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EXAMINATION STRESS;
EFFECTS ON THYROID HORMONES

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ABSTRACT... Objective: 1: To examine the effects of examination stress in young adult male and female medical students on cardiovascular system and thyroid gland (i.e. thyroid hormones; T_3,T_4).2:To find out whether the responses are sex dependent or not. **Setting:** Department of Biochemistry NMC Multan (1997-1998). **Patients and method:** Examination stress was studied in 28 young female and 21 young male volunteer medical students, 0.5 hour before Biochemistry examination (stress condition), at 10-12 a.m. and about six weeks after examination (control condition) at the same time in the year 1997. Estimation of Thyroxine (T_4) and Triiodothyronine (T_3) and T_3 /T_4 was done in patients and control subjects. **Results:** There were no differences in body mass index of male and female groups in control and stress group. Subsequent analysis between two sexes showed that males subjects had significantly higher systolic (124.7±40.1 mmHg) and diastolic blood pressure (76.56±2.48 mmHg). Heart rate (84.6±2.63) increases in stress condition, in both sexes, but in males the increasing of heart rate is more than in females. Whereas females had higher respiratory frequency in stress condition, as compared to males. The levels of T_3 in female stress group were higher than male stress group but statistically not significant. The mean values of T_4 were highly significant in female stress group than in male stress group. **Conclusions:** Stress responses to examination are different between two sexes. The differences in responses to examination stress between male and female showed a greater increase in systolic and diastolic blood pressure, heart rate, respiratory rate and also thyroid hormones in response to stress. It is suggested that as the examination is a stressful condition and different effects of stress on male and female medical students should be considered. The clinical presentation is palpitations, tremors, nervousness, apathy, fatigue, thirst, and emotional un-stability is due to the increase of thyroid hormones. Students are guided to remain relaxed, as neurotransmitters and hormones are released which may effect the overall performance of the students. Further study may be down to find out the effects of stress on other systems of the body which may be helpful in future to avoid the poor mental health status during the examination.

Key Words: Cardiovascular; Endocrine; Biochemistry Examination; Sex Difference; Thyroid Hormones, Stress.

INTRODUCTION

Stress is the specific and nonspecific response of the body to any kind of physiologic pressure or unwanted forces due to environment or peripheral effects. Stress acts in different axes including hypothalamus-pituitary adrenal axis, hypothalamus-pituitary-gonads axis and hypothalamus-pituitary –thyroid axis[1,2]. In addition, there are autonomic responses by sympathetic nervous system to the stressful condition i.e. the activation of sympathetic nervous system and the activation of the above axes specially hypothalamic pituitary axis occur, simultaneously[2,3]. Different kinds of stress call for the responses of endocrine glands; for example, responses to the stress of temperature, hypoglycemia, surgery, pain, occupations, or decreasing energy , are mediated by different endocrine glands. There are differences in cardiovascular and neuroendorine responses to stress, i.e cardiovascular complications include hypertension and increased heart rate, gastric ulcer, migraine, headache, palpitation, and asthma[2].

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Among neuroendocrine stress reactions the releasing of catecholamines, i.e adrenaline and noradrenaline play a key role in human adjustment to environmental demands, for example, augmentation of the peripheral catecholamine level is accompanied by a series of changes in cardiovascular and metabolic function which facilitate adaptation to a wide range of stimulus conditions[2].

Human studies suggest that cardiovascular responses to stress are sex-dependent and in females they differ during the menstural cycle[4,5]. Women usually have lower blood pressure and adrenaline in response to stress than do men[6], suggesting that determinants of women's stress responses may differ from mens responses[7]. Most of the studies on different responses to stress were carried out in middle aged men and women, and there were not many reports that investigated the effects of stress on the young medical students. The examination stress was accounted as an acute physiologic stress in some subjects. Examinations are anecdotally viewed as an extremely stressful condition[8]. Patients with acne may experience worsening of the disease during examinations[9]. A study in Netherlands on PhD students showed that although the blood pressure did not change significantly by the examination stress, but peripheral benzodiazepine receptor density, all opregnanolon, and cortisol concentration were significantly increased during examination[10]. It is crucial to survey the determinants of response to stress induced by examination in young males and females. Therefore the general aim of this study was; firstly, to assess the cardiovascular and neuroendocrine (thyroid hormones) responses to examination stress in young medical students, secondly, to find whether the responses are sex dependent. No work has been done before on the stress response of thyroid hormones, so an attempt is made to find out the effect of stress (examination) on the most metabolically active hormones in the adult healthy volunteers.

MATERIALS AND METHODS

Examination stress was studied in 28 young females and 21 young males. 19-23 years old volunteer medical students were included in the study and there was no difference in age between males (21 .5± 1.3 years) and females (20.4±1 years). Students were asked to fill in a questionnaire about the stressful examinations and to specify which subject is more stressful. After reviewing the questionnaires it was revealed that Biochemistry examination is the most stressful condition. For the control of stress condition and elimination of the interfering factors, all the individuals who were suffering from other stresses (except the examination) e.g. psychological problems or taking medication were excluded from the study. The effect of stress was investigated half an hour before annual Biochemistry examination in 1997 (stress condition) and about six weeks after examination (control condition). The body mass index , systolic and diastolic blood pressure ,heart rate respiratory frequency, T_3, T_4 and T_3/T_4 ratio were measured at control and stress conditions. Blood pressure and heart rate were measured using sphygmomanometer and stethoscope. Blood samples were taken 30 minutes before examination and about six weeks after examination at 1-12 a.m. Thyroid hormones(T_3,T_4) were measured by radio-immunoassay (RIA) method. All subjects gave their informed written consent for participation in the study. The experimental design and the procedures followed were in accordance with the ethical standards laid down for human studies.

Data was analyzed by analysis of variance (ANOVA) to compare the differences between groups. The data are presented as Mean ± S.EM. and $p<0.05$ and $P<0.001$ were considered as statistically significant.

RESULTS

The results of this study are summarized in (Table I-III). Table I summarizes some demographic characteristics of the female and male students. Both weight and height of male are significantly higher than females ($P<0.001$), but there was no significant difference in body mass index between two sexes.

Table -I. Selected demographic characteristics of the female and male students in the biochemistry examination stress and control condition. Data represents mean ±SEM				
Variables	Conditions			
	Control Group		Stress Group	
	Female	Male	Female	Male
Weight (Kg)	54.78±1.21	***59.35±3.86	55.6±1.2	***66.68±1.8
Height (cm)	163.56±0.97	***175.1±1.4	164.32±0.97	***175±0.98
BMI (Kg m-2)	20.40.4	21.52±0.46	20.56±0.45	21.84±0.57
Age (Years)	21.4±1.5	22.5±1.75	21.7±1.4	22.9±1.65
*** Significant Sex Difference, P<0.001.n = 28 for females and 21 males.				

Table II shows the mean of systolic and diastolic blood pressure , heart rate and respiratory frequency for male and female students in stress male group and control group. According to data, the systolic blood pressure is significantly higher in males than females (p<0.01).In males systolic blood pressure is significantly higher in stress than control group (P<0.05).Diastolic blood pressure in stress condition is significantly increased in males as compare to females (p<0.01).

Heart rate of females in stress condition is significantly increased as compared to control; this is the same for males. In control condition heart rate for females is significantly greater than males (p<0.001). However in males the increase in heart rate is significantly higher than females in stress condition. Respiration frequency (RF) of females was more than males in both control and stress conditions (P<0.05).

Table-II. Mean and standard errors for systolic blood pressure , diastolic blood pressure , heart rate , and respiratory frequency (RF) in female and male students under Biochemistry examination ,stress group ,and in control s. Data represent Mean ± SEM.				
Variables	Conditions			
	Control Group		Stress Group	
	Female	Male	Female	Male
SBP (mmHg)	112.34±1.6	116.±2.7*	110.8±2.25	124.766±4.01**
DBP (mmHg)	67.96±1.27	74.2±1.9	68.22±2.03	76.56±2.48*
Hr (beat Min^{-1})	77.09±1.04	70.2±1.64	84.9±1.25***	17.12±0.28
RF (beat Min^{-1})	18.48±0.28	16.88±0.21	20.81±0.52	170.12±0.28
*p<0.05 significant difference in male under stress and control group. **p<0.01 significant sex difference under stress group p<0.001 significant sex difference under stress condition.				

Mean values of serum T_3,T_4,and T_3/T_4 ratio are shown in table-III. Mean level of T_3 expressed in ng/dl observed in control subject was (1.58±0.09). in female and (1.60±0.96) in male subjects. Mean levels of T_3 in stress

group (2.60±0.56) in females were higher than in male group (2.75±0.65).The values are higher in stress group but statistically insignificant as compared with control group. The mean levels of T_4 expressed in µg/dl were observed (8.17±0.41) in female controls and (7.50±0.65) in male controls. In stress female group the mean value of T_4 was (11.45±2.09) and in male (9.05±1.96) respectively and higher to the control but was not statistically significant as compared with control group. Mean levels of T_3/T_4 Quotient observed in control subjects was (55.87±5.57) in female and (53.06±5.02) in male controls. T_3/T_4 ratio in stress female group is (48.3±6.09)and (50.50±5.06) in male patients respectively. These values are statistically highly significant.

Table-III. Means of (T_3) and (T_4) and T_3/T_4 ratio in female and male students under Biochemistry examination (stress group) and control conditions. Date represent Mean ± SEM.

Variables	Conditions			
	Control Group		Stress Group	
	Female	Male	Female	Male
T_3 mg/dl	1.58±0.09	1.60±0.96	2.60±0.56	2.75±0.65
T_4 µg/dl	8.17±0.14	7.50±0.65	11.45±2.09	9.05±1.96
T_3/T_4	55.87±5.57	53.06±5.02	48.13±6.09	50.50±5.06
**** Significant Sex difference, P< 0.001. n = 28 for females and 21 males.*				

DISCUSSION

The results of this study showed that there were no differences in body mass index of male and female groups in control and stress conditions. Male group had higher systolic and diastolic blood pressure and increased heart rate in stress condition as compared to those of females, whereas, females had higher respiratory frequency in stress condition as compared to that of males. Our findings in cardiovascular responses are in agreement with the studies of Matthews, that reported sex differences in systolic blood pressure and diastolic blood pressure responses during stress in middle age individuals[6] and Tersman who found increase in systolic blood pressure[11]. Zeller et al. have recently shown that during medical licensing examination, diastolic blood pressure was significantly increased but the systolic blood pressure did not change significantly[12].The present report shows that, the sex difference also exists in young adult individuals, but is in oppose to the results of Bijlani[13]. This difference was suspected because Bijlani experiments were done one week before examination, but our experiment was on the day of examination. Increase heart rate in this study is in agreement with the results of Stoney[5] and Mathews[6] who determined the cardiovascular responses to physical and psychological stresses. It has been shown that subchronic physiological stress in human increases alpha2-adrenergic receptor density, which is related to stress-induced anxiety[15]. Examination stress causes a decrease in the parasympathetic influences on the heart rate[16]. Examination stress also changes the activity of sympathetic and parasympathetic nervous system[17]. The finding in respiratory frequency suggests that increase in respiratory frequency along with increasing the activity of vagus nerve instead of accompanying with decrease of sympathetic activity, it is also possible that females may be more sensitive to stimulation of vagus nerve than males. Thyroxine and triiodothyronine are the only physiologically active hormones and ratio of T_4/T_3 will be proportional to thyroid function.Estimation of T_4andT_3 would be considered as better index of thyroid function. he process of synthesis of these two hormones is the same but they differ in rapidity and intensity of action. Triiodothyronine is about four time as potent as T_4 but it is present in blood in much smaller quantities and persists for a shorter time than does thyroxine. A primary action of thyrotropin is to activate thyroid adenylate cyclase and to increase the glandular cyclic adenosine mono-phosphate (cyclic AMP)[3,5]; Gillman and Rall, 1986. Cyclic AMP acting as the intracellular mediator of

thyrotropin appears to be able to produce the important actions of the hormone. .It has been reported that human thyroid tissues appear to possess a single set independent receptors sites for thyroid stimulating hormones. The receptors have a high binding affinity in stress. Thyroid hormone increases metabolism in the tissues and causes more rapid utilization of oxygen, cardiac output and heart rate. Thyroid hormone probably has direct effect on the excitability of heart which in turn increases heart rate .These effects were also observed by Buccino et. al. (1967) that thyroid hormone augments the contractile state of isolated cardiac preparations by a mechanism not involving catecholamines. Sterling in1979 observed that increase may be due to hypersensitivity of heart to catecholamines in stress state and reports indicates that the number of myocardial- adrenergic receptors are increased. The mean levels of T_4 in stress group (17.79 P<0.02)was significantly higher as compared to the control group. The mean levels of T_4/T_3 ratio in control subjects (55.87) is within normal limits. But in stress group the values are statistically significant (35.92,p<0.01). The results of this study are in agreement with the findings of Johansson that has shown the hormonal change in male and female medical students in response to examination stress[20].

A study in Netherlands on PhD students showed that although the blood pressure did not change significantly by the examination stress, but peripheral benzodiazepine receptor density, all opregnanolon, and cortisol concentration were significantly increased during examination[10]. Results showed that the plasma ACTH in male students is higher than female in both control and stress group. Also the levels of cortisol in male is increased under stress whereas in females it was not changed [12]. These results are in agreement with the result of other investigators[4,11,19]. Martinek studied the effects of routine written examination on salivary cortisol and Johansson had shown the hormonal change in male and female medical students in response to examination stress[20]. Komesaroff showed that only under stress conditions the amount of cortisol in luteal phase is greater than follicular phase, whereas, in control condition there is no significant change[21]. Tersman also measured the cortisol concentration in different phases[11].

CONCLUSION

It is concluded that there are difference in physiological and endocrinal i.e. biochemical (thyroid hormones, T_3,T_4) responses to examination stress between males and females showed a greater increase in systolic and diastolic blood pressure, heart rate, respiratory rate and also thyroid hormones in responses to stress. Therefore it is suggested that as the examination is stressful condition, different effects of stress on male and female medical students should be considered. The clinical presentations e.g. palpitation, tremors, nervousness, apathy, fatigue, thirst and emotional liability is due to the increased level of thyroid hormones. Students are advised to remain relaxed, as biochemical neurotransmitters are released which may effect the over all performance of even the highly intellectual students. Further studies are suggested to know the effects of stress of other systems of the body that may be helpful in future to avoid the poor mental health during the examination.

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