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Relationship between High Sensitivity C-Reactive Protein Level and Depression in Elderly Patients

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Abstract

Background: *Depression is one of the highly prevalent disorders in elderly people and leads to an increased risk of mortality. Depressive illness is projected to be the second leading cause of disease burden after ischemic heart disease. Inflammation and depressive symptoms seem to be associated in large epidemiological cross-sectional studies. Among a lot of inflammatory markers, high-sensitivity C reactive protein (hs-CRP) is a specific inflammatory marker.*

Objective: *This study aimed to investigate the possible association between the serum level of high-sensitivity C reactive protein (hs-CRP) and depressive symptoms in the geriatric population.*

Material and Methods: *The study was carried out on 100 subjects (from both sexes (male and female) aged 60 years or older) divided into Group I (Control): including 50 subjects healthy volunteers, Group II (Depressed patients): including 50 patients who must fulfill a score of 5 or more over 15 of the Geriatric Depression Scale-short Form (GDS-15) and a score of 10 or more over 27 of the Patient Health Questionnaire (PHQ-9).*

Results: *hs-CRP levels in group II (cases) ranged from 0.67 – to 7.0. with a mean value (S.D) of 2.44 ± 1.91. hs-CRP among group I (control) ranged from 0.34 – 0.99 with a mean value (S. D) of 0.66 ± 0.18. hs-CRP was insignificantly higher among the cases group (p <0.001)*

Conclusion: *There was a statistically significant difference between the serum levels of hs-CRP in group II (cases) and group I (control).*

Keywords: *Depression; Inflammation; High-sensitivity C reactive protein (hs-CRP).*

Introduction

According to the World Health Organization (WHO), the global population is aging so rapidly that between2015 and 2050, the proportion of individuals over the age of 60 years will nearly double, from 12% to 22%.[1]

Depression is one of the highly prevalent disorders in elderly people and leads to an increased risk of mortality. Depressive illness is projected to be the second leading cause of disease burden after ischemic heart disease. [2,3]

Depression is both underdiagnosed and undertreated in primary care settings. Symptoms are often overlooked and untreated because they co-occur with other problems encountered by older adults. [1]

Elevated depressive symptoms have been associated with an array of poor physical health outcomes, including increased risk of diabetes and coronary heart disease. [4,5]

Late-life depression (LLD) refers to the presence of significant clinical depression in individuals over 60 years of age, findings of epidemiological studies suggest that late-life depression is a strong risk factor for normal subjects progressing to mild cognitive impairment. Moreover, late-life depressive mood disorders could carry additional risk for disability, family caregiver burden, medical comorbidity, and suicide. [6, 7]

The underlying mechanisms for depressive symptoms in old age remain unclear, but the inflammatory host response is repeatedly inferred in the pathogenesis of neuropsychiatric conditions. [8]

Inflammaging denotes an upregulation of the inflammatory response that occurs with age, resulting in a low-grade chronic systemic proinflammatory state. [9]

Inflammaging differs significantly from the traditional five cardinal features of acute inflammation in that it is a (a) low-grade, (b) controlled, (c) asymptomatic, (d) chronic, and (e) systemic state of inflammation. [10]

Inflammation and depressive symptoms seem to be associated in large epidemiological cross-sectional studies. [11]

Among other inflammatory factors, high-sensitivity C reactive protein (hs-CRP) is a specific marker that has the following two advantages: 1) it is easily measured in blood samples, and 2) it provides a reliable marker of active inflammation. [12, 13]

Acute-phase proteins, such as CRP, are rapidly upregulated under these conditions, most commonly within hepatocytes, under the control of cytokines produced at the site of pathology. During infection and inflammation within the human body, CRP levels will rise acutely to elicit a sufficient immune response. Interleukin 6, 1 and transforming growth factor-β are responsible for the rise in plasma levels of the acute phase protein, due to the accelerated transcription of their genes within the liver. [14]

Consistent with the hypothesis that inflammation is present in a particular subgroup of depressed patients, the anti-inflammatory drug infliximab showed antidepressant properties only in treatment-resistant depressed patients who have high levels of the inflammatory marker C-reactive protein.[15]

This study aimed to investigate the possible association between the serum level of high-sensitivity C reactive protein (hs-CRP) and depressive symptoms in the geriatric population.

Subjects

The study was carried out on 100 subjects (from both sexes (male and female) aged 60 years or older) divided into:

- **Group I (Control):** include 50 subjects healthy volunteers.
- **Group II (Depressed patients):** include 50 patients who must fulfill a score of 5 or more over 15 of the Geriatric Depression Scale-short Form (GDS-15) and a score of 10 or more over 27 of the Patient Health Questionnaire (PHQ-9).

Patients with one or more of the following were excluded

1. History of stroke.
2. History of diabetes mellitus.
3. History of angina pectoris or myocardial infarction.
4. History of mental illness other than depression.
5. Patients with hearing or speech impairment. [16,17]
6. Patients with any identifiable acute, intermittent, or chronic infection or being on routine anti-inflammatory or immunosuppressive therapy.

Methods

The following data were obtained for each patient:

- **Socio-demographic data:** [18]
  - Name.
  - Age (in years).
  - Sex (male and female).
  - Occupation (employed, unemployed, or retired……etc).
  - Marital status (single-married-divorced-widow).
  - Smoking (smoker -non-smoker).
  - Sleep duration will be collected in hours per day (h/day).
- **Full history taking for the present condition regarding** duration, course, medication, and received
- **Complete physical examination** was done for all participants.
- **Depression was assessed using:**
  1. Geriatric Depression Scale-Short Form (GDS-SF) (annex I) [19]
  2. Patient Health Questionnaire (PHQ-9) (annex II). [20]
- **The following laboratory investigation was done for Control and cases:**
  - Complete blood count (CBC). [21]
  - Erythrocyte sedimentation rate (ESR). [22]
  - Liver enzymes: ALT, AST. [23]
  - Serum protein, albumin, and total bilirubin. [24]
  - Renal function tests: blood urea, serum creatinine, complete urine analysis. [25]
  - Fasting blood sugar and post-prandial. [6]
  - High-sensitivity C-reactive protein (hs-CRP) was measured by nephelometry using a BN II nephelometer (Siemens). [27]

Results

Statistical analysis of the data

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation, and median. The significance obtained results were judged at the 5% level.

The used tests were

1 - Chi-square test

For categorical variables, to compare between different groups

2 - Fisher's Exact or Monte Carlo correction

Correction for chi-square when more than 20% of the cells have an expected count less than 5

3 - Student t-test

For normally distributed quantitative variables, to compare between two studied groups

4 - Mann Whitney test

For abnormally distributed quantitative variables, to compare between two studied groups

Table (1): Comparison between the two studied groups according to demographic data

	Control (n = 50)		Depressed (n = 50)		Test of Sig.	p
	No.	%	No.	%		
Sex						
Male	27	54.0	28	56.0	χ^2= 0.040	0.841
Female	23	46.0	22	44.0		
Age						
Min. – Max.	60.0 – 81.0		60.0 – 81.0		t= 0.105	0.917
Mean ± SD.	69.94 ± 6.53		69.80 ± 6.80			
Median	69.50		69.0			
Occupation						
Employed	0	0.0	0	0.0	χ^2= 0.464	^{MC}p= 0.793
Private work	15	30.0	12	24.0		
Retired	16	32.0	17	34.0		
Housewife	19	38.0	21	42.0		
Marital status						
Married	30	60.0	41	82.0	χ^2= 5.877*	0.015*
Single	0	0.0	0	0.0		
Widows	20	40.0	9	18.0		
Divorced	0	0.0	0	0.0		

χ^2: **Chi-square: Monte Carlo** **t: Student t-test**
p: p-value for comparison between the two studied groups
*: Statistically significant at $p \leq 0.05$

Table (2): Comparison between the two studied groups according to smoking and sleep duration

	Control (n = 50)		Depressed (n = 50)		Test of Sig.	p
	No.	%	No.	%		
Smoking						
Nonsmoker	27	Non-smoker	31	62.0	χ^2= 0.891	0.640
Smoker	15	30.0	11	22.0		
Ex-smoker	8	16.0	8	16.0		
Sleep duration						
Min. – Max.	5.0 – 9.0		5.0 – 10.0		t= 0.322	0.748
Mean ± SD.	6.82 ± 1.26		6.74 ± 1.23			
Median	7.0		7.0			

χ^2: **Chi square test** **t: Student t-test**
P: p-value for comparison between the two studied groups

Table (3): Comparison between the two studied groups according to blood picture

Blood picture	Control (n = 50)	Depressed (n = 50)	Test of Sig.	p
WBCs (x10^9/L)				
Min. – Max.	4.10 – 11.0	4.20 – 11.0	t= 0.495	0.622
Mean ± SD.	7.78 ± 1.83	7.59 ± 2.04		
Median	7.85	7.35		
RBCs (x 10^{12}/L)				
Min. – Max.	4.50 – 6.50	4.50 – 6.50	t= 0.330	0.742
Mean ± SD.	5.44 ± 0.60	5.48 ± 0.67		
Median	5.35	5.45		
HB (g/dl)				
Min. – Max.	9.20 – 12.50	8.50 – 11.80	t= 7.975*	<0.001*
Mean ± SD.	12.05 ± 0.47	11.22 ± 0.57		
Median	12.10	11.35		
Platelet (x 10^9/L)				
Min. – Max.	156.0 – 429.0	176.0 – 438.0	U= 1180.0	0.629
Mean ± SD.	277.1 ± 81.15	281.6 ± 77.52		
Median	254.5	258.5		

t: Student t-test **U: Mann Whitney test**
p: p-value for comparison between the two studied groups
p: p-value for comparison between the two studied groups

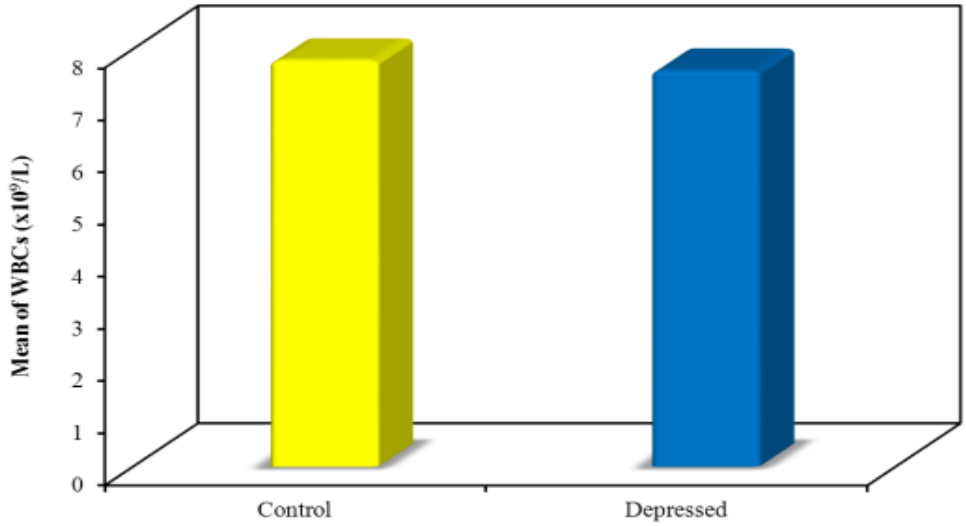

Figure (1): Comparison between the two studied groups according to WBCs

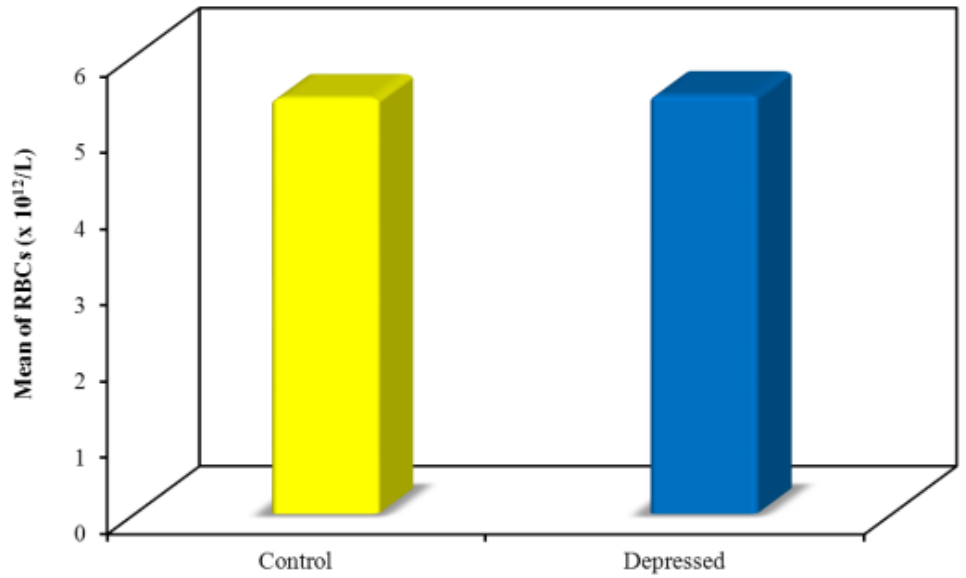

Figure (2): Comparison between the two studied groups according to RBCs

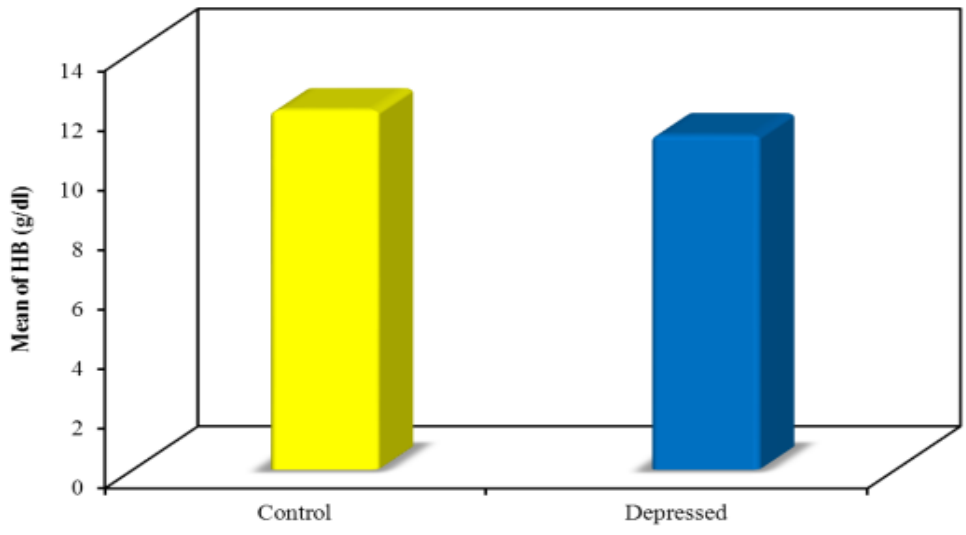

Figure (3): Comparison between the two studied groups according to HB

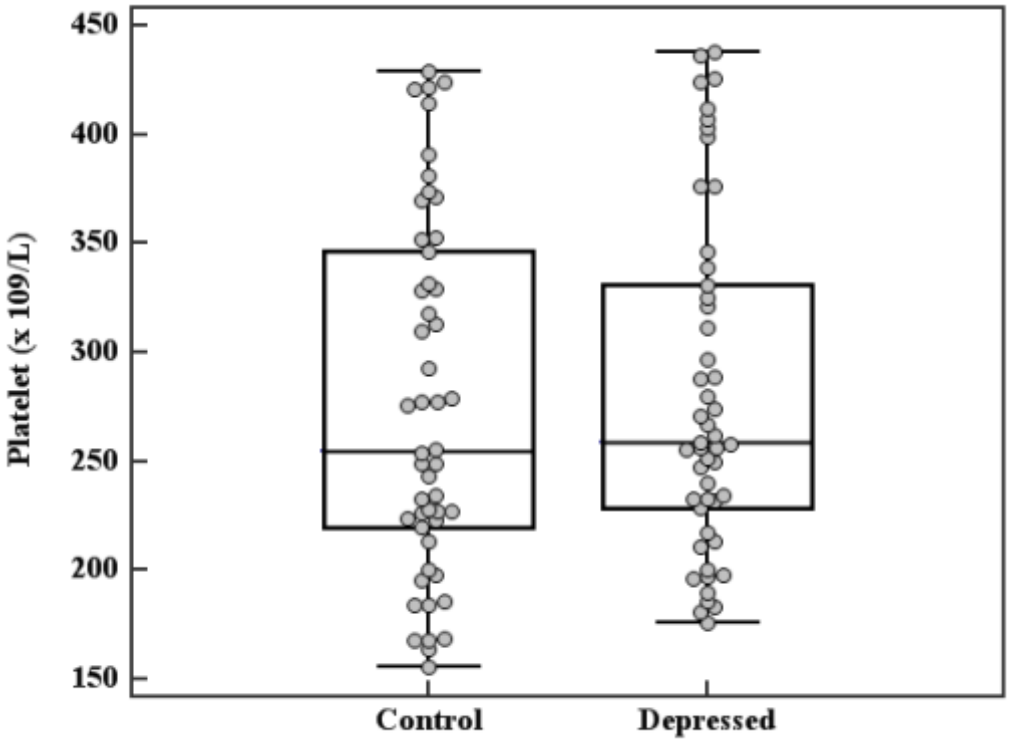

Figure (4): Comparison between the two studied groups according to platelet

Table (4): Comparison between the two studied groups according to liver function

Liver function	Control (n = 50)	Depressed (n = 50)	Test of Sig.	p
ALT (u/l)				
Min. – Max.	22.0 – 40.0	22.0 – 40.0	t= 0.000	1.000
Mean ± SD.	30.92 ± 6.08	30.92 ± 4.94		
Median	31.0	30.50		
AST (u/l)				
Min. – Max.	21.0 – 34.0	21.0 – 34.0	t= 0.623	0.535
Mean ± SD.	27.70 ± 3.75	27.20 ± 4.25		
Median	27.50	27.0		
Serum protein (g/l)				
Min. – Max.	5.40 – 6.20	5.40 – 6.10	t= 1.109	0.270
Mean ± SD.	5.82 ± 0.26	5.76 ± 0.25		
Median	5.90	5.80		
Albumin (g/dl)				
Min. – Max.	3.40 – 5.0	3.40 – 5.0	t= 0.081	0.936
Mean ± SD.	4.20 ± 0.49	4.21 ± 0.50		
Median	4.15	4.20		
Total bilirubin (mg/dl)				
Min. – Max.	0.24 – 1.20	0.24 – 1.17	U= 1218.00	0.825
Mean ± SD.	0.73 ± 0.31	0.72 ± 0.28		
Median	0.71	0.71		

U: Mann Whitney test **t: Student t-test**
p: p-value for comparison between the two studied groups

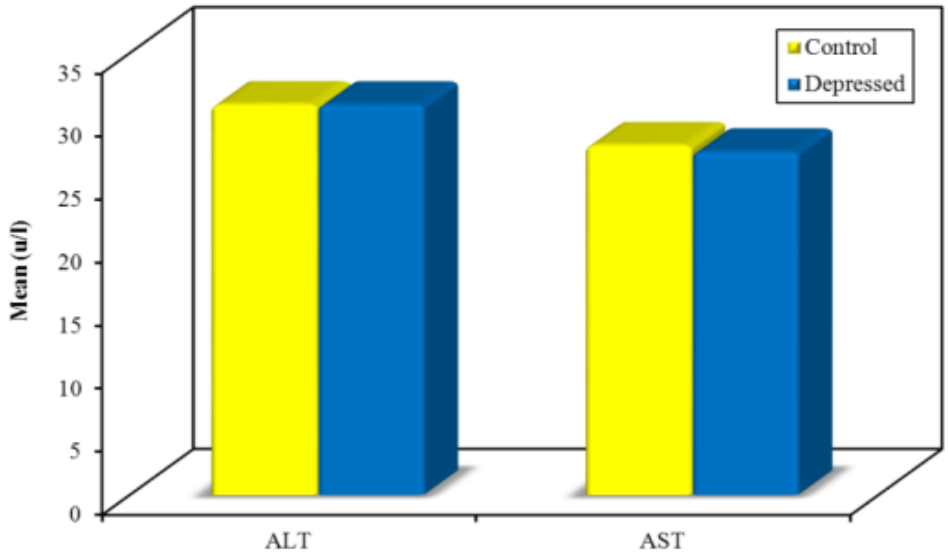

Figure (5): Comparison between the two studied groups according to ALT and AST

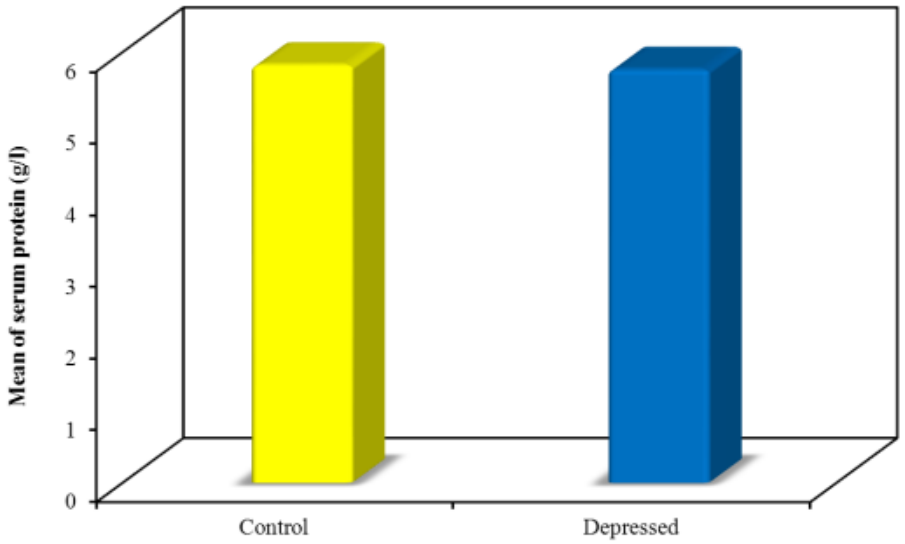

Figure (6): Comparison between the two studied groups according to serum protein

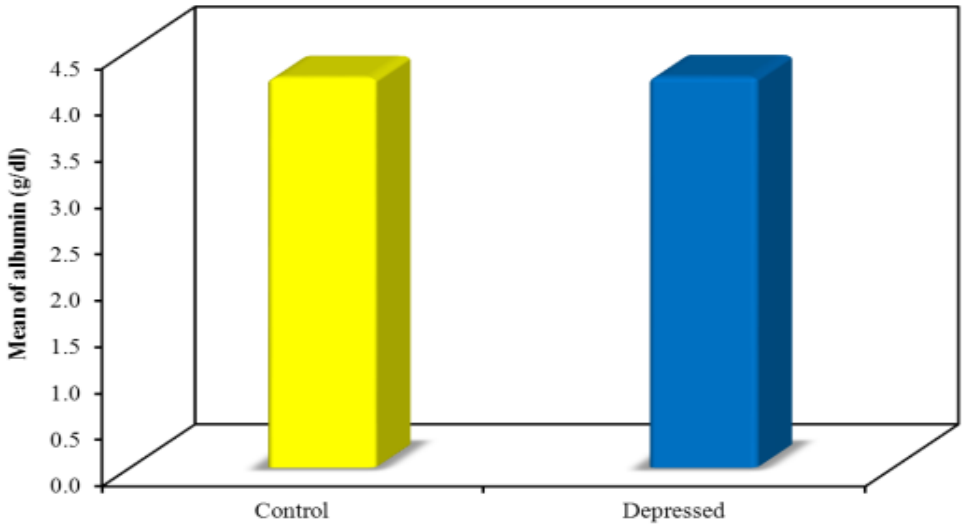

Figure (7): Comparison between the two studied groups according to albumin

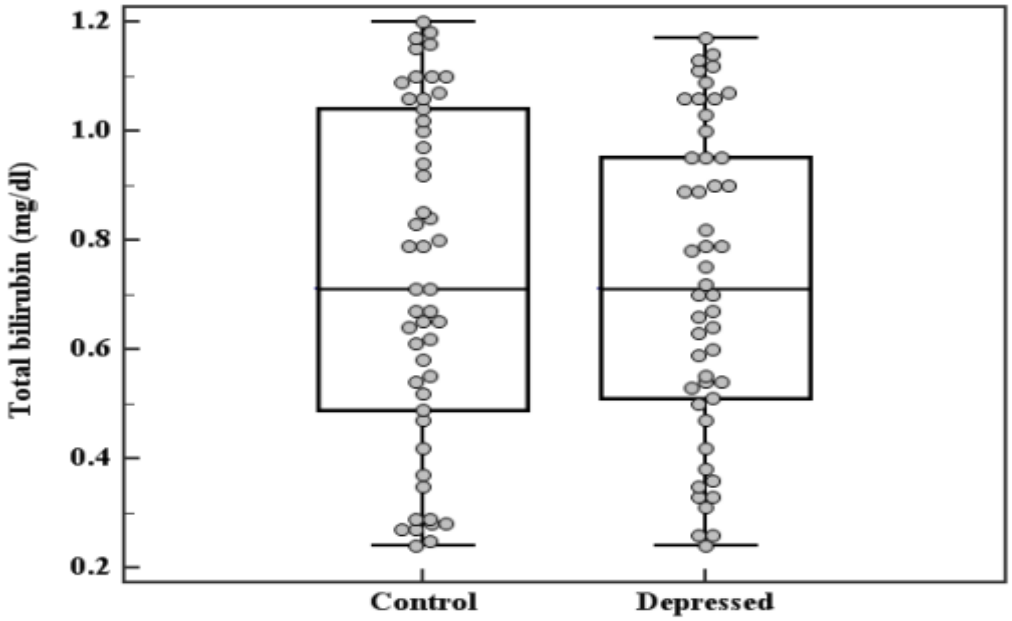

Figure (8): Comparison between the two studied groups according to total bilirubin

Table (5): Comparison between the two studied groups according to renal function

Renal function	Control (n = 50)	Depressed (n = 50)	U	p
Blood urea (mg/dl)				
Min. – Max.	17.0 – 31.0	17.0 – 60.0		
Mean ± SD.	24.48 ± 4.13	26.20 ± 7.23	1128.50	0.401
Median	24.50	25.0		
Serum creatinine (mg/dl)				
Min. – Max.	0.62 – 1.05	0.64 – 2.20		
Mean ± SD.	0.83 ± 0.13	0.91 ± 0.34	1188.50	0.671
Median	0.82	0.86		

U: Mann Whitney test p: p-value for comparison between the two studied groups

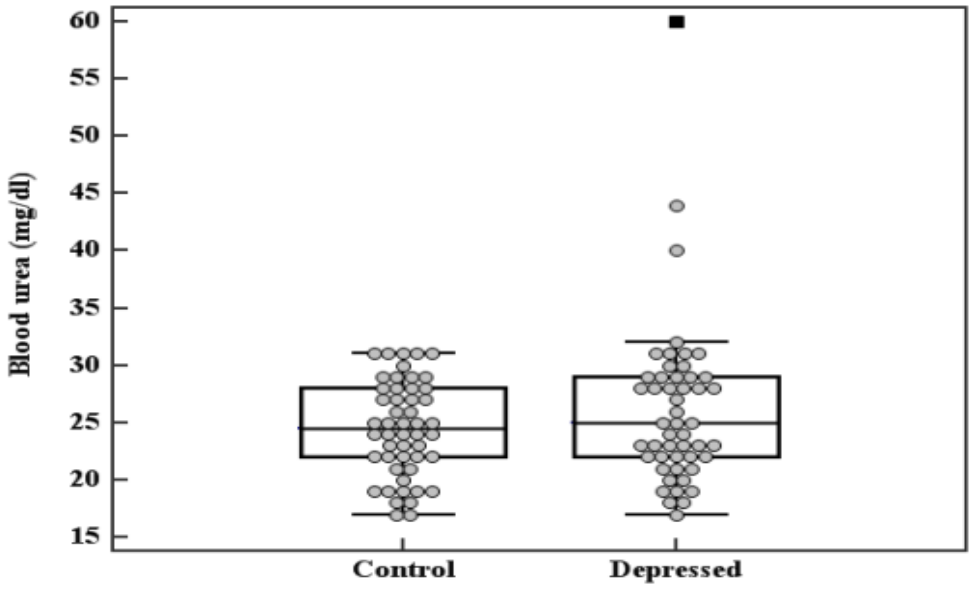

Figure (9): Comparison between the two studied groups according to blood urea

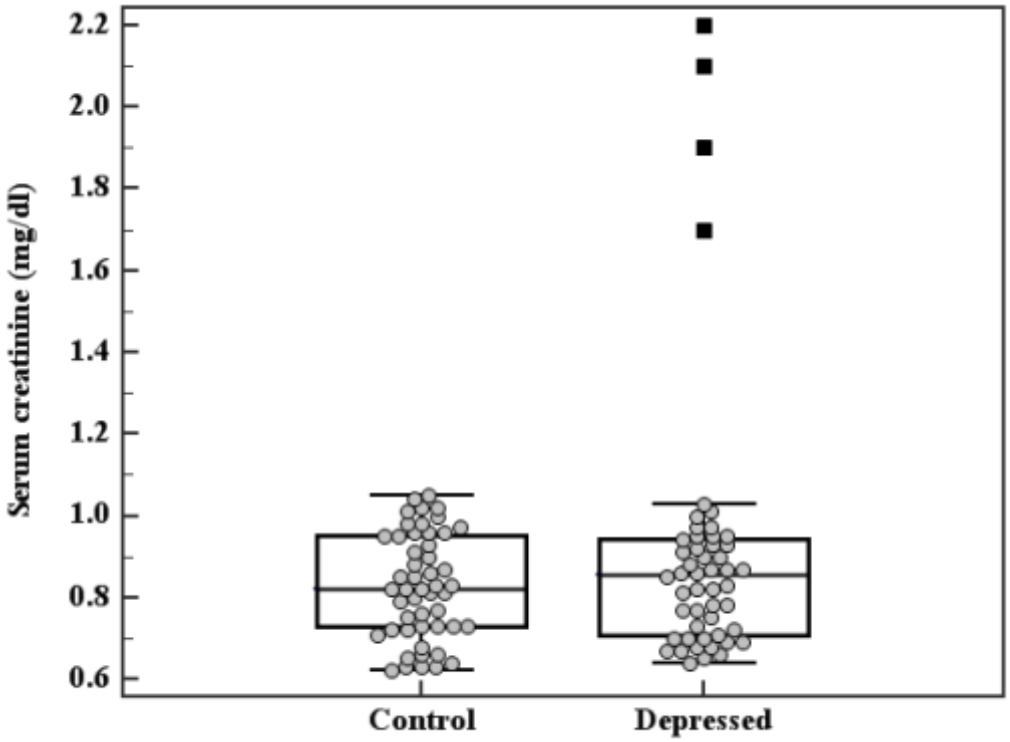

Figure (10): Comparison between the two studied groups according to serum creatinine

Table (6): Comparison between the two studied groups according to glycemic parameters:

Sugar picture	Control (n = 50)	Depressed (n = 50)	t	p
FBG (mg/dl)				
Min. – Max.	83.0 – 125.0	82.0 – 125.0		
Mean ± SD.	102.3 ± 12.65	99.56 ± 11.74	1.106	0.271
Median	100.0	97.0		
PPBG (mg/dl)				
Min. – Max.	118.0 – 167.0	117.0 – 172.0		
Mean ± SD.	143.0 ± 12.86	140.2 ± 13.91	1.037	0.302
Median	143.5	137.5		

t: Student t-test p: p-value for comparison between the two studied groups

Table (7): Comparison between the two studied groups according to ESR

	Control (n = 50)	Depressed (n = 50)	U	p
ESR (1st hour / mm)				
Min. – Max.	2.0 – 18.0	2.0 – 18.0		
Mean ± SD.	9.42 ± 4.87	9.14 ± 5.01	1207.50	0.769
Median	9.0	8.50		

U: Mann Whitney test
p: p-value for comparison between the two studied groups

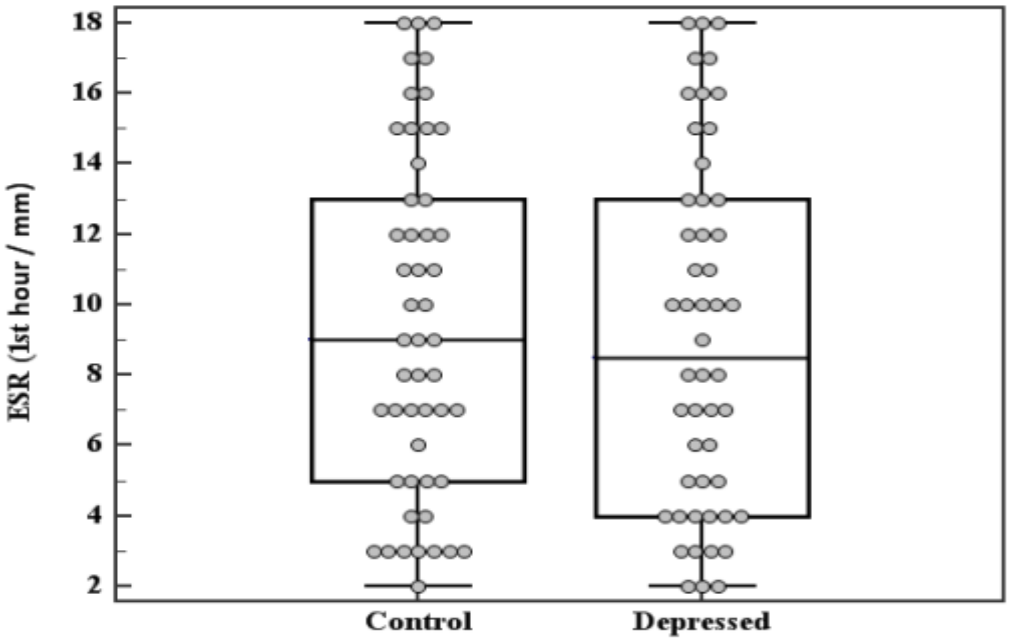

Figure (11): Comparison between the two studied groups according to ESR

Table (8): Comparison between the two studied groups according to hs-CRP

hs-CRP (mg/dl)	Control (n = 50)	Depressed (n = 50)	U	p
Min. – Max.	0.34 – 0.99	0.67 – 7.0		
Mean ± SD.	0.66 ± 0.18	2.44 ± 1.91	83.000*	<0.001*
Median	0.67	1.57		

U: Mann Whitney test

p: p-value for comparison between the two studied groups

*: Statistically significant at $p \leq 0.05$

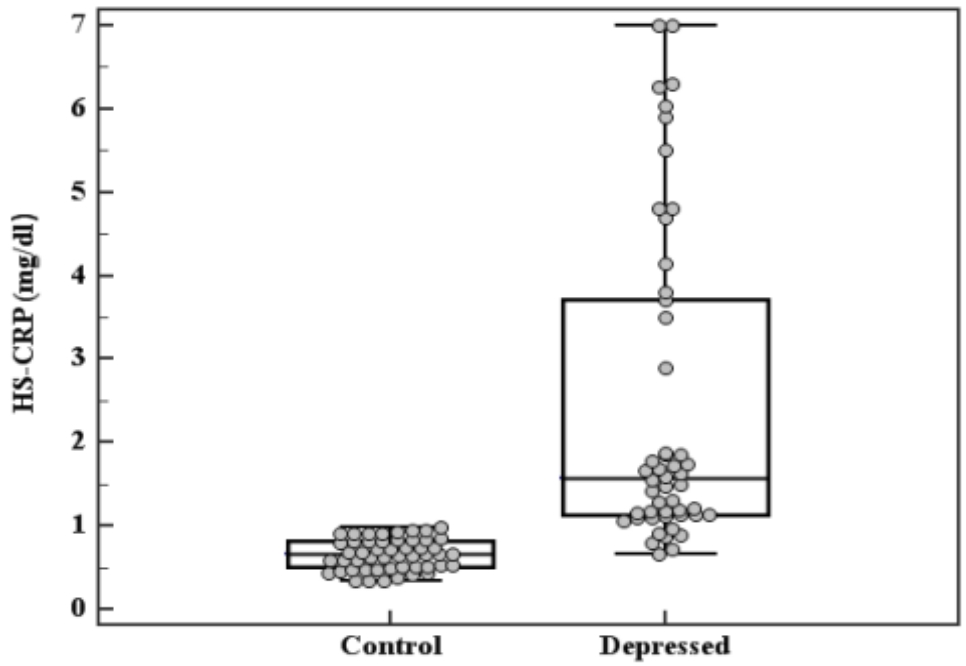

Figure (12): Comparison between the two studied groups according to hs-CRP

Table (9): Comparison between the two studied groups according to depression scores

Depression scores	Control (n = 50)	Depressed (n = 50)	U	p
GDS-15				
Min. – Max.	1.0 – 5.0	5.0 – 14.0		
Mean ± SD.	2.96 ± 1.48	9.52 ± 3.06	33.000*	<0.001*
Median	3.0	10.0		
PHQ-9				
Min. – Max.	2.0 – 11.0	10.0 – 23.0		
Mean ± SD.	6.04 ± 2.59	16.22 ± 4.22	13.000*	<0.001*
Median	6.0	15.50		

U: Mann Whitney test
p: p-value for comparison between the two studied groups
*: Statistically significant at $p \leq 0.05$

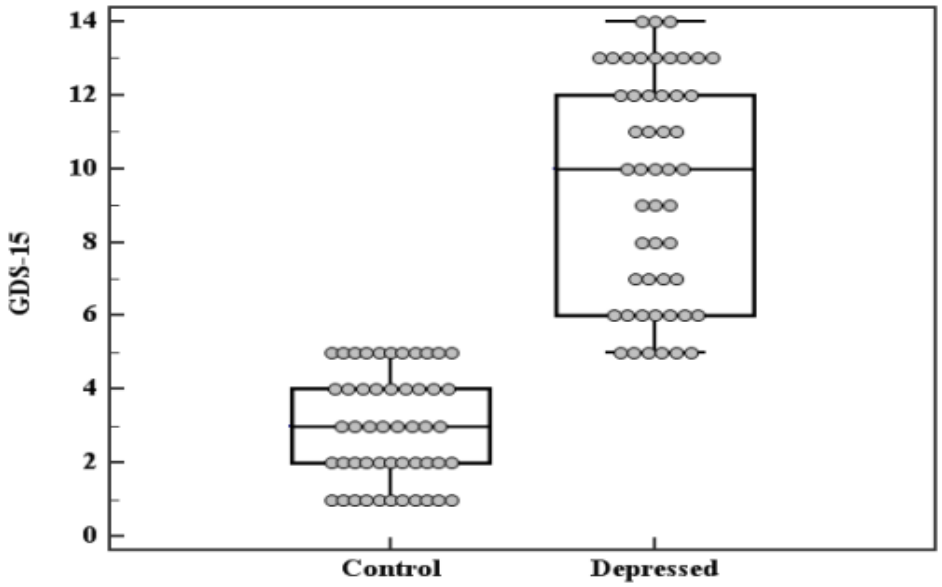

Figure (13): Comparison between the two studied groups according to GDS-15

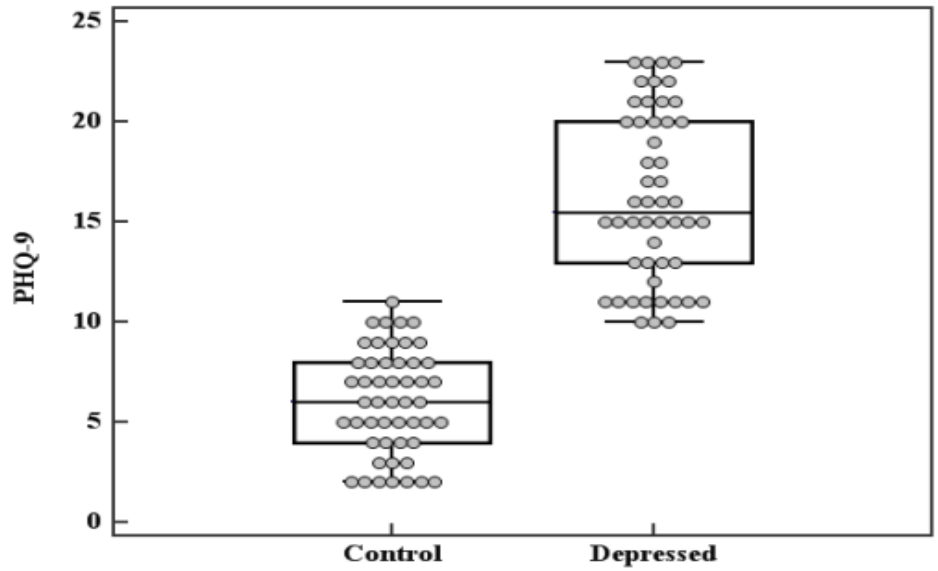

Figure (14): Comparison between the two studied groups according to PHQ-9

Discussion

The elderly population is growing worldwide and has been accompanied by a concurrent increase in physical or psychological disabilities. [28]

Depression in late life is common and has serious consequences on function, medical co-morbidity, quality of life, and use of medical services. [29]

Our major goal was to find if there is a possible association between hs-CRP and depression in the elderly population.

In our study, hs-CRP results were different between both groups. The mean value of hs-CRP was 2.44 ± 1.91 mg/dl in group II (cases) and 0.66 ± 0.18 mg/dl in group I (control). Comparing the two groups showed a statistically significant difference between them regarding the hs-CRP ($p<0.001$).

In the prospective Sydney Memory and Aging Study, Baune et al. found that hs-CRP levels were not associated with depressive symptoms, whereas IL-8 was associated with depressive symptoms at baseline and 2-year follow-up. [30]

In the Health, Aging, and Body Composition Study, high levels of inflammatory markers including CRP, interleukin 6 (IL-6), and tumor necrosis factor α (TNF-α) were associated with depressive symptoms. [31]

In disagreement with our results, Kop et al found that there was no association between elevated CRP levels and depressed mood in a large sample of persons aged 65 years or older. [32] Also, Zalli et al found no cross-sectional association of CRP with depressive symptoms in 656 elderly depressed men and women,[33] while Song et al confirmed this association only in men, but not in women. [34] Penninx et al reported different results, showing the association between depressed mood and markers of inflammation, including elevated CRP levels. [31]

In agreement with our results, Grosse et al. found that activation of the inflammatory response system contributes significantly to the maintenance of symptoms of depression and might be more relevant in people who are more severely ill. [35]

Carvalho et al. identified this relationship in patients resistant to antidepressant treatment.[36,37]

Jones et al. and Moussavi et al. found an association between depressive symptoms and inflammation in individuals who have co-morbid depression with other mental and physical illnesses.[38,39]

Ford and Erlinger recorded this association in patients suffering from recurrent depression. [40]

Raison et al. showed that the anti-inflammatory drug infliximab showed antidepressant properties only in treatment-resistant depressed patients who have high levels of the inflammatory marker C-reactive protein.[41]

van den Biggelaar and colleagues showed that baseline levels of CRP significantly predicted incident depression at 5-year follow-up in elderly participants of >85 years old. [42]

Matsushima et al. and Krogh et al. reported no cross-sectional association between baseline values of hs-CRP and depressive symptoms in community-dwelling older participants. [43,44]

Conclusions

The main finding of the study is that hs-CRP was significantly higher in depressed subjects than in normal subjects. This indicates two main conclusions:

1) Geriatric depression appears to be an inflammatory process or at least a result of the inflammatory process.
2) hs-CRP may serve as markers for early diagnosis of late-life depression.

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