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Exam-related changes in salivary oxytocin and cortisol levels of preclinical medical students

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ABSTRACT

Objective: The relationship between exam conditions with the peripheral oxytocin and cortisol levels and psychological characteristics by gender were investigated.

Participants and Methods: Thirty-six preclinical medical students gave saliva samples in exam-free and pre-and post-exam conditions and completed a comprehensive psychometric questionnaire.

Results: Before the theoretical exam, cortisol levels were elevated in females but not in males, whereas, oxytocin levels were similar in both sexes under exam conditions. Genders were equalized in terms of most psychometric properties. Females did not feel prepared for the exam and experienced more anxiety before the exam than males. Females had higher cortisol levels before the exam than after the exam, but no change was observed in the cortisol levels of males by the exam conditions. Oxytocin levels did not differ significantly for any condition or group.

Conclusion: Females may need to be supported in study planning and time management to increase exam preparedness and stress management to increase coping with stress. The study's small sample size casts a shadow on the generalizability of the results. In future studies, the research process can be spread over a longer period and more people can be reached by not giving up strict selection rules.

Keywords: Test anxiety, Medical education, Oxytocin, Gender, Cort

1. INTRODUCTION

A safe academic environment supports academic development and positively affects the moral constructs and behaviors of medical students [1, 2]. However, the undergraduate medical education is regarded globally as a long, stressful and anxiety-provoking stage [3-5]. It was emphasized that taking an exam or having poor academic performance was associated with high levels of perceived stress and cortisol in the university students [6-8]. In parallel, mental health of medical students was negatively affected during their training, and higher levels of perceived stress, anxiety and depressive symptoms were evident as compared to non-medical students [9-12]. A recent study demonstrated that physical and mental health of students were worsened at the end of the first-year of the medical training, but were then improved throughout the rest of the education, while perceived stress levels have still remained high [13].

The neuropeptide oxytocin (OXT) was proposed to exert anti-stress and anti-anxiety effects [14, 15]. Studies have shown that activation of the hypothalamo-pituitary-adrenal axis (HPA), induced by a psychosocial stress causes a cortisol response, which is accompanied by an elevated OXT secretion showing a positive correlation with the elevated cortisol levels [16, 17]. It was suggested that the stress-relieving effect of OXT does not occur at the initial phase of the HPA hyperactivity, but high levels of OXT secretion accelerates vagal recovery during the later phase of stress [17]. On the other hand, stress reduction activities and social engagement are proposed to yield an enhanced secretion of OXT and a resultant vagal upregulation [18, 19].

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One of the major causes of stress among university students is the "exam anxiety", which may frequently disturb academic performance and result in several psychological problems [20, 21]. The impact of exam anxiety was evaluated in non-medical students, and salivary cortisol concentrations were found to be elevated before the exams with a higher cortisol response in the oral exams as compared to written tests [7, 22-24]. The facilitating effect of oxytocin on coping with stress has been examined in terms of situations that cause social stress: Studies show that intranasal OXT intake reduces social stress-induced anxiety in women, increases the positive effect of social support [25], and decreases cortisol concentration in stress situations with interpersonal difficulties [26]. Endogenous OXT rises before cortisol when the exam period approaches and contributes to the management of the stress response by regulating the effect of cortisol, which subsequently increases [27]. However, the contribution of OXT response to exam-induced anxiety in medical students, and the impact of gender, coping styles, social relationships and the personality characteristics on their exam-induced anxiety were not elucidated before. Since exam stress and how this stress is managed may be related to a number of psychometric properties, personality and cognitive characteristics of the participants and their coping styles were also evaluated in the present study with valid and reliable scales. While evaluating the relationship between gender, exam condition, cortisol and OXT levels, if a difference has arisen in any of the mentioned psychometric features, the correlation between this feature and stress-induced CORT and OXT response was also examined.

The aim of the present study was to investigate the effect of anticipated written exams on the salivary OXT and cortisol responses of the pre-clinical medical students who were evaluated in various psychometric characteristics. The main hypotheses of the study were as follows: 1. Females have a higher pre-exam anxiety level than males; 2. Females have higher CORT levels before and after the exam; 3. OXT levels in females both before and after the exam are higher than those in males.

2. PARTICIPANTS and METHODS

Participants and the research design

The study was approved by the Marmara University, School of Medicine, Ethics Committee for Clinical Research (06.03.2016-09.2016.390). The aim and the inclusion criteria of the study were announced on the Marmara University School of Medicine (MUSM) campus using the bulletin boards, and three meetings were held by the researchers to explain the procedures. Inclusion criteria were determined as: not having diagnosed with a psychological or a neurological disease, not having a systemic disease, not being pregnant or lactating, not smoking and not being on a legal or an illegal drug during the study period.

Forty-one students studying at MUSM participated in the study. Despite regular calls for participation in the research, the number of participants could not be increased more. On the other hand, 5 students missed one or two salivary measurements, and thereby the statistical analyses were executed by using the data of 36 students (19 females and 17 males with a mean age of 18.97± 0.86 years), which revealed a similar sample size that has been used in many studies, as reported in the meta-analysis of Spilijak et al. [28]. The participants were at the 1st (n=11), 2nd (n=7), or 3rd (n=18) year of the medical school at the time of the research. During these preclinical years, the theoretical exams for different subject committees are prepared in similar formats and are given as multiple-choice exams to be answered within 90 to 100 minutes. In order to eliminate a possible bias in the study that could be caused by the participation of high-achieving students, exam performance data were compared with the median of the whole class using a one-sample non-parametric test and the results indicated that the median of the study sample is not significantly different from that of the whole class (data not shown).

In an exam-free period (45 to 60 days before the exam) students were gathered in groups in one classroom, where all the questionnaire-filling and saliva-collecting activities would be done, and then they were given a training on the saliva collection method (Figure 1). During this session, they were also asked to fill in two questionnaires. Within the same week, they were asked to come over again to fill in a second set of questionnaires, and to collect their baseline saliva samples. During this second session, the students stated on the given forms whether they have experienced any stressful events within the last 6 months and the severity degree of the experienced stress. A day before the collection day (baseline or exam day), the students were sent an e-mail or a text message which reminded them the time and requirements for saliva collection. The times at which saliva samples were collected during the exam-free period were matched with the times at which saliva samples were collected during the exam period (between 09:00 am to 10:00 am and 11:30 am to 12:30 pm).

Before exams, the students were asked to what extent they felt ready for the exam (1-I am not ready to 5-I am too ready) and how anxious they were about the exam (1-I am not worried at all 5-I am extremely worried). At 30 min before the exam, and at 15 min immediately after the exam, the students collected their saliva into tubes.

Questionnaires and Inventories

People's responses to stress situations can be determined by many factors including environmental, physiological and psychosocial. In this study, all students were undergoing the same examination system and strict selection criteria were used to eliminate possibilities that could affect the physiology of the individual. In addition to these, certain personality traits can be related to appraisal, coping styles and coping effectiveness [29]. Burgess et al., showed a positive correlation between "agreeableness" and problem-focused coping strategies [30]. Also, a significant negative correlation exists between "agreeableness" and negative emotional reactions [31]. Since, the metacognitions are closely related to different dimensions of test anxiety [32, 33], the need for controlling thoughts, cognitive confidence, and negative beliefs about the uncontrollability of

thoughts and danger were reported to be positively correlated with anxiety [34, 35]. Also, People may activate different coping mechanisms in line with their personality traits and different circumstances [36]. Problem-focused coping predicted the reduction of academic stress [37] and decreased cortisol levels [38]. Due to these variabilities in effect, this study included comprehensive psychological tools to measure possible individual differences.

The research sample was evaluated in terms of the following psychometric features that may be related to coping with stress. The Scale of Dimensions of Interpersonal Relationships, which has 53 items with 4 dimensions, was used to predict the interpersonal relationships [39]. The Cronbach's alpha coefficients of this scale's dimensions vary between 0.78 and 0.85. The Turkish version Metacognition Questionnaire-30 (MQ-30) was adapted by Tosun and Irak and, has 30 items with 5 dimensions [40]. Any increase in the scores means that the specific metacognitive activity has increased and may cause anxiety in the participants. The Ten-Item Personality Inventory was also adapted to Turkish and it consists of 10 items and 5 dimensions [41]. The Cronbach's alpha values of the dimensions vary between 0.81 and 0.86. The higher the score for a dimension, more dominant is the dimension as a personality trait for the participant. MQ-30's total Cronbach's alpha score is 0.93 and its dimensions' Cronbach's alpha values are between 0.72-0.93. Brief Coping Styles Scale's (COPE) validity and reliability study was done by Bacanlı et al., and, the dimensions' Cronbach's alpha values vary between .39 and .92. It has 28 items and shows a 14-factor structure [42]. State-Trait Anxiety Inventory (STAI) was used only to measure "state anxiety" using a 20-item form with one dimension [43]. The Cronbach's alpha coefficient for the state anxiety inventory is 94. Higher scores in STAI indicate greater anxiety.

Collection of saliva samples and the measurement of salivary oxytocin and cortisol levels

Saliva collection was first made during the exam-free period and then repeated before and after the exam (Figure 1). By collecting saliva samples, it was aimed to eliminate the anxiety of repeated invasive sampling by blood withdrawal [44]. The students were asked to wash their mouth with water and spit it out. They were then instructed to place a roll of cotton (SalivaBio Oral Swab, Salimetrics, Carlsbad, CA, USA) under their tongue, tilt their head forward and accumulate saliva in their mouth without swallowing for 40 s. Then, the students with their surgical gloves on, placed the wet cottons into the Salivettes® (Sarstedt, Rommersdolf, Germany) that were previously labeled with codes. The Salivettes were kept ice-chilled for at most 1 h until they were centrifuged at 4 °C and 1500 g for 15 min. The liquid samples obtained after centrifugation were then stored at −80 °C. Salivary OXT and cortisol levels were measured using the commercial enzyme linked immunosorbent assay (ELISA) kits (Human OXT Cat. Number: 201-12-1047; Human cortisol Cat. Number: 201-12-1004; Sunlong Biotech, China). OXT level was expressed in ng/μg protein with a sensitivity of 1.775 pg/ml and cortisol levels in nmol/μg protein with a sensitivity of 7.186 nmol/L. After each saliva collection, sandwiches and fruit juices were offered to all students.

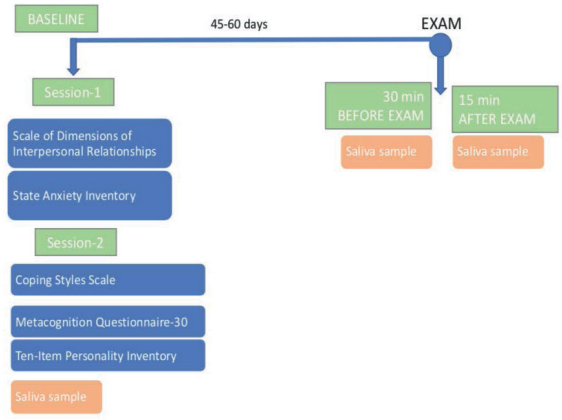

Figure 1. *Psychometric measurement and biological data collection design*

Statistical Analysis

The sample size was determined with the OpenEpi program (https://www.openepi.com/). Estimating the difference in saliva cortisol level between the groups [45], sample size was calculated as n=16 with 80% power and 95% Confidence interval (2-sided).

Saliva levels of OXT and cortisol were analyzed by One-Way repeated measures of ANOVA using GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA) program. Jamovi 2.3.21 was used to compare genders in psychometric properties. The Mann-Whitney U were used due to the low sample size and not normal distribution. Significance level was determined as $p<0.05$ and Bonferroni correction was used when necessary.

3. RESULTS

Psycho-biological characteristics of the participants

Table I shows the mean and median scores for each psychometric measurement, gender differences and baseline biological variables. Mean salivary OXT and cortisol changes for genders are presented in Figure 2 and 3. In females, cortisol levels measured before the exam were higher than the cortisol levels determined after the exam ($p=.047$). However, salivary cortisol levels in males were not significantly different among measurements ($p>.05$). OXT levels in males or female students have not significantly changed before or after the examination (for both males and females $p>.05$).

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Table I. *The inventory/questionnaire scores and baseline salivary cortisol/oxytocin levels in the baseline conditions.*

Metacognition Questionnaire-30				
	Min-max score can be obtained	Mean (Standard deviation)	Median	Interquartile ranges
Positive beliefs about worry	7-24	14.83 (3.74)	15.50	5.75
Negative beliefs about uncontrollability of thoughts and danger	7-28	15.20 (3.40)	15.00	6
Cognitive confidence	6-24	12.29 (4.45)	12.00	5.25
Cognitive self-consciousness	1-24	18.42 (3.16)	18.00	4
Beliefs about need to control thoughts[a]	1-20			
All participants		13.97 (3.28)	14.00	6
Female		15.10 (3.26)	16.00	5
Male		12.62 (2.84)	11.00	4
Ten-Item Personality Inventory				
Emotional stability	2-14	8.41 (2.07)	8.00	3
Openness to experiences	2-14	7.94 (1.63)	8.00	2
Conscientiousness	2-14	7.97 (2.20)	8.00	3.25
Extraversion	2-14	8.97 (1.69)	8.50	2
Agreeableness	2-14	8.66 (2.24)	8.00	2.5
Brief Coping Styles Scale				
Using Instrumental Social Support	2-8	6.48 (1.29)	7.00	1
Humor	2-8	5.41 (1.84)	5.50	3
Substance use	2-8	2.22 (0.76)	2.00	0
Acceptance	2-8	6.63 (1.37)	7.00	2
Denial	2-8	4.77 (0.98)	5.00	2
Behavioral Disengagement	2-8	2.82 (1.01)	3.00	1
Mental Disengagement	2-8	5.16 (1.34)	5.00	2
Suppression of Competing Activities	2-8	5.80 (1.25)	6.00	2
Turning to Religion	2-8	6.08 (1.90)	6.50	3.75
Restraint coping	2-8	4.97 (1.38)	5.00	2
Positive Reinterpretation	2-8	6.36 (1.33)	6.00	2
Planning	2-8	7.08 (1.15)	7.00	1.75
Focus on and Venting of Emotions	2-8	5.41 (1.22)	5.00	1.75
Using Emotional Social Support[b]	2-8			
	All participants	5.66 (1.24)	6.00	2
	Female	6.10 (1.04)	6.00	1
	Male	5.17 (1.28)	5.00	2
Scale of Dimensions of Interpersonal Relationships				
Approval dependence	15-60	35.88 (8.09)	36.00	11
Empathy	9-36	29.45 (3.43)	29.00	5
Trust for others	15-60	42.46 (4.41)	41.50	6
Emotional awareness	14-56	42.91 (4.80)	43.50	7.25
State Anxiety Inventory (min 20 – max 80 for the inventory)				
	20-80	35.63 (7.54)	35	10.75
Cortisol in saliva (nmol/µg protein) in the non-exam period				
		4.76 (1.78)	4.85	2.86
Oxytocin in saliva (ng/µg protein) in the non-exam period				
		4.97 (2.47)	5.15	2.79

Note. All data were compared regarding the gender of the students. Except the indicated statistical significances, the rest of the data were not different between males and females.
a Females have higher scores than males (U=83.5, z=-2.28, p= .002)
b Females have higher scores than males (U=86.00, z=-2.46, p= .013)

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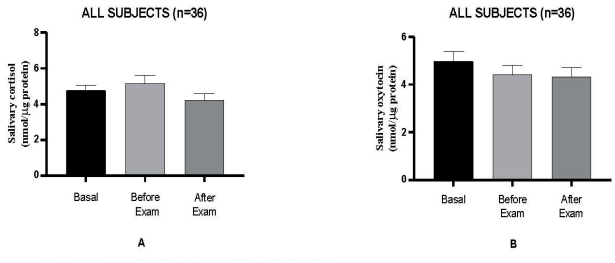

Figure 2. *Salivary cortisol (A) and oxytocin (B) levels in all students*

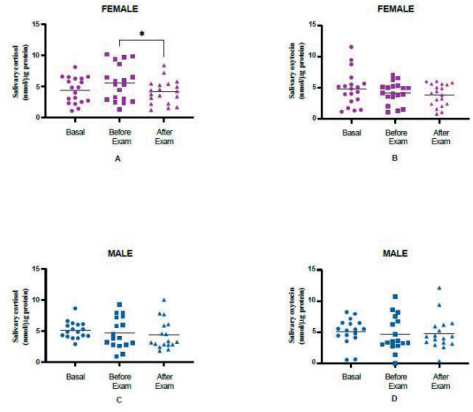

Figure 3. *Salivary cortisol (A & C) and oxytocin (B & D) levels in females (n=19) and males (n=17) * p<0.05*

Perceived stress, perceived preparedness before the exam

Subjective anxiety before the written exam was higher in females than that in males (U = 66.50, z = – 1.85, p = .033) (For females 3.56 (SD=1.09), *Median* = 3, for males *2.75 (SD=.096) Median =3)*. For the written exam, the males' level of feeling prepared for the exam was 3.58 out of 5 (*SD* = .96, *median*=3.5), that of the females was 2.47 (*SD*= .72, *median*=3.0) (U = 43.00, z = – 3.05, p = .001). There was a negative correlation between feeling prepared before the theoretical exam and cortisol levels before the exam (r=-.627, p=.01) and after the exam (r=-.511, p=.01) only in women.

Psychological variables in relation to biological differences

Most of the psychometric characteristics of the participants were similar between genders which helped us to attribute the differences in biological changes to the exam type and related perceived stress. Only in "Beliefs about need to control of thought" and "Using emotional social support" dimensions females had higher scores than males (Table I). The aforementioned correlation for females between perceived readiness for the exam and cortisol levels before and after the exam was checked by partial correlation analysis by controlling for those dimensions. The correlation between perceived preparedness and before exam cortisol levels was still significant (p=.028). Also, the correlation between perceived readiness and cortisol levels after the exam was verified for females even after controlling for the psychometric dimension (p=.016).

4. DISCUSSION

Our data revealed that salivary cortisol levels of the female students were significantly elevated before the exam, but the salivary cortisol levels of the male students were not altered by the exam, while no statistically significant difference was present among the salivary OXT levels of male or female students. Brown et al. [46] pointed out that there was no correlation between the gender distribution and the peripheral OXT and cortisol concentrations, but others [47] have indicated sex-related differences in the cortisol levels. The elevated cortisol response in the female students may be explained by their lower perceived readiness as compared to males, which was reported by the students before the exam. Other studies have also shown that female students experience more stress than male students [48-51] and especially the academic stress in male students is reduced during the school years, while the stress level of female students remains the same throughout the education [48, 52]. Taken together, higher readiness and lower test anxiety of the male students may explain their unchanged cortisol levels before the theoretical exam.

In contrast to their higher salivary cortisol levels, the OXT levels of female students were not changed before the written exam. The emergence of a stressful situation or receiving social support when a stressful stimulus is experienced cannot always be associated with the OXT response and different experimental designs can have confounding effects [13, 53, 54]. People may activate different coping mechanisms in line with their personality traits under different circumstances [36].

Some studies have reported a correlation between metacognitions and test anxiety [32, 33]. However, the MCQ-30 dimension that predicts test anxiety is generally the "negative beliefs about the uncontrollability and danger of worry" dimension [34, 35]. Therefore, it can be expected that the dimension "beliefs about need to control thought", which is a different dimension than the one mentioned above, does not change the correlation between feeling prepared before the exam and cortisol.

The main limitation of this study is that a larger sample size could not be reached. Possible reasons for this may be the strict criteria for inclusion in the study and the choice of not participating in a practice that may create extra stress before the exams, which is already a stressful situation. In future studies, it may be beneficial to reward participation in order to increase the motivation of students to participate. Since the sampling was made at 15 min before and after the exam, the hormonal responses were detected at these time points. Future studies could be planned to make saliva sampling at more frequent intervals in the exam room immediately before and after the stressor, which was not applicable to exam rules in our institution. On the other hand, the study is based on the comparison of gender groups that are largely similar in terms of some personality traits and coping styles, showing no difference between the baseline biological measurements, it provides reliable results about

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the change in biological data due to exam anxiety. In further studies, exam conditions requiring active communication with another individual can be selected or experimentally created to capture the possible change in OXT. In addition, semi-structured interviews with students can be conducted before and after the exam to reveal their metacognitions, coping styles, and perceptions of interpersonal relationships. Thus, it may be more accurate to interpret biological measurements based on cognitions at the time of the measurements.

Although, the differences observed in cortisol levels in the study differed according to gender, the findings suggest certain recommendations that are appropriate for all medical students. In the training program, it may be considered to implement practices that support students, especially female students, in stress management. These practices could include guidance and psychological counseling to provide a realistic basis for self-assessment of anticipatory performance and competence, regulation of unrealistically high expectations, effective studying and development of self-regulated learning skills during the course period prior to stressful situations such as examinations, which could help manage academic anxiety.

As both the related literature and this study show, academic anxiety can be high among students in the faculty of medicine. Considering that one of the environmental variables that determine coping with anxiety is the structure of the education program, the following can be suggested for this study: Institutionally, designing the assessment and evaluation system in a way that supports learning, reasonably organizing the time, place and duration of exams, ensuring exam validity and reliability, and using exams not only for decision-making but also for formative purposes will reduce students' uncertainty about exams and make it easier for them to see exams as a natural and learning-supportive part of education, which can have a positive impact on coping with academic anxiety.

Conclusion and limitations

Our data suggest that in preclinical medical school students, the cortisol levels of the females measured before the exam were higher than those of the males, implicating a higher stress level in females. However, oxytocin levels were similar in the exam conditions of both genders.

Strict selection rules were applied to minimize the possibility of biological data being influenced by variables other than test stress. However, this also limited the number of participants. In addition to the aforementioned selection rules, it was also questioned whether the participants had recently experienced stress for another reason. Nevertheless, the study population may have differed from the study universe at certain points. For example, curiosity about scientific research, being in contact with researcher professors. Those who did not participate in the study despite meeting the criteria may not have wanted to increase their existing anxiety because the study covered the exam period, or they may not have wanted to disrupt the order they were used to for reasons such as extra anxiety or biological sampling. Therefore, these characteristics and their effects may not have been reflected in the results.

The fact that there was no difference in cortisol for males but there was for females may be related to the fact that girls experience academic stress more intensely, as mentioned in the introduction. In this study, females felt less prepared for the exam during the exam period and this may be related to the fact that they were more anxious. The fact that oxytocin levels did not differ according to exam periods and gender can be explained by the view that changes in biological measurements may not always reflect those in psychometric measurements [13, 32, 33].

In this study, saliva was analyzed in order not to put the participants under extra stress and to prevent the inclusion of participants who might be concerned about invasive methods and to reduce the sample size further. Blood analyses would have provided more robust results and a clearer correlation with psychometric measurements, but the non-invasive method was not preferred for the reasons mentioned above.

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Compliance with Ethical Standards

Ethical approval: The study was approved by the Marmara University School of Medicine Ethics Committee for Clinical Research (06.03.2016-09.2016.390).

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Conflict of interest: The authors declare that there is no conflict of interest.

Author contributions: SYI, FEB, SS and BCY: Research design, SYI, FEB, SS, SAT and BCY: Methods, SYI, SS, BCY and SAT: Data collection, SYI, SS and BCY: Statistical analysis, SYI, FEB, SS, SAT and BCY: Manuscript preparation. All authors read and approved the final manuscript.

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