factors (Turecki and Brent, 2016). Among biological factors, immune-inflammatory processes appear to play a key role in the neurobiology of suicidal behavior. Recent systematic reviews and meta-analyses link suicide-related events with a pro-inflammatory state, including increased levels of blood tumor necrosis factor-alpha (TNFa), C-reactive protein (CRP) and interleukin-6 (IL-6), and decreased levels of IL-2 (Chen et al., 2020; Serafini et al., 2020; Miola et al., 2021).

In this context, the routine analysis of serum CRP concentrations as a measure of inflammation remains one of the most widely utilized assays in medicine. High-sensitivity CRP (hs-CRP) is a relevant alternative for research, because of the short half-life of other cytokines, and because of its detectability at lower levels (Courtet et al., 2016). Previous studies focusing on CRP levels in patients with suicidal behaviors revealed contradictory results. Few studies with relatively small sample size showed no significant associations between CRP and suicidal behavior (Karlović et al., 2012; Vargas et al., 2013), while others showed significant associations in patients with mental disorders (O'Donovan et al., 2013; Courtet et al., 2015; Gibbs et al., 2016; Loas et al., 2016; Cáceda et al., 2018). In some of these studies focusing on the relationship between CRP and suicide attempt, increased CRP and pro-inflammatory cytokines have been described in individuals following recent (Ganança et al., 2016; Gibbs et al., 2016) and remote (Courtet et al., 2015) suicide attempts. In addition to inflammatory markers, there is evidence of altered metabolic profiles in suicidal patients (e.g., diminished serum triglycerides, body mass index -BMI- and waist circumference in suicide attempters with mood disorders) compared to those with no history of suicide attempts (da Graca Cantarelli et al., 2015). Altered metabolic profiles in turn are related to childhood adverse experiences (e.g., lower total cholesterol levels) and to high CRP levels (e.g. high triglycerides and low HDL cholesterol) (Ekinci and Ekinci, 2017; Kraav et al., 2019). Additionally, based on recent GWAS data, it appears that the robust genetic correlations between high CRP levels and depressive

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symptom severity are of similar (small) size as the robust genetic correlations between high BMI and depressive symptom severity (Kappelmann et al., 2021). However, to the best of our knowledge, the relationships between hs-CRP concentrations, glycaemia and serum lipid levels in suicide attempters have been understudied.

Thus, our study aimed to investigate the relationship between recent suicide attempt, metabolic (serum lipid profile and glucose levels), inflammatory (hs-CRP levels) and psychopathological variables following suicide attempt in hospitalized psychiatric patients.

2. Methods

2.1. Participants

Twenty-nine inpatients recruited at the Psychiatric Ward of Padova University Hospital, Italy, from 1st January 2018 to 31st July 2020, and a control group of twenty-eight healthy blood donors matched by sex and age participated in the study. The inclusion criteria were: a) being hospitalized in an emergency psychiatric ward for a suicide attempt; b) age 18–75 years; c) male patients d) the willingness to participate in the study by signing a written informed consent.

The exclusion criteria were: a) female patients; b) having a positive history of neoplasia, severe cardiomyopathies with ejection fraction <50, severe renal failure, acute neurological injuries, or neurodegenerative illnesses including Parkinson's, Huntington's Chorea, amyotrophic lateral sclerosis, multiple sclerosis, and dementia; c) the assumption of lipid-lowering or anti-inflammatory drugs. In addition, all patients with hs-CRP values greater than 10 mg/L were excluded because these values were likely attributable to an ongoing acute inflammatory disease.

This study was approved by the local Ethics Committee and undertaken in accordance with the guidelines of the Helsinki Declaration of 1975. All participants accepted voluntarily to participate in the study and provided their written informed consent after receiving a complete explanation of the procedures.

2.2. Assessments and procedures

Socio-demographic, laboratory, and clinical data of recruited patients were investigated during hospitalization through a standardized clinical chart. The inquired patients' domains included age, nationality, marital, occupational and socioeconomic status, education level, circumstances of the recent suicide attempt (method, lethality and intentionality), as well as lifetime history and number of previous suicide attempts. In addition, the presence of recent (in the previous 12 months) conflictual situations or relationships, or deaths of someone close, history of child trauma, and psychiatric history including diagnosis, age of onset and number of episodes were carefully recorded. Psychiatric diagnoses were set according to the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5) (APA, 2013). We adopted the following definition of "suicide attempt": an act characterized by self-inflicted, potentially injurious behavior with non-fatal outcome for which there is evidence - either explicit or implicit - of the intent to die (Silverman et al., 2007).

Laboratory data obtained for all participants and included in our analysis were hs-CRP and a fasting glucose and lipid panel consisting of total, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol, and triglycerides. Admission laboratory data are routinely used to screen patients for medical instability prior to admission, and are drawn routinely, within 24 h of admission, between 7:00 and 8:30 a.m. after at least 10 hour fasting. CRP levels were measured by hs-CRP assay. For the control group, only hs-CRP data from samples drawn in connection with blood donation were available.

The overall severity of affective symptoms in the patient group was assessed using the 17-item Hamilton Rating Scale for Depression (HAM-D) (Hamilton, 1960), and suicidal impulsiveness and intent through the BIS (Barratt Impulsiveness Scale) (Patton et al., 1995) and the ISS (Pierce Suicidal Intent Scale) (Pierce, 1977), respectively. Additionally, the Italian versions of the SCL-90-R (Symptom Checklist-90-Revised) (Prunas et al., 2012) and the CTQ (Child Trauma Questionnaire) (Innamorati et al., 2016) were administered to assess psychopathological profiles and history of childhood maltreatment.

2.3. Statistical analysis

All statistical analyses were performed with R software version 3.5.1 (R Core Team, 2019), with the value of statistical significance set at $p<0.05$. Continuous variables were represented as mean and standard deviation (SD) or median and interquartile range (IQR), as appropriate, while categorical variables were represented as frequency and percentage.

Median hs-CRP values in the patient and in the control groups were compared using the Wilcoxon signed-rank test. Age-controlled correlation analyses between hs-CRP values and total, HDL and LDL cholesterol, triglyceride and blood glucose values in the group of attempted suicides were performed via Spearman's test. Additionally, possible associations between hs-CRP values and sociodemographic variables, as well as clinical and psychopathological measures (HAM-D, ISS, SCL-90-R and CTQ scores) were tested in the group of suicide attempters through the Mann-Whitney U test or the Kruskal Wallis test, as appropriate.

3. Results

A total of 29 inpatients after an attempted suicide were initially recruited. After exclusion of two individuals whose hs-CRP levels were higher than 10 mg/L, a final sample of 27 patients was retained for the analyses. Their basic characteristics are reported in Table 1. Of the 28 initially recruited healthy controls, one was excluded due to hs-CRP levels higher than 10 mg/L.

Median hs-CRP levels were significantly higher in the suicide attempters (2.83, IQR 1.34 to 5.00) compared to controls (0.54, IQR 0.35 to 1.06, $p<0.001$) (Fig. 1).

The levels of hs-CRP in the group of attempted suicide cases did not differ according to the patient's psychiatric diagnosis, method of attempted suicide, severity of depressive symptoms, history of child trauma, recent losses, or relational problems (Table 2).

The levels of hs-CRP in individuals who attempted suicide were not significantly correlated to any metabolic biomarkers, nor to levels of severity of depressive symptoms, suicidal intent, impulsiveness and overall psychopathology (Table 3).

The results did not change when including individuals with hs-CRP levels higher than 10 mg/L in the analyses (Supplementary Figure 1, Supplementary Table 1 and Supplementary Table 2).

4. Discussion

We found significantly higher levels of hs-CRP in subjects who had recently attempted suicide compared to age- and sex-matched healthy subjects. Moreover, the levels of hs-CRP in attempted suicide cases were not related to background, metabolic or psychopathological characteristics, nor to the methods of attempted suicide.

Our findings of higher hs-CRP levels in relation to suicidal attempts are in line with previous results. While general population studies have produced mixed findings (Batty et al., 2016; Park and Kim, 2017; Russell et al., 2020, 2021), possible biomarkers of suicidality in psychiatric, especially depressed patients have been quite consistently identified. According to a recent meta-analysis, CRP levels in suicidal depressive patients (ranging from suicidal thoughts to completed suicide) are higher when compared to both non-suicidal depressed patients and healthy controls (Chen et al., 2020). In specific, even though with some inconsistencies (Coryell et al., 2018, 2020), CRP levels appear to be

Table 1
Basic characteristics of the patients ($n = 27$) hospitalized after an attempted suicide.

	N (%) / mean (SD) / median (IQR)
***N* = 27**	
Civil status	
Single	9 (33.3%)
Married/cohabiting	11 (40.7%)
Divorced/Widowed	7 (25.9%)
Living conditions	
With partner (with or without children)	12 (44.4%)
Alone/with children only	8 (29.6%)
With parents	7 (25.9%)
Level of education	
Low	11 (40.7%)
Medium/high	16 (59.3%)
Socioeconomic level	
Low	12 (44.4%)
Medium	15 (55.6%)
Psychiatric diagnosis	
Mood disorder	14 (51.9%)
Personality disorder	7 (25.9%)
Substance abuse/dependence	3 (11.1%)
Other	3 (11.1%)
Suicidal method	
Poisoning	15 (55.6%)
Hanging/Jumping/Drowning	7 (25.9%)
Cutting	5 (18.5%)
Relational problems/past 12 months (yes)	18 (66.7%)
Any loss/past 12 months (yes)	3 (11.1%)
Total Cholesterol mmol/L (mean (SD))	5.12 (1.27)
HDL Cholesterol mmol/L (median [IQR])	1.25 [1.09, 1.37]
LDL Cholesterol mmol/L (median [IQR])	3.17 [2.66, 4.19]
Triglyceridesmmol/L (median [IQR])	1.29 [1.16, 1.86]
Glucosemmol/L (median [IQR])	5.10 [4.50, 5.40]
HAMD total score (mean (SD))	20.15 (5.54)
Depressive symptoms (HAMD)	
Mild	4 (14.8)
Moderate	8 (29.6)
Severe	5 (18.5)
Very severe	10 (37.0)
ISS total score (mean (SD))	14.30 (4.22)
SCL90-R-GSI total score (median (IQR))	0.82 (0.47–1.67)
BIS total score (mean (SD))	64.37 (12.83)
CTQ Emotional Abuse	
None	17 (63.0%)
Low	7 (25.9%)
Moderate/Severe	3 (11.1%)
CTQ Physical Abuse	
None	21 (77.8%)
Low	1 (3.7%)
Moderate/Severe	5 (18.5%)
CTQ Sexual Abuse	
None	22 (81.5%)
Low	2 (7.4%)
Moderate/Severe	3 (11.1%)
CTQ Emotional Neglect	
None	16 (59.3%)
Low	4 (14.8%)
Moderate/Severe	7 (25.9%)
CTQ Physical Neglect	
None	17 (63.0%)
Low	2 (7.4%)
Moderate/Severe	8 (29.6%)
CTQ Total score (median (IQR))	33.0 (29.0, 46.0)

BIS, Barratt Impulsiveness Scale; CTQ, Child Trauma Questionnaire; HAMD, Hamilton Depression Rating Scale; ISS, Pierce Suicidal Intent Scale; SCL90-R-GSI, Symptom Checklist-90-Revised Global Severity Index.

higher in those with than in those without a history of suicide attempt, irrespective of potential confounders such as psychiatric comorbidity or chronic illness, or time since the attempt (Courtet et al., 2015; Loas et al., 2016). Less clear is the relationship between inflammatory markers and suicidal ideation (Bergmans et al., 2019; Courtet et al., 2015; O'Donovan et al., 2013). In spite of results suggestive of a similar pattern of association (Chang et al., 2017; O'Donovan et al., 2013), Caceda et al. (2018) reported a relationship between high CRP levels and number of lifetime suicide attempts, but not severity of current suicidal ideation among depressed patients. Instead, severity of suicidal ideation was correlated with physical pain, but not with depression severity or psychological pain. Based on these findings the authors concluded that the inflammation status detected in relation to suicidal behavior may be an abiding suicidal trait rather than marker of acute suicidality (Caceda et al., 2018). While this hypothesis partly contrasts with previous findings of high CRP in relation to past, but not recent (during the previous month) attempted suicide (Dickerson et al., 2017), it is partly in line with our results. In fact, the lack of correlations in our study between hs-CRP levels (measured shortly after the attempted suicide) vs. other metabolic biomarkers, indicators of depression severity and other psychological symptoms further suggests that inflammation may be specifically related to suicidal behavior, rather than to underlying or triggering conditions.

Accumulating evidence has shown that many psychiatric conditions (such as depression, schizophrenia, bipolar disorder) are characterized by an inflammatory status as identified by high levels of CRP (Fernandes et al., 2016a, 2016b; Osimo et al., 2019). Thus, it cannot be ruled out that different hs-CRP levels between suicide attempters and controls in our study are in fact due to underlying psychopathology. However, the hypothesis of inflammation as an independent marker of suicidality has been supported by a recent meta-analysis of psychiatric patients, showing that CRP levels are higher in individuals with suicidal ideation or behavior when compared to non-suicidal subjects or to those with lowest suicidality, irrespective of the underlying psychiatric diagnosis. This observation points to increased CRP as a transdiagnostic marker of suicidal ideation and attempt (Miola et al., 2021), and is in line with our finding of similarly high hs-CRP levels across different psychiatric diagnoses in the group of suicide attempters. A possible mechanism underpinning the association between peripheral inflammation (as indicated in our study by high levels of hs-CRP) and suicidal behavior could be the enhanced permeability of the blood-brain barrier, and consequent direct or indirect effects on the central nervous systems. In fact, peripheral inflammation and consequent inflammatory molecules can disrupt the blood–brain barrier, causing dysfunction and increased permeability, abnormalities typically found in many Central Nervous System diseases (Huang et al., 2021). Additionally, alterations of the immune function and increased blood levels of cytokines and inflammatory factors (e.g., IL-1, IL-6, TNFa) have been identified in psychiatric disorders such as schizophrenia and depression, and many neurons have receptors for inflammatory cytokines. In this way, inflammation could have direct effects on neuronal functioning, possibly leading to modifications in the levels of neurotransmitters, and thus to altered mood and/or behavior (Steiner et al., 2013; Brundin et al., 2015; Huang et al., 2021).

The main limitation of this study is the small number of participants, which did not allow us to detect possible influences of psychiatric diagnosis, childhood trauma and metabolic parameters on hs-CRP levels. Another limitation arises from the lack of background information in the control group, including their mental health-related characteristics and previous and current suicidality. However, because the controls were selected from blood donors after application of stringent exclusion criteria, they were likely to be healthy individuals. The lack of laboratory data in the control group did not allow us to examine differences between suicide attempters and healthy controls in parameters other than hs-CRP levels. Moreover, we did not have information on participants' BMI, which is known to be highly related to CRP levels (Lear et al., 2003). Additionally, by including only male participants, we ruled out possible hormone-related variations in hs-CRP levels. Moreover, cases and controls were matched by age, and correlation analyses in the attempted suicide group were controlled by age. Given the short time interval between the attempted suicide and the hs-CRP measurement, we cannot rule out that the detected difference between cases and controls is due to the stress or physical traumatism and tissue damage

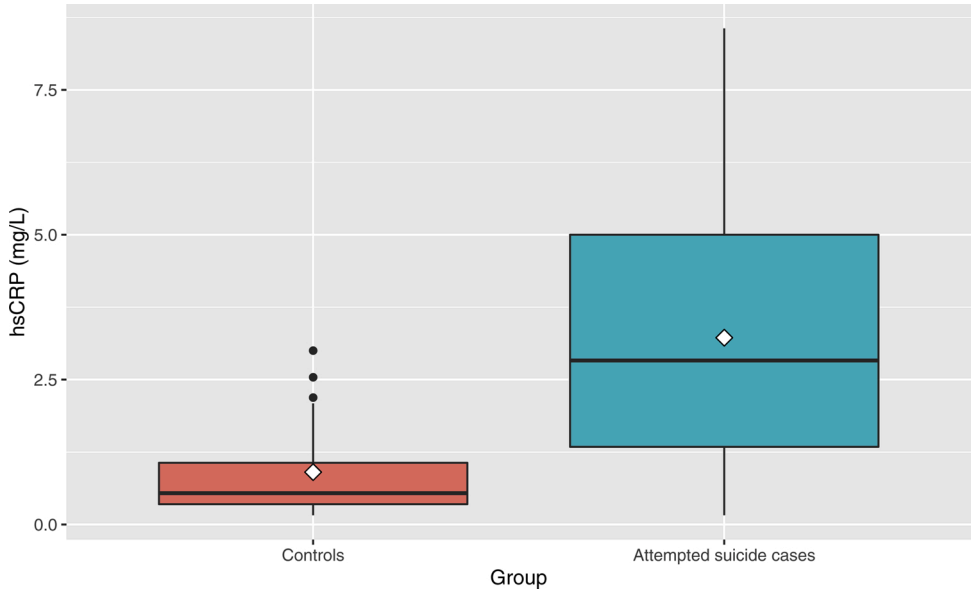

Fig. 1. hs-CRP concentrations in suicide attempters and healthy controls. Boxes represent interquartile ranges, black lines represent median values, diamonds are mean values, and vertical bars are minimum and maximum values.

Table 2
Associations between categorical background characteristics and hs-CRP levels.

	hs-CRP mg/L (median, IQR)		*p*-value *
	Event, yes	Event, no	
History of child trauma, emotional abuse	2.56 (1.09 to 3.82)	2.90 (1.89 to 5.13)	0.725
History of child trauma, physical abuse	2.56 (1.29 to 6.22)	2.90 (1.68 to 4.87)	0.977
History of child trauma, sexual abuse	2.67 (2.17 to 7.40)	2.87 (1.17 to 4.63)	0.532
History of child trauma, emotional neglect	2.67 (1.34 to 6.72)	2.87 (1.65 to 3.87)	0.570
History of child trauma, physical neglect	3.62 (1.29 to 7.06)	2.67 (1.68 t o3.53)	0.328
Any loss/past 12 months	1.89 (1.41 to 2.03)	3.00 (1.51 to 5.14)	0.232
Relational problems/past 12 months	2.75 (1.22 to 4.86)	2.90 (1.68 to 4.87)	0.777
Depressive symptoms (HAMD)	Severe/Very severe: 3.09 (2.24 to 5.24)	Mild/ Moderate: 1.92 (0.92 to 3.72)	0.213
Psychiatric diagnosis			0.882**
Mood disorder	2.44 (1.11 to 5.10)	—	
Personality disorder	3.09 (1.83 to 5.24)	—	
Substance abuse/dependence	2.45 (1.50 to 2.90)	—	
Other	2.90 (2.54 to 3.21)	—	
Suicidal method			0.927**
Poisoning	2.45 (0.95 to 5.24)	—	
Hanging/Jumping/Drowning	3.09 (2.26 to 4.11)	—	
Cutting	2.90 (1.89 to 3.91)	—	

* p-value from Mann-Whitney U test.
** p-value from Kruskal-Wallis test comparing hs-CRP values across psychiatric diagnoses or suicidal methods.

caused by the suicidal act itself. However, the levels of hs-CRP did not differ across suicidal methods, suggesting that the introduced bias is likely limited. Similarly, we cannot rule out that higher hs-CRP levels in attempted suicide cases may be partly caused by psychotropic drug use.

Table 3
Age-controlled Spearman correlation between continuous background characteristics and hs-CRP levels.

	hs-CRP ρ	p-value
Total Cholesterol	0.20	0.372
HDL Cholesterol	−0.11	0.627
LDL Cholesterol	0.20	0.384
Triglycerides	−0.12	0.602
Glucose	0.06	0.765
HAMD score	0.27	0.189
ISS total score	−0.04	0.839
SCL90-GSI total score	0.20	0.320
BIS total score	0.03	0.902

BIS, Barratt Impulsiveness Scale; HAMD, Hamilton Depression Rating Scale; ISS, Pierce Suicidal Intent Scale; SCL90-R-GSI, Symptom Checklist-90-Revised Global Severity Index.

In conclusion, our matched case-control study confirms previous observations of high levels of the inflammation marker hs-CRP in patients who have attempted suicide, irrespective of their underlying type and levels of psychopathology.

Declaration of Competing Interest

All the authors have no conflict of interest.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jadr.2022.100381.

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