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Original Article

Assessment of Cortisol, Brain-Derived Neurotropic factor, C - reactive protein, Interleukin-6 levels and cognitive decline after trauma exposure

Shamoon Noushad[1,2], Ujala Sajid[3], Sadaf Ahmed[2,3] & Basit Ansari[1]

[1]Department of Health & Physical Education, University of Karachi, Karachi-Pakistan.
[2]Psychophysiology Research Lab, MAHQ Biological Research Centre, University of Karachi, Karachi-Pakistan.
[3]Department of Physiology, University of Karachi, Karachi-Pakistan.

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Corresponding Author Email: ujalasajid97@gmail.com

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Abstract

Background: Studies have found that multiple neurobiological mechanisms are underlying the cause of Posttraumatic stress that influence the nervous and immune system leading to neurodegenerative and psychiatric comorbidities. The present study aims to assess and evaluate the serum Cortisol, C - reactive protein (CRP), Interleukin-6 (IL-6), Brain-Derived Neurotropic Factor (BDNF) levels and cognitive decline among subjects with trauma exposure and to determine the relationship between the above-specified stress biomarkers.

Methodology: Two groups with trauma exposure (including natural disaster, any accident, physical and/or verbal violence, or any stressful condition) in the last twelve months were recruited. Groups were majorly divided based on TSC-40 (Trauma Symptom Checklist - 40) scores. Subjects with a TSC score > 40 were kept in the traumatized group, while those with TSC score < 40 were included in the control group. A total of 188 subjects above the age of 18 were recruited following inclusion criteria, cognition was measured using the Six-Item Cognitive Impairment Test (6-CIT), and serum samples were obtained for cortisol, CRP, BDNF, and IL-6 levels.

Results: There was a significant difference in the serum BDNF ($p<0.001$) level among the traumatized subjects, i.e. 15.68 ± 3.55 ng/dl as compared to controls 26.65 ± 2.47 ng/dl; no significant difference was found in CRP levels (ns) in both groups with a slight increase among the traumatized subjects as compared to the controls, i.e. 4.29 ± 1.50 mg/dl vs. 3.42 ± 1.11 mg/dl. As indicated by the 6-CIT score, the cognitive decline was more pronounced among the traumatized subjects, i.e. 8.54 ± 2.13 compared to the control group 5.0 ± 1.81, with a significant positive difference ($p<0.001$).

Conclusion: The finding suggests that traumatic stress is associated with Cognitive decline, BDNF and cortisol, whereas a non-significant association was found with IL-6 and CRP levels.

Keywords

Traumatic Stress, Cognitive Decline, Brain-Derived Neurotrophic Factor, C - reactive protein, Interleukin-6, Cortisol.

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Introduction

Traumatic events and associated stress have been known to trigger several physical or mental health disabilities, including fatigue, sleep disturbances, anxiety disorder, depression etc. A debate has continued for decades until several studies have proposed a significant link between traumatic stress and its psychological impact on individuals' health and well-being[1, 2]. The drastic or life-threatening events, including accidents, natural disasters, physical and/or verbal violence, or any other stressful condition that is a source of trauma and alters the body's homeostasis, leads to traumatic stress[3]. Individuals with mental health problems such as Post-Traumatic Stress Disorder (PTSD) and major depressive disorder (MDD) or even psychiatric problems had mostly experienced certain traumatic incidences like early childhood trauma, sexual abuse, verbal abuse, and physical violation[2,4-6]. Moreover, the traumatic subjects tend to have a reduced ability to cope with fear and usually feel helpless most of the time[7]. This coping disability generally leads to PTSD that is considered a heterogeneous condition[6] and characterized by successive traumatic reminders, avoidance of cue related to trauma, negative cognition, etc[3, 8].

In the current era, traumatic events are very common in one's life, leading to severe psychotic distress and neuronal impairment; it should be assisted by clinicians, psychologists or psychotherapists, either by interviewing the traumatized individual any formal psychometric testing or any assessment tool[9]. Early assessment and effective management has shown positive growth among the traumatized individuals depending upon the type and number of experiences of the traumatic event[10]. Normal brain development needs to be reviewed at different life stages to understand how traumatic stress initiates[5]. From childhood to later in life, the human brain undergoes several changes, be it structural or functional. It is essential to be well aware of the normal developmental changes to differentiate them based on the pathologies[5]. It is important to understand the changes in individual behaviour, both mentally and socially, caused by any stressful situation or trauma experiencing. Previous evidence from studies has associated childhood victimization or trauma, decades after exposure, with an elevation of inflammatory biomarkers measured[8].

Evidence suggests that the subjects who had suffered from childhood victimization or trauma have elevated levels of inflammatory biomarkers, including IL-6 and CRP, while relatively low levels of BDNF[8,10]. The involvement of neurobiological inflammatory markers in the pathogenesis of trauma is quite obvious. CRP is the most validated and widely studied biomarkers of the peripheral inflammation associated with trauma[9], and elevated CRP levels indicate the increased risk of degenerative disorders[11]. Similarly, BDNF is one of the most extensively researched neurotrophic factors with the most established evidence of influencing synaptic plasticity and has a significant role in cellular proliferation and brain pathologies[12,13]. The down regulation of BDNF in association with traumatic history results in long-term changes in the neurobiology of the brain, suggesting BDNF as an essential biomarker of pathological conditions[14].

In the behavioural literature, both of the molecules that is IL-6 and CRP regarded as inflammatory biomarkers and used mostly in assessing the presence and severity of low-grade inflammation[15-17]. Chronic stress leads to various disease states through the activation of two major systems i.e. HPA –

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axis and the other is the sympathetic nervous system (SNS) axis, usually by the up-regulation of glucocorticoids (cortisol in humans) and catecholamines (epinephrine and norepinephrine)[18]. These two secreted molecules then perform their function by acting through their separate receptor mechanism on different cell types, including the immune cells and nerve cells[18,16]. Besides, it is suggested that chronic stress usually inhibits the secretion of proinflammatory cytokines that usually mediate cellular immunity. On the other hand, the stress can activate the anti-inflammatory cytokine that mediates humoral immunity. Based on this general hypothesis was led that chronic stress particularly leads towards the disease state through immunosuppression.

However, there is still a gap in understanding the overall association of HPA axis activation that leads to alteration in the serum BDNF, IL-6, cortisol and CRP levels under pathological conditions. The present study aimed to assess and compare serum cortisol, CRP, IL-6, and BDNF levels among subjects with trauma exposure and to determine the relationship between the above-specified stress biomarkers. The outcome of this study suggests a significant association between severity of trauma and decrease level of BDNF, along with slight elevation in the serum cortisol, CRP and IL-6, highlighting the possible involvement of BDNF, CRP and IL-6 in the development of post-traumatic stress.

Methodology

This cross-sectional study was conducted from September to December 2019. Two groups with trauma exposure (including natural disaster, any accident, physical and/or verbal violence, or any stressful condition) in the last twelve months were recruited. Groups were majorly divided based on TSC-40 scores. Subjects with a TSC score > 40 were kept in a traumatized group, while those with < 40 scores were included in the control group.

Subjects were recruited from the following three sites, i.e. University of Karachi, Markaz-e-Umeed and Kohi Goth Hospital. A total of 188 subjects above 18 years of age were recruited, with no evidence of any metastatic disease, were enrolled in the study. According to DSM-V, subjects having any codified psychiatric disorder, those on psychopharmacological treatment during the last three years and those who had gone through any structural, psychological intervention for at least six months during the last three years were kept under exclusion criteria. Pakistan medical association committee on ethics approved all recruitment and assessment procedures. All subjects included provided written informed consent after receiving a complete description of the study.

For the investigation of traumatic symptoms, TSC-40 was used[19]. TSC-40 is a self-reported 40-item inquiry form based on a 4-point Likert scale. It evaluates symptomatology in adults associated with childhood or adult traumatic experiences and measures aspects of posttraumatic stress and other symptom clusters found in some traumatized individuals. TSC-40 consisting of six subscales: Anxiety, Depression, Dissociation, Sexual Abuse Trauma Index (SATI), Sexual problems and sleep disturbances; it requires approximately 10-15 minutes to complete. Cognition was measured using the 6-CIT[18]. This short 2-3-minute test contains items on orientation, memory and concentration. Scoring ranges from 0-28, with higher scores indicating more cognitive impairment. Patients with a 6-CIT score of 10 points or lower were considered normal cognition; those with 6-CIT score ≥ 11 were categorized as cognitive

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impairment[20]. Venous blood was collected For estimation of CRP, Cortisol, IL-6 and BDNF into sampling tubes in the morning, the concentration of CRP (mg/dl), BDNF (ng/dl), Cortisol (mcg/dl), IL-6 (pg/ml) was measured using enzyme-linked immunosorbent assay.

All the continuous variables like age, Cortisol, CRP, BDNF, and TSC-40 score were expressed as mean and standard deviation. In contrast, the categorical variables, including gender, ethnicity, occupation and religious preference, etc., were given frequency and percentages.

Chi-square test and One-way Analysis of Variance (ANOVA) were used for comparison between the groups, and $p<0.05$ was considered statistically significant. Data were analyzed using SPSS Version 22.0.

Results

Out of 188 subjects, there were 88 traumatized and 100 controls. The majority were females, i.e. 75%, and only 25% were males, with a mean age of 29 ± 7.8 years. Most of the subjects belonged to different ethnicity, had different occupational statuses, religious preferences and political views, as shown in (Table 1).

Table 1: Demographic characteristics of the subjects enrolled in the study.

Baseline Characteristics		**n(%)**
Gender	Male	47(25)
	Female	141(75)
Ethnicity	Sindhi	24(12.76)
	Balochi	23(12.23)
	Punjabi	18 (9.57)
	Pathan	21(11.17)
	Muhajir	80(42.55)
	Others	15(7.97)
	Prefer not to respond	7(3.19)
Occupation	Student (not working)	133(70.74)
	Student (part-time job/business)	13(6.91)
	Student (full-time job or business)	14(7.44)
	Business	11(5.85)
	Salaried Person	17(9.04)
Religious preference	Agnostic	2(1.06)
	Religious	165(87.76)
	Not religious but spiritual	14(7.44)
	Others	7(3.72)
Political View	Conservative	30(15.95)
	Moderate	118(62.76)
	Liberal	40(21.27)

*Values are given as Mean ± SD or n(%)

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Individuals with trauma (TCS Score > 40) had significantly lower levels of BDNF, i.e. 15.68 ± 3.55 ng/dl, and slightly higher levels of CRP 4.29 ± 1.50 mg/dl as compared to controls (Table 2).

Table 2: Comparative assessment of traumatic symptom and biomarkers among the traumatized and control subjects

Variable	Traumatized (Group)	Controls (Group)	p-value
	Mean ± SD		
TSC-40 Score	56.72±11.91	27.76±9.28	<0.001*
6-CIT Score	8.54±2.13	5.0±1.81	<0.001*
CRP (mg/dl)	4.29±1.50	3.42±1.11	ns
BDNF (ng/dl)	15.68±3.55	26.65±2.47	<0.001*
Cortisol (mcg/dl)	26.17±3.65	20.37±3.71	<0.001*
IL-6 (pg/ml)	2.90±0.63	2.44±2.08	ns

*p-value < 0.05 is considered significant; ns: non-significant

*TSC-40-Traumatic Symptom Checklist; 6-CIT-Six Item Cognitive Impairment Test; CRP-C-reactive protein; BDNF-Brain Derived Neurotropic Factor; IL-6-Interleukin 6

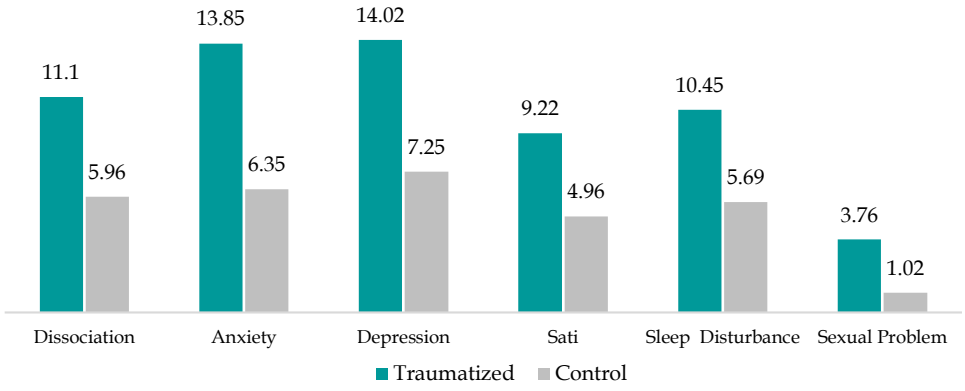

Figure 1: Comparison of subscales scores of TSC-40 among the control and traumatized groups of study

Figure 1 shows the mean value of the subscales score of TSC-40 among the traumatized and control subjects. Depression was significantly very high in traumatized subjects ($\bar{X}$=14.02) compared to the control subjects ($\bar{X}$=7.25). In contrast, the anxiety level was significantly also very high in traumatized residents ($\bar{X}$=13.85) as compared to the control subjects ($\bar{X}$=6.35). Dissociation, SATI, and Sleep disturbance level were almost equal in traumatized subjects with a mean value of 11.11, 9.22 and 10.45. Among all the subscales scores, both traumatize subjects and control subjects scored the lowest in the Sexual problem subscale; traumatized subjects ($\bar{X}$=3.76) and control subjects ($\bar{X}$=1.02).

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Discussion

The present study aimed to investigate the role of biomarkers in post-traumatic stress, focusing on the serum concentration of cortisol, BDNF, IL-6 and CRP among the traumatized and control subjects. The subjects who were deemed traumatized as per the findings from TSC-40, with comparatively high depression and anxiety index, were compared to those who scored less and considered as controls (Figure 1).

The BDNF and CRP level was measured to find the association of inflammation with the underlying posttraumatic stress mechanism. Rosen et al., 2017 have suggested that systemic inflammation is associated with stress pathology with a positive CRP association with posttraumatic stress severity[21]. Moreover, a meta-analysis of random effects suggested that individuals who had experienced any type of childhood trauma (sexual, physical or emotional) had elevated baseline peripheral CRP levels[17]. A follow-up study by Laurin and his colleagues suggested that psychological distress is associated with increased CRP concentration and inflammatory mechanisms reflecting processes that further contribute to cognitive decline in later life[22]. Similarly, in our study, the mean CRP level was elevated among the traumatized subjects compared to the controls, i.e. 4.29 ± 1.50 mg/dl vs. 3.42 ± 1.11 mg/dl (Table 2). Although the association wasn't significant as per the evidence, there was a prominent variation in the mean CRP level among the two groups.

We found significant down regulation in the serum BDNF concentration among the traumatic subjects 15.68 ± 3.55 ng/dl as compared to the controls 26.65 ± 2.47 ng/dl ($p<0.05$) (Table 2). A recent study confirmed that the serum BDNF level decline among individuals with a history of a traumatic event or those with mental health illnesses[14]; the study indicated a significant decline in the serum BDNF concentration among patients reporting childhood sexual abuse and depressive episodes[21]. Moreover, Angelucci et al., in their study, suggested the involvement of BDNF in the pathophysiology of PTSD[23]. The role of BDNF in enhancing learning and memory in the hippocampus is evident[24], and the present study revealed a positive correlation in the down-regulation of BDNF (Table 2).

Our results show the positive correlation of cortisol with the TSC-40 score. The positive correlation shows that if the TSC-40 score increases, then the cortisol level also increases and vice versa. The increased score of TSC-40 indicates that people whose scores were above 40 have a high level of cortisol and the people whose TSC-40 score was below 40 have a low level of cortisol[25]. As a biomarker of stress, the cortisol is linked to the TSC-40 score, which determines the level of cortisol and trauma of an individual[26]. Thus, our finding also indicates higher the TSC-40 score, the higher the level of cortisol and this increase in cortisol level, the person can be identified in a chronic traumatic stress[27]. TSC-40 scores below 40 showed a decrease in levels of the IL-6, while the TSC-40 scores above 40 showed an increase in IL-6 levels though it was insignificant, as shown in table1that may indicate the initiation of low-grade inflammation[28].

Cognitive impairment is one of the core features of degenerative disorders, and studies showed a significantly high association between traumatic events, degeneration of brain cells and cognitive dysfunction[29]. The cognitive impairment among the traumatized subjects was significantly high compared to the control group, with a decreased level of BDNF. Studies have suggested that BDNF plays a

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critical role in enhancing learning and memory in the hippocampus[30]. The results of 6-CIT of a traumatized group show a positive correlation between the decreased level of BDNF levels with cognitive impairment pathology. There was a slight elevation in CRP and IL6 concentration in traumatized subjects compared to the control group, suggesting that higher CRP levels may be a marker of memory and learning impairment in traumatic subjects. Noble, J. M. et al., 2010, in a cross-sectional analysis, suggested that increased CRP level can be a marker of memory and an increased risk of cognitive decline[31]. Since the results show a very slight elevation in CRP levels of traumatized individuals, hence basis on the results, we cannot suggest an association between cognitive impairment and an increase in IL6 and CRP.

These overall results indicate that some other undefined factors may be modifying the observed associations of traumatic events with degeneration of brain cells, related immune influences, and susceptibility to cause psychiatric conditions later in life by way of inflammatory processes[32]. Still, it is possible that changes in BDNF and cortisol while non-significance of IL6 and CRP can be assumed to certain specific characteristic symptoms of traumatic stress[32,33]. However, further exploration of the role of environmental interactions and immune mechanisms is still a challenge[34]. The limitations of the current study that hinder further insight include its focus on a cross-sectional association based on one-time assessments of inflammatory markers, undervaluing the explicit inflammation markers' role in stress disorders and lack of longitudinal study design. The symptomatic expositions and potential confounders interfering with the immune system should be monitored in longitudinal and case-control settings to clarify these ambiguities.

Conclusion

The finding suggests that traumatic stress is associated with Cognitive decline, BDNF and cortisol, highlighting the possible involvement of these biomarkers in developing associated symptomatic neurobiological alterations. Whereas the changes in IL-6 and CRP were non-significant in the association with traumatic scores. However, there is a possible role of the explicit inflammation markers, and related mechanisms that are needed to be explored by further large-scale descriptive studies or randomized controlled trials are required to elucidate the mechanism.

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References

1. Jeenger J, Singroha V, Sharma M, Mathur DM. C-reactive protein, brain-derived neurotrophic factor, interleukin-2, and stressful life events in drug-naive first-episode and recurrent depression: A cross-sectional study. Indian J psychiatry. 2018;60(3):334.
2. Giacobbo BL, Doorduin J, Klein HC, Dierckx RA, Bromberg E, de Vries EF. Brain-derived neurotrophic factor in brain disorders: focus on neuroinflammation. Mol neurobiology. 2019;56(5):3295-312.
3. Brooks M, Graham-Kevan N, Robinson S, Lowe M. Trauma characteristics and posttraumatic growth: The mediating role of avoidance coping, intrusive thoughts, and social support. Psychol Trauma. 2019;11(2):232.
4. Noushad S, Ansari B, Ahmed S, Saleem Y. Effect of Nature-based physical activity on post-traumatic growth among Healthcare providers with post-traumatic Stress: Protocol for a randomized controlled trial.

ISSN 2412-3188 (Online) | 2410-1354 (Print)

Int. j. endorsing health sci. res. 2020; 8(4):295-301.
5. Speer K, Upton D, Semple S, McKune A. Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. J inflam Res. 2018;11:111.
6. Hoerster KD, Campbell S, Dolan M, Stappenbeck CA, Yard S, Simpson T, Nelson KM. PTSD is associated with poor health behavior and greater Body Mass Index through depression, increasing cardiovascular disease and diabetes risk among US veterans. Prevent Med reports. 2019;15:100930.
7. Jenewein J, Erni J, Moergeli H, Grillon C, Schumacher S, Mueller-Pfeiffer C, Hassanpour K, Seiler A, Wittmann L, Schnyder U, Hasler G. Altered pain perception and fear-learning deficits in subjects with posttraumatic stress disorder. J pain. 2016;17(12):1325-1333.
8. Baldwin JR, Arseneault L, Caspi A, Fisher HL, Moffitt TE, Odgers CL, Pariante C, Ambler A, Dove R, Kepa A, Matthews T. Childhood victimization and inflammation in young adulthood: A genetically sensitive cohort study. Brain Behav Immun. 2018;67:211-217.
9. Ahmed S, Noushad S, Shahzad S, Azher SZ, Aziz A, Saleem MT. Post-traumatic Stress Disorder in Karachites due to random events of violence. Int J Endors Health Sci Res. 2014;2(1): 42-45.
10. Miller MW, Maniates H, Wolf EJ, Logue MW, Schichman SA, Stone A, Milberg W, McGlinchey R. CRP polymorphisms and DNA methylation of the AIM2 gene influence associations between trauma exposure, PTSD, and C-reactive protein. Brain Behav Immun. 2018;67:194-202.
11. Nestler E, Barrot M, DiLeone RJ, Eisch AJ, Gold SJ. Monteggia LM. Neurobiology of depression. Neuron. 2002;34:13-25.
12. Alexandrov PN, Kruck TP, Lukiw WJ. Nanomolar aluminum induces expression of the inflammatory systemic biomarker C-reactive protein (CRP) in human brain microvessel endothelial cells (hBMECs). J inorganic biochemist. 2015;152:210-213.
13. Dimitriadis M, van den Brink RH, Comijs HC, Voshaar RO. Prognostic effect of serum BDNF levels in late-life depression: Moderated by childhood trauma and SSRI usage?. Psychoneuroendocrinol. 2019;103:276-283.
14. Aas M, Dieset I, Mørch R, Steen NE, Hope S, Reponen EJ, Laskemoen JF, Ueland T, Aukrust P, Melle I, Agartz I. Reduced brain-derived neurotrophic factor is associated with childhood trauma experiences and number of depressive episodes in severe mental disorders. Schizophrenia Res. 2019;205:45-50.
15. Fagundes CP, Way B. Early-life stress and adult inflammation. Curr Dir Psychol Sci. 2014;23(4):277-283.
16. Miller GE, Chen E, Parker KJ. Psychological stress in childhood and susceptibility to the chronic diseases of aging: moving toward a model of behavioral and biological mechanisms. Psychol. Bull. 2011;137(6):959.
17. Baumeister D, Akhtar R, Ciufolini S, Pariante CM, Mondelli V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. Mol psychiatry. 2016;21(5):642-649.
18. Hänsel A, Hong S, Cámara RJ, Von Kaenel R. Inflammation as a psychophysiological biomarker in chronic psychosocial stress. Neurosci Biobehav Rev. 2010;35(1):115-121.
19. Briere J, Runtz M. Trauma Symptom Checklist 33 and 40: TSC-33 and TSC-40. Available at: http://www.scalesandmeasures.net/files/files/Trauma%20Symptom%20Check.pdf.
20. Abdel-Aziz K, Larner A. 6CIT for detection of dementia and cognitive impairment. J Neurol Neurosurg Psychiatry.2014;85(10):e4.
21. Rosen RL, Levy-Carrick N, Reibman J, Xu N, Shao Y, Liu M, Ferri L, Kazeros A, Caplan-Shaw CE, Pradhan DR, Marmor M. Elevated C-reactive protein and posttraumatic stress pathology among survivors of the 9/11

ISSN 2412-3188 (Online) | 2410-1354 (Print)

World Trade Center attacks. J Psych Res. 2017;89:14-21.
22. Aas M, Dieset I, Hope S, Hoseth E, Mørch R, Reponen E, Steen NE, Laskemoen JF, Ueland T, Aukrust P, Agartz I. Childhood maltreatment severity is associated with elevated C-reactive protein and body mass index in adults with schizophrenia and bipolar diagnoses. Brain Behav Immun. 2017;65:342-349.
23. Angelucci F, Ricci V, Gelfo F, Martinotti G, Brunetti M, Sepede G, Signorelli M, Aguglia E, Pettorruso M, Vellante F, Di Giannantonio M. BDNF serum levels in subjects developing or not post-traumatic stress disorder after trauma exposure. Brain Cog. 2014;84(1):118-122.
24. Leal G, Bramham CR, Duarte CB. BDNF and hippocampal synaptic plasticity. Vitamins and hormones. 2017 Jan 1;104:153-195.
25. Bergman B, Ahmad F, Stewart DE. Work family balance, stress, and salivary cortisol in men and women academic physicians. Int J Behav Med. 2008;15(1):54-61.
26. Simeon D, Yehuda R, Cunill R, Knutelska M, Putnam FW, Smith LM. Factors associated with resilience in healthy adults. Psychoneuroendocrinol. 2007;32(8-10):1149-1152.
27. Do Yup Lee EK, Choi MH. Technical and clinical aspects of cortisol as a biochemical marker of chronic stress. BMB reports. 2015;48(4):209.
28. Bob P, Susta M, Gregusova A, Jasova D. Dissociation, cognitive conflict and nonlinear patterns of heart rate dynamics in patients with unipolar depression. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(1):141-145.
29. Sahu G, Malavade K, Jacob T. Cognitive impairment in schizophrenia: interplay of BDNF and childhood trauma? A review of literature. Psychiatric Quart. 2016;87(3):559-569.
30. Yu H, Zhang Z, Shi Y, Bai F, Xie C, Qian Y, Yuan Y, Deng L. Association study of the decreased serum BDNF concentrations in amnestic mild cognitive impairment and the Val66Met polymorphism in Chinese Han. J clin psychiatry. 2008;69(7):1104-1111.
31. Noble JM, Manly JJ, Schupf N, Tang MX, Mayeux R, Luchsinger JA. Association of C-reactive protein with cognitive impairment. Arch neurol. 2010;67(1):87-92.
32. Tursich M, Neufeld RW, Frewen PA, Harricharan S, Kibler JL, Rhind SG, Lanius RA. Association of trauma exposure with proinflammatory activity: a transdiagnostic meta-analysis. Transl psychiatry. 2014;4(7):e413.
33. Kim TD, Lee S, Yoon S. Inflammation in post-traumatic stress disorder (PTSD): a review of potential correlates of PTSD with a neurological perspective. Antioxidants. 2020;9(2):107.
34. Wieck A, Barbosa IG, Teixeira AL, Bauer ME. Immunology of Post-Traumatic Stress Disorder (PTSD). Immunopsychiatry: A Clinician's Introduction to the Immune Basis of Mental Disorders. UK: Oxford University Press; 2019:227.