Zagazig University Medical Journal
www.zumj.journals.ekb.eg

Manuscript ID ZUMJ-1909-1523
DOI **10.21608/zumj.2019.16998.1523**

ORIGINAL ARTICLE

C-reactive protein in patients with major depressive disorder in Zagazig university hospitals.

Rafik Reda Abd El-Latif [1], Amany El-Shabrawy Mohamed [1], Abdallah Saad Ibrahim [1], Alaa Ashraf Mansour [1].
[1]Department of psychiatry, Zagazig university

Corresponding author: Alaa Ashraf Ahmad Mansour, resident psychiatry, 01017230589, alaaashraf157@hotmail.com

Submit Date	2019-09-16
Revise Date	2019-10-21
Accept Date	2019-10-24

ABSTRACT

Background*:* The relationship between inflammation and psychiatric disorders has been widely debated. Psychiatric patients had features of inflammation, such as high levels of inflammatory markers. This study was conducted to assess plasma C-reactive protein level (CRP) in patients with major depressive disorder (MDD) and compare them with healthy controls.

Methods*:* A sample of 196 participants (98 cases, 98 controls) was taken, cases satisfied the diagnosis of MDD according to Diagnostic and statistical manual of mental disorder (DSM-5). Blood samples were collected from patients and controls to measure plasma levels of CRP. Severity of depression in patients was assessed by Beck depression inventory and the Hamilton depression rating scale.

Results*:* There was a statistically significant elevation of CRP levels in patients with MDD compared to control group with P value 0.009. Also there was a significant correlation between CRP level and degree of severity of depression.

Conclusion*:* CRP was elevated in patients with MDD and associated with severity of MDD. This result supports the previous findings that inflammatory hypothesis has a great role in major depressive disorder pathogenesis.

Keywords: Major depressive disorder, Inflammation, C-reactive protein.

INTRODUCTION

Inflammatory hypothesis had been evident to play an important role in major depressive disorder (MDD) evidenced by elevated levels of inflammatory markers [1]. Normalization of these inflammatory markers was detected after remission of symptoms of MDD [2]. Also chronic inflammatory diseases, such as systemic lupus erythematosus and rheumatoid arthritis were highly comorbid with depression [3]. C-reactive protein (CRP) is a plasma protein synthesized in liver, elevated in response to tissue injury or inflammation, CRP is a suitable inflammatory marker as it is readily available, relatively stable in stored biological specimens; not affected by time of day or meal intake [4].

Several mechanisms had been found to link inflammation with MDD. These mechanisms focus mainly on the influence of inflammatory cytokines on neurotransmitters as serotonin, microglia, the Hypothalamic pituitary adrenal axis and neuroplasticity [5]. Inflammatory cytokines were found to stimulate indolamine 2,3-dioxygenase (IDO) to convert tryptophan

and decrease levels of serotonin [6] .Inflammatory processes activate microglia and over activation of the microglia causes decreased neuroplasticity, decreased neuronal function [7] and inhibition of glutamate catabolism which was observed in patients with MDD [8]. Inflammatory cytokines also stimulate the hypothalamic-pituitary-adrenal axis leads to increase cortisol level leading to depressive symptoms [9]. Chronic course of MDD was found to be linked with inflammation and the inflammatory processes were found to increase risk of further depressive episodes and participate in the progressive course of depression [10].

Methods

The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. Written informed consent was obtained from all participants and the study was approved by the research ethical committee (Institutional Review Board, Faculty of Medicine, Zagazig University). The study was performed in psychiatric department, Zagazig University hospitals, Sharkia, Egypt. The sample size was 196 (98 cases and 98 control group). The sample was selected by simple random technique. *Inclusion criteria* include: All patients met The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) criteria for major depressive disorder, patients have not taken any antidepressant for current episode yet, patients of either sex, within the age limit of 18–60 years and all socioeconomic classes were included. *Exclusion criteria:* Age below 18 or above 60, patients who were taking any antidepressant medication within 6 months prior to study, previous history of manic or hypomanic episodes in patients or first degree relatives, patients with any infection, e.g.(bacterial/viral/fungal) within 1 month prior to study, patients who were on any other medication that affects CRP (anti-inflammatory drugs and antibiotics), patients with any inflammatory disease (such as arthritis, Asthma Autoimmune diseases, Allergy), patients with trauma due to surgery, fractures, burns within 1 month prior to study, patients with malignancies, pregnant women or who were pregnant within 6 months prior to study, women are using oral contraceptive pills within 6 months prior to study and substance abuse patients (but nicotine smoker were included in the study).

Participants enrolled in the study were subjected to the following:

a) A specially designed semi-structured interview derived from the Zagazig psychiatric sheet was used to cover the following parameters: Demographic data, including; age, gender, marital state, education, residence and occupation. Also body mass index, smoking, number of previous episodes were obtained.

b) Psychometric assessment for the patients includes the following:

- The Beck Depression Inventory

The Beck Depression Inventory (BDI) is the most widely scale used for depression, consists of twenty-one items that cover emotional, somatic and behavioral symptoms in depressed patients [11].

BDI cut-off (≥13) was used to identify the disorder. Scores (10-18) indicate mild to moderate depression, (19-29) indicate moderate to severe, (≥ 30) indicate severe depression [12]. Validated Arabic version of the scale was used in this study [13].

- The Hamilton Depression Rating Scale.

The Hamilton Depression Rating Scale (HAM-D) widely used to detect depression severity. More than 20 versions of the Hamilton depression scale were published. The commonly used one in various studies was the original 17-item version. Total score for depression severity: (<8) no depression, mild depression (6-13), moderate (14-18), severe (19-23) and very severe (≥24) [14]. Validated Arabic version of the scale was used in this study [15].

c) Venous sample was withdrawn under complete aseptic conditions from all subjects and analyzed at Zagazig university hospitals laboratories for CRP assessment.

Statistical Analysis

The collected data were computerized and statistically analyzed using SPSS (Statistical Package for Social Science) program software version 25. Qualitative data were represented as frequencies and Pearson's chi square ($\chi 2$) test was used to calculate difference between qualitative variables. Quantitative data were expressed as mean ± SD (Standard deviation). Mann Whitney test (MW) was used to analyze continuous data between two groups. Independent T test was used to calculate difference between quantitative variables in 2 groups in normally distributed data. Spearman's correlation coefficient (r) was used to test correlation between CRP and continuous variables. We consider (+) sign as indication for direct correlation i.e. increase frequency of independent lead to increase frequency of dependent & (-) sign as indication for inverse correlation i.e. increase frequency of independent lead to decrease frequency of dependent.

The level of statistical significance(S) was set at 5% ($P<0.05$), highly significant difference was present if $p\leq 0.001$ (HS) and p-value ≥ 0.05 was considered statistically insignificant(NS).

RESULTS

There was no statistical significant difference between the two studied groups in age, BMI, gender, education, occupation, marital status, residence or smoking as showed in table (1). MDD was common in female in our sample by percentage 64%. The number of episodes ranged from 1 to 10 with mean 2.02 as showed in table (2).

As showed in table (3), scores of Beck depression inventory ranged from 17 to 55 with mean 39.94. According to BDI, 1% of patients had mild MDD, 6.1% had moderate MDD and 92.9% had severe MDD. And according to The Hamilton depression rating scale, scores ranged from 14 to 45 with mean 32.92. 2% of patients had moderate MDD, 7.1% had severe MDD and 90.8% had very severe MDD.

There was a highly statistical significant increase in CRP level among cases compared to control group with P value 0.009 as showed in table (4). There was a highly statistical significant increase in CRP level among female, regarding smoker patients they represented 74.5% of patients and were found to had significant elevation in CRP levels compared with non-smoker patients, also there was positive statistically significant correlation between CRP and BMI as showed in tables (5 & 6).

There was statistically significant increase in CRP level among severe cases compared to mild to moderate case with P value 0.03.

Table (1): Demographic data of the two studied groups:

Variable	Cases (*n*=98)		Control (n=98)		t	p
Age : (year)						
Mean ± SD	38.82 ± 12		39.15 ± 11.54		0.20	0.84
Range	18 - 60		21 - 58			NS
BMI: (Kg/m^2)						
Mean ± SD	29.84 ± 3.70		29.60 ± 3.29		0.47	0.64
Range	21 – 41.6		23 - 35			NS
Variable	**No**	**%**	**No**	**%**	**χ^2**	**P**
Gender:						
Male	34	34.7	41	41.8	1.06	0.30
Female	64	65.3	57	58.2		NS
Marital status:						
Single	20	20.4	15	15.3		
Married	59	60.2	64	65.3	0.92	0.82
Widow	9	9.2	9	9.2		NS
Divorced	10	10.2	10	10.2		
Education:						
Illiterate	13	13.2	16	16.3		
Basic	34	34.7	40	40.8	2.31	0.51
High school	35	35.7	32	32.7		NS
College	16	16.3	10	10.2		
Occupation:						
Working	45	45.9	46	46.9	0.02	0.89
Not Working	53	54.1	52	53.1		NS
Residence:						
Urban	32	32.7	36	36.7	0.36	0.55
Rural	66	67.3	62	63.3		NS
Smoking:						
Yes	73	74.5	71	72.4	0.11	0.75
No	25	25.5	27	27.6		NS

SD: Standard deviation t: Independent t test χ2: Chi square test
NS: Non significant (P>0.05)

Table (2): Number of episodes among cases group:

Variable	Cases (*n*=98)
Number of episode:	
Mean ± SD	2.02 ± 1.73
Median	1
Range	1 - 10

Table (3): Scores of Beck depression inventory and Hamilton depression scale score among the cases group:

Beck Depression Inventory:	**Cases (*n*=98)**	
Mean ± SD	39.94 ± 7.29	
Range	17 – 55	
Classes:	**No**	**%**
Mild to moderate	1	1
Moderate to severe	6	6.1
Severe	91	92.9
Hamilton depression scale:	**Cases (*n*=98)**	
Mean ± SD	32.92 ± 6.80	
Range	14 - 45	
Classes:	**No**	**%**
Moderate	2	2
Severe	7	7.1
Very severe	89	90.8

Table (4): Comparison of CRP among the two studied groups:

Variable	Cases (*n*=98)	Control (n=98)	MW	p
CRP: (mg/dl)				
Mean ± SD	4.19 ± 4.29	2.34 ± 2.26	**2.61**	**0.009****
Median	2.31	1.63		
Range	0.21 – 22.63	0.5 – 8.12		

SD: Standard deviation MW: Mann Whitney test **: Highly significant (P<0.01)

Table (5): Relation between gender, smoking and severity of depression among the cases group and CRP:

Variable	No	CRP				MW	P
		Mean	Sd	Median	Range		
Gender:							
Male	34	2.55	2.74	1.52	0.21-11.04	**2.80**	**0.005****
Female	64	5.07	4.7	4.60	0.21-22.63		
Smoking:							
Yes	73	4.89	4.58	3.16	0.21-22.63	**2.87**	**0.004****
No	25	2.16	2.35	1.3	0.31-9.25		
Severity of depression:							
Mild to moderate	7	1.70	2.72	8.32	0.21-7.83	**2.21**	**0.03***
Severe	91	4.39	4.33	1.78	0.31-22.63		

SD: Standard deviation MW: Mann Whitney test
*: Significant (P<0.05) **: Highly significant (P<0.01)

Table (6): Correlation between CRP and age, BMI and number of episodes among cases group:

Variable	CRP (n=98)	
	r	P
Age (years)	0.09	0.37 NS
BMI (Kg/m^2)	**0.26**	**0.009 ****
Number of episode	0.14	0.17 NS

r: Spearman correlation coefficient
NS: Non significant (P>0.05)
**: Highly significant (P<0.01)

DISCUSSION

Recently personalized medicine and personalized psychiatry are given more attention in research and inflammation could be considered as an important component in personalized psychiatry [16]. CRP is not only an inflammatory marker, but also shares in pathogenesis of many mental and physical disorders [17]. CRP is easier to be used in studies with a higher reliability than that of other markers [16]. CRP had an effective role in modulating inflammatory processes [18].

- **Regarding sociodemographic data:**

Our study include 196 person divided into 98 patients with MDD and 98 healthy controls, both groups were matched in sociodemographic data. No statistical significance difference between both groups in age, gender, education level, occupation, marital status and residence. Also there was no statistical significance difference between both groups in BMI and smoking.

Ages of patients group ranged from 18-60 years old with their mean 38.8, the group included 64 females representing 65.3% of the cases group, majority of patients were married representing 61.2%, 67.3% of patients were from rural areas, 74.5% of the patients were smokers.

Recent studies were consistent with our results showing that MDD disorder was more prevalent among women [19,20]. Not in the line with our findings, a study found that majority of depressed people were from urban environment (62.7%), and were living alone "widow or single" (52.5%) [19].

- **Regarding severity of MDD:**

We assessed severity of MDD by Beck depression inventory and Hamilton depression scale, we found that approximately 90% of our

patients had severe depression. Another study used a different methodology found that 46.8% of patients with MDD had severe depression [20].

large number of patients with severe depression in our study may be because all our patients were in acute episode and didn't receive any antidepressants during the episode. Also [20] was a survey to detect prevalence of MDD and didn't include inpatients with MDD.

- **CRP among cases group and control group:**

Our study found that CRP levels were highly significant elevated in patients than control group with P value 0.009, our results were consistent with several studies which supported the evidence that MDD have elevated levels of CRP [21,22].

A study found that there was no significant difference in CRP levels in depressed patients compared to healthy control [23]. But at the same study, significant elevation in IL-6 was detected in patients compared to healthy people, the differences in findings of IL-6 and CRP may contrast with what expected, known that IL-6 promotes CRP production, this may due to post-transcriptional mechanisms that modulate expression of CRP [24] and could explain that difference in IL-6 and CRP findings

Another studies found this difference only related to the gender of the patients. The association of CRP with depression seen only in females not males, this finding could be explained by the high proportion of females in this study compared to males, also marital status and residence could explain this variation [25].

- **CRP and covariates in case group:**

Regarding gender, our study found that CRP was higher in female patients than male patients. Our results were consistent with [26] who found a significant higher levels of CRP in females compared to males with MDD, Elevated levels of CRP in females as compared to males is consistent with other previous reports [27, 28].

Increased adipose tissue may play a role in elevated level of CRP in female patients, as Female patients with MDD were found to have increase in weight and appetite when compared with male patients [29]. Also effect of sex hormones in the production of inflammatory mediators may also explain this variation [27].

These results were not in line with other studies which reported no significant difference in CRP between male and female patients with MDD [23, 30].

This discrepancy could be explained by the use of antidepressants agents. Since the latest two studies [23, 30] didn't exclude patients on antidepressant treatments. Antidepressants had been found in previous study to cause significant decrease in CRP [31]. Also other variables affecting CRP as age, BMI, smoking, and degree of severity of MDD, besides comorbidities with diseases or use of any drugs affecting CRP in patients included in studies could explain this discrepancy.

Regarding smoking, our results showed that there is significant increase in CRP among smoker patients. The relationship between nicotine and CRP which has been found in many studies [32], immune defense mechanisms were found to be weakened by nicotine [33], and associated with elevated CRP levels [34]. Smoking is often comorbid with depression, so there was debate if they share some etiological vulnerabilities [35].

Regarding BMI, our study found that there was positive significant correlation between CRP and BMI in depressed patients. This finding was consistent with [24, 32] who reported that higher BMI was strongly associated with higher CRP levels in patients with MDD. In the other hand, a study [30] found that there was no significant relation between BMI and CRP. This inconsistency can be clarified by effect of other variables affecting CRP as age, gender, smoking and degree of severity of MDD. Also inclusion of patients on antidepressant medications in the latest study may clarify this inconsistency.

Indicators of obesity, such as BMI and waist circumference are associated with elevated levels of CRP [36]. Adipocytes and tissue-resident macrophages were found to

produce large amount of inflammatory markers. Obesity was associated with chronic activation of inflammatory mechanisms which may play an important role to the development of neuropsychiatric disorders in obese patients [37].

Regarding severity of depression, our study found that there was significant correlation between CRP and severity of depression measured by Hamilton depression scale and Beck depression inventory. Our result was consistent with many studies with reported that elevated levels of CRP in MDD are significantly associated with greater severity of depressive symptoms [25, 38].

Previous studies were not in line with others which found that there were no significant association between severity of depression and CRP [23, 30]. Inconsistent findings of the association between CRP levels and severity of depression may be due to other factors that had a key role in CRP level in depressed patients as BMI, age, gender and the use of antidepressants agents, also variations in the sample size among studies could explain this inconsistency.

Greater severity of depression activates inflammation via many mechanisms as decreased parasympathetic stimulation [39] and decreased physical activity [40].

CONCLUSION

MDD patients had significally elevated CRP compared with control group. There was a significant correlation between CRP and severity of depression.

All these results support the previous findings that inflammatory hypothesis had a great role in pathogenesis of MDD.

LIMITATIONS

The sample size was relatively small, and all the patients were taken from psychiatry department in Zagazig university hospitals (outpatients and inpatients), which limits the generalization of our results. We didn't include other clinical data that could affect CRP as age of onset of the disease, duration of illness and family history of MDD.

RECOMMENDATIONS

Further studies including large sizes samples are required, with adjustment of variables that could affect CRP. Future gene studies have to shed the light on the role of different polymorphisms of CRP gene on the susceptibility of major depressive disorder. Also follow up studies are required to detect CRP levels in MDD patients after improvement.

Conflict of Interest: Non declared.
Funding: No funding sources.

REFERENCES

1. **Gardner A. & Boles RG.** Beyond the serotonin hypothesis: mitochondria, inflammation and neurodegeneration in major depression and affective spectrum disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2011; 35(3):730-743.
2. **Cattaneo A, Gennarelli M, Uher R, Breen G, Farmer A, Aitchison KJ, et al.** Candidate genes expression profile associated with antidepressants response in the GENDEP study: differentiating between baseline 'predictors' and longitudinal 'targets'. Neuropsychopharmacology 2013; 38(3): 377.
3. **Schmidt FM, Schröder T, Kirkby KC, Sander C, Suslow T, Holdt LM, et al.** Pro- and anti-inflammatory cytokines, but not CRP, are inversely correlated with severity and symptoms of major depression. Psychiatry research 2016; 239: 85-91.
4. **Jha MK, Minhajuddin A, Gadad BS, Greer T, Grannemann B, Soyombo A, et al.** Can C-reactive protein inform antidepressant medication selection in depressed outpatients? Findings from the CO-MED trial. Psychoneuroendocrinology 2017; 78: 105-113.
5. **Lazar MA. & McIntyre RS.** Novel Therapeutic Targets for Major Depressive Disorder. In Neurobiology of Depression. Academic Press. 2019; 383-400.
6. **Capuron L, Neurauter G, Musselman D L, Lawson D H, Nemeroff C B, Fuchs D, et al**. Interferon-alpha–induced changes in tryptophan metabolism: relationship to depression and paroxetine treatment. Biological psychiatry 2003; 54(9):906-914.

7. **Rosenblat J D, Cha D S, Mansur R B, & McIntyre R S.** Inflamed moods: a review of the interactions between inflammation and mood disorders. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2014; 53: 23-34.
8. **Hashimoto K, Malchow B, Falkai P, & Schmitt A.** Glutamate modulators as potential therapeutic drugs in schizophrenia and affective disorders. European archives of psychiatry and clinical neuroscience 2013; 263(5): 367-377.
9. **Sigalas P D, Garg H, Watson S, McAllister-Williams R H, & Ferrier I N.** Metyrapone in treatment-resistant depression. Therapeutic advances in psychopharmacology 2012; 2(4):139-149.
10. **Moylan S, Maes M, Wray NR, & Berk M.** The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. Molecular psychiatry 2013; 18(5): 595.
11. **Beck A, Ward C, Mendelson M, Mock J, & Erbaugh J.** An inventory for measuring depression. Archives of General Psychiatry 1961; 4: 561–571.
12. **Beck AT. & Beamesderfer A.** Assessment of depression: the depression inventory. In *Psychological measurements in psychopharmacology*. Karger Publishers 1974; 7: 151-169
13. **Abdel-Khalek A.** Beck Depression Inventory. the Arabic version. *Cairo, Anglo-Egyptian Bookshop* 1996
14. **Hamilton M.** A rating scale for depression. *Journal of neurology, neurosurgery, and psychiatry* 1960; *23*(1): 56.
15. **Fateem L.** Arabic manual of Hamilton Depression Scale, translated and adapted by Lotfy Fateem. *The Anglo-Egyptian bookshop* 1998
16. **Lamers F, Milaneschi Y, & Penninx BW.** Depression Subtypes and Inflammation: Atypical Rather Than Melancholic Depression Is Linked With Immunometabolic Dysregulations. In Inflammation and Immunity in Depression. Academic Press 2018; 455-471
17. **Wysokiński A, Margulska A, Strzelecki D, & Kłoszewska I.** Levels of C-reactive protein (CRP) in patients with schizophrenia, unipolar depression and bipolar disorder. Nordic journal of psychiatry 2015; 69(5): 346-353.
18. **Sproston NR. & Ashworth JJ.** Role of C-reactive protein at sites of inflammation and infection. Frontiers in immunology 2018; 9: 754.
19. **Clignet F, Houtjes W, van Straten A, Cuijpers P, & van Meijel B.** Unmet care needs, care provision and patient satisfaction in patients with a late life depression: a cross-sectional study. Aging & mental health 2019; 23(4): 491-497.
20. **Hasin DS, Sarvet AL, Meyers JL, Saha TD, Ruan WJ, Stohl M, et al.** Epidemiology of adult DSM-5 major depressive disorder and its specifiers in the United States. JAMA psychiatry 2018; 75(4): 336-346.
21. **Chamberlain SR, Cavanagh J, de Boer P, Mondelli V, Jones DN, Drevets WC, et al.** Treatment-resistant depression and peripheral C-reactive protein. The British Journal of Psychiatry 2019; 214(1): 11-19.
22. **Smith KJ, Au B, Ollis L, & Schmitz N. (2018).** The association between C-reactive protein, Interleukin-6 and depression among older adults in the community: a systematic review and meta-analysis. Experimental gerontology 2018; 102: 109-132.
23. **Lamers F, Milaneschi Y, Smit JH, Schoevers RA, Wittenberg G, & Penninx, B. W.** Longitudinal association between depression and inflammatory markers: Results from the Netherlands Study of Depression and Anxiety. Biological psychiatry 2019; 85(10): 829-837.
24. **Kim Y, Hooten NN, Dluzen DF, Martindale JL, Gorospe M, & Evans MK.** Posttranscriptional regulation of the inflammatory marker C-reactive protein by the RNA-binding protein HuR and microRNA 637. Molecular and cellular biology 2015; 35(24): 4212-4221.
25. **Köhler-Forsberg O, Buttenschøn HN, Tansey KE, Maier W, Hauser J, Dernovsek MZ, et al.** Association between C-reactive protein (CRP) with depression symptom severity and specific depressive symptoms in major depression. Brain, behavior, and immunity 2017; 62: 344-350.
26. **Jha MK, Minhajuddin A, Chin-Fatt C, Greer TL, Carmody TJ, & Trivedi MH.** Sex differences in the association of baseline c-

reactive protein (CRP) and acute-phase treatment outcomes in major depressive disorder: Findings from the EMBARC study. Journal of psychiatric research 2019; 113: 165-171.

27. **Lee S, Oh SS, Jang SI, & Park EC.** Sex Difference in the Association between High-sensitivity C-reactive Protein and Depression: The 2016 Korea National Health and Nutrition Examination Survey. Scientific reports 2019; 9(1): 1918.
28. **Song BM, Lee JM, Choi W, Youm Y, Chu SH, Park YR, et al.** Association between C reactive protein level and depressive symptoms in an elderly Korean population: Korean Social Life, Health and Aging Project. BMJ open 2015; 5(2): e006429.
29. **Marcus SM, Kerber KB, Rush AJ, Wisniewski SR, Nierenberg A, Balasubramani GK, et al.** Sex differences in depression symptoms in treatment-seeking adults: confirmatory analyses from the Sequenced Treatment Alternatives to Relieve Depression study. Comprehensive psychiatry 2008; 49(3): 238-246.
30. **Zhang J, Yue Y, Thapa A, Fang J, Zhao S, Shi, W., et al.** Baseline serum C-reactive protein levels may predict antidepressant treatment responses in patients with major depressive disorder. Journal of affective disorders 2019; 250: 432-438.
31. **Crnković D, Buljan D, Karlović D, & Krmek M.** Connection between inflammatory markers, antidepressants and depression. Acta clinica Croatica 2012; 51(1): 25-32.
32. **Hastie CE, Haw S, & Pell JP.** Impact of smoking cessation and lifetime exposure on C-reactive protein. Nicotine & Tobacco Research 2008; 10(4): 637-642.
33. **Lee J, Taneja V, & Vassallo R.** Cigarette smoking and inflammation: cellular and molecular mechanisms. Journal of dental research 2012; 91(2): 142-149.
34. **Gonçalves RB, Coletta RD, Silvério KG, Benevides L, Casati MZ, Da Silva JS, et al.** Impact of smoking on inflammation: overview of molecular mechanisms. Inflammation Research 2011; 60(5): 409-424.
35. **Dierker LC, Avenevoli S, Stolar M, & Merikangas KR.** Smoking and depression: an examination of mechanisms of comorbidity. American Journal of Psychiatry 2002; 159(6): 947-953.
36. **Horn SR, Long MM, Nelson BW, Allen NB, Fisher PA, & Byrne, M. L.** Replication and reproducibility issues in the relationship between C-reactive protein and depression: A systematic review and focused meta-analysis. Brain, behavior, and immunity 2018; 73: 85-114.
37. **Delgado I, Huet L, Dexpert S, Beau C, Forestier D, Ledaguenel P, et al.** Depressive symptoms in obesity: Relative contribution of low-grade inflammation and metabolic health. Psychoneuroendocrinology 2018; 91: 55-61.
38. **Wium-Andersen MK, Ørsted DD, & Nordestgaard BG (2014).** Elevated C-reactive protein, depression, somatic diseases, and all-cause mortality: a mendelian randomization study. Biological psychiatry 2014; 76(3): 249-257.
39. **Carney RM, Freedland KE, & Veith RC.** Depression, the autonomic nervous system, and coronary heart disease. Psychosomatic medicine 2005; 67:S29-S33.
40. **Hamer M, Sabia S, Batty GD, Shipley MJ, Tabák AG, Singh-Manoux A, et al..** Physical activity and inflammatory markers over 10 years: follow-up in men and women from the Whitehall II cohort study. Circulation 2012; 126(8): 928-933.

How to Cite

ashraf, A., Abd El-Latif, R., El-Shabrawy, A., Ibrahim, A. C-reactive protein in patients with major depressive disorder in Zagazig university hospitals.. *Zagazig University Medical Journal*, 2021; (501-510): -. doi: 10.21608/zumj.2019.16998.1523