

## THE EFFECTS OF DEPRESSION ON ENDOCRINE AND IMMUNE SYSTEMS

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### ABSTRACT

To study the effect of depression on the endocrine and immune systems, 557 male freshman and sophomore medical students (20-30 years old) were given Beck's Depression Inventory. Students with marks 5 or above were selected as the control (n=26) and those with marks of 20 or higher were chosen as the test group (n=27). All of the students were subjected to the following tests: CBC, differential, total cholesterol (TC), triglycerides (TG), HDL-c, VLDL-c, fibrinogen (Fibr), cortisol (Cort), prolactin (PRL), testosterone (Test), triiodothyronine (T<sub>3</sub>), thyroxine (T<sub>4</sub>), total serum immunoglobulins (Ig), IgA, IgG, IgM, creatine kinase (CK), and C3 and C4 components of the complement system.

Results indicated statistically significant increases of the following parameters in the test group as compared with the controls: TC (P < 0.05), LDL-c (P < 0.05), CK (P < 0.025), Fibr (P < 0.01), Test (P < 0.05), Cort (P < 0.025), IgG (P < 0.025) and Ig (P < 0.025). The results were in accordance with the anticipated hormonal and cell-mediated immunity alterations caused by depression, which affected both cytokines and endorphin levels.

In spite of the limited number of subjects used in this study and lack of the dexamethasone suppression test (DST), the overall approach of this study is encouraging; nevertheless, further studies using a larger sample are required.

**Keywords:** Depression, behavioral diseases, affectional abnormalities and schizophrenia

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### INTRODUCTION

Depression has been known as the most common affectional disorder by Avicenna and Razi who have described it as "a kind of behavioral disorder" and Hippocrates who referred to it as "melaina chole" in 450 B.C.<sup>1</sup>

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The most commonly understood types of depression are acute, chronic, reactive, endogenous, exogenous, bipolar, unipolar, and others; scientific classifications are now available and designated in the DSM-III-R<sup>2,3</sup> which are beyond the scope of this study. Most depressions are caused by anxiety due to the incorrect appraisal and misinterpretation of oneself, caused by a lack of understanding the reality about the environment and its interactions with one's feelings, resulting in a series of symptoms which usually occur as vicious cycles. The lack of control on intrapersonal relationships, feelings of subjugation, being abused and subject

Table I. Comparison of serum lipids and lipoproteins of depressed (D) and normal (N) control students.

Triglycerides (TG)			Total cholesterol (TC)			LDL-cholesterol			HDL-cholesterol			VLDL		
mg/dl	D	N	mg/dl	D	N	mg/dl	D	N	mg/dl	D	N	mg/dl	D	N
31-99	55.65	46.15	110-132	11.11	26.92	83-85	11.11	26.92	26-32	18.52	23.10	7.8-16.7	66.66	50.00
100-147	35.92	23.07	133-155	35.92	30.76	86-105	40.79	50.00	33-39	48.15	42.35	16.8-25.7	18.51	30.76
148-195	7.40	19.23	156-176	22.22	19.23	106-125	18.51	7.69	40-46	25.92	26.92	25.8-34.6	3.70	11.53
196-244	0.00	7.96	177-198	18.52	11.53	126-145	11.11	15.38	47-53	0.00	7.71	34.7-43.6	7.40	3.84
245-291	7.40	0.00	199-220	22.22	11.53	146-165	18.51	0.00	> 54	7.41	0.00	43.7-52.5	3.70	3.84
292-340	3.70	3.84	-	-	-	-	-	-	-	-	-	-	-	-
$\mu \pm S.D.$			$\mu \pm S.D.$			$\mu \pm S.D.$			$\mu \pm S.D.$			$\mu \pm S.D.$		
D	N		D	N		D	N		D	N		D	N	
114.7 $\pm$ 71.6	123.7 $\pm$ 58.8		168.3 $\pm$ 30.98	152.9 $\pm$ 26.3		112.8 $\pm$ 29.43	96.6 $\pm$ 21.44		37.6 $\pm$ 8.0	37.3 $\pm$ 5.02		17.8 $\pm$ 10.9	18.99 $\pm$ 9.06	
N.S.			P < 0.05			P < 0.025			N.S.			N.S.		

to cruelty, injustice, forceful obedience, and exaggeration, socioeconomical, emotional and spiritual losses are among the causes of most exogenous and reactive depressions.

Biochemical studies on the molecular basis of depression and deduced from the mechanism of action of antidepressants<sup>4,5</sup> have shown that the illness is due to alterations in the concentration of neurotransmitters (Nt). Tricyclic drugs inhibit the reuptake of Nts (e.g. epinephrine, serotonin, etc.) at nerve terminals<sup>6,8</sup> whereas monoamine oxidase inhibitors (MAOI) prevent the oxidation of monoamine antidepressants (e.g. catecholamines), resulting in an increase in concentration which leads to euphoria in patients with bipolar depression.<sup>5,7</sup> Similarly, neuroleptic antidepressants used for treating schizophrenia inhibit dopamine receptors in the brain causing decreased dopamine absorption and resulting in an inhibition of adenylate cyclase-mediated reactions.<sup>9</sup>

Advances in molecular genetics have revealed that mood disorders, e.g., bipolar depression, schizophrenia, etc. are genetically transmitted; therefore there is hope that definitive treatment may become available following establishment of the specific deficiency.<sup>10,11</sup>

The purpose of this study was to determine the effects of depression(s) on hematological, biochemical, hormonal and immunochemical parameters routinely used for the diagnosis of various diseases. Although similar research has been carried out in experimental animal models,<sup>12</sup> the primary importance of this study is that a variety of parameters have been measured in a single sample, in humans with similar goals and in one geographical area.

## MATERIALS AND METHODS

### Subjects

A group (n=570) of male first and second year medical students selected on a voluntary basis (with ages ranging from 20-30 years) were asked to complete "Beck's Depression Inventory" after proper explanation by a psychiatrist. According to this scale, 21 multiple choice questions are asked which each may receive 0-3 points, along with eight questions to serve as a "lie detector test". From 570 students, 55 did not deliver the test results, 43 did not answer the questions completely and 24 received higher than 8 points in the lie detector test (a total of 122) who were excluded from the study. Students with a score of 5 or below were assigned as the control group (n=26) and those with scores higher than 20 were chosen as the test group (n=27). All subjects were healthy with no apparent clinical symptoms as confirmed by the physician, and were not taking any psychotropic medication(s).

### Collection of specimens

Fasting blood, 3 ml oxalated and 17 ml anticoagulant-free, were withdrawn in the morning. Sera were prepared immediately, dispensed in appropriate aliquots and stored at -20°C. Oxalated blood samples were subjected to CBC and differential counts and sera obtained after centrifugation of non-oxalated blood samples were used for parameter analysis.

### Chemicals

All chemicals were obtained from commercial sources and were of analytical grade. Special chemicals

**Table II.** Comparison of serum levels of FBS, CK and fibrinogen of depressed (D) and normal (N) control students.

FBS			Fibrinogen			Creatine kinase (CK)		
mg/dl	D	N	mg/dl	D	N	mg/dl	D	N
41-55	3.7	3.8	125-249	60.0	100.0	48-164	88.9	96.0
56-70	11.11	3.8	250-370	40.0	0.00	165-280	7.40	4.60
71-85	33.33	57.70	-	-	-	281-396	30.70	0.00
86-100	48.15	23.10	-	-	-	-	-	-
101-115	3.70	7.70	-	-	-	-	-	-
> 116	0.00	3.80	-	-	-	-	-	-
$\mu \pm S.D.$			$\mu \pm S.D.$			$\mu \pm S.D.$		
D	N		D	N		D	N	
83.50 $\pm$ 13.10	83.60 $\pm$ 13.06		210 $\pm$ 69.06	140 $\pm$ 31.40		127.4 $\pm$ 65.60	99.04 $\pm$ 28.60	
N.S.			P < 0.001			P < 0.025		

and various kits employed for chemistry and enzyme assays were purchased from the following pharmaceutical companies: glucose, high density lipoproteins (HDL-c), total cholesterol, control sera and creatine kinase, from Human Co., USA; cortisol kits from DSL Co., triiodothyronine, T<sub>3</sub>-resin uptake, thyroxine and prolactin kits from BYK Co.; testosterone kits from ISD; radial immunodiffusion (RID) plates for analysis of Ig, C3 and C4 components of complement, Ig and complement controls from Behring Co., Germany and CRP kits from Sclavo Co., Japan.

### Equipment

All hematological indices were determined by a Hematology H-1 (Technicon Co., USA), biochemical parameters were measured by an RA-1000 automatic analyzer (Technicon Co., USA) and gamma radiations were counted via a Kontron gamma counter. Centrifugations were done in a clinical centrifuge and when necessary in a refrigerated Sorvall centrifuge (Sorvall Co., USA).

### Biochemical determinations

The following parameters were measured by commercially available kits based on the methods mentioned below.

Glucose, glucose oxidase-peroxidase reaction; triglycerides, lipase-glycerol kinase-glycerol phosphate oxidase-peroxidase coupled reactions; total cholesterol, cho. esterase-cho. oxidase-peroxidase method; HDL-c, phosphotungstic acid-magnesium as precipitant; very low density lipoproteins (VLDL-c) and low density lipoproteins (LDL-c) by using Friedwald's equation. CK was assayed by the procedure of Demetriou and

Drewes.<sup>13</sup> Ig classes, C3 and C4 were determined by the RID method of Mancini. Hormones were measured by radioimmunoassay (RIA) procedures as described: PRL, by the method of Hwang et al;<sup>14</sup> testosterone, by the procedure of Ismail et al;<sup>15</sup> T<sub>3</sub>, according to Ellis et al;<sup>16</sup> cortisol as described by Sokolof et al;<sup>17</sup> T<sub>3</sub>RU by the method of Clark and Brown;<sup>18</sup> and T<sub>4</sub> by SPAC-T<sub>4</sub> kit. C-reactive protein was determined by latex agglutination, Sclavo kit (Sclavo Co., Japan) and fibrinogen by the microheat precipitation procedure.

### RESULTS

All data were subjected to statistical analysis by "Quatra Package Computer Software" and comparisons were made by Student's t-test and P-values < 0.05 were considered statistically significant. Table I shows the results obtained from serum lipids and lipoproteins. As shown, TG concentrations were the same in test and control groups, while TC and LDL-c levels were significantly higher in the test group compared to controls (P<0.05 and <0.025, respectively). There were no significant differences in VLDL-c and HDL-c concentrations.

There was no difference in fasting blood sugar as shown in Table II. CK and fibrinogen concentrations in the test group were significantly higher as compared to those of controls (P<0.025 and P<0.001, respectively).

The results of hormones assayed are summarized in Table III. As seen, there were no differences in the concentrations of T<sub>3</sub>RU, T<sub>4</sub> and prolactin, whereas cortisol and testosterone levels of the test group sera were

Table III. Comparison of serum hormone levels of depressed (D) and normal (N) control students.

% T <sub>3</sub> RU			T <sub>4</sub>			Cortisol			Testosterone			Prolactin		
%	D	N	µg/dl	D	N	µg/dl	D	N	ng/dl	D	N	mIU/L	D	N
32.0-34.0	3.70	0.00	6.6-7.9	11.11	0.00	6.40-11.17	0.00	38.51	3.10-5.7	3.20	23.07	125-195	11.11	7.00
34.1-37	11.11	26.92	7.91-9.3	22.20	19.2	11.18-15.95	33.3	15.4	5.71-8.29	37.03	34.61	196-266	29.62	34.61
37.1-40	51.58	34.61	9.31-10.6	51.90	38.5	15.96-20.73	44.5	30.76	8.30-10.89	40.74	23.07	267-337	29.62	7.69
40.1-43	14.81	30.76	10.61-11.95	14.80	34.6	20.74-25.51	11.11	3.85	10.9-13.50	18.51	19.23	338-408	18.51	15.38
43.1-46	18.51	7.87	11.96-13.30	0.00	7.69	25.52-30.30	11.11	11.53	-	-	-	409-480	11.11	15.58
µ ± S.D.			µ ± S.D.			µ ± S.D.			µ ± S.D.			µ ± S.D.		
D	N		D	N		D	N		D	N		D	N	
39.6±3.04	39.4±2.62		9.64±1.20	10.31±3.6		18.6±4.65	15.16±6.82		9.1±2.34	7.9±2.76		300±85.0	273.1±112.3	
N.S.			N.S.			P < 0.025			P < 0.05			N.S.		

Table IV. Comparison of the frequency of differential counts in depressed (D) and normal (N) control students.

PMN			Lymphocytes			Monocytes			Eosinophils			Basophils		
No./mm <sup>3</sup>	D	N	No./mm <sup>3</sup>	D	N	No./mm <sup>3</sup>	D	N	No./mm <sup>3</sup>	D	N	No./mm <sup>3</sup>	D	N
1980-3870	66.7	61.53	1510-2510	51.9	65.4	160-360	22.2	26.9	< 100	18.5	19.2	11-30	29.6	19.2
3880-5770	33.3	30.76	2520-3520	40.8	34.6	365-565	55.6	57.7	100-290	55.6	69.2	31-50	29.6	42.3
5780-7670	0.00	7.69	3530-4530	7.40	0.00	570-770	22.2	11.5	300-490	3.70	3.9	51-70	26.0	37.6
-	-	-	-	-	-	> 770	0.00	3.9	500-690	11.10	7.7	71-90	15.0	3.90
-	-	-	-	-	-	-	-	-	≥ 700	11.10	0.00	-	-	-
µ ± S.D.			µ ± S.D.			µ ± S.D.			µ ± S.D.			µ ± S.D.		
D	N		D	N		D	N		D	N		D	N	
1450±3620	1470±3670		2638±630	2332±532		474±147	420±240		230±190	190±150		50±20	49±15	
N.S.			N.S.			N.S.			N.S.			N.S.		

significantly higher than those of the control group ( $P < 0.025$  and  $P < 0.05$ , respectively).

Hematological results are compared in Table IV. No significant differences were observed concerning neutrophils and lymphocytes (percent or total count). Similar results were obtained for monocytes and basophils, but the eosinophil total count of the test group was higher than that of controls; nevertheless, this difference was not statistically significant.

Analysis of immunoglobulins are shown in Table V. Total Ig and IgG levels of the test group were higher than controls ( $P < 0.025$  in both cases), but no difference was found in IgA and IgM content between the two groups.

Results obtained for C3 and C4 components of the complement system (Table IV) showed no significant difference between test and control groups.

## DISCUSSION

Affective disorders are associated with physiological, biochemical and neuroendocrine changes. The mechanisms governing these phenomena are not known at present. However, there is evidence which indicates that neurotransmitters and hormones stimulate macrophages, leading to IL-1 and prostaglandin secretion.<sup>19,20</sup> The hypothalamus is believed to trigger the secretion of releasing hormones, resulting in the formation of active hormones which cause changes in intracellular physiological mechanisms.<sup>20</sup>

### Human subjects

In this study, the test students chosen on the basis of Beck's test were considered depressed, therefore results are limited to the accuracy of this test and should not be

Table V. Comparison of serum concentrations of immunoglobulin of depressed (D) and normal (N) control students.

Total Ig			IgG			IgA			IgM		
g/L	D	N	g/L	D	N	g/L	D	N	g/L	D	N
15.8-21.40	14.8	28.0	11.3-16.3	11.11	36.00	1.44-2.54	37.03	28.00	1.16-1.91	25.96	24.00
21.41-27.10	37.0	44.0	16.4-21.4	40.79	32.00	2.55-3.65	37.03	36.00	1.92-2.67	14.81	32.00
27.11-32.71	33.3	24.0	21.5-26.5	29.62	28.00	3.66-4.76	22.22	24.00	2.68-3.43	29.62	28.00
32.72-38.35	11.1	4.00	26.6-31.6	14.81	4.00	4.77-5.88	37.00	12.00	3.44-4.19	22.22	8.00
38.36-44.01	3.7	0.00	31.7-36.8	3.700	0.00	-	-	-	4.20-4.95	7.40	8.00
μ ± S.D.			μ ± S.D.			μ ± S.D.			μ ± S.D.		
D	N		D	N		D	N		D	N	
27.90±6.25	24.40±4.75		21.70±5.48	18.40±2.60		2.98±0.93	3.30±1.25		2.90±0.94	2.65±0.99	
P < 0.025			P < 0.025			N.S.			N.S.		

generalized. Although noticeable contradictions have been observed in similar research carried out, there are common characteristics acceptable by all researchers in this field, i.e. several neuroendocrine and immunological parameters are altered in all depressed individuals. Some examples are (1) increased plasma lipids;<sup>21,22</sup> (2) an increase of cortisol secretion;<sup>27</sup> increased CK levels;<sup>23</sup> depression-induced modulation of the immune response;<sup>19,24</sup> an increase in  $\beta$ -endorphin;<sup>28</sup> decreased FTI levels and involvement of the hypothalamus-pituitary-adrenal axis.<sup>30</sup>

### Serum lipids and lipoproteins

Results of TC and LDL-c levels obtained in this study are in accordance with those reported by McCann et al.<sup>21</sup> and Morgan et al.,<sup>32</sup> as both parameters had higher concentrations in depressed persons. It is proposed that increased epinephrine levels result in an elevation of TC and  $\beta$ -adrenergic blockers cause a decrease in TG and increased LDL-c values.<sup>28</sup> In this study, although the test group had higher TC and LDL-c levels, no difference was observed between the TG content of test sera compared to controls. In spite of appreciable numerical differences in the control vs. test group, no linear correlation was obtained between TC and LDL-c levels and depression scores. The same was true for several other laboratory parameters, which may be due to the following reasons: (1) a difference of a few marks in the test used for selection may not be reliable for distinguishing between normal and depressed individuals, due to the fear of students to answer questions without bias. A constructed psychoanalytical interview by a psychiatrist and the dexamethasone suppression test (DST)<sup>32</sup> should be performed; (2) in spite of the emphasis on

Table VI. Comparison of serum concentration of C3 and C4 components of the complement system in depressed (D) and normal (N) control students.

C3 Component			C4 Component		
g/dl	D	N	g/dl	D	N
0.56-0.82	14.81	28.00	0.180-0.240	18.51	12.00
0.83-1.09	51.82	48.00	0.251-0.301	33.33	36.00
1.10-1.36	25.92	24.00	0.302-0.362	18.51	24.00
1.37-1.62	7.30	0.00	0.363-0.423	22.22	12.00
-	-	-	0.424-0.484	7.40	4.00
-	-	-	0.485-0.565	0.00	12.00
$\mu \pm S.D.$			$\mu \pm S.D.$		
D	N		D	N	
1.02±0.22	0.96±0.16		0.313±0.08	0.241±0.09	
N.S.			N.S.		

discontinuation of drug use by students, it is possible that some of the test students may have been taking psychotropic medications, and (3) the sample size was too small to show a wide range of variations.

### Blood sugar

High glucose levels have been reported in depressed individuals to be due to increased levels of cortisol, epinephrine and glucagon which stimulate glycogenolysis and gluconeogenesis.<sup>27,41</sup> In addition, increased HbA<sub>1c</sub> concentrations in depressed subjects is an acceptable indicator of glucose elevation in serum.<sup>34</sup> Although no difference was observed in FBS values of the two groups, glucose tolerance tests should be performed

in order to substantiate these results.

### Creatine kinase

The increased CK activity found in the test group is supported by the results of studies conducted by Metzler who showed that primary muscle isozymes (M-isozymes) were increased in depressed patients.<sup>23</sup> The presence of numerous hematomas in people with chronic bipolar depression confirms the presence of muscular disorders, which lead to an increased activity of CK-M-isozymes.

### Immunoglobulins and complement components

Data showed a reliable increase in total Ig and IgG in the test group with a positive linear correlation between Ig contents of the two groups ( $P=0.036$ ,  $r=0.43$ ). Among Ig classes, IgM levels showed a positive linear correlation with depression scores of the control group ( $P = 0.02$ ,  $r=0.47$ ), whereas IgG levels gave a positive but non-linear correlation ( $P=0.11$ ,  $r=0.33$ ).

In spite of the contradictory reports concerning Ig concentration, according to Glaser et al., students under examination stress and those suffering from inadequate social support showed a noticeable delay in the synthesis of antibody against hepatitis B surface antigen.<sup>37</sup> It has also been shown that work pressure and stress lead to increased IgG levels,<sup>38</sup> which confirm the data reported in the present investigation. It is believed that increased IgG levels are due to reduction of the activity of immune cells.<sup>34,35</sup> Studies by Dunn<sup>12</sup> have shown that the number of T-cells and subtypes  $T_s$ ,  $T_h$ , B cells and natural killer cells (NK) were the same in depressed and control groups, but the response to mitogen was defective in depressed individuals. Also, cell-mediated immunity in response to herpes virus was not sufficient to control the infection in depressed patients;<sup>12</sup> Evans reported that the NK cell number and their killing efficacy was decreased in depressed individuals.<sup>39</sup>

Concerning the functions of the neuroendocrine system, it is believed that this system is required for ontogeny of the immune system and the two systems have mutual interactions.<sup>12,19</sup> Sympathetic nerves in immune organs such as the thymus and spleen produce not only norepinephrine, but neuropeptides such as endorphin which affect the immune system.<sup>28,43</sup> In contrast to sympathetic systems that carry cytokine receptors, cholinergic and  $\beta$ -adrenergic receptors have been identified on the surface of lymphocytes.<sup>34,40,42</sup>

### Hormonal analyses

Among the serum hormones tested, only cortisol and testosterone levels of the test group were higher than

those of controls; no significant linear correlation was found between hormone levels and depression scores. This is probably due to the method of selection of the depressed individuals.

It is classically believed that high cortisol levels enhance the occurrence of depression (the basis of DST) and data reported herein are in agreement with those reported elsewhere.<sup>27,33,41</sup> Elevated testosterone levels have been reported in dominant and aggressive people.<sup>41,43</sup> This elevation in depressed subjects seemingly contradicts the expected decreased sexual activity often observed in this group. Recent evidence obtained demonstrate that the decreased level of testosterone is not directly related to sexual drive, since testosterone is biochemically a prohormone that is converted to the active forms, dehydrotestosterone and estradiol, processes that may be inhibited during the course of depression. In addition, in some phases of bipolar depression, patients may become hypersexual.<sup>43</sup> The level of prolactin increases during depression due to increased  $\beta$ -endorphin (a natural antidepressant), which in turn decreases dopamine concentration.<sup>40</sup>

In this study, university students have been used as subjects, a group who are vulnerable to depression due to agoraphobia secondary to change of environment, homesickness, disorientation, loneliness, maladaptation to college life, etc. The major contribution of this study is that a large number of laboratory parameters have been measured in a single sample of human subjects with similar long-term goals in one geographical area.

In conclusion, the data presented herein indicate that some laboratory parameters are altered during certain phases of depression(s). Such studies are very difficult to perform in the Western hemisphere due to rigid laws, limitations and severe consequences of using human subjects in biomedical research.<sup>44</sup> It is suggested that the dexamethasone suppression test be used for selection of clinically depressed individuals, and a thorough study of the immune system be carried out in order to evaluate the endocrinological and immunological changes occurring during the course of depression.

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