Does State Anxiety Affect the Outcome of an Oral Glucose Tolerance Test?

Durum Anksiyetesi Oral Glukoz Tolerans Test Sonuçlarını Etkiler mi?

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ABSTRACT

Aim: Some experimental studies reported that state anxiety is mediated by sympathetic effect of autonomic nervous system with an increase in norepinephrine secretion regulated by the catechol-o-methyltransferase gene. We conducted a prospective study investigating the effect of state anxiety of the subjects prior to oral glucose tolerance test (OGTT) on the test outcomes.

Material and Methods: State-Trait Anxiety Inventory (STAI) TX-1 form was given to the patients whom OGTT was indicated for this prospective study. OGTTs were performed by the same nurse and in the same test room during this study. STAI TX-1 form consisted 20 items and each one of them had weighted scores from 1 to 4.

Results: We included 516 patients to whom OGTT was performed and who completed STAI TX-1 form. No significant association between state anxiety score and OGTT outcomes was found. Pairwise comparisons showed BMI and waist circumference in the group of married were significantly higher than those in the group of single. Similarly, the percentage of DM diagnosis following OGTT in the group of married was significantly higher than that in the group of single.

Conclusion: Our study demonstrated that test-dependent state anxiety had no impact on OGTT outcomes. Evaluating state anxiety of the patients right before OGTT may not be required; however, as described in the literature, it is worthwhile to remember chronic anxiety could affect the outcomes of OGTT and a randomized prospective study is necessary to help determine if evaluating trait anxiety is required prior to OGTT.

Keywords: Oral glucose tolerance test, State anxiety, Norepinephrinergic sympathetic activity

ÖZ

Amaç: Bazı deneysel çalışmalarda, durum anksiyetesinin, katekol-o-metiltransferaz geni tarafından düzenlenen ve norepinefrin sekresyonunda artışa neden olan otonom sinir sisteminin sempatik etkisi tarafından düzenlendiği bildirmiştir. Bu nedenle, oral glukoz tolerans testi (OGTT) öncesi olan durum anksiyetesinin test sonuçlarına etkisini araştıran prospektif bir çalışma planladık.

Gereç ve Yöntemler: Bu prospektif çalışma için OGTT endike olan hastalara test öncesinde, Durumluk Sürekli Kaygı Envanteri (STAI) TX-1 formu dolduruldu. OGTT'ler bu çalışma sırasında aynı hemşire tarafından ve aynı test odasında yapıldı. STAI TX-1 formu 20 maddeden oluşmakta ve bu maddelerin her biri 1'den 4'e kadar değişen skorlara sahipti.

Bulgular: OGTT yapılan ve STAI TX-1 formunu dolduran 516 hastayı çalışmamıza dahil ettik. Durum anksiyete skoru ile OGTT sonuçları arasında anlamlı bir ilişki bulunmadı. İkili karşılaştırmalar, evli grupta vücut kütle indeksinin ve bel çevresinin bekar gruba göre anlamlı olarak daha yüksek olduğunu gösterdi. Benzer şekilde, evli grupta OGTT sonrası diyabet tanı yüzdesi, bekar gruptan anlamlı derecede daha yüksekti.

Sonuç: Çalışmamız, teste bağlı durum anksiyetesinin OGTT sonuçları üzerinde bir etkisi olmadığını gösterdi. Hastaların durum anksiyetesinin OGTT'den hemen önce değerlendirilmesi gerekmeyebilir; ancak, literatürde açıklandığı gibi, kronik anksiyetenin OGTT sonuçlarını etkileyebileceğini hatırlamakta fayda vardır. Kronik anksiyetenin OGTT'den önce değerlendirilmesinin gerekli olup olmadığını belirlemeye yardımcı olmak için randomize prospektif çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Oral glukoz tolerans testi, Durum anksiyetesi, Norepinefrinerjik sempatik aktivite

INTRODUCTION

Anxiety can be described as a feeling of tension, worry or nervousness which is difficult to control causing unfavorable outcomes such as impairment or major distress. The outcomes of a recent survey reported in 2017 showed that an anxiety disorder was the most common mental health disorder, estimating the prevalence as 3.8% (284 million) of the global population (1). The association between anxiety and some other disorders, such as musculoskeletal disorders, hypertension, metabolic syndrome (MetS) and diabetes mellitus (DM) were demonstrated by a number of studies (2-4).

A recent study of 1255 patients showed a significant interaction between insulin resistance and social anxiety (5). Batelaan et al. had also demonstrated that anxiety is associated with increased risk for DM (6). Clinical chronic anxiety was also 20% higher among individuals with diabetes compared to those without diabetes in a surveillance study (7). Norepinephrinergic sympathetic nervous system and hypothalamic-pituitary-adrenal axis (HPA) are two different stress pathways which have been suspected to be involved in the development of MetS (8).

In addition to that, short-term norepinephrinergic sympathetic activity has been considered related to state anxiety which has been known to increase blood pressure, e.g., white coat hypertension (9). Some experimental studies reported that state anxiety is mediated by sympathetic effect of autonomic nervous system and that activity *per se*, triggers the elevation in blood pressure by secreting norepinephrine, regulated by the catechol-o-methyltransferase (COMT) gene (10). Based on these data in the literature, we conducted a prospective study investigating the effect of state anxiety of the subjects prior to oral glucose tolerance test (OGTT) on the test outcomes.

MATERIAL and METHODS

Individuals who referred to our Endocrinology clinic were evaluated between February-July 2020. The patients whom OGTT was indicated in the evaluation of impaired fasting glucose (IFG), obesity or reactive hypoglycemia were recruited for this prospective study. State-Trait Anxiety Inventory (STAI) TX-1 form was given to the patients who gave their informed consent to evaluate their state anxiety right before OGTT. STAI TX-1 form consisted 20 items and each one of them had weighted scores from 1 to 4. In order to obtain the scores for the S-anxiety, before starting the calculation, the scoring weights for the anxiety-absent items (1, 2, 5, 8, 10, 11, 15, 16, 19, 20) were reversed, i.e., 1, 2, 3, 4 were replaced by 4, 3, 2, 1, respectively. When this process was done, all scores were added which made up a cumulative state anxiety score (SAS) varying from a minimum of 20 to a maximum of 80.

Considering the patients' self-declaration, a history of any psychiatric disease or a disease which causes insulin resistance, such as Cushing's syndrome, acromegaly, polycystic ovary syndrome (PCOS); active glucocorticoid, anxiolytic, antidepressant or antipsychotic drug use, pregnancy, age less than 18 years were the exclusion criteria of our study. OGTTs were performed by the same nurse and in the same test room during this study. 5 groups were established according to OGTT outcomes: Normal - fasting plasma glucose (FPG) level < 100 mg/dL and 2-h plasma glucose (PG) level < 140 mg/dL, IFG - FPG level between 100 - 125 mg/dL and 2-h PG level < 140 mg/dL, impaired glucose tolerance (IGT) - FPG level < 100 mg/dL and 2-h PG level between 140 - 199 mg/dL, IFG and IGT - FPG level between 100 - 125 mg/dL and 2-h PG level between 140 - 199 mg/dL, and DM - FPG level ≥ 126 mg/dL or 2-h PG level ≥ 200 mg/dL. In addition to OGTT results and STAI scale scores, patients' demographic characteristics including sex, education and marital status, history of diabetes in the first-degree relatives were noted. Height, weight and waist circumference of the patients were measured and body mass index (BMI) was calculated. There was no routine pre-test psychiatric evaluation to diagnose any unrevealed psychiatric disorder.

All statistical analyses were performed using the SPSS for Windows, version 21.0 (IBM Inc., Chicago, IL, USA). The Kolmogorov-Smirnov and the Shapiro-Wilk tests were used to assess the assumption of normality. Continuous variables were presented depending on normal distribution; normally distributed data as mean±standard deviation (SD)

and non-parametric data as median (25th-75th percentile). Categorical variables were summarized as counts (percentages). Comparisons of continuous variables between groups were carried out using the independent samples t test or the Mann-Whitney U test and the Kruskal-Wallis test, whichever was appropriate. The Dunn's test was used for pairwise multiple comparisons. Associations between continuous variables were determined by the Spearman correlation analysis and the association between two categorical variables was examined by the Chi-square test. Multinomial logistic regression analysis was used to determine the factors affecting the outcome variable. All statistical analyses were carried out with a 5% significance and a two-sided p-value < 0.05 was considered statistically significant. Ethical approval was obtained from the ethics committee of Kocaeli University, Faculty of Medicine (Date:27.02.2020, No: KÜ GOKAEK 2020/3.09-2020/50) and all the patients gave their written informed consent to the study.

RESULTS

In this study, we included 516 patients to whom OGTT was performed and who completed STAI TX-1 form. Our group consisted of 158 (30.6%) men and 358 (69.4%) women with a mean ± SD age of 42.62 ± 14.20. Demographic and clinical characteristics including OGTT outcomes are described in Table 1. In unadjusted analyses, there was no significant correlation between SAS and age ($r = 0.075$, $p = 0.089$), education ($r = -0.080$, $p = 0.071$), BMI ($r = -0.013$, $p = 0.765$) and waist circumference ($r = 0.004$, $p = 0.923$). As described in Table 2, median (25th-75th) SAS was 39 (32-45) in women and 38 (32-46) in men which showed no significant difference between two groups by Mann-Whitney U test ($p = 0.926$). Kruskal-Wallis test showed there

Table 1: Demographic characteristics, OGTT outcomes and STAI scores of the patients (n = 516).

Characteristics	Values
Age (years ± SD)	42.62 ± 14.20
Height (cm± SD)	166.44 ± 8.94
Weight (kg± SD)	84.44 ± 20.39
Waist circumference (cm± SD)	104.85 ± 15.93
Body Mass Index (kg/m^2± SD)	30.46 ± 6.96
STAI Score± SD	38.84 ± 9.41
Demographics	**Cases [n (%)]**
Sex	
Male	158 (30.6)
Female	358 (69.4)
Marital Status	
Married	373 (72.3)
Single	110 (21.3)
Widow	33 (6.4)
Education	
Nonliterate	17 (3.3)
Literate	12 (2.3)
Elementary school	112 (21.7)
Middle school	50 (9.7)
High school	135 (26.2)
College	190 (36.8)
Diabetes in first-degree relatives	
Yes	271 (52.5)
No	245 (47.5)
OGTT outcomes	
Normal	288 (56.1)
IFG	30 (5.9)
IGT	37 (7.2)
IFG and IGT	9 (1.8)
DM	149 (29.0)

DM: Diabetes mellitus, **IFG:** Impaired fasting glucose, **IPG:** Impaired plasma glucose, **OGTT:** Oral glucose tolerance test, **SD:** Standard deviation, **STAI:** State-Trait Anxiety Inventory.

Table 2: The relationship between demographic characteristics of the patients and the STAI Score.

	STAI Score*	p
Sex		
Male	38.00 (32.00 - 46.00)	0.926^α
Female	39.00 (32.00 - 45.00)	
Marital Status		
Married	38.00 (32.00 - 46.00)	
Single	39.00 (31.75 - 46.00)	0.993^β
Widow	40.00 (34.00 - 43.50)	
Education		
Nonliterate	41.00 (32.00 - 49.00)	
Literate	43.00 (32.25 - 50.00)	
Elementary school	39.00 (33.00 - 46.00)	0.344^β
Middle school	37.50 (32.00 - 45.00)	
High school	41.00 (32.00 - 47.00)	
College	38.00 (31.00 - 44.00)	
	STAI Score**	
Diabetes in first-degree relatives		
Yes	38.51 ± 9.22	0.408^Ω
No	39.20 ± 9.62	

STAI: State-Trait Anxiety Inventory
*Data are expressed as median (25th - 75th percentile)
**Data are expressed as mean ± standard deviation
^{α}Evaluated by the Mann-Whitney U Test
^{β}Evaluated by the Kruskal-Wallis Test
^{Ω}Evaluated by the Independent Samples t Test

was no association between marital status of the patients and SAS (*p* = 0.993) (Table 2). However, pairwise comparisons showed BMI and waist circumference in the group of married were significantly higher than those in the group of single (*p* = 0.017 and *p* < 0.001, respectively). No significant relationship between SAS and education status/family history of DM was shown (*p* = 0.344 and *p* = 0.408, respectively) (Table 2).

In multinomial logistic regression analysis as given in Table 3, there was no significant association between SAS and OGTT outcomes (IFG vs Normal OR 0.996, 95% CI 0.956-1.037, *p* = 0.883; IGT vs Normal OR 1.014, 95% CI 0.997-1.052, *p* = 0.475; IFG and IGT vs Normal OR 0.999, 95% CI 0.931-1.071, *p* = 0.972; DM vs Normal OR 1.005, 95% CI 0.982-1.027, *p* = 0.689) after adjustment for all other covariates such as age, BMI, waist circumference and family history of DM. A significantly higher age and waist circumference in the DM group was demonstrated com-

pared to the normal group (OR 1.043, 95% CI 1.027-1.059, *p* < 0.001 and OR 1.044, 95% CI 1.019-1.069, *p* = 0.001, respectively).

While there was no correlation between OGTT outcomes and SAS (*p* = 0.856) in unadjusted analysis, there was a significant relationship between OGTT outcomes and age, weight, BMI and waist circumference (*p* < 0.001) (Table 4). Chi-square test demonstrated that the percentage of DM diagnosis following OGTT in the group of married was significantly higher than that in the group of single (123/370 [33.2%] and 18/110 [12.1%], respectively, *p* = 0.003), as given in Table 4. There was no association between OGTT outcomes and family history of DM (*p* = 0.220) (Table 4). Additionally, the analyses showed that the odds of being diagnosed with DM in college graduates (38/190 [20.0%]) was significantly lower compared to those in other education levels (*p* = 0.007). According to the results calculated by Dunn's test, all those significant correlations were in

Table 3: Multinomial logistic regression analysis for the factors related with OGTT outcomes.

OGTT outcomes*		OR	95% CI for OR	p
IFG	Intercept			**0.012**
	Age	1.011	0.983-1.040	0.441
	BMI	1.036	0.951-1.129	0.414
	Waist circumference	1.003	0.963-1.044	0.898
	STAI score	0.996	0.956-1.037	0.833
	FH of DM (yes vs no)	1.646	0.750-3.614	0.214
IGT	Intercept			**< 0.001**
	Age	1.040	1.013-1.066	**0.003**
	BMI	0.985	0.903-1.075	0.739
	Waist circumference	1.024	0.984-1.065	0.241
	STAI score	1.014	0.977-1.052	0.475
	FH of DM (yes vs no)	1.424	0.700-2.898	0.329
IFG and IGT	Intercept			0.058
	Age	1.005	0.958-1.055	0.832
	BMI	1.041	0.896-1.208	0.602
	Waist circumference	1.009	0.939-1.083	0.811
	STAI score	0.999	0.931-1.071	0.972
	FH of DM (yes vs no)	0.471	0.114-1.954	0.300
DM	Intercept			**< 0.001**
	Age	1.043	1.027-1.059	**< 0.001**
	BMI	0.974	0.923-1.027	0.329
	Waist circumference	1.044	1.019-1.069	**0.001**
	STAI score	1.005	0.982-1.027	0.689
	FH of DM (yes vs no)	1.205	0.787-1.844	0.391

*The reference category is: NORMAL

BMI: Body mass index, **CI:** Confidence interval, **DM:** Diabetes mellitus, **FH:** Family history, **IFG:** Impaired fasting glucose, **IGT:** Impaired glucose tolerance, **OGTT:** Oral glucose tolerance test, **OR:** Odds ratio, **STAI:** State-Trait Anxiety Inventory

between normal and DM groups. Older age, weight, BMI and waist circumference were observed in the newly diagnosed DM group compared to those in the totally healthy group in terms of OGTT outcomes.

DISCUSSION

In the present study, there was no association between pretest state anxiety and OGTT outcomes. To the best of our knowledge, this is the first study examining that relationship, albeit a cross-sectional study including 82 women with PCOS examined the association of state anxiety with the clinical features of the patients (11). The authors reported that the only significant relationship was shown between BMI and state anxiety; however, anxiety had no effect on insulin resistance. Some other articles reported a positive correlation between chronic anxiety and MetS/insulin resistance (3). In a meta-analysis, a significant positive correlation between anxiety and MetS risk was demonstrated in which one cohort study examining 432 subjects (3). The direction of this association is still unclear, which makes it inconvenient to conclude which one of them is a cause or an outcome.

The first possible mechanism causing that correlation is the activation of the HPA axis by chronic clinical anxiety which induces the release of counter-regulatory hormones such as adrenalin, noradrenalin, glucagon, growth hormone and cortisol (12). When this protective mechanism becomes chronically active, predisposing factors for DM such as insulin resistance, exacerbation of abdominal fat deposition and dyslipidemia are triggered (13). In addition to that, in turn these counter-regulatory hormones and the outcomes induced by them such as larger waist circumference cause higher levels of inflammatory markers such as interleukin-6 and C-reactive protein which are responsible for a variety of metabolic dysfunctions (14,15). It should be underlined that all these findings are due to the effects of chronic clinical anxiety; however, in our study, it was shown that the short-term state anxiety prior to OGTT had no impact on insulin sensitivity and blood glucose level.

From another point of view, it was also suggested that diabetes led to anxiety. Clinical anxiety symptoms may develop at the time of diagnosis with DM or during the period after the diagnosis. The patients may possibly feel distressed about the management of the disease, undesirable lifestyle changes and the long-term diabetes-related micro and mac-

Table 4: The association of OGTT outcomes with the demographic/clinical characteristics of the patients and the STAI score.

	OGTT Outcomes[γ]					
	Normal	**IFG**	**IGT**	**IFG&IGT**	**DM**	**p***
STAI Score	39.00 (31.00-45.75)	36.00 (27.75-46.75)	41.00 (33.00-45.00)	38.00 (36.00-43.00)	39.00 (32.00-46.50)	0.856
Age	38.00 (27.25-49.00)	40.50 (33.50-50.00)	45.00 (39.00-55.50)	38.00 (28.50-52.00)	48.00 (38.50-58.50)	**< 0.001**
Weight	77.00 (67.00-94.00)	85.50 (75.50-94.25)	88.00 (75.50-96.00)	81.00 (71.50-94.50)	88.00 (76.00-97.50)	**< 0.001**
BMI	28.12 (24.56-33.78)	29.92 (27.25-33.30)	30.08 (25.71-35.30)	32.39 (27.43-35.15)	31.24 (28.09-34.79)	**< 0.001**
Waist Circumference	101.00 (92.00-111.75)	109.00 (97.75-113.25)	104.00 (98.50-113.00)	108.00 (95.50-116.00)	110.00 (100.00-118.50)	**< 0.001**
	OGTT Outcomes[¥]					
	Normal	**IFG**	**IGT**	**IFG&IGT**	**DM**	**p****
Marital Status						
Married	191 (51.6)	22 (5.9)	30 (8.1)	4 (1.1)	123 (33.2)	
Single	80 (72.7)	6 (5.5)	3 (2.7)	3 (2.7)	18 (16.4)	**0.003**
Widow	17 (51.5)	2 (6.1)	4 (12.1)	2 (6.1)	8 (24.2)	
Diabetes in first-degree relatives						
Yes	141 (52.4)	19 (7.1)	22 (8.2)	3 (1.1)	84 (32.2)	
No	147 (60.2)	11 (4.5)	15 (6.1)	6 (2.5)	65 (26.6)	0.220

BMI: Body mass index, **DM:** Diabetes mellitus, **IFG:** Impaired fasting glucose, **IGT:** Impaired glucose tolerance, **OGTT:** Oral glucose tolerance test, **STAI:** State-Trait Anxiety Inventory

[γ]Data are expressed as median (25th - 75th percentile), [¥]Data are expressed as n (%)

*Evaluated by the Kruskal-Wallis Test, **Evaluated by the Chi-Square Test

ro-vascular complications which causes poorer adherence to diabetes care regimens (16). Diabetes related anxiety was reported in approximately 60% of patients with DM and it was shown that anxiety provokes poorer glycemic control and higher incidence of diabetes-related complications (17).

Other considerable results in this study were the significant association between new-onset DM diagnosis according to OGTT outcomes and marital status/waist circumference. In adjusted analyses, only age and waist circumference were significantly higher in the diabetes group than those in the normal group, which may indicate waist circumference is one the most substantial predictive parameters for type 2 DM, even better predictor than BMI. In accordance with our finding, in a population-based cross-sectional study which was conducted in Iran, the authors reported waist circumference and waist-to-height ratio were slightly better discrimination parameters than BMI for diabetes (18).

In a brief review by Jawad and Kalra (19), the interaction between marriage and diabetes was discussed. Patients with diabetes may encounter some concerns and challenges which are derived from the fear of self-disclosure, subfertility, financial implication and lack of "marriageability"/ability to maintain a high level of marital quality. As a result, clinical anxiety could be elevated by all these factors disrupting the adherence to diabetes care regimens. Likewise, Liu et al. (20) emphasize the importance of marital quality for both the development and management of DM with a comprehensive analysis in a national longitudinal study. In agreement with those studies, the present study showed that the percentage of DM diagnosis following OGTT in the group of married was significantly higher than that in the group of single; however, there was no significant association between SAS and marital status. From these two findings, it can be concluded that aforementioned predisposing factors due to marriage might increase the odds for development of diabetes, despite even the absence of clinical anxiety. Moreover, alteration in eating habits and decline in frequency of daily exercise after getting married could be other factors increasing the development ratio of diabetes.

Our study demonstrated that test-dependent state anxiety had no impact on OGTT outcomes, unlike the effect of chronic clinical anxiety as described in the literature. Our primary aim was to enlighten that relationship between those two entities and in case of a presence of a significant association, conducting STAI-TX1 scale to subjects could be a routine procedure prior to OGTT and it could be postponed for the individuals with increased state anxiety score. According to our results, it can be concluded that evaluating the state anxiety of patients right before OGTT may not be required; however, it is worthwhile to remember the chronic anxiety could affect the outcomes of OGTT and a randomized prospective study is necessary to help determine if evaluating trait anxiety is required prior to OGTT.

Author Contributions

Concept: **Emre Gezer, Yeliz Demirhan,** Design: **Emre Gezer, Yeliz Demirhan,** Supervision: **Berrin Çetinarslan, Zeynep Cantürk, Alev Selek,** Resources: **Emre Gezer, Yeliz Demirhan, Ayfer Peker Karatoprak,** Materials: **Yeşim Yeliz Demirhan, Ayfer Peker Karatoprak,** Data Collection and/or Processing: **Yeliz Demirhan, Ayfer Peker Karatoprak,** Analysis and/or Interpretation: **Emre Gezer, Berrin Çetinarslan, Alev Selek, Zeynep Cantürk,** Literature Search: **Emre Gezer, Mehmet Sözen, Yeliz Demirhan,** Writing Manuscript: **Emre Gezer, Mehmet Sözen,** Critical Review: **Alev Selek, Berrin Çetinarslan, Zeynep Cantürk.**

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethical Approval

Approval was obtained from the ethics committee of Kocaeli University, Faculty of Medicine (Date:27.02.2020, No: KÜ GOKAEK 2020/3.09-2020/50)

Review Process

Extremely peer-reviewed and accepted.

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