



Oxidative Stress Markers, Neuroendocrine Hormones, Serum Vitamins (C, and E) among Minia University Postgraduate Students caused by Exam Stress: Impact on Performance

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ABSTRACT

Objective: We thought to examine the effect of exam stress on serum cortisol, leptin, CRP, IL-6, and vitamins (C, E) levels among postgraduate students and their impact on academic performance. **Method:** Minia University postgraduate nursing students were involved in this study. Stress was measured by the Kessler 10 Psychological Distress instrument (K10). Sera leptin, cortisol, Vitamins (C, E), C-Reactive Protein (CRP), total anti-oxidant capacity (TAC) and Malondialdehyde (MDA) were assessed for each subject twice, the first time was one month before the exam date and the second time was one hour before the exam time. **Results:** 52 female postgraduate nursing students had participated in the study (mean age of 25 ± 3.4 years). The stress percentage increased from 51.9 % to 82.7% at the exam day. There was moderate negative significant correlation between vitamin C and cortisol levels only during examination stress ($r = -0.44$, $p < 0.001$). There was a moderate negative significant correlation between vitamin E and leptin levels only in stress ($r = -0.41$, $p = 0.002$). The most contributing significant metabolic parameters affecting the academic performance was leptin followed by TAC and Vitamin C. **Conclusion:** The academic performance was better in mild and moderate stresses and the most contributing variables were leptin levels, TAC levels, and IL-6 levels. Exam stress caused an increase in leptin and cortisol levels and a decrease in vitamin C and TAC levels. Vitamin C by its correlation to cortisol may decrease stress response anxiety and improve academic performance.

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INTRODUCTION

Stress induces a wide range of biochemical and behavioral injurious effects of the body. Examination is a realistic stressor that disturbing human health and cortisol is a known stress hormone involved in this adaptation.¹

In the 1994s, leptin, an adipocyte-derived hormone that regulates energy metabolism, was discovered. Psychological stress can induce sympathetic stimulation showing leptin effect in humans clearly. Acute stressors can upregulate levels of some circulating inflammatory markers including interleukin-6 (IL-6).²

Reactive oxygen species have essential physiological roles in homeostasis and intracellular cell signaling.³ Oxidative damage has a major impact in the pathogenesis of stress. Product of lipid peroxidation, malondialdehyde (MDA), is the product of lipid peroxidation, can cause damage to cell proteins resulting in cellular apoptosis. So, prevention of the dangerous effects of reactive oxidative stress (ROS) are of critical importance and may be controlled by non-enzymatic antioxidants (e.g., Glutathione, vitamin C and E) and enzymatic antioxidants.⁴

Vitamin C (Ascorbic acid) has a great effect in the body. It is necessary for the synthesis of collagen. It is also necessary for the synthesis of hormones and neurotransmitters. It is more than an antioxidant which reduces potentially damaging Reactive Oxygen Species (ROS), forming relatively stable ascorbate free radicals.⁵ It also, reduces stress and distress, reduces anxiety, and elevates mood.⁶

Vitamin E (α -tocopherol) is a key lipophilic antioxidant protecting lipoproteins, cellular and intracellular membranes from damage.⁷ This property also enables the molecule to play a significant role in stress. Anxiety during exam increases the negative mood and tends to destroy cellular immunity while conserving humeral immunity.⁸ They reported meta-analysis of more than 3 hundred articles recording a relationship between stress and the immune system parameters in human.

The effect of exam stress on β -endorphin, blood elements, inflammatory cytokines and some endocrine hormones are previously discussed but with much controversy.⁹ So, this research was carried out to study the relationship between perceived stress level, endocrine hormones (cortisol and leptin), some inflammatory markers and antioxidant activities (TAC, vitamins C, and E) among postgraduate nursing students undergoing examination stress and their impact on performance and if there is any role of vitamins depletion on performance during exam stress.

METHOD

This longitudinal study conducted during the period from November 2019 to January 2020 in Minia University. A written consent was obtained before the beginning of the research, accepted by the ethical committee of Minia University.

Fifty-two postgraduate nursing students (age ranged from 25 \pm 3.4 years - females) were participated in the study. All postgraduate nursing students enrolled in Minia University during the year 2019- 2020 were included into the research. The exclusion criteria were: the use of possible or known drugs that may affect memory, the use of vitamins during the previous 6 months and severe neurological or psychiatric illness.

Stress was measured by the Kessler-10 Psychological Distress Scale subjective stress test.¹⁰ This scale has

been used thoroughly in epidemiological research to assess the level of current psychological stress, then it was translated into many languages, as well as Arabic. This instrument was used in two stages, one month and one hour before the exam. The WHO World Mental Health applied it as a stress measure in many studies.^{11,12} The Kessler-10 scale contains ten questions as "how often in the last month did you suffer from ..." and offers some complaints, such as exhausted for no obvious cause, upset, nervous or distressed. The five possible answers for each question range from 'none of the time' to 'all of the time' and were scored from 1 to 5 respectively. Scoring was interpreted as: a score of < 20 does not mean stress of any level while a score of 20-24 means mild stress, 25-29 means moderate stress, and 30-50 means severe stress.¹³ The questionnaire had also contained some demographic data like students' age, residence, questions related to academic performance, and sources of stress. This instrument was self-administered and used in two stages, one month and one hour before the exam. The reliability of the questionnaire was tested by Cronbach alpha = 0.90 (95% confidence interval (CI) 0.89-0.91). Performance was assessed as the percentage score acquired in a specific examination, and classified into good (60% and more), and bad (less than 60%).

Biochemical analysis: Two blood samples were collected from each participant, one month and one hour before the exam at 11.00 AM. 2ml of blood was taken from each participant. A venous blood sample was taken by a small cannula from an ante cubital vein. Plasma CRP was determined by turbidimetry (biosystems, Egypt). Plasma MDA and TAC concentration were determined using colorimetric assay kit according to manufacturer's instructions (Bio diagnostic, Dokki, Giza, Egypt). Plasma leptin was determined by DSL (Webster, TX) 10 -23100 ACTIVE Human Leptin enzyme-linked immunosorbent ELISA, an enzymatically amplified "two steps" immunoassay. IL-6 was determined in serum samples by using AviBion Human IL-6 ELISA kit, Finland). Cortisol level was determined by applying the spectrophotofluorometric method (Shimaduz RF-5000, Japan). This technique principally involves an extraction of free 11-hydroxycorticosteroids from serum, mainly, cortisol, by methylene chloride followed by condensation with an acidic fluorescence

Table (1): Metabolic parameters and vitamins level changes during academic stress in postgraduate nursing students.

	Baseline	On the day of examination	P-value
Distribution of stress according to Kessler-10 psychological distress scale (K10), n (%)			
-No stress < 20	25 (48.1)	9 (17.3)	<0.001
-Mild stress = 20-24	4 (7.7)	16 (30.8)	
-Moderate stress = 25-29	10 (19.2)	4 (7.7)	
-Severe stress = 30-50	13 (25)	23(44.2)	
-Total K 10 score	23.8±9.9	28.8±9.9	
Leptin (µg/L)	11.1±7.6	13.5±7.1	<0.001
Cortisol (ng/mL)	79.4±9.6	93.9±9.2	<0.001
SBP (mmHg)	118.1±2.6	124.3±3.6	<0.001
MDA (mmol/L)	4.4±0.81	5.2±0.98	<0.001
IL6 (pg/ml)	4.5 (3.5-5.5)	4.6 (3.5-5.6)	0.300
CRP (mg/dL)	1.45 (0.6-2.4)	1.47 (1.2-3.51)	0.060
TAC (mmol/L)	1.79±0.5	1.54±0.4	0.003
Vit C(mg/dL)	1.07±0.39	0.86±0.32	<0.001
Vit E (µg/mL)	9.8±3.48	9.25±2.89	0.260

Data were presented as mean±SD, unless mentioned otherwise. P-values were obtained using Wilcoxon Signed ranks test or paired t-test. P < 0.05 for baseline (one month before exam day) vs. under exam stress for all hormone changes; SBP: Systolic Blood Pressure; MDA: Malondialdehyde, IL6: interleukin 6; CRP: C- reactive protein; TAC: Total reagent.

The induced fluorescence is measured at 510 nm after excitation at 450 nm (Silber, Busch, & Oslapas, 1958). Vitamin C (Ascorbic acid) was antioxidant capacity; Vit C: Vitamin C; Vit E: Vitamin E measured by colorimetric assay kit according to the instructions of manufacturer (Biodiagnostic, Dokki, Giza, Egypt) or Sigma-Aldrich. Vitamin E was determined by ELISA kits (bio compare)

Statistical analysis: Data were analyzed using SPSS version 20. Normal distribution was tested by the Kolmogorov-Smirnov test, and the parametric variables with normal distribution were interpreted as mean ± SD. For the nonparametric variables (IL6, and CRP); the median, along with the minimum and maximum values, were demonstrated in the descriptive tables. Comparisons between measurements of the parametric parameters were determined by paired and unpaired samples t-test. Statistically significant differences were tested with the nonparametric Mann Whitney U test for quantitative items, and with the nonparametric Wilcoxon Signed ranks test for paired observations. Multiple linear regression analysis (stepwise method) was used to assess the relations between percentage of

academic performance and metabolic parameters. Pearson's correlation coefficients and spearman correlation coefficients were performed to examine the correlations between vitamins and metabolic parameters. The P-value of < 0.05 was statistically significant.

RESULTS

Fifty-two female postgraduate nursing students had participated in the study (mean age of 25±3.4 years). The stress perceived by the students before and during the exam stressful condition is represented in (Table1). In stressful conditions, students were found to have higher significant levels of cortisol, leptin, MDA, and TAC in comparison to the baseline situation. A similar response was noticed in IL-6 levels although were statistically not significant. In addition, vitamin C levels showed a significant reduction in the exam stress time in comparison with the baseline time.

The stress mean score based on K10 scoring was significantly more in the exam time than baseline (28.8±9.9, and 23.8±9.9, respectively, p<0.001). The percentage of all types of stress among the postgraduate students one month before the

Table (2): Relationship between Metabolic parameters with respect to Kessler-10 psychological distress scale

	No stress (K10 score <20)	Stress (K10 score ≥20)	P-value
Leptin (µg/L)	11.1±7.6	13.6±6.3	0.17
Cortisol (ng/mL)	79.3±9.8	95.5±9.7	<0.001
MDA (mmol/L)	4.9±0.7	5.3±1.2	0.3
IL6 (pg/ml)	4.7 (3.5-6.7)	4.6 (0.5-6.57)	0.1
CRP (mg/dL)	1.3 (0.7-3.7)	1.47 (0.7-3.8)	0.7
TAC (mmol/L)	1.5±0.37	1.55±0.4	0.3
Vit C(mg/dL)	1.07±0.39	0.88±0.35	0.2
Vit E (µg/mL)	9.8±3.48	9.35±2.96	0.6

Data were presented as mean±SD. P-values were obtained using Wilcoxon Signed ranks test or paired t-test. MDA: Malondialdehyde; IL6: interleukin 6; CRP: C- reactive protein; TAC: Total antioxidant capacity; Vit C: Vitamin C; Vit E: Vitamin E

Table (3): Correlation between vitamin C and vitamin E with other metabolic parameters in and without stress

	Vitamin C		Vitamin E	
	No stress	Stress	No stress	Stress
Leptin (µg/L)	0.10 (0.4)	-0.8 (0.5)	0.079 (0.5)	-0.41 (0.002)
Cortisol (ng/mL)	-0.088 (0.5)	-0.44 (0.001)	0.38 (0.7)	-0.18 (0.1)
MDA (mmol/L)	-0.13 (0.3)	-0.04 (0.7)	0.14 (0.3)	-0.10 (0.4)
IL6 (pg/ml)	0.11 (0.4)	-0.5 (0.7)	0.01 (0.9)	-0.03 (0.7)
CRP (mg/dL)	0.10 (0.4)	0.4 (0.7)	0.07 (0.6)	0.13 (0.3)

Data were presented as r (p-value)

examination day was 51.9 % (7.7% suffered stress mildly, 19.2% suffered stress moderately while 25% suffered stress severely), while on the examination day it was 82.7% (30.8% suffered stress mildly, 7.7% suffered stress moderately and 44.2% suffered stress severely). In this study, the mean values of systolic blood pressure (SBP) during exam time were higher and were statistically significant ($p < 0.001$) when compared with the pre-examination values (Table 1). It was observed that cortisol levels were higher among students whose (K10) score is ≥ 20 and it was highly statistically significant ($p < 0.001$). Table 2 shows relationship between Metabolic parameters with respect to Kessler-10 psychological distress scale. There was higher cortisol with stress ($p < 0.001$). Table 3 shows a moderate negative significant correlation between vitamin C and cortisol levels only during examination stress ($r = -0.44$, $p < 0.001$). There was a moderate negative significant correlation between vitamin E & leptin levels only in stress ($r = -0.41$, $p = 0.002$). About half of the participants, 12 students (46.2%) who had got good

exam performance were having mild examination stress (Table 4), However, 16 (61.6%) of students who had got bad exam performance were having severe examination stress. The difference was statistically significant ($p = 0.01$). The most contributing significant metabolic parameters affecting the academic performance was leptin followed by TAC and Vitamin C (Table 5). Figure 1 depicts a correlation between serum leptin, and cortisol levels. Serum leptin levels showed a significant moderate positive correlation with serum cortisol levels ($r = 0.38$ $p = 0.04$).

DISCUSSION

Academic exam is a common model used in stress research because it is a predictable and standardized example of real-life stressors. Exam stress induced a significant neurohormonal change.^{9,14}

Results of this study showed increased levels of stress among postgraduate nursing students in Minia, Egypt. The overall percentage of exam stress was 82.7%, which is higher than a study which was done among medical students in Saudi Arabia which was 61.1%¹⁵

Table (4): Effect of perceived examination stress on the academic performance

	No stress	Mild stress	Moderate stress	Severe stress	Total	p-value
Bad	3 (11.5)	4 (15.4)	3 (11.5)	16 (61.6)	26 (100)	0.02
Good	6 (23.1)	12 (46.2)	1 (3.8)	7 (26.9)	26 (100)	
Total	9 (17.3)	16 (30.8)	4 (7.7)	23 (44.2)	52 (100)	

P-values were obtained using Fisher exact test

Table (5): Multiple linear regression predicting factors affecting the academic performance

	Beta	p-value	95% CI (lower)	95% CI (upper)
Age	-0.13	0.33	-5.14	1.9
Sex	-0.1	0.46	-18.3	8.5
Leptin	-0.55	0.014	-7.1	-9.6
Cortisol	0.05	0.3	-0.5	0.5
IL6	-0.24	0.08	-4.5	0.33
CRP	-0.215	0.1	-8.5	1.02
TAC	0.35	0.017	2.9	0.35
Vitamin C	0.25	0.04	9.09	13.6
Vitamin E	0.13	0.3	-2.8	8.09

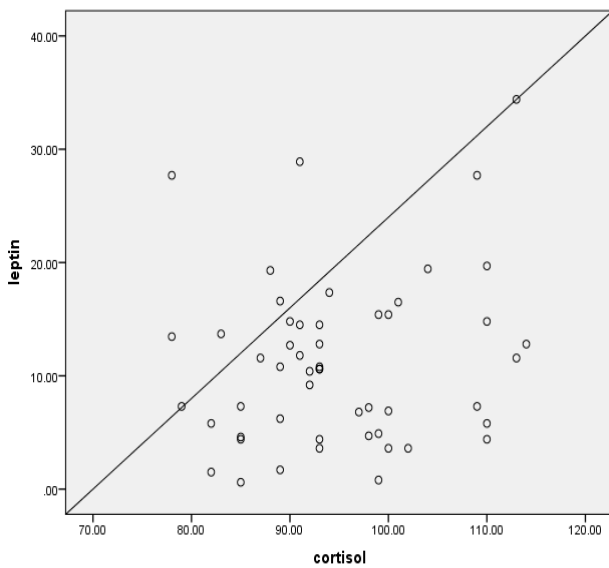


Figure (1): Correlation between cortisol and leptin levels

which used the K10 stress scale. Our explanation is that our study was done among postgraduate students who may have more stress regarding their jobs and financial worries.

Cortisol and corticosterone are the endogenous glucocorticoids in humans and rodents, respectively used as biomarkers of stress.¹⁶ Initially, this induces a reaction of body to acute stress initiating a ‘fight or flight’ response. Chronically altered cortisol levels cause pathological processes named ‘allostatic overload’, resulting in diseases such as type-II diabetes

mellitus, metabolic syndrome, increased susceptibility to addiction and psychic diseases, depression and anxiety, as well as neurocognitive disorders.¹⁷

Studies have showed contradictory results regarding the potential effects of exam stress on cortisol levels. Previous studies reported lower levels of cortisol during examination stress.¹⁸ Another study was conducted by Larson et al., reported no difference in plasma cortisol before, during and after examination.¹⁹ In the present study, because of stressful situations, students were found to have higher significant concentrations of leptin and cortisol in comparison to the baseline situation. Stress causes an increase in blood cortisol levels by stimulation of hypothalamo-pituitary-adrenal (HPA) axis. Cortisol is a potent stimulator of leptin secretion through a direct action on adipose tissue.²⁰ However, reduction in leptin plasma levels during academic stress in other research was explained by the inhibitory impact of SNS on leptin response to stress.⁹

Leptin may be involved in the acute stress response, regulating inflammatory parameters as both structure and function, leptin resembles IL-6.²¹ Leptin also, modifies the activity of the HPA axis. Elevation of leptin level during stress can also modulate various physiological and psychological processes to overcome stress.²² For example, stress increased leptin level can reduce depression induced by stress.²³

Vitamin C is an antioxidant required by all cells to control various biochemical reactions. Vitamin E is an antioxidant that protects cell membrane from lipid peroxidation. Stress may also damage the antioxidant defense system.²⁴ The present results found that exam stress have induced lowering of vitamin C and E levels and decreased TAC level without change in diet or nutritional intake. Decreased level of antioxidant vitamins (Vitamin C & E) was previously detected among stressed rats as showed by a study²⁵ and decreased vitamins (A & C) during exam time as showed by.²⁶

There was a moderate positive significant correlation between vitamin C and cortisol levels only during examination stress ($r= 0.44$, $p<0.001$). This could be explained as Vitamin C is needed for the synthesis of cortisol by the adrenal cortex in stress time.²⁶ Examination might have caused higher demand of vitamin C by the adrenal tissue for formation of cortisol in stress response course.²⁷ The body antioxidant capacity is decreased leading to the insufficient dealing with the free radicals generated more MDA before exam time as reported in this study. Vitamin C is considered the brain antioxidant because of its highest concentrations in neuron rich areas. Vitamin C can neutralize free radical damage which is generated during normal metabolism of cells and is therefore essential for its neuroprotective function. As well as to its antioxidant function, Vitamin C acts as a co-factor in different enzymatic reactions that help the secretion of neurotransmitters in the brain such as dopamine and noradrenalin needed for motivation, alertness, concentration, and memory in exam.²⁴

Oxidative stress may cause neuropsychological disorders in stress time of exam. Medical undergraduate students had elevated oxidative stress as revealed by oxidative damage to DNA and sensitivity to lipid oxidation with decreased level of antioxidant status on the day of exam as in previous research.²⁸ Vitamin E in animal research revealed that decreased α -tocopherol concentrations in the brain down regulates the genes associated with myelination and neuronal vesicle transport which element of healthy brain functions.²⁹ Vitamin E prevents the activation of p38MAPK, whose activity is important for phosphorylation of neuronal tau molecules and prevents the formation of major Alzheimer biomarkers.³⁰

Academic performance in an examination stress has been discussed in many studies.^{1,31} Stress changes brain functioning causes memory and learning problems. Examination stress varies from mild to severe. These different levels of stress can cause learning problems with different degree. In our study the academic performance was better in mild and moderate than high stress groups and this is matched with a previous study carried out among Pakistani university students which noticed that the academic performance was also better in moderate than high stress groups. This could be explained as exam stress increases on individual who does his best performance, and this beneficial stress helps to concentrate on his target but not so much to distort his performance. But if this stress continues it will affect the performance and elevated stress has been demonstrated previously to have a negative effect on performance.³²

Multiple linear regression analysis showed that the most contributing significant metabolic parameters affecting the academic performance was leptin followed by TAC and Vitamin C. leptin improves examination performance by decreasing mental distress, its antidepressant effect²⁶ and its role in hippocampal synapse and memory formation.³³ Leptin increases synaptic plasticity by altering short-term potentiation of synaptic transmission into long-term potentiation (LTP), which is a neurophysiological base of memory formation and learning.³⁴ Leptin also has neuroprotective actions, by decreasing apoptosis, increasing the synthesis of neurotrophic factors, protecting against oxidative stress, and increasing proliferation of hippocampal progenitor cells.³⁵ Antioxidants have a vital role in antagonizing the harmful effect induced by oxidative stress among persons suffering from stress and anxiety during exam time, and this may enhance academic achievement. Vitamin C has also been found to act as a neuromodulator which may decrease anxiety and enhance academic achievement.³⁶

The academic performance was affected by IL-6 levels. Esteban-Cornejo and others have studied the relation between inflammatory biomarkers and academic achievement among 238 girls aged 10.6 ± 3.4 years. Results showed that, IL-6, CRP and white Blood count were associated negatively with all academic indicators (β values ranging from -0.094 to -0.217 , all P value <0.05).³⁷ Inflammatory markers may impair

academic performance by their effects on memory as in previous research conducted among healthy and depressed elderly adults found that both encoding and recall of memories were associated negatively with serum IL-6. ³⁸

Limitations of the study: The small sample size of the participating students followed up might contribute to type 2 errors in associations that would have been avoided having bigger sample size.

CONCLUSIONS

Leptin and cortisol are biomarkers of stress perception with positive correlation between them in exam stress while leptin is the most contributing factor affecting academic performance by facilitating memory. The exam stress can result in oxidative stress by increased level of MDA and decreased TAC and vitamin C levels in serum. Vitamin C was negatively correlated with serum cortisol in stress exam so that supplementation of Vitamin C may treat anxiety and improve academic performance in exam by increasing blood cortisol level as anti-stress response.

Ethics Approval

The study obtained all required approvals from the ethics committee of Minia University.

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