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C-reactive protein in anhedonia among patients with major depressive disorder and its relation to suicidal ideation

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Abstract

Background There is evidence that major depressive disorder (MDD) with its cardinal symptoms, anhedonia and suicide, are linked with raised inflammatory markers like C-reactive protein (CRP). This case–control study investigated the correlation between high sensitive CRP (Hs-CRP), anhedonia, suicidal ideation, and depression severity in MDD patients.

Methods Forty-one MDD patients and 47 healthy controls were recruited. MDD diagnosis was confirmed using DSM-5 criteria. Depression severity, anhedonia, and suicidal ideation were assessed using standardized scales. Serum Hs-CRP levels were measured as an inflammatory marker.

Results MDD cases had significantly greater Hs-CRP levels compared to controls. Additionally, Hs-CRP levels were positively correlated with both anhedonia and suicidal ideation in MDD cases. Depression severity was significantly linked with both anhedonia and suicidal ideation.

Conclusion This study suggests a link between inflammation, anhedonia, suicidal ideation, and depression severity in MDD patients. Additional research is necessary to find out the principal mechanisms.

Keywords Depressive disorder, Anhedonia, Suicide, Inflammatory markers, CRP

Background

The hallmarks of major depressive disorder (MDD) are a number of impairing symptoms, particularly in two main areas: increases in negative mood and affect and decreases in positive affect. An approximated 40% of cases relapse within 2 years after receiving antidepressant treatments [21] or standard-of-care psychotherapies involving cognitive behavioral medication [13, 14]. Up to 40–50% of cases do not respond appropriately

to either of these treatments. The primary indicator of depression is anhedonia, which is characterized by a lack of motivation and/or enjoyment. It is frequently enduring, particularly in those who do not get better after trying treatment [16, 36]. One of the biggest challenges to global public health is suicide. Ninety percent of suicide victims have one or more psychiatric disorders, of these, MDD alone accounts for 59 to 87% of suicides [11, 39]. Anhedonia is correlated with an elevated possibility of future suicidal behaviors [4]. Anhedonia and inflammation have been shown to interact to contribute to the pathophysiology of MDD, particularly to anhedonia symptoms [52]. According to Felger et al. [18], a significant percentage of MDD cases show evidence of inflammation in the peripheral and central nervous systems, including elevated levels of inflammatory cytokines and the acute phase reactant CRP. Reduced reactivity to conventional antidepressant drugs is linked with elevated

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inflammation [20, 26, 28], most possible as a result of known effects on neurotransmitter systems and associated neurocircuits. Certainly, mesolimbic dopamine and corticostriatal reward circuits are impacted by inflammation, both naturally occurring and caused by experimentation, and these circuits are connected to changed motivational states and anhedonia [17].

Aim of the work

This study's aim was to investigate the correlation between high sensitive CRP (Hs-CRP), anhedonia, suicidal ideation, and depression severity in an Egyptian sample of MDD patients.

Subject and methods

This research is a cross-sectional case–control study. The research was authorized via the scientific and ethical committee of the Faculty of Medicine, Fayoum University, in (M 668, 13 August 2023).

The cases were enrolled from the Psychiatry Outpatient Clinic, Fayoum University, which is performed 3 days weekly via the time from September 2023 until February 2024 by consecutive sampling.

Every study participant had to provide written consent. In order to verify the subject's information and documentation, the principal investigator had to go over consent forms that had been signed. The principal and co-investigator were the only people with access to the coded and secure patient data on a personal computer. A semi-structured interview derived from the psychiatric sheet of the Fayoum Psychiatry Department was used to interview the cases who met the inclusion criteria. The interviews were structured clinical interviews dependent on the DSM-5 (SCID-5-RV) to diagnose MDD, the Beck Depression Inventory scale to assess the depression's severity, the Snaith Hamilton Pleasure Scale to identify and measure anhedonia, and the Suicidal Ideation's Beck Scale to identify and measure the suicidal ideation's severity. Both the patients' and the control group's serum Hs-CRP levels were then assessed.

➤ Group A (patients group)

Forty-one cases with the sample size were detected as minimum as 35 cases with effect size 0.7 in two-sided (two tails) type I error 0.05 and power of 80%. MDD has diagnosed patients from the Outpatient Psychiatric Clinic at Fayoum University Hospital using SCID-5-RV. All cases fulfilled the inclusion criteria (both genders, age ranges between 18 and 50 years, not receiving any medications, substances, or electroconvulsive treatment in the last 6 months).

As regards exclusion criteria, patients with organic medical conditions, organic brain disease, inflammatory, and infectious and autoimmune diseases and patients with another mental disorder, substance use disorder, and pregnant women were excluded.

➤ Group B (control group)

Forty-seven (47) healthy volunteers, matched by gender and age to the case group, were recruited from the hospital staff. No prior neurological, medical, psychiatric conditions or substance abuse. All volunteers provided written informed consent to take part in the study.

Methods

1. Psychiatric assessment: All cases were interviewed by utilizing the semi-structured interview resulting from the psychiatric sheet of Fayoum Psychiatry Department; relevant data involve the following: marital status, sociodemographic data, occupation, age at substance use onset, period of substance use, and family history.
2. Structured Clinical Interview for DSM-5 Disorders-Research Version (SCID-5-RV): The SCID-5-RV [19].
3. Psychometric evaluation.
 - (a) Beck's Depression Inventory (BDI) [7], Arabic translated version [1, 2]): Beck Depression Inventory scale was originally developed to measure the depressive symptoms' severity among patients with depressive illness. The highest possible score for the whole test would be 63, and the lowest possible score for the test would be 0.
 - (b) Snaith Hamilton Pleasure Scale (SHAPS) [47]: Arabic translated version [50]: In recent days, this scale has questioned the hedonic capacity. The 14-item questionnaire has four response options: strongly/definitely disagree, disagree, agree, and strongly/definitely agree. The overall result may vary from 0 to 14. Items marked as disagree and strongly/definitely disagree receive a score of 1, while agree, strongly/definitely agree, and agree responses receive a score of 0 [47]. The anhedonic group is made up of participants who score three or greater. The Arabic version was obtained from.
 - (c) The Arabic version of the Beck Scale of Suicidal Ideation (BSSI) [5]: The efficacious interviewer-rated version of the Scale for Suicide Ideation [6] acted as the model for the 1988 development of the original BSSI. In the self-report version of the BSI, the case is asked to read

through 19 groups of statements and choose the one that most accurately describes their feelings over the last week, including today. Three statements total for each group, ranging in severity from 0 to 2 on a 3-point rating system. Thus, the range of total scores is 0 to 38. Suicidal ideators can also be identified using the first five items of the BSI [5]. The patient is instructed to skip the next 14 items, which include detailed information about their plans and attitudes and if they score 0 on either of the 2 items: item 4 (active suicidal desire) or item 5 (passive suicidal desire). If not, the previous 14 items receive a rating.

(4) Laboratory tests and specimen collection

To confirm the plasma Hs-CRP level, blood samples were taken from each participant. Each participant had a venipuncture to obtain a 5-ml anticoagulant-free aliquot of blood. Centrifugation was performed 60 min after collection to remove serum from the coagulated or packed cells after complete clot formation. Items that are not examined within a day of being collected are frozen at -20°C . ELISA conducted the measurements [51].

Statistical analysis

All data was gathered, encrypted, and safely stored on a personal computer that was only accessible by the principal investigator. After the data was analyzed with the Statistical Package for Social Sciences (SPSS) software version 22 in Windows 7 (SPSS Inc., Chicago, IL, USA), the relevant statistical tests were selected. The size of the study sample was determined utilizing GPower[®] software version 3.1.7 (Institute of Experimental Psychology, Heinrich Heine University, Dusseldorf, Germany). To confirm normality, the quantitative data from the study were first run via the one-sample Kolmogorov–Smirnov test for each study group. Dependent on the findings, inferential statistical tests were chosen. When dealing with quantitative parametric data, comparisons of quantitative measures between more than two independent groups were made using the one-way ANOVA test, and comparisons between two independent groups were made using the independent samples *t*-test. The Mann–Whitney test was employed to compare two independent groups, and the Kruskal–Wallis test was utilized when comparing more than two independent groups in quantitative nonparametric data. The chi-square test was applied to the qualitative data in order to compare two or more qualitative groups. You can employ the bivariate Pearson correlation test

to determine the relationship between two quantitative parametric variables. One tool used to investigate the relationship between nonparametric, quantitative variables is the bivariate Spearman's correlation test.

Results

Table 1 showed no significant results between the study groups as regards sociodemographic data.

Figures 1, 2 and 3 demonstrated that the mean Beck Depression Inventory (BDI) score was 33.39 ± 8.4 , mean Snaith-Hamilton Pleasure Scale (SHAPS) score was 5.93 ± 3.77 , and mean Beck Scale for Suicidal Ideation (BSSI) score was 9.95 ± 9.9 . A total of 43.9% of cases showed severe level of BDI, and 41.5% showed extremely severe level. For SHAPS levels, 80.5% of study group were positive, and 63.4% of them were positive BSSI. (This means that 43.9% of cases had severe depression, 41.5 had extremely severe depression, 80.5% had anhedonia, and 63.4 had suicidal ideation.)

Table 2 explained that there was statistically significant high level of hs-CRP with p -value < 0.001 among cases in comparison to controls. (This means that hs-CRP level is elevated in cases of depression.) Also, this table indicated that there was no statistically significant difference with p -value > 0.05 in hs-CRP levels between various levels of BDI. (This means that hs-CRP level was not affected by depression severity.) In contrast, there was a statistically significantly greater level of hs-CRP level among cases with positive SHAPS and BSSI with p -value 0.03. (This means that there is high hs-CRP level in cases with anhedonia and suicidal ideation.)

Table 3 illustrated that among cases, there was statistically significant *positive* correlation with p -value < 0.05 between Hs-CRP level and both SHAPS and BSSI scores. (This means that the increase in the severity of anhedonia and suicidal ideation was linked with higher Hs-CRP level.)

In contrast, there was no statistically significant link with p -value > 0.05 between level of Hs-CRP and any of age of patients or BDI. (This means that the increase in age and the depression's severity were not linked with greater hs-CRP level.)

Figures 4, 5 and 6 illustrated that among cases, there was statistically significant *positive* correlation between BDI score and both SHAPS, and BSSI scores of patients, which indicated an *elevation* in depression severity, will associate with *elevation* in anhedonia severity and suicidal ideation. Furthermore, there was a statistically significant link between SHAPS and BSSI scores of patients, which indicated an *increase* in

Table 1 Comparisons of different sociodemographic characteristics in study groups

Variables	Cases (N=41)		Control (N=47)		p-value	Sig.
Age (years)						
Mean ± SD	28.63 ± 9.9		29.28 ± 8.38		0.74	NS
Gender						
Male	6	14.6%	13	27.7%	0.19	NS
Female	35	85.4%	34	72.3%		
Marital status						
Single	19	46.3%	15	31.9%	0.18	NS
Married	20	48.8%	32	68.1%		
Widow	1	2.4%	0	0%		
Divorced	1	2.4%	0	0%		
Educational level						
Illiterate	11	26.8%	5	10.6%	0.11	NS
Basic	5	12.2%	8	17%		
Secondary	5	12.2%	13	27.7%		
University	20	48.8%	21	44.7%		
Occupation						
Unemployed	31	75.6%	28	59.6%	0.08	NS
Employer	3	7.3%	12	25.5%		
Free business	7	17.1%	7	14.9%		

BDI levels among cases

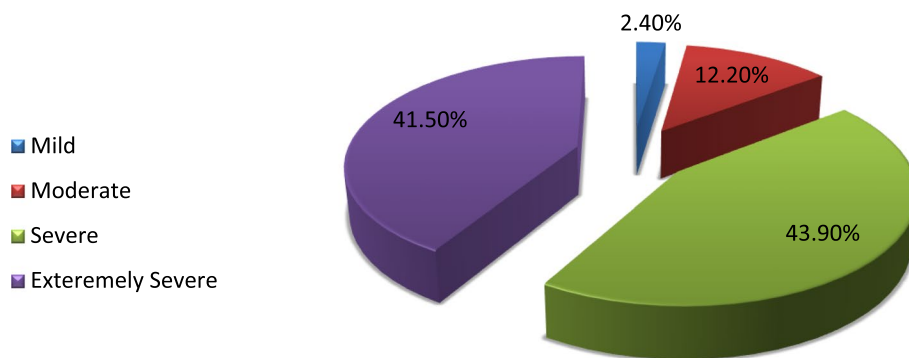


Fig. 1 BDI levels among cases

anhedonia score will associate with *increase* in suicidal ideation scores.

Discussion

As regards suicide and anhedonia in our study group, 80.5% were positive for anhedonia, and 63.4% of study group were positive for suicide (Figs. 2 and 3). This result is consistent with Cao et al. [10] who found that anhedonia occurrence is about 70% in individuals with MDD. Also, consistent with [34] who noted 86.2% of the cases had a SHAPS > 5, which can be deemed as a severe anhedonia in a specimen of 1657 cases with MDD.

Furthermore, this result corresponds with Kaggwa et al. [29], who stated that approximately half of those who screened positive for depression had suicidal ideation. Also in line with [55] who showed that 56–88% of cases had suicidal ideation in some of the evaluations, but only 8–44% in all of them. But inconsistent with the meta-analysis that showed that only 37.7% of the MDD patients had suicidal ideation [8]. This difference may be owing to the sample size and population and whether the participants with MDD were clinical sample or from general population as those who enrolled in clinics have more severe symptoms with greater incidence of suicide.

SHAPS levels among cases

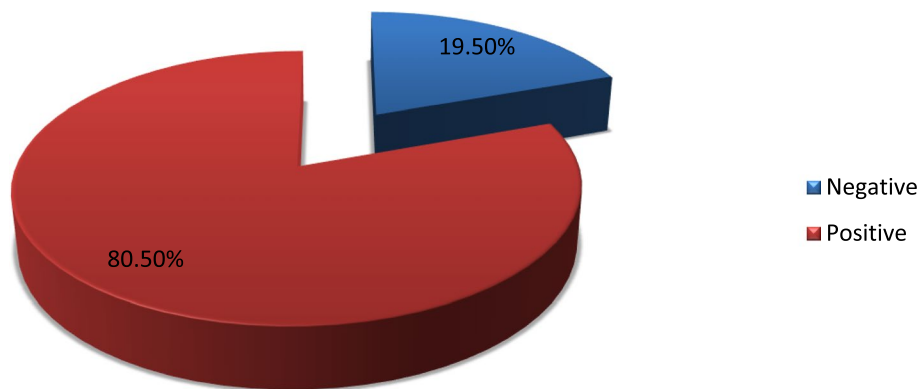


Fig. 2 SHAPS levels among cases

BSSI levels among cases

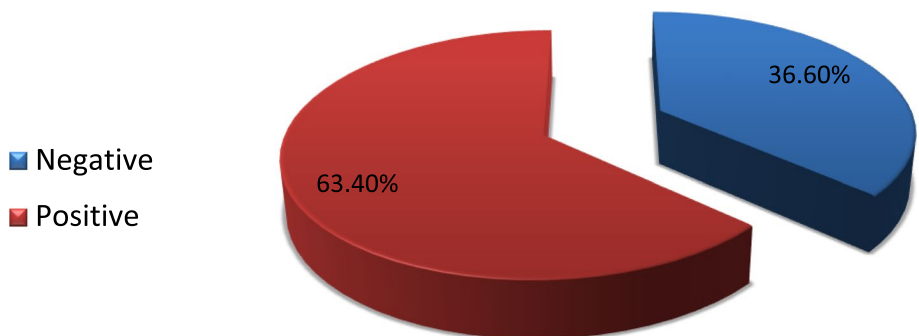


Fig. 3 BSSI levels among cases

This study demonstrated a statistically significant difference in serum Hs-CRP level between controls and MDD group (51.3 ± 27.3 vs. 79.8 ± 24.3 in both groups consecutively) (p -value < 0.001) (Table 2). This result is in agreement with a latest meta-analysis that noted that serum CRP levels were extreme in depressive cases than those in non-depressive ones [18, 40, 41]. Numerous observational studies have supported a link with greater CRP levels among depression’s cases [23, 30, 35]. In contrast, studies using general population specimens found no link between depression and raised serum CRP after adjusting for lifestyle, sociodemographic, and disease covariates [48, 54, 57]. Additionally, two studies noted negative correlation, i.e., depression was linked with less CRP levels [9, 25]. These inconsistencies could be the

result of modifications for potentially confounding variables, methods for measuring depression, or variations in the study populations with regard to sex, age, or race/ethnicity, so our study may add a relative consideration to the importance of CRP among MDD in Egyptians.

According to the existing study, there was a statistically significant difference (p -value = 0.037) in the serum Hs-CRP level between cases who had suicidal thoughts and patients who did not (Table 2). This is in line with research by Chen et al. [12], which found that CRP levels were greater in patients with suicidal depression than in non-suicidal depression patients or healthy controls. It is also in line with research by Miola et al. [38], which discovered that CRP levels were higher in people exhibiting suicidal ideation or behavior than in non-suicidal

Table 2 Comparisons of Hs-CRP level in diverse study groups and comparisons of Hs-CRP level in different psychiatric problems among cases

Variables	Hs-CRP (ng/ml)		p-value	Sig.
	Mean ± SD			
Cases	79.8 ± 24.3		<0.001*	HS
Control	51.3 ± 27.3			
Variables	Median	Range	p-value	Sig.
BDI levels				
Mild	--	--	0.069	NS
Moderate	68.8	25.65–102.28		
Severe	70.8	15.19–119.93		
Extremely severe	90.12	63.06–112.60		
SHAPS levels				
Negative	57.46	15.19–108.10	0.035*	S
Positive	88.5	54.86–119.93		
BSSI levels				
Negative	70.18	15.19–119.93	0.037*	S
Positive	90.36	54.86–111.19		

*p value < 0.05

**p value < 0.001

Table 3 Correlation between Hs-CRP with psychiatric problem scores among cases

Variables	Hs-CRP (ng/ml)		Sig.
	R	p-value	
Age	0.006	0.96	NS
BDI score	0.29	0.063	NS
SHAPS score	0.49	0.001	HS
BSSI score	0.32	0.039	S

*p value < 0.05

**p value < 0.001

subjects. This finding, however, conflicts with that of Russell et al. [44], who discovered no link between CRP and adult suicide in Taiwan. It is probable that different populations have different causes of systemic inflammation, and that different populations have different relationships between inflammatory markers and suicide. Additionally, compared to Caucasian populations, East Asian populations had lower levels of CRP, according to Saito et al. [45].

The current investigation revealed a statistically significant difference (p -value=0.035) in the serum Hs-CRP level between patients with and without anhedonia (Table 2). This finding is consistent with that of Raison & Miller [42], who discovered that anhedonia and psychomotor slowing are caused by elevated inflammation

as determined by CRP. Additionally, Li et al.'s [32] study demonstrated a positive correlation between the serum levels of cortisol, CRP, and IL-6 and the SHAPS score. The theory that inflammation could be the root cause of depression's anhedonia symptom could explain this. Remarkably, resistance to standard antidepressant medications has been independently linked to both inflammation and anhedonia [37, 53]. Furthermore, a number of studies show that anti-cytokine therapies that block inflammation specifically lessen anhedonia symptoms in cases with depression [31, 43, 46].

This study indicated that raised plasma levels of Hs-CRP have no significant correlation with depression intensity (p -value=0.069) (Table 3). These findings are in line with Huckvale et al. [27] who noted no link between CRP and depressive symptom severity but inconsistent with Liu et al. [33], Orsolini et al. [40], and Tayefi et al. [49] who noted extreme depressive symptom intensity with greater CRP levels. The correlation between the intensity of depression and CRP levels has been found to be inconsistent. This could be attributed to factors such as age, gender, smoking status, BMI, and sample size differences between studies that significantly influenced CRP levels in depressed patients.

This study showed that among cases, there was statistically significant positive correlation with p -value < 0.05 between severity of depression, anhedonia, and suicide (Figs. 4, 5 and 6) which indicated an increase in severity of depression will be associated with increase in severity of anhedonia and severity of suicidal ideas. Furthermore, these findings are consistent with Gabbay et al. [22], who observed that a greater level of anhedonia was linked with more severe clinical outcomes, including a higher degree of overall illness severity, longer episodes, higher suicidality scores, and a higher number of MDD episodes. Likewise, further studies demonstrated a positive link between concurrent levels of anhedonia and suicide ideation, and anhedonia may have predictive value for future levels of suicide ideation as was indicated by Ducasse et al. [15], Gillis-sie et al. [24], and Winer et al. [56]. In a study analyzing data from 103 cases who either tried to kill themselves or died by suicide throughout the STEP-BD trial, anhedonia and the severity of suicide ideation elevated in the months preceding suicidal behavior [3]. Research evaluating ketamine as a suicidality intervention observes that although lower will to live was linked to anhedonia before ketamine treatment, lower anhedonia levels were linked to fewer suicidal thoughts and higher causes to live after ketamine medication [4]. Thus, combining psychopharmacological intervention with anhedonia-specific intervention strategies could improve the efficacy of suicidality medication.

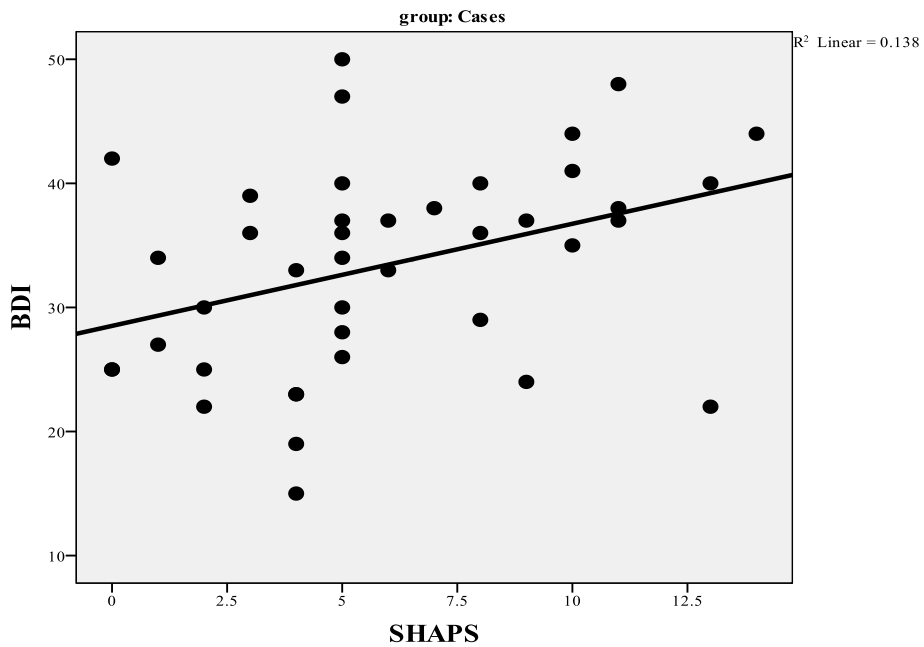


Fig. 4 Link between BDI scores and SHAPS scores among cases

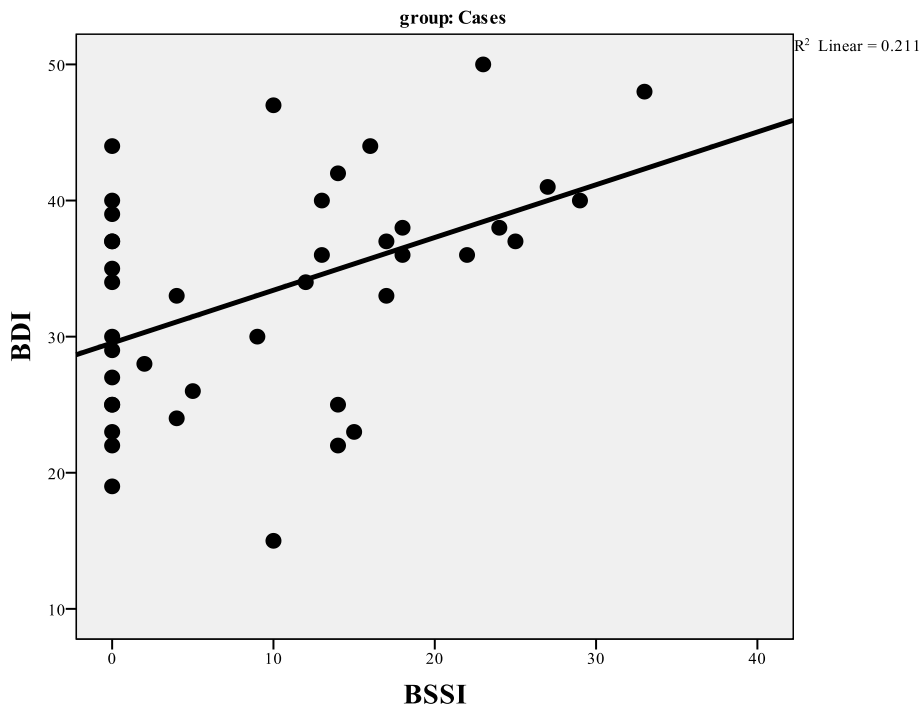


Fig. 5 Link between BDI scores and BSSI scores among cases

Conclusion

People with MDD have much higher levels of CRP than healthy controls. Anhedonia and suicidal thoughts are associated with elevated CRP in

individuals with MDD. Suicidal thoughts and anhedonia are linked to depression severity. Anhedonia is linked with increase in suicidal ideation in MDD cases.

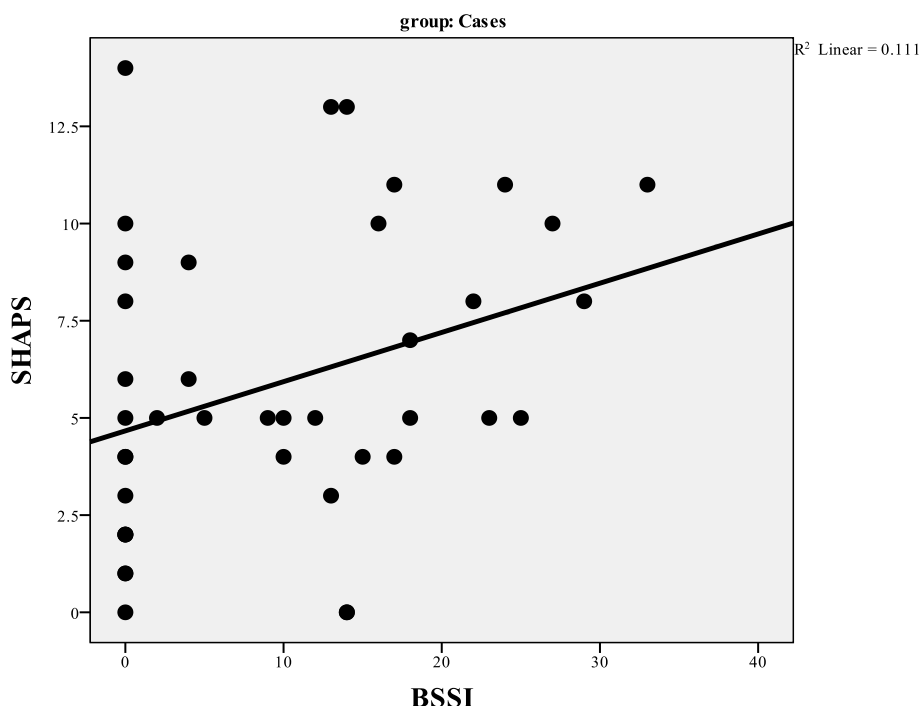


Fig. 6 Link between SHAPS scores and BSSI scores among cases

Limitation

Utilizing case–control studies can help avoid drawing conclusions about causal relationships because the participants showed enough insight to recognize that their symptoms were excessive or distressing because they were seen in a hospital-based treatment clinic. However, sample size calculation was done, and our sample size is still a limitation because of vast number of previous research in the relation between CRP and depression and suicide with contradictory results. Yet, to the best of our knowledge, only few numbers of articles have studied the relation of CRP to anhedonia especially in Egypt. Consequently, low numbers of patients with mild symptoms may reduce the power to detect meaningful associations. The present research evaluated the mood disorder’s current episode rather than its lifetime incidence, meaning that follow-up studies may be necessary after episodes have remitted to explore such a relationship between CRP and MDD. Not excluding smoking may constitute a confounding factor as it may impact CRP. Utilizing only Hs-CRP can affect the conclusion about the significance of inflammatory markers in depression as it is not specific for neuropsychiatric disorders, so further studies with other inflammatory markers and larger sample should be investigated.

Abbreviations

- BDI Beck’s Depression Inventory
- BSSI Beck Scale of Suicidal Ideation
- Hs CRP High sensitive C-reactive protein
- MDD Major depressive disorder
- SHAPS Snaith Hamilton Pleasure Scale

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Authors’ contributions

HD¹ was the main supervisor in revising the research. MS² prepared the main idea, revise the data, and analyzed the data. AR³ was the principal investigator and was responsible for collecting data and samples and interpreting the results of psychological tools. MD⁴ was the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Funding

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Availability of data and materials

NA.

Declarations

Ethics approval and consent to participate

The research was authorized by the scientific and ethical committee of the Faculty of Medicine, Fayoum University in (M 668, 13 August 2023). The principal and co-investigator were the only individuals with access to the coded and secure patient data on a personal computer.

Consent for publication

All authors agreed the manuscript and give their consent for submission and publication.

Competing interests

The authors declare that they have no competing interests.

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