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ORIGINAL ARTICLE

The relationship between oxytocin-copeptin levels and cognition-anxiety in patients with type I diabetes mellitus

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Abstract

Background Type I diabetes mellitus can lead to the development of cognitive dysfunction and anxiety due to chronic hyperglycemia, recurrent hypoglycemia, and micro - and macrovascular complications. It is known that oxytocin and copeptin have effects on neuropsychiatric activities such as learning, memory, and social adaptation and have anxiolytic properties. In this study, we aimed to search the relationship between oxytocin and copeptin levels and cognition and anxiety in patients with type I diabetes mellitus.

Methods The study included 39 type I diabetes mellitus patients aged 18–50 years and 39 age- and sex-matched healthy controls. The Montreal cognitive assessment inventory for cognitive assessment and the State and Trait anxiety scales for anxiety assessment were administered to all participants by the same psychologist. Plasma oxytocin and copeptin levels were measured with ELISA kits and compared with the mentioned tests results.

Results There were significant differences in oxytocin and copeptin levels between the two groups ($p = 0.001$). There was no difference in Montreal cognitive assessment and state anxiety scales between the groups, but trait anxiety scales levels were higher in patients ($p < 0.001$). However, there was no correlation between the oxytocin and copeptin levels and the results of both tests.

Conclusions In conclusion, although there was no difference between the groups in terms of cognitive functions and state anxiety, trait anxiety scores were found to be significantly higher in type I diabetes mellitus patients. However, no correlation was found between oxytocin and copeptin levels and these cognition and anxiety scores in either group.

Keywords Type I diabetes mellitus · Oxytocin · Copeptin · Cognition · Anxiety

Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease that causes destruction of insulin-producing β cells of pancreas and is known to be associated with cognitive dysfunction. In a study, the incidence of cognitive impairment was 28% in adult patients with childhood onset T1DM compared to 5% in those without diabetes [1]. Different types of

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cognitive dysfunction may develop in adult patients with T1DM. Some have worse memory performance than non-diabetic controls, and many also had significantly reduced psychomotor efficiency, sustained attention, and information processing speed. In addition, executive functions in anticipation, cognitive flexibility and concept formation may be impaired [2]. Age of onset and duration of disease, hyperglycemia, hypoglycemia, diabetic ketoacidosis, angiopathy, neuropathy, high body mass index (BMI), and hypertension are the most important factors on cognitive functions and may cause structural changes in the brain over time [3].

Living with T1DM interferes with normal activities and can lead to psychological distress. Anxiety symptoms are common in T1DM, although one study has shown it to occur in approximately 13–21% of this population [4]. Previous studies have shown that trait anxiety is associated with lower quality of life, self-management, and poor glycemic control in youth with T1DM [5]. In patients with T1DM, issues such as the physical and psychosocial changes that occur in adolescence, managing oneself and peers, and negotiating with their parents about the daily treatment regimen, gaining more autonomy and independence, the impact of hypoglycemia and hyperglycemia on daily life, and future complications of diabetes are various potential sources of anxiety [6]. However, no clear causal conclusions can be drawn from these findings because different causes are likely to exist in a wide variety of life situations.

Oxytocin (OXT) and arginine-vasopressin (AVP), synthesized in the hypothalamus, are structurally homologous neuropeptides and differ by only two amino acids. After being synthesized, they are transported to the neurohypophysis via the hypothalamic-pituitary tract and then secreted into the systemic circulation. The main function of OXT is contraction of uterine smooth muscles during childbirth and myoepithelial cells of the mammary gland during lactation [7]. Known as the antidiuretic hormone, AVP is released into the bloodstream in response to changes in serum osmolality and neurohormonal and hemodynamic stimuli, increasing the reabsorption of water in the renal tubules and thus retaining fluid in the organism [8]. Although their actions are often contradictory, there is substantial evidence of functional overlap [9]. OXT and AVP are also released in the central nervous system (CNS) and act as neuromodulators and regulate various forms of social behavior that vary with age and gender. Both of them have pivotal regulatory functions in socio-emotional and cognitive processes such as social exploration and recognition, attachment and anxiety in humans and animals [10]. OXT regulates parental, emotional, loyalty, and sexual behaviors, while AVP regulates social behavior and emotions, particularly anxiety, fear and aggression [11, 12].

Recently, observational studies have been conducted examining OXT and its association with diabetes complications. OXT has been suggested to reduce anxiety-related behaviors or neuroendocrine stress responses in humans [13]. There are few studies investigating OXT in people with T1DM. In a study examining the role of OXT during hypoglycemia, circulating OXT concentrations after insulin-induced hypoglycemia were found to be higher in individuals with T1DM than in controls [14]. However, Kujath et al. found OXT levels to be lower in premenopausal women with T1DM than in controls [15]. Whereas Seelig et al. showed an increase in copeptin level during hypoglycemia in patients with T1DM due to hypoglycemia awareness [16]. Additionally several studies have demonstrated associations between increased copeptin and worsening of diabetes complications in adults with T1DM [17].

In humans, direct assessment of neuropeptide levels in the brain is not possible, so investigations often rely on peripheral measurement of endogenous neuropeptide levels. We hypothesized that women with T1DM would have lower OXT but higher levels of copeptin, and that these reviews would be associated with cognitive dysfunction and anxiety levels. Therefore, in this study, we aimed to investigate the relationship between OXT & copeptin levels and cognition & anxiety in patients with T1DM.

Materials and methods

Patients and study design

This cross-sectional study included 39 patients with T1DM between the ages of 18–50, followed by the endocrinology outpatient clinic of Ankara training and research hospital, and 39 healthy controls matched for age and gender. T1DM was defined according to the World Health Organization criteria and all patients with T1DM were under intensive insulin therapy four times a day.

Those with hypothyroidism, iron or vitamin B12 deficiency anemia, hypertension, chronic comorbidity or drug use, recent or ongoing infection, CNS disease and known psychiatric disease, and those during pregnancy and lactation were excluded from the study.

Demographic details such as age, gender, marital status, comorbidities, and anthropometric measurements were recorded. Participants were also asked about duration of illness, age at diagnosis, current medications, and family history.

Serum samples of all participants were obtained in the morning after an overnight fasting and centrifuged at 1000×*g* for 15 min, and the serums were stored at -80°C until analysis. In addition to routine biochemical tests, Human Oxytocin Elisa kits and Human Copeptin Elisa kits (Shanghai Sunred Biological Technology Co. Ltd) were analyzed manually with double-antibody sandwich enzyme-linked immunosorbent measurement method. Washing was

done with ELx 50 Auto strip washer (BIO-TEK Instruments,INC/ USA) and reading was done with ELx 800 Microplate Reader (BIO-TEK Instruments,INC/ USA). Measuring range of OXT kit: 2–600pg/ml, sensitivity: 1.775 pg/ml and measuring range of copeptin kit: 0.07–20 ng/ml and sensitivity: 0.067ng/ml.

The Montreal cognitive assessment (MOCA) inventory for cognitive assessment and the state and trait anxiety scales for anxiety assessment (STAI-I, STAI-II, respectively) were administered to all participants by the same psychologist.

MOCA is a neuropsychological tool that takes approximately 15 min to assess conditions such as attention, executive functions, memory, language, visual-structural skills, and orientation. It was created as a screening test to detect mild cognitive perception and has a cut-off score of 24 points out of 30.

The State-Trait Anxiety Inventory (STAI) was used to measure state and trait anxiety symptoms in adolescents. The STAI has 40 items, half of which represent current emotions (state scale) and the other half relate to emotions in general (trait scale). The items are answered on a 4-point Likert scale ranging from 1 (not at all) to 4 (very much), the total score ranges from 20 to 80, the cut-off point is 40, and higher scores indicate higher levels of anxiety symptoms.

Statistical analysis

Statistical analysis was performed with the Statistical Package for Social Sciences (SPSS) program version 21.0 for Windows (SPSS Inc., Chicago, IL). Normality tests were made with Kolmogorov-Smirnov test. Normally distributed parameters were reported as mean and standard deviation, and non-normally distributed parameters were reported as median and interquartile range [IQR]. A comparison between groups of continuous variables was performed using Mann–Whitney *U* test. The Chi-square test was used to investigate the difference between the groups regarding the categorical variables. Correlation between variables was analyzed using Spearman's rank correlation coefficients. Differences were considered to be statistically significant if p values were < 0.05.

Results

There was no difference between the two groups in terms of age, gender, education level, and BMI. There was a significant difference in OXT and copeptin levels between the groups ($p = 0.001$). The median of OXT: 100.6 pg/ml (12–1000) and copeptin: 1.63 ng/ml (0.36-16.85) in the type I DM group and the median of OXT 313.4 pg/ml (36.87–926.62) and copeptin: 2.90 ng/ml (0.36–14.77) in the control group (Table 1).

There was no difference in MOCA and STAI-I levels between the groups, but STAI-II levels were higher in type I DM patients ($p < 0.001$) (Table 1). However, there was no correlation between OXT and copeptin levels and MOCA and STAI-I and II tests between the groups (Table 2). Also no correlation was found between both OXT and copeptin with MOCA and STAI test results in only T1DM patients.

There was no correlation between both OXT and copeptin and fasting blood glucose (FBG), HbA1c level and BMI in both groups too. But there was a positive correlation between disease duration and OXT, but not with copeptin ($r = 0.448$, $p = 0.015$; $r = 0.121$, $p = 0.532$, respectively). However, OXT and copeptin were positively correlated with each other ($r = 0.764$, $p = < 0.001$) (Table 2).

There was no correlation between MOCA, STAI-I, and STAI-II scores and FBG, postprandial blood glucose (PPG) and HbA1c in the type I DM group, and no correlation was found between FBG in the control group (Table 3).

Discussion

In this study, in accordance with previous studies, OXT levels were lower in the type 1 DM group than in the control group; however, contrary to the literature, copeptin levels were also lower, and there was a statistically significant difference between the two groups in terms of both parameters. MOCA and STAI-I levels were similar between the two groups, but STAI-II levels were higher in patients with T1DM. However, there was no correlation between OXT and copeptin levels and MOCA and STAI I and II tests both between the groups and only in the T1DM group.

The impact of T1DM on the developing brain remains controversial. In a study inspecting neurocognitive outcomes in young adults with early-onset T1DM, this group of patients had no difference in memory, general intellectual ability, and emotional difficulties compared to healthy controls [18]. Similarly, in another study, no significant difference was found between siblings with T1DM and their unaffected siblings in terms of cognitive and academic achievement, speech articulation measures, and behavioral variables [19]. However, in the study of Nunley et al., clinically relevant cognitive impairment is quite common among middle-aged adults with childhood-onset T1DM [1]. Similarly, in a study examining the effect of statins on cognitive functions, it was shown that cognitive functions were impaired in T1DM patients when compared to control subjects without diabetes [20]. In our study, the cognitive functions of patients with diabetes were evaluated with the MOCA test, and the results were not different from the healthy ones.

Anxiety symptoms are about 2–3 times more common in young people with T1DM than in the general youth population [21]. Anxiety symptoms are associated with both

Table 1 Baseline demographic, biochemical characteristics of the participants, and scale results

	T1DM patients (*n*=39)	Controls (*n*=39)	*p* value*
Age (years)[a]	30.97 ± 7,99	33.82 ± 7,09	0.10
BMI (kg/m2)[a]	25.27 ± 4,59	25.99 ± 3,96	0.59
FBG (mg/dl)[a]	251.67± 109,07	88.36 ± 7,90	**<0.001**
PPG (mg/dl)[a]	190.9 ± 121.97	-	
HbA1c (%)[a]	9.92 ± 2.44	-	
GFR (mL/dk/1.73m^2)[a]	113.93 ± 18,19	107.57 ± 10,83	0.16
ALT (U/L)[b]	18,00 (12,00- 22,00)	21,50 (15,75- 33,75)	0.11
AST (U/L)[b]	18,00 (13,00-22,00)	19,50 (17,00- 26,50)	0.10
Hgb (g/dl)[a]	15.04 ± 2,08	14.58 ± 1,32	0.36
TSH (mIU/L)[b]	1,86 (1,14- 2,98)	1,62 (1,08- 2,48)	0.59
fT4 (ng/dL)[a]	1.21 ± 0,23	1.00 ± 0,20	**0.002**
Oxytocin (pg/ml) [b]	100,67 (61,67- 151,91)	308,61 (77,66- 524,35)	**0.001**
Copeptin (ng/ml)[b]	1,64 (1,15- 2,13)	2,69 (1,61- 8,25)	**0.002**
MOCA score[b]	24,00 (21,00- 26,00)	24,00 (22,00- 27,00)	0.38
STAI-I score[b]	46,00 (42,00- 48,00)	46,00 (41,00- 48,00)	0.39
STAI-II score[b]	49,00 (47,00- 53,00)	46,00 (43,00- 51,00)	**0.02**

BMI, body mass index; *FBG*, fasting blood glucose; *GFR*, glomerular filtration rate; *ALT*, alanine aminotransferase; *AST*, aspartate aminotransferase; *Hgb*, hemoglobin; *TSH*, thyrotropin; *fT4*, free thyroxine; *MOCA*, Montreal cognitive assessment; *PPG*, postprandial glucose; *STAI-I*, State anxiety scale; *STAI-II*, Trate anxiety scale

[a] Mean ± standard deviation

[b] Median (interquartile range)

p val < 0.05 denoted as statistically significant (in bold)

*Student's *T*-test; Mann-Whitney *U* test

physiological and psychosocial adverse outcomes, including poorer self-management, poorer glycemic control and lower diabetes-specific quality of life [22]. Two types of anxiety have been defined in the literature: state anxiety, which reflects a temporary emotional fear or tension, and trait anxiety, which is defined as the tendency to feel anxious [23]. While there is still debate about whether state and trait anxiety are directly correlated with each other or should be treated separately, it is clear that both are associated with poor diabetes outcomes. In a study by Rechenberg et al.in patients with T1DM, higher state anxiety was associated with poorer glycemic control and poorer self-management. Teenagers with high-state anxiety tend to be older and have many general and diabetes-specific stressors, such as daily coping situations, in- and after-school activities, and integrating their diabetes treatment regimen into them. However, higher trait anxiety was associated with poorer self-management and diabetes-specific quality of life, but not with poorer glycemic control [24]. Notably, in a study by Herzer et al., adolescent-state anxiety was significantly associated with HbA1c values, blood glucose monitoring (BGM) frequency, and depressive symptoms. Adolescent-trait anxiety was associated with BGM frequency and depressive symptoms, but not with HbA1c values [25]. In our study, STAI-I scores were similar between the two groups, but STAI-II scores were higher in the type 1 DM group. However, no correlation was found between STAI-II score and OT and copeptin levels.

Table 2 Correlation analysis table for all participants

	Oxytocin		Copeptin	
	r	*p*	*r*	*p*
Age (years)	-0,044	0,701	-0,120	0,297
BMI (kg/m2)	0,015	0,923	0,079	0,619
FBG (mg/dl)	-0,268	0,063	-0,249	0,084
HbA1c (%)	-0,189	0,336	-0,160	0,417
Duration of disease (years)	**,448***	**0,015**	0,121	0,532
MOCA score	0,106	0,357	0,214	0,059
STAI-I score	0,046	0,691	0,058	0,612
STAI-II score	-0,152	0,185	-,257*	0,023
Oxytocin(pg/ml)	1,000		**,764****	**< 0,001**
Copeptin(ng/ml)	**,764****	**< 0,001**	1,000	

BMI, body mass index; *FBG*, fasting blood glucose; *MOCA*, Montreal cognitive assessment; *STAI-I*, State anxiety scale; *STAI-II*, Trate anxiety scale

**Correlation is significant at the 0.01 level (2-tailed)

*Correlation is significant at the 0.05 level (2-tailed)

r Correlation coefficient; for Spearman's rank correlation

Table 3 Correlation analysis between glycemic status and cognition-anxiety scores

	T1DM patients						Controls	
	FBG (mg/dl)		PPG (mg/dl)		HbA1c (%)		FBG (mg/dl)	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*
MOCA score	-0,241	0,225	-0,626	0,053	-0,261	0,197	-0,162	0,472
STAI-I score	0,336	0,087	0,443	0,200	0,253	0,212	0,238	0,286
STAI-II score	-0,093	0,643	0,438	0,206	0,076	0,712	-0,075	0,741

FBG, fasting blood glucose; *MOCA*, Montreal cognitive assessment; *PPG*, postprandial glucose; *STAI-I*, State anxiety scale; *STAI-II*, Trate anxiety scale

*Correlation is significant at the 0.05 level (2-tailed)

*r*Correlation coefficient; for Spearman's rank correlation

While OXT is known to reduce anxiety, low levels of STAI-II have also been shown to increase the effects of OT in humans [26]. Although we could not find a relationship between them, the low levels of OXT and high STAI-II levels in the T1DM are consistent with the literature. On the other hand, Katan et al. defined copeptin as an individual stress marker and showed that to correlate with cortisol levels [27]. However, in our study, copeptin levels were lower in the T1DM group and were not correlated with anxiety scores.

The study by Schiel et al. found no difference in copeptin concentrations in adolescents with T1DM compared to those without diabetes. However, the sample size was small in their studies, the gender and BMI of the participants were not similar between the groups, and their age, which is one of the important factors affecting the copeptin level, was also young [28]. In adults, however, several studies have shown that copeptin concentrations are elevated in people with T1DM [17].

In the study of Jensen et al. in T1DM patients, they could not find any relationship between copeptin and FBG, HbA1c and BMI, but copeptin level was found to be higher in the T1DM group than their peers [29]. In our study, we could not find a correlation between copeptin and the same parameters, but copeptin levels were found to be lower in the T1DM group. Similarly, no correlation was found between OXT and these parameters. Studies have shown that copeptin levels in patients with T1DM are associated with increased cardiovascular risk, which is an inevitable chronic complication and poor glycemic control. However, in our study, there was a positive correlation between disease duration and OXT, but not with copeptin. Half of our diabetes patient group was within the first decade of diagnosis and HbA1c was not correlated with copeptin despite poor glycemic control. The small sample size may have contributed to this situation. Also copeptin levels may not have risen as expected, since almost all of our diabetic patients in our study do not have comorbid diseases and known diabetes complications.

Despite the data supported in the literature, in terms of glycemic status, in our study, no correlation was observed between MOCA, STAI-I and STAI-II scores and FPG, PPG, HbA1c levels in the type I DM group, and no correlation was found between these scores and FFG in the control group. This is probably due to the small sample size of our study.

This study has important limitations such as cross-sectional design and small sample size. As it is a human study, OXT and copeptin levels were analyzed from peripheral blood samples, not from the CNS. Lifestyle and frequency of hypoglycemia, which can affect OXT and copeptin levels, were not included in the study. Glomerular filtration rate (GFR) is an important factor affecting the analysis, but it is an advantage that there is no difference in GFR between the groups. In addition, if this study had been designed as a prospective study rather than a cross-sectional one, and psychological scores and oxytocin and copeptin levels were re-examined after glycemic control was achieved, it would have provided us with more explanatory results in this regard. However, it is a valuable study in terms of having data on the parameters available for adults with and without T1DM, and providing perspective on cognition and anxiety, which are important but overlooked problems of diabetes.

In conclusion, no difference was found between adult T1DM patients and their peers without T1DM in terms of cognitive functions and state anxiety states. Trait anxiety scores were found to be significantly higher in T1DM patients. However, no correlation was found between OXT and copeptin levels and these cognition and anxiety scores in both groups. Possible interventions to reduce anxiety are known, such as cognitive behavioral therapy, coping skills training, or mindfulness-based stress reduction. However, as the molecular connections become clearer in the future, the use of OXT in treatment may come to the fore, especially because of its anxiety-reducing effect. Longitudinal studies are needed to better define the role of OXT and copeptin in cognitive functions and the pathogenesis of anxiety in adults with and without T1DM.

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Author contribution All authors contributed significantly to the design of the study, collected study data, contributed to the analysis, interpretation, and writing, critically reviewed the manuscript, read and approved the final version of the manuscript to be published.

Declarations

Ethics approval The study was approved by the local ethics committee of Ankara Training and Research Hospital (No:4738/2014).

Consent to participate The study was in compliance with the Declaration of Helsinki and written informed consent was obtained from all participants prior to entry into the study.

Competing interest The authors declare no competing interests.

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