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Immunological Markers and Brain Derived Neurotrophic Factor in Major Depressive Disorder

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KEYWORDS

Brain Derived Neurotrophic Factor, Immunological Markers, Major Depressive Disorder.

ABSTRACT:

Background: Therapeutic approaches for major depressive disorder (MDD) are accessible; however, outcomes remain suboptimal, with approximately 50% of patients failing to achieve adequate response. The objective of this study was to evaluate immunological markers and brain-derived neurotrophic factor (BDNF) levels in a cohort of drug-free persons diagnosed with MDD, in a group of healthy first degree relatives of those cases diagnosed with MDD matched for sex and age, assessment of immunological markers and BDNF in a group of healthy control subjects matched for sex and age, comparison between 3 mentioned groups and assessment of correlation between severity of MDD and (immunological markers and BDNF) in patients' group.

Methods: This cross sectional study involved 90 persons. All cases were selected by simple random sampling and randomized into 3 equal groups: Patients' group with MDD diagnosed according to DSM-5 criteria, first degree relatives group; Healthy first degree relatives matched for sex and age and control group; Healthy control subjects matched for sex and age. All participants underwent general and neurological examinations and relevant investigations.

Results: TNF-α, IL6, hs-CRP, and IFN-γ were significant increase in cases had MDD than their first degree relatives and healthy control ($P<0.001,<0.001,<0.001,<0.001$). hs-CRP, IL6, TNF-α and IFN-γ were significantly higher in relatives group than healthy control group ($P<0.001,<0.001,<0.001,<0.001$). BDNF was significantly decrease in cases group than both 1th degree relatives group ($P=0.001$) and healthy control group. ($P<0.001$). Relatives group was significantly decrease in BDNF than healthy control group ($P=0.011$).

Conclusions: MDD cases demonstrate a higher concentration of inflammatory markers (hs-CRP, IL6, TNF-α, IFN-γ) than 1th-degree relatives and control subjects. MDD cases exhibited reduced levels of BDNF than first-degree relatives and control subjects.

Introduction

Major Depressive Disorder (MDD) is a highly debilitating condition worldwide, exerting significant adverse effects on daily functioning, quality of life, cognitive abilities, employment status, and workplace productivity [1]. Therapeutic approaches for MDD, including antidepressant pharmacotherapy, are accessible; however, the outcomes remain suboptimal, as approximately 50% of patients do not achieve adequate response [2].

Therapeutic strategies for MDD, including antidepressant pharmacotherapy, are available; however, the results remain suboptimal, with approximately 50% of patients failing to attain a sufficient response. Two significant biological risk factors for depression merit specific consideration: Inflammatory response and diminished levels of brain-derived neurotrophic factor (BDNF) [3]. Research indicates that innate immunity primarily contributes to pathophysiology of depressive disorder. It is hypothesized which anti-inflammatory agents maintain immune system homeostasis may contribute to the alleviation of depressive symptoms. Pro-inflammatory cytokine levels are frequently higher in individuals had depression, notably in those exhibiting resistance to antidepressant therapy [4].

Novel mechanisms, particularly the associated processes and consequences of cell-mediated immunity activation and inflammation, have been acknowledged in depression. These include, for example, indoleamine 2,3-dioxygenase (IDO) activation, diminished antioxidant

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levels, heightened oxidative stress, and mitochondrial injury. Concurrently with advancements in understanding inflammation and cell-mediated immune activation, recent studies have identified progressive neuroanatomical impairments in depression, including neurodegeneration, elevated neuronal apoptosis, and diminished levels of neurotrophic factors [5].

Another important biological risk factor for depression is deficiency in BDNF, a member of the neurotrophin family of growth factors which is a small protein expressed by the BDNF gene on chromosome eleven in humans. BDNF has been extensively researched regarding its involvement in pathogenesis of MDD and antidepressant treatment effectiveness [6].

Researchers have dedicated several decades of research to BDNF as a prospective biomarker for depression. Clinical data often suggest that individuals diagnosed with major depressive condition demonstrate a heightened propensity for alterations in their BDNF-TrkB (BDNF-tropomycin receptor kinase B) signaling activity. Multiple investigations have indicated that individuals diagnosed with depression display diminished concentrations of BDNF than healthy control (HCs), and that various antidepressant therapies elevate circulating BDNF levels, highlighting the significance of BDNF deficiency in depression pathogenesis [3].

This study aimed to evaluate immunological markers and BDNF concentrations in a cohort of medication-free cases diagnosed with MDD, as well as a group of healthy 1th-degree relatives of these cases, matched for age and sex. Furthermore, immunological markers and BDNF levels were evaluated in a control group of healthy individuals matched for sex and age.The study involved a comparative analysis among the three groups and an investigation of the correlation between MDD severity and the levels of immunological markers and BDNF within the patient group.

Patients and Methods

This cross sectional study involved ninety persons at Department of Neuropsychiatry and The Center of Psychiatry, Neurology and Neurosurgery, Tanta University from November 2022 through December 2024. A informed written consent was obtained from the patients. The investigation was conducted subsequent to obtaining approval from the Ethics Committee of the Faculty of Medicine, Tanta University (approval code: 35994/10/22).

The inclusion criteria regarding cases' group was drug-free cases diagnosed with MDD according to Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 (first major depressive episode, patients were not under treatment before or currently using any medications), age from 18 to 45 years, both males and females, first degree relatives group and control group criteria were age and sex matched with the patient group and negative current or past history of psychiatric conditions. Negative family history of psychiatric disorders in control group.

The exclusion criteria were present and past history of autoimmune disorders, current infections or allergies, current inflammatory conditions or tissue injury, current surgical condition or physical illness, intellectual developmental disorder, neurocognitive disorders or other mental disorder, abnormal body mass index (<18.5 and >25), co-morbid substance use disorders including smoking, taking psychotropic medications, hormonal agents, antiinflammatory agents, anti-hypertensive drugs or antihyperlipidemic drugs and pregnancy and lactation.

Randomization:

All patients were selected by simple random sampling and randomized into 3 equal groups:

- Patients' group (n=30): Cases had MDD diagnosed according to DSM-5 criteria.
- First degree relatives group (n=30): Healthy first degree relatives matched for sex and age.
- Control group (n=30): Healthy control subjects coordinated to sex and age.

All participants in the study underwent a full history recording, which included socio-demographic characteristics and body mass index (BMI), also general and neurological examinations, along with relevant investigations such as psychometric assessments and laboratory tests.

Mini international neuropsychiatric interview (MINI) [7]:

Arabic version 7.0.2 [8]. According to the diagnostic criteria specified in the DSM-IV and the International Classification of Diseases, Sheehan et al. [7] established Mini International Neuropsychiatric Interview to

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examine a few psychiatric diseases. Validated versions in additional languages are also made available along with updates to the Mini International Neuropsychiatric Interview every few years. Originally intended for use in multicenter clinical trials and epidemiological investigations, it was created to address the demand for a brief, valid, and reliable mental interview [9]. The validated English version of Mini International Neuropsychiatric Interview 7.0.2 was employed and subsequently translated into Modern Standard Arabic. The estimated completion time is approximately 15 to 30 minutes.

This instrument was explicitly designed for application in clinical practice and research activities within psychiatric and primary healthcare environments. The assessment consisted of 130 questions requiring "yes" or "no" responses, formulated to assess 16 Axis I DSM-5 disorders and one personality disorder. Each of sixteen components commences with a screening inquiry intended to eliminate particular analyses, potentially leading to module skipping if answered in the negative, or to an exploration of symptom severity if replied in the positive [8].

Hamilton depression rating scale (HAM-D):

The Hamilton Depression Rating Scale (HAM-D), initially devised by Max Hamilton in 1960, comprised 21 items. Nevertheless, scoring was predicated solely on the first 17 items [10]. Hamilton advised that the scores for the final 4 items (paranoid symptoms, diurnal variation, depersonalization/derealization, and obsessional and compulsive symptoms) be excluded from the total score, as these either were not deemed essential to the disorder, were infrequent, or were not considered indicative of severity [11]. In 1976, National Institute of Mental Health facilitated dissemination of an exhaustive reference encompassing widely used psychiatric rating scales. A revised edition of HAM-D was featured in that volume, becoming the most widely utilized version in the United States [12].

By 1980, the HAM-D was widely recognized as a standards for evaluating other depression assessment instruments and served as the standard criterion for determining the antidepressant efficacy of treatments [13]. More than any other individual, Per Bech has rendered significant contributions to the body of literature concerning HAM-D. In 1986 Bech et al. [14] a succinct compilation of rating scales was published, featuring an alternative version of HAM-D which explicitly defined criteria for assessing each individual item. By 1990, multiple variants of the HAM-D had been developed, leading researchers and clinicians to become confused about the available options and their respective features. No individual iteration of HAM-D or a standardised set of conventions has achieved universal acceptance [15]. These operational criteria were formulated in collaboration with Hamilton himself. A subscale version of the HAM-D, known as the Melancholia Scale (MES), has been employed in numerous research studies, especially across Europe [16]. This study used the Arabic version translated by Lotfy Fateem [17].

High sensitivity C reactive protein (hs-CRP), Interleukin-6(IL-6), Tumor necrosis factor alpha (TNF-α), Interferon gamma (IFN-γ) and Brain derived neurotrophic factor (BDNF):

The levels of hs-CRP, IL-6, TNF-α, IFN-γ, and BDNF in the samples were measured utilizing a double-antibody sandwich enzyme-linked immunosorbent assay (ELISA) reagent. TNF-α, hs-CRP, IL-6, IFN-γ, and BDNF were integrated into a monoclonal antibody enzyme plate, which was pre-coated with human-specific monoclonal antibodies directed against hs-CRP, IL-6, TNF-α, IFN-γ, and BDNF. Following incubation, biotin-labeled antibodies targeting IL-6, hs-CRP, IFN-γ, TNF-α, and BDNF were introduced and subsequently combined with Streptavidin-HRP to generate an immune complex. Subsequently, incubation was carried out, and the well was rinsed again to eliminate any unbound enzymes. Subsequently, add Chromogen Solution A and B; the liquid's color transitions to blue. Following the addition of acid, the colour subsequently shifts to yellow. The chromaticity of the pigment and the levels of human biomarkers hs-CRP, IL-6, TNF-α, IFN-γ, and BDNF in the sample exhibited a positive correlation.

Statistical analysis:

The present study was statistically analyzed and presented using SPSS V25. Among the statistical methods employed were analysis of variance (ANOVA), chi-square, person's correlation coefficient, standard deviation, and mean. Make a chi-square test for the independence of the row and column variables without stating the direction or intensity of the link. Probability ratio and Pearson chi-square tests two types of statistical

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tests: chi-square and t-tests. For purpose of detecting correlation between 2 quantitative variables within a single group, the linear correlation coefficient was employed. As stated in the Windows version of SPSS. When comparing quantitative data collected at different times within the same group, the ANOVA test was employed.

Results

There is insignificant difference among 3 groups concerning age and education. Depression was higher in females than males in patients group with insignificant difference between the 3 studied groups. Depression was more in married patients in patients group with insignificantly different among 3 groups according to marital state. Most of patients group were unemployed with insignificant difference between the three studied groups (P- value= 0.065). Mean BMI in patients group was 22.830 ± 1.338, in first degree relatives group was 22.643 ± 1.480 and in control group was 22.867 ± 1.062 with insignificant difference among 3 groups regarding BMI. **Table 1**

Table 1: Age, gender, marital state, education distribution, occupation, BMI across the three studied groups.

		Groups				P-value
		Patients	Relatives	Control	Total	
Age (Years)		28.933 ± 5.407	26.500 ± 4.524	26.433 ±4.854	----	0.089
Gender	**Male**	8 (26.67%)	4 (13.33%)	4 (13.33%)	16 (17.78%)	0.296
	Female	22 (73.33%)	26 (86.67%)	26 (86.67%)	74 (82.22%)	
Marital state	**Single**	8 (26.67%)	10 (33.33%)	17 (56.67%)	35 (38.89%)	0.114
	Married	20 (66.67%)	17 (56.67%)	10 (33.33%)	47 (52.22%)	
	Divorced	2 (6.67%)	3 (10.00%)	3 (10.00%)	8 (8.89%)	
Education distribution	**Illiterate**	4 (13.33%)	3 (10.00%)	2 (6.67%)	9 (10.00%)	0.893
	Primary School	3 (10.00%)	4 (13.33%)	2 (6.67%)	9 (10.00%)	
	Secondary School	6 (20.00%)	5 (16.67%)	9 (30.00%)	20 (22.22%)	
	High institute	4 (13.33%)	4 (13.33%)	6 (20.00%)	14 (15.56%)	
	University	13 (43.33%)	14 (46.67%)	11 (36.67%)	38 (42.22%)	
Occupation	**Employed**	9 (30.00%)	14 (46.67%)	18 (60.00%)	41 (45.56%)	0.065
	Unemployed	21 (70.00%)	16 (53.33%)	12 (40.00%)	49 (54.44%)	
BMI		22.830 ± 1.338	22.643 ±1.480	22.867 ± 1.062	---	0.777

Data are presented as mean ± SD or frequency (%). BMI: Body mass index,* significant as P-value ≤ 0.05.

Hs-CRP was significant increase in cases had MDD than their first degree relatives and healthy control (P<0.001). Hs-CRP was significant increase in relatives group than healthy control group (P<0.001). IL 6 was significantly increase in cases group than both first degree relatives group and healthy control group. (P<0.001). IL 6 was

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significantly increase in relatives group than healthy control group. (P<0.001). TNF-α was significantly increase in cases group than both first degree relatives group and healthy control group (P<0.001). TNF-α was significantly increase in relatives group than healthy control group. (P<0.001). IFN-γ was significantly increase in cases group than both 1th degree relatives group and healthy control group. (P<0.001). IFN-γ was increase in relatives group than healthy control group with insignificant statistical difference. (P=0.105). BDNF was significantly decrease in patients group than both 1th degree relatives group (P=0.001) and healthy control group. (P<0.001). BDNF was significantly decrease in relatives group than healthy control group. (P=0.011). **Table 2**

Table 2: hs-CRP, IL 6, TNF alpha, IFN gamma and BDNF across the three studied groups

	Groups			**P-value**
	Patients	**Relatives**	**Control**	
hs-CRP (mg/l)	2.253 ± 0.473	1.327 ± 0.485	0.743 ± 0.107	**<0.001*** **P1<0.001*** , **p2<0.001*** , **p3<0.001***
IL 6 (pg/ml)	18.760 ± 1.491	15.738 ± 0.983	5.382 ± 1.519	**<0.001*** **P1<0.001*** , **p2<0.001*** , **p3<0.001***
TNF alpha (pg/ml)	5.6038.602± 5	27.34 2.08 ± 97	18.9± 3.33707	**<0.001*** **P1<0.001*** , **p2<0.001*** , **p3<0.001***
IFN gamma (pg/ml)	91.208 ± 9.640	44.373 ± 18.101	36.709 ± 14.250	**<0.001*** **P1<0.001*** , **p2<0.001*** , **p3<0.001***
BDNF (ng/ml)	0.516 ± 0.227	0.713 ± 0.246	0.866 ± 0.089	**<0.001*** **P1<0.001*** , **p2<0.001*** , **p3<0.001***

Data are presented as mean ± SD or frequency (%).hs-CRP : high sensitivity C reactive protein, BMI: Body mass index, TNFalpha: Tumor necrosis factor α, IFN gamma: Interferon γ, BDNF:Human Brain derived neurotrophic factor.* significant as P-value ≤ 0.05.p1: p value between Patients and Relatives, p2: p value between Patients and Control, p3: p value between Relatives and Control.

Distribution of cases with and without suicidal ideation (SI) within patients group showing that patients with no suicidal ideation (NSI) is more prevalent (70.00%) compared to patients with SI (30.00%). Hs-CRP was significantly increase in cases had SI than patients with NSI within patients group (P=0.005). IL6 was significantly increase in cases with SI than cases with NSI within patients group (P<0.001). TNF alpha was

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increase in cases with SI than cases with NSI within patients group with insignificant difference (P=0.065). IFN gamma was increase in cases with SI than cases with NSI within patients group with insignificant difference. BDNF was decrease in cases with SI than cases with NSI within patients group with insignificant difference (P=0.079) **Table 3**

Table 3:Comparison between patients with and without suicidal ideation within patients group regarding high sensitivity C reactive protein (hs-CRP), IL 6, TNF alpha IFN gamma and BDNF.

	Patients		**P-value**
	Suicidal ideation (n=9)	**No suicidal ideation (n=21)**	
hs-CRP (mg/l)	2.611 ± 0.237	2.100 ± 0.468	**0.005***
IL 6 (pg/ml)	20.197 ± 1.266	18.144 ±1.120	**<0.001***
TNF alpha (pg/ml)	41.479 ± 6.472	37.369 ± 4.846	0.065
IFN gamma (pg/ml)	92.859 ± 12.601	90.500 ± 8.335	0.549
BDNF (ng/ml)	0.405 ± 0.117	0.563 ± 0.248	0.079

Data are presented as mean ± SD.hs-CRP: high sensitivity C reactive protein, IL 6: Interleukin-6, TNF alpha: Tumor necrosis factor α, IFN gamma: Interferon γ, * significant as P-value ≤ 0.05.

Significant positive correlation between depression severity as detected by HAM-D score and hs-CRP (P-value= 0.013) meaning the more depression severity, the higher the hs-CRP level. Significant positive correlation between severity of depression as detected by HAM-D score and IL-6 (P-value= 0.038) meaning the more severity of depression, higher the IL-6 level. Significant positive correlation between depression severity as detected by HAM-D score and TNF alpha (P-value= 0.015) meaning the more the severity of depression, the higher the TNF alpha level.Significant positive correlation between depression severity as detected by HAM-D score and IFN gamma (P-value= 0.029) meaning the more the severity of depression, the higher the IFN gamma level. Significant negative correlation between severity of depression as detected by HAM-D score and BDNF (P-value= 0.002) meaning the higher the severity of depression, the lower the BDNF level. **Table 4**

Table 4: Hamilton depression rating scale (HAM-D) score in patients group assessing depression severity, correlation between severity of depression as detected by (HAM-D) score and high sensitivity CRP (hs-CRP), interleukin-6 (IL-6), TNF alpha, interferon gamma (IFN-γ) and brain derived neurotrophic factor (BDNF)

HAM-D score	17.733 ± 2.703	
	HAM score	
	R	**P-value**
hs-CRP (mg/l)	0.446	**0.013***
IL 6 (pg/ml)	0.380	**0.038***
TNF alpha (pg/ml)	0.442	**0.015***

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IFN gamma (pg/ml)	0.400	**0.029***
BDNF (ng/ml)	-0.544	**0.002***

Data are presented as mean ± SD. hs-CRP: high sensitivity C reactive protein, IL 6: Interleukin-6, TNF alpha: Tumor necrosis factor α, IFN gamma: Interferon γ, BDNF: Human Brain derived neurotrophic factor, * significant as P-value ≤ 0.05.

Discussion

C-reactive protein (CRP), a marker of acute-phase inflammatory response, has been widely utilized to evaluate low-grade inflammation in psychiatric disorders and has yielded significant insights into the diagnosis and risk assessment of cardiovascular diseases [18].

In our study, hs-CRP was significantly increase in cases had MDD than their 1th degree relatives and healthy control (P<0.001).

Prior investigations have similarly demonstrated a significant correlation between depression and increased serum hs-CRP levels [19].

On the other side, some authors found no or even inverse relation between depression and hs-CRP levels. Chocano-Bedoya et al., [20] did not establish a significant relation between inflammatory markers, as CRP, and depression observed over a follow-up period of 6 to 18 years.

Our research represents inaugural laboratory study to evaluate hs-CRP levels in healthy first-degree relatives of individuals had depression. We observed that hs-CRP levels were significantly elevated in relatives group than healthy control group.

In our study, interleukin-6 was significantly increase in cases group than both first degree relatives group and healthy control group.

Also, pro-inflammatory cytokines IL-1α and interleukin-6 were significant increase in those with MDD than HCs according to Elgellaie et al,[21]. Nevertheless, some investigations report insignificant differences in interleukin-6 levels between cases with MDD and healthy volunteers [20].

Our research represents the first laboratory investigation to evaluate interleukin-6 levels in healthy 1th-degree relatives of individuals had depression. We observed that interleukin-6 levels were significant increased in relatives group than healthy control group.

TNF-α was significantly increase in cases group than both first degree relatives group and healthy control group.

In Fan et al., [22] study, they show that depressive patients exhibit increased interleukin-6 and TNF-α levels, whereas interleukin-18 levels are reduced than controls. Furthermore, levels of TNF-α and interleukin-6 were significant positive correlation with HAM-D17 scores in cases with depression, indicating that higher HAM-D scores and greater severity of depression are related to increased levels of TNF-α and interleukin-6.

Contrary to this study, in Brambilla et al., [23] study, peripheral concentrations of TNF-α in controls differed insignificantly from MDD patients before and after therapy.

Our study is the first laboratory study to assess tumor necrosis factor alpha in healthy first degree relatives of depressed cases. In our study, relatives group was significantly increase in TNF-α than healthy control group.

In this study, IFN-γ was significantly increase in patients group than both first degree relatives group and healthy control group. (P<0.001)

This aligns with Chen et al., [24] showed serum IFN-γ levels were signicantly increase in MDD than those in HCs.

In contrast to our results, Daria et al., [25] showed significantly reduced serum IFN-γ levels in cases had MDD than HCs. They also showed that decreased serum levels of IFN-γ are inversely related to depression severity.

Our study represents the initial laboratory examination aimed at evaluating IFN-γ levels in healthy 1th-degree relatives of individuals had depression. In our study, IFN-γ was increase in relatives group than healthy control group with no statistical difference.

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In our study, BDNF was significantly decrease in cases group than both first degree relatives group and healthy control group.

This is also consistent with Liu et al., [26] A study involving 90 cases with first-episode, unmedicated MDD and HCs was conducted. Baseline BDNF levels were considerably decrease in individuals had MDD than HCs.

According to Emon et al., [27], demonstrated that serum levels of BDNF were significant reduced in drug-naïve cases had MDD than HCs. Serum BDNF levels did not exhibit significantly different between drug-treated cases and HCs.

Gupta et al., [28] indicated which serum BDNF levels were markedly decreased in cases had MDD relative to HCs. Following treatment with fluoxetine and agomelatine in cases had MDD, serum BDNF levels were elevated. Furthermore, a study established which serum BDNF levels were significant lower in drug-naive MDD cases than those receiving antidepressant treatment or HCs.

In our study, BDNF was significantly decrease in relatives group than healthy control group.

This is inconsistent with Knorr et al., [29]. In their case-control investigation, they found that blood BDNF protein levels were significant elevated in persons had a family history of depressive disorder.The current data indicates that a family history of depression may be associated with an increased level of BDNF in healthy individuals. Based on present findings, establishing a causal relationship between peripheral blood BDNF concentrations and depression is not possible. Nevertheless, we suggest which increased BDNF levels may serve as a potential compensatory or protective response in persons at depression risk [29].

The SI was assessed using item 3 (suicide) of the HAM-D. This item presents following alternative claims: 0 = absent; 1 = indicates a perception that life is not worth living; 2 = expresses a desire to be deceased or recurrent thoughts of death; 3 = includes SI; and 4 = involves suicide attempts. In the current study, persons scoring either 1 or 0 were categorized as having NSI. A score of 2 or increase was indicative of SI presence. This cutoff value has been employed in prior research [30-32].

In our study, cases with SI was significantly increase in hs-CRP than patients had NSI within patients group.

In Huang et al., [33], reported that cases had SI increase CRP levels than those without SI and controls.

Also, Bai et al. [34], reported significant higher in CRP in MDD cases had SI in comparison with those without SI.

Nevertheless, Courtet et al., [35] find insignificant difference in CRP levels between cases with and without SI.

In our study, IL6 was significantly increase in cases had SI than patients had NSI within patients group.

This is consistent with Guo et al., [36]. They show that MDD cases with SI exhibited significantly elevated IL-6 level than HCs and MDD cases without SI.

Nevertheless, Gabbay et al., [37] show insignificant difference in plasma IL-6 level in adolescent MDD patients with SI than adolescent MDD patients with NSI.

In our study, TNF alpha was increase in cases had SI than cases with NSI within patients group with insignificant difference.

This aligns with O'Donovan et al., [38] who reported significantly increase TNF-α levels in cases with increase levels of SI than in those with decrease levels of SI.

In contrast to this and according to Gabbay et al., [37], plasma concentrations of TNF-alpha were markedly reduced in suicidal adolescents with MDD than nonsuicidal MDD cohort.

In our study, IFN gamma was increase in cases had SI than patients with NSI within patients group with insignificant difference.

This aligns with Yang et al., [39], inflammatory cytokines assessment in cases of MDD categorised by suicide risk revealed which, had increasing suicide risk, peripheral blood levels of IL-6, TNF-alpha, and IFN-gamma progressively elevated, whereas levels of IL-2 and IL-8 steadily decreased.

In this study, BDNF was decrease in cases had SI than patients with NSI within patients group with insignificant difference (P=0.079).

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This aligns with Khan et al., [40], They assessed serum BDNF levels in 68 physically healthy, unmedicated individuals diagnosed with MDD (for a minimum duration of six weeks), of whom 40 reported NSI and 28 endorsed SI without active suicidal intent, as well as in 76 healthy control participants (HC). Serum BDNF levels were markedly reduced in individuals had MDD and SI in comparison to those with NSI MDD.

In our study, there is a significant positive correlation between depression severity, as measured by HAM-D score, and hs-CRP levels (P-value = 0.013), indicating that greater depression severity is related to increase hs-CRP levels.

This is consistent with Agnihotri et al., [41]. This was a crosssectional study conducted on a sample of 40 participants. Sociodemographic data was noted, and the HAM-D was applied to rate depression severity. Blood samples were obtained at 8 a.m. to record hs-CRP. Hs-CRP was significantly increased showing an underlying inflammatory pathology. Also, it is noteworthy that hs-CRP was positively correlated with depression severity.

In Nishuty et al., [42], study enrolled 88 patients with MDD and 86 control subjects matched for gender, BMI and age. The Ham-D was administered to all patients to assess depression severity.

Serum CRP levels were assessed utilizing commercially available ELISA assays. Patient Ham-D scores demonstrated a positive correlation with serum CRP levels.

According to Orsolinia et al., [43], A cross-sectional, population-based investigation investigated the association between depression and hs-CRP within a group of 6,126 adults. Subjects exhibiting depressive symptoms demonstrated an average CRP concentration exceeding that of the HCs. Furthermore, the authors identified a positive correlation between depression severity and hs-CRP levels.

In this study, a significant positive correlation was showed between depression severity, as measured by HAM-D score, and IL-6 levels (P-value = 0.038), indicating that higher depression severity is related to elevated IL-6 levels.

Nishuty et al., [42] the study enrolled 88 individuals diagnosed with MDD and 86 control subjects, who were matched according to gender, age, and BMI. The HAM-D was administered in all instances to assess depressive symptoms severity. Serum levels of IL6 were analyzed by commercially available ELISA kits. Ham-D scores of cases were positively correlated with serum IL6.

This is consistent with Fan et al., [22], Serum levels of TNF-α, IL-6, and IL-18 were quantified through enzyme-linked immunosorbent assay in 64 individuals diagnosed with depression and 80 healthy control subjects. Depressive symptoms in the subjects were evaluated utilising the HAM-D-17. Depressive cases demonstrated elevated serum levels of TNF-α and IL-6, while exhibiting reduced IL-18 concentrations in comparison to controls. TNF-α and IL-6 levels demonstrated a significant positive correlation with Hamilton Depression Scale-17 scores in cases had depression.

In our study, there is significant positive correlation between depression severity as detected by HAM-D score and TNF alpha (Pvalue= 0.015) meaning the more the severity of depression, the higher the TNF alpha level.

This aligns with Fan et al., [22], showed that cases had depression exhibit raised levels of TNF-α and IL-6, while IL-18 concentrations are reduced than controls. Furthermore, levels of IL-6 and TNF-α demonstrated a significant positive correlation with HAMD-17 scores in cases had depression, Indicating that higher concentrations may be related to more severe depressive symptoms.

Das et al., [44] study was found the elevated serum interleukin1β (IL-1β) and TNF-α levels were detected among MDD cases. These increased levels of peripheral markers exhibited a positive correlation with depression severity. So, increased serum levels of IL-1β and TNF-α may function as biomarkers for evaluating the likelihood of depression.

In our study, there is significant positive correlation between depression severity as detected by HAM-D score and IFN gamma (P-value= 0.029) meaning the more the severity of depression, the increase IFN gamma level.

On the other side, Daria et al., [25] case-control study and showed that serum IFN-γ levels were significant reduced in MDD cases than HCs. A significant negative

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correlation was showed between HAM-D scores and serum IFN-γ levels.

In this study, there is significant negative correlation between depression severity as detected by HAM-D score and BDNF (Pvalue= 0.002) meaning higher depression severity, the lower BDNF level.

This is consistent with Gonul et al., [45], who revealed that baseline BDNF levels of patients were significantly decrease than those of controls and were negatively correlated with HAM–D scores. After eight weeks of treatment, BDNF levels of cases was higher significantly and no more exhibited significantly different from control group. These findings endorse the hypothesis which BDNF may be a key factor in MDD pathophysiology, and that effective antidepressant therapy elevates the diminished BDNF levels in persons had depression.

Emon et al., [45] In both groups of medication-naive and drug treated individuals treated MDD, statistically significant negative correlations were identified between serum BDNF concentrations and scores on Ham-D.

In another study, thirty cases passing the DSM-IV criteria for MDD and 40 normal control subjects were recruited for the study. Cases had not been administered psychotropic medications. The depression extent was evaluated using HAM-D. Serum BDNF concentrations were assessed using ELISA. The study findings indicated that serum BDNF concentrations were significantly reduced in patient cohort diagnosed with depression relative to the healthy control group; Nevertheless, no relation was known between serum BDNF levels in patients and their corresponding HAM-D scores [46].

Therefore, studying a limited number of inflammatory markers, although in the study we have tried best to cover all possible confounders, numerous factors may still influence serum cytokine levels and brain function–derived neurotrophic factor levels could not be controlled in this study and we had one healthy control group but not another group of patients with different mental disorder, such as bipolar disorder, for comparison.

Conclusions

MDD cases exhibited elevated levels of inflammatory markers (IL-6, hs-CRP, IFN-γ,TNF-α) compared to first-degree relatives and control subjects. MDD cases showed lower levels of BDNF than 1th degree relatives and control subjects. Compared to control subjects, first degree relatives showed increase levels of inflammatory markers (hs-CRP, TNF-α, IL6, IFN-γ) and decrease BDNF levels, levels were intermediate between depressed cases and control subjects. Cases had SI showed increase levels of inflammatory markers (TNF-α, hs-CRP, IL6, IFN-γ) and decrease levels of BDNF than patients without SI.

Therefore, regular follow up of 1th degree relatives of cases had MDD if possible for early detection and treatment for better outcome and given the limited efficacy of currently available antidepressants, further exploration of inflammatory mechanisms may open a new era for better treatment for MDD.

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BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CRP	C-reactive protein
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSM-5 criteria	Diagnostic and Statistical Manual of Mental Disorders 5th edition
ELISA	Enzyme-linked immunosorbent assay
HAM-D	Hamilton depression rating scale
HCs	healthy controls
hs-CRP	High sensitivity C reactive protein
IFN-γ	Interferon γ
IL-1β	interleukin1β
IL-6	Interleukin-6
MDD	Major depressive disorder
MES	Melancholia scale
MINI	Mini international neuropsychiatric interview
TNF-α	Tumor necrosis factor α