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## Correlation of Elevated Serum Serotonin Levels with Regular Aerobic Exercise is Associated with Alterations in Monocyte Count and Hemoglobin Levels during Winter Season

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### ABSTRACT

Central fatigue pheromone is not satisfactory to explain altered serum serotonin sSER. Thus the aim of this study is to detect some potential peripheral predictors of altered sSER at rest on the day without any exercise during winter season. One hundred and one university male students aged (21.5±1.5) year's. Participants were divided into two groups: The NES (non exercising) and RES (regular aerobic exercising) subject groups. BMI was calculated for all subjects. Fasting blood samples were collected and tested for blood glucose, blood indices, lipid profile, serum serotonin, leptin vitamin B<sub>12</sub>, folic acid and salivary stress hormones (cortisol and DHEA). T test showed an elevation in serum serotonin levels of RES group with significant mean difference (p = 0.031) between the study groups RES and NES. Total WBC count and obesity values for mean of BMI, weight and leptin were significantly higher in NES group. Granulocytes count (R<sup>2</sup> = 0.114), hemoglobin levels (R<sup>2</sup> = 0.193), WBC count (R<sup>2</sup> = 0.289), LDL levels (R<sup>2</sup> = 0.362) and serum leptin levels (R<sup>2</sup> = 0.423) were selected by stepwise regression analysis as predictive variables of regular aerobic exercise for serum serotonin. These predictors together explained 42% of the variance in serum serotonin. In NES potential predictors were; monocyte count (R<sup>2</sup> = 0.102) and platelets count (R<sup>2</sup> = 0.275). This study indicates that a positive correlation between regular aerobic exercise and serum serotonin levels in winter season is associated with significant changes in monocyte count.

**Key words:** Aerobic exercise, blood indices, serum serotonin, leptin, lipid profile, Jordanian

### INTRODUCTION

Exercise induces physiological changes that make it an effective therapeutic method of intervention in many physical and health disorders including mental health (Childs and De Wit, 2014). Biological influence of exercise training induces neurobiological alterations as antidepressant drug by elevating the levels of serotonin (Melancon *et al.*, 2014). Therefore, prevention of depression can be added to the other benefits of exercise.

Mechanisms through which exercise produces antidepressant effects may occur via the central serotonergic

system (Greenwood and Fleshner, 2011) by increasing synthesis, concentration and metabolism of serotonin in the brain (Caperuto *et al.*, 2009). Many studies have suggested that central fatigue after exercise was attributed to elevated serotonin levels (Teixeira-Coelho *et al.*, 2014) as demonstrated in animal and human studies (Cordeiro *et al.*, 2014). However, central fatigue hypothesis could be accepted to explain elevated serotonin levels after acute exercise according to many previous studies but this is unacceptable to explain peripheral changes in serotonin levels (Fernstrom and Fernstrom, 2006). This raises the possibility of serotonin levels in exercising individuals may be modulated by certain

peripheral mediators. Evidences taken from previous studies indicate that the interactions between external stimuli such as exercise and brain disorders may be reflected in peripheral predictors facilitating their use as potential diagnostic markers (Carboni, 2013). Consequently, peripheral blood cells seem to be significant predictors of serotonergic transmission and serotonin levels alterations according to recent studies (Tazehkand and Topaktas, 2014). Particularly, clearance of serotonin from the ECF by serotonin transporters SERT expressed by peripheral blood cells genes (Wipfli *et al.*, 2011) might be one of the mechanism's key factors that explain exercise effect on serum serotonin. Drawing on these findings, the study is designed to proof if the association of serum serotonin alterations during winter season with exercise is mediated by peripheral changes as a part of physiological adaptation in exercising individuals or it is mainly a response to direct effect of exercise according to central fatigue hypothesis. Therefore, aim of the study is to detect which of some potential predictors in the peripheral circulation are involved in the alterations of serum serotonin during winter time in the relation to aerobic regular exercise.

## MATERIALS AND METHODS

**Study design and participants:** The present work was a cross sectional study carried out in the Applied Science University, Amman, Jordan during the period from January to April 2010. This study was performed using a protocol for the protection of human subjects approved by the Applied Science University Ethical Committee no DRGS-2009-7. Student filled out questioner including anthropometric and clinical characteristics. One hundred and one male nursing students aged  $21.5 \pm 1.5$  years. Participants were divided into two groups: The NES (non exercising,  $n = 51$ ) and RES (regular aerobic exercising,  $n = 50$ ) subject groups. The majority of Jordanian nursing students in the college were males (more than 90 %), therefore the present study was conducted on male participants. To avoid confounding factors subjects with chronic diseases ( $n = 4$ ) such as diagnosed cardiovascular diseases, cerebrovascular disease, dyslipidemia, stable hypertension treated by drugs, chronic hepatic disease, renal problems, or taking any kind of medications during the previous two months were excluded.

**Body Mass Index (BMI):** On the day of evaluation, height (cm), weight (kg) and BMI ( $\text{kg m}^{-2}$ ) of participated students were recorded and then classified according to the body mass index BMI: Normal weight students,  $20 \text{ BMI} < 25$ ; overweight students,  $25 \text{ BMI} < 30$  and obese group,  $\text{BMI} > 30$ .

**Blood glucose and lipid profile:** Fasting venous blood samples were obtained, centrifuged and stored at  $-20^\circ\text{C}$  until assayed. Fasting blood glucose samples were collected at 8 am. Blood glucose was confirmed by using one touch test strips (Lifescan; Johnson and Johnson, Palmitas, CA). Triglycerides, total cholesterol and High Density Lipoprotein

Cholesterol (HDL) was determined using enzymatic colorimetric kits (Linear Chemicals, Barcelona, Spain). Low density lipoprotein cholesterol (LDL-C) was calculated from the equation recorded in a previous study (Friedewald *et al.*, 1972).

**Serum serotonin and leptin:** Fasting serum leptin and serotonin samples liquated and stored in polypropylene vials at  $-20^\circ\text{C}$  until analysis which was performed after two weeks at Al-Khalidy Medical Centre Laboratories, Amman, Jordan. Commercial Serotonin EIA kits were obtained for quantitative determinations of serum serotonin (Labor Diagnostika Nord GmbH and Co, KG, Nordhorn, Germany). Analytical sensitivity, as reported by the manufacturer, was  $5 \text{ ng mL}^{-1}$ . Leptin samples were assayed with an enzyme immunoassay kit (DRG Diagnostics, Marburg, Germany) with analytical sensitivity about  $1.0 \text{ ng mL}^{-1}$  according to the manufacturer.

**Serum Vitamin B<sub>12</sub> and folic acid:** The serum was isolated by centrifugation. The electro chemiluminescence immunoassay was used on Cobase immunoassay analyzer (Roche Diagnostics) for serum vitamin B<sub>12</sub> and folic acid using electro chemiluminescence immunoassay (ECLIA) kits (Roche Diagnostics). Quantitative measurement of leptin in serum was performed by enzyme immunoassay or ELISA kit (DRG Diagnostics, Marburg, Germany), according to the manufacturer's instructions.

**Salivary cortisol and DHEA:** Salivary cortisol and DHEA were collected from the participants at morning between the hours of 8 and 9 am and at evening between the hours 11 and 12 pm 23:00 pm and 24:00. To collect salivary samples, participants were provided with a salivette sampling device (cotton) along with both verbal and written instructions for usage. The instructions stated that participants were to collect saliva themselves. Participants were asked to drool passively through a straw into a tube which then were kept on ice in order to precipitate mucin and then centrifuged ( $10,000 \times g$ , 15 min,  $4^\circ\text{C}$ ). The supernatant (1 mL) was collected and stored at  $-20^\circ\text{C}$  until the day of assay which was after two weeks. Salivary cortisol and DHEA were measured by an enzyme-linked immunosorbent assay (ELISA) (SLV-2930 and SLV-3012, respectively, DRG International, Inc., USA) at Ibn Alhytham Hospital Laboratories, Amman, Jordan. The limits of detection of this assay were  $1.48 \text{ pmol L}^{-1}$  for salivary cortisol and  $0.324 \text{ pmol L}^{-1}$  for DHEA.

**Hematology parameters:** Clinical hematology parameters were measured for all volunteers, platelets count, total leukocyte count, differential leukocyte counts, hematocrit, hemoglobin and RBC indices (Mean Cell Hemoglobin [MCH], Mean Cell Volume [MCV], Mean Cell Hemoglobin Concentration [MCHC]), mean platelets count. Complete blood count was performed on the COBAS MICROS OT 18, Roche, France.

**Statistical analysis:** The statistical analyses were performed using a statistical software package SPSS, version 19.0 for Windows (Chicago, IL, USA). The t test was used to test for significant differences in independent variables between the two groups. To find if there is any correlation between participant's characteristics and serum serotonin levels Pearson analysis was applied. Stepwise linear regression was used to determine which factors are the highest predictors of variance in serum serotonin levels.

## RESULTS

**Descriptive characteristics of the participants (n = 101):** Table 1 shows descriptive characteristics of the participants (n = 101). A total of 101 Jordanian male subjects. Twenty seven subjects were excluded because they did not meet the requirements for participating in the study. The results indicate that, except for BMI and leptin, all parameters were within the normal range.

**Effects of regular aerobic exercise on anthropometric values and blood parameters:** The comparison showed an elevation in serum serotonin levels in RES group with significant mean difference (p = 0.031) between the study groups RES and NES. Obesity values for mean of BMI, weight and leptin were significantly higher in NES group p = 0.002, p = 0.004 and p = 0.009, respectively compared with RES group subjects (Table 2). Except the significant decrease in WBC count of RES group (p = 0.021), no significant differences were observed in the mean values for

lipid profile, hematological parameters, B<sub>12</sub>, folate or salivary diurnal steroid hormones cortisol and DHEA between the two study groups (Table 2).

**Correlations of serum serotonin with anthropometric features and blood parameters:** Table 2 presents serum serotonin correlation coefficients for eight selected variables in the both study groups. In RES group, winter serum serotonin levels were inversely correlated with GRA count (r = 0.337, p<0.001), HGB (r = 0.440, p = 0.022) and serum leptin levels (r = 0.651, p = 0.04). In the same group serum serotonin levels were positively correlated with WBC count r = 0.537, p = 0.004 and LDL cholesterol r = 0.602, p = 0.01. In NES group, serum serotonin levels were positively correlated with platelets count r = 0.524, p = 0.040 and negatively with monocytes count (r = 0.448, p = 0.002) and morning salivary cortisol r = 0.319, p = 0.032 (Table 2).

**Stepwise regression analysis:** Stepwise regression analysis was performed to investigate which independent variables accounted for these associations with serum serotonin changes. Accumulatively, granulocytes count (R<sup>2</sup> = 0.114, p< 0.001), hemoglobin levels (R<sup>2</sup> = 0.193, p = 0.022), WBC count (R<sup>2</sup> = 0.289, p = 0.004), LDL levels (R<sup>2</sup> = 0.362, p = 0.01), serum leptin levels (R<sup>2</sup> = 0.423, p = 0.04) were selected as predictive variables of regular aerobic exercise for serum serotonin. These predictors together explained 42% of the variance in serum serotonin levels in subjects who exercised (RES group). Also the results showed two predictive variables

Table 1: Descriptive characteristics of the participants (n = 101)

Variables	Mean	Std dev	Max.	Min.	Median	10 (%)	90 (%)
Age	21.543	1.481	24.00	18.00	21.00	20.00	23.00
Serotonin (ng mL <sup>-1</sup> )	231.3	80.2	535.0	64.2	214.0	157.3	313.5
Fasting blood glucose (mg dL <sup>-1</sup> )	86.8	8.2	112.0	60.0	88.0	77.0	97.2
Leptin (ng mL <sup>-1</sup> )	12.6	9.74	39.7	2.0	9.5	2.98	28.09
Body weight (kg)	82.84	14.18	112.0	60.0	79.0	67.10	105.90
Height (cm)	175.49	5.6	186.0	160.0	176.0	167.70	182.30
BMI (kg m <sup>-2</sup> )	26.986	4.438	40.000	20.50	25.800	22.000	33.060
Morning cortisol (nmol L <sup>-1</sup> )	9.11	3.59	18.00	2.80	8.50	4.85	15.00
Night cortisol (nmol L <sup>-1</sup> )	3.794	1.462	10.000	1.700	3.600	2.450	6.000
Morning DHEA (nmol L <sup>-1</sup> )	1.602	0.334	2.60	0.880	1.570	1.310	1.944
Night DHEA (nmol L <sup>-1</sup> )	0.890	0.322	1.50	0.176	0.850	0.480	1.440
TG (mg dL <sup>-1</sup> )	117.49	27.56	197.0	63.0	117.0	82.6	147.9
TC (mg dL <sup>-1</sup> )	179.275	29.555	268.0	129.0	175.0	140.6	216.3
HDL (mg dL <sup>-1</sup> )	49.529	7.126	66.0	36.0	50.0	40.70	59.30
LDL (mg dL <sup>-1</sup> )	104.216	30.455	216.0	29.0	100.0	78.10	137.0
Serum vit B <sub>12</sub> (pg mL <sup>-1</sup> )	252.114	94.026	556.4	64.20	235.4	160.50	370.220
Serum folic acid (ng mL <sup>-1</sup> )	9.712	3.087	18.0	3.48	10.05	5.660	13.255
WBCs (10 <sup>9</sup> L <sup>-1</sup> )	6.047	1.661	9.50	1.90	5.80	4.170	8.490
RBCs (×10 <sup>12</sup> L <sup>-1</sup> )	5.320	0.682	8.20	4.21	5.220	4.632	6.111
Hb (g dL <sup>-1</sup> )	16.061	0.946	18.8	13.80	16.00	14.710	17.0
PCV (%)	46.229	3.959	56.8	36.20	46.20	41.680	51.310
MCV (fL)	88.059	3.645	98.0	80.00	87.00	84.0	93.60
MCH (pg)	30.469	3.036	35.1	14.70	30.70	28.210	32.890
MCHC (g dL <sup>-1</sup> )	34.153	2.263	38.0	25.50	34.00	31.790	36.70
Lymph No (×10 <sup>9</sup> L <sup>-1</sup> )	34.604	4.881	45.5	20.20	34.80	28.610	39.50
Mono (%)	5.667	0.864	7.6	3.10	5.80	4.770	6.930
Gran No. (×10 <sup>9</sup> L <sup>-1</sup> )	59.116	5.810	74.7	41.70	59.0	53.280	66.37
Platelets (×10 <sup>9</sup> L <sup>-1</sup> )	253.292	65.021	405.1	31.90	255.0	172.9	321.7

**Table 2: Effect of regular aerobic exercise on serum serotonin, anthropometric and blood characteristics among Jordanian young men during winter season**

Variables	NES (n = 51) Mean±SD	RES (n = 50) Mean±SD	Mean difference	p-value
Serotonin	231.36±80.62	273.28±102.49	41.925	0.031
FBG	86.725±9.673	86.660±7.044	0.0655	0.969
Serum leptin	12.60±9.78	8.13±6.82	-4.466	0.009
Weight	82.843±14.251	75.04±6.107	-7.803	0.004
Height	175.49 ±5.64	175.18±5.33	-0.310	0.791
BMI	26.986±4.60	24.40±3.41	-2.578	0.002
M Cor	9.108±3.610	8.53±2.87	-0.580	0.375
N Cor	3.79±1.46	3.718±1.34	-0.0760	0.788
M DHEA	1.62±0.33	1.63±0.42	0.00024	0.997
M DHEA	0.89±0.32	0.866±0.41	-0.024	0.744
Triglycerides	117.49±27.70	113.950±29.04	-3.540	0.532
Total cholesterol	179.27±29.7	174.86±30.85	-4.415	0.426
HDL	49.52±7.16	50.28±7.5	0.751	0.608
LDL	104.21±30.6	100.206±31.31	-4.010	0.377
B12	341.408±130.95	354.712±120.683	13.304	0.602
Folate	9.712±3.103	10.535±4.043	0.823	0.258
WBC	6.108±1.569	5.38±1.54	-0.728	0.021
RBC	5.32±0.685	5.328±0.63	0.0082	0.950
HGB	16.06±0.95	15.804±1.384	-0.257	0.279
PCV	46.23±3.98	46.692±5.061	0.463	0.610
MCV	88.06±3.663	86.620±4.793	-1.439	0.093
MCH	30.469±3.051	29.702±2.252	-0.767	0.155
MCHC	34.153±2.274	33.828±1.933	-0.325	0.441
Lymphocytes	34.604±4.906	36.808±7.766	2.204	0.091
Monocytes	5.667±0.868	5.764±1.245	0.0973	0.649
GRA	59.116±5.839	57.490±9.350	-1.626	0.192
PLT	257.720±57.765	257.26±63.421	-0.460	0.970

NES: Non-exercising subjects, RES: Regular exercising subjects, MCV: Mean cell volume, MCH: Mean cell hemoglobin, MCHC: Mean cell hemoglobin concentration, PCT: Packed cell volume, WBC: White blood cell, BMI: Body mass index and RBC: Red blood cell

**Table 3: Pearson correlation and association of selected independent variables by stepwise regression analysis with serum serotonin in NES and RES study groups**

Group and independent variables	r	Coefficient (B)	R <sup>2</sup>	p-value
<b>NES</b>				
Monocytes	0.319	-35.86	0.102	0.002
Platelets	0.524	0.294	0.275	0.040
<b>RES</b>				
Granulocytes	0.337	-5.782	0.114	<0.001
Hemoglobin	0.440	-22.587	0.193	0.022
WBC	0.537	25.453	0.289	0.004
LDL	0.602	1.094	0.362	0.010
Leptin	0.651	-3.93	0.423	0.040

NES: Non exercising subject, RES: Regular exercising subject

may explain 27% of the variance in seasonal serum serotonin levels of NES group. These predictors were; monocyte count (R<sup>2</sup> = 0.102, p = 0.002) and platelet count (R<sup>2</sup> = 0.275, p = 0.04) (Table 3).

## DISCUSSION

The results of this study point to significant elevation of the serum serotonin sSER levels in regular aerobic exercising subjects RES compared with their peers in non exercising subject NES group. Elevated sSER in RES group was negatively associated with granulocyte count, hemoglobin levels and serum leptin. In NES study group significant positive associations were observed for the WBC count and LDL cholesterol. Decreased sSER monocyte count in all peripheral blood cells (Arzt *et al.*, 1991).

The present observations are partially consistent with previous studies that examined the effects of a physical

activity on the serum levels of serotonin (He *et al.*, 2012). Also significant decrease in serum leptin, body weight and BMI values in RES group were reviewed in previous studies (Akbarpour, 2013). Surprisingly, except for serum leptin. Similar results were found by Kim *et al.* (2012) for the same obesity parameters in fourteen men sample after 12 weeks of regular exercise. This confirms that altered adipokine level during aging is accompanied with significant changes in ob gene expression (Nogalska *et al.*, 2003). It has pointed to a complicated association of exercise with central or peripheral changes of serotonin levels (Fernstrom and Fernstrom, 2006). This may be due the contradictory evidences on the relationship between physical activity and the risk of depressive symptoms including sSER alterations in male young adulthood (Strohle, 2009).

The association of peripheral blood cells PBCs activities with alterations of sSER levels was noted before. It seems to be reflected by serotonin transporters SERT levels in ECF (Beikmann *et al.*, 2012). The same gene for SERT expression has been shown in the brain AND in peripheral blood cells (Jennings *et al.*, 2010) displaying similar structural and functional properties in both tissues. Outside the CNS, SERT takes up 5-HT from plasma, keeping its levels very low (Yubero-Lahoz *et al.*, 2013). This makes peripheral SERT expression one of the causal factors that regulate sSER levels. Accordingly, the present findings seem to be in consistent with Yang *et al.* (2007) who concluded that platelets, lymphocytes and monocytes have major action to express peripheral SERT. Obviously, the present findings showed that platelets and monocyte counts were the most potential

predictors that associate with sSER alterations in NES group whereas lymphocytes and monocytes in RES group when adjusted to the regular aerobic exercise effect. Lymphocyte and monocyte count showed a positive association with sSER in RES group, whereas the same association was negative in NES group only for monocyte count.

Taken together, regular aerobic exercise seems to be a physiological SERT inhibitor in a potential mechanism by which elevated monocyte count with or without role for lymphocytes elevates sSER levels in RES by facilitating SERT clearance from ECF or throughout changing on SERT expression by monocytes and lymphocytes which are thought to express SERT (Yang *et al.*, 2007). This potential influence of exercise on sSER may occur throughout induction of Ca<sup>2+</sup> influx in monocytes and immature MoDC (Idzko *et al.*, 2004). Moreover elevated monocytes were also associated with slight elevation of LDL levels in RES group. This confirms the importance of exercise against suppression of anti-oxidative power of monocyte by ox-LDL observed in mild and moderate exercise models (Wang *et al.*, 2006). Therefore, exercise regulate the expression of certain genes of monocytes in a way that could limit pro-inflammatory function and drive monocytes to prevent atherosclerosis (Radom-Aizik *et al.*, 2014). Finally, although many studies showed a positive association between hemoglobin levels and exercise performance (Lipinski *et al.*, 2009) this is first study that indicate the effect of hemoglobin levels on serum serotonin in exercising individuals. Strengths of this study also include homogenous sample in the terms of age, gender and ethnicity, also the blood samples were collected in the time out of exercise during depressive season. It was not possible to measure serotonin transporter levels in both study groups to confirm our findings.

## CONCLUSION

In conclusion, this study indicate a positive association between regular aerobic exercise and serum serotonin levels in winter season via peripheral mechanism including some changes in peripheral blood cells particularly monocyte count.

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