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Oxidative status and prolidase activities in generalized anxiety disorder

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ABSTRACT

Objective: Prolidase (Pro), an intracellular enzyme necessary for collagen turnover, matrix remodelling and cell growth has been shown to be related to Oxidative Stress (OS). To our knowledge, serum Pro activity in generalized anxiety disorder (GAD) has not been documented yet. In this study, we aimed to evaluate OS and its relation with Pro activity in patients diagnosed with GAD.
Method: Thirty untreated GAD patients and 30 healthy controls were included in the study. Blood samples were collected from all subjects to quantify total oxidant status (TOS), total antioxidant status (TAS) and Pro activity. Oxidative stress index (OSI), the ratio of TOS to TAS, is calculated to evaluate the balance between antioxidants and oxidants. Hamilton Anxiety Rating Scale (HARS) was used to determine the anxiety levels of all subjects.
Results: GAD group demonstrated statistically significantly higher TOS, OSI and Pro levels, when compared with the control group ($t = 2.947$, $p = 0.005$; $t = 2.874$, $p = 0.006$; and $t = 9.396$, $p < 0.001$ respectively). HARS scores were found to be positively correlated with TOS, OSI and Pro levels ($p = 0.008$, $r = 0.338$; $p = 0.008$, $r = 0.339$; and $p < 0.001$, $r = 0.751$ respectively).
Conclusion: The degree of severity of OS is correlated with the levels of Pro. Thus, Pro might be the target enzyme, promising to be a marker for the follow-up of GAD patients. To the best of our knowledge, this study is the first to report a significant relation between Pro activity and GAD.
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1. Introduction

Within the last decades, the knowledge of the link between oxidative stress (OS) and psychiatric disorders has been surging (Ng et al., 2008). Noteworthy susceptibility to OS of the brain arouses curiosity to reveal the role of OS in neuropsychiatric disorders (Berk et al., 2008). Although researches investigating the relations OS has with schizophrenia, bipolar disorder and depression are more frequent; studies concerning obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, social phobia, autism, substance abuse and attention deficit hyperactivity disorder are also published (Atmaca et al., 2004; Attari et al., 2002; Berk et al., 2008; Ersoy et al., 2008; Kuloglu et al., 2002a, 2002b; Ng et al., 2008; Sogut et al., 2003).

In simple terms, an imbalance of oxidative status in favor of free metabolic by-products of aerobic life, in other words free radicals (FR) lead to OS (Davies, 1995; Halliwell and Gutteridge, 2000). Oxidative processes such as electron transport system, cytochrome P450 activation and monoamine oxidation; activation of immune system and phagocytes; lipid peroxidation; and oxidative stress caused by trauma or ischemia results in production of FR

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(Esterbauer et al., 1991; Gutteridge, 1995; Lohr, 1991; Mahadik and Mukherjee, 1996). FR produced under physiological states are believed to trigger aging process but when the redox homeostasis is out of balance towards FR, due to over-production or insufficiency of antioxidant defense mechanisms, OS becomes endamaging (Finkel and Holbrook, 2000; Sies, 1997).

Free radicals, principally reactive oxygen and nitrogen species threaten the brain, is considered vulnerable to oxidative damage (Halliwell, 2006; Ng et al., 2008; Valko et al., 2007). This vulnerability is due to (i) constitution which is rich in polyunsaturated fatty acids that provides substrates for oxidation; (ii) relatively high oxygen consumption and hence FR production; (iii) presence of catalytic metals such as iron and copper; (iv) poor antioxidant content; and (v) secondary damage caused by oxidative cell injury and necrosis via inflammatory processes (Esterbauer et al., 1991; Halliwell, 2006; Mahadik and Mukherjee, 1996). Damaging of phospholipid fatty acids and cholesterol based cell membranes alter viscosity resulting in seratonergic and catecholaminergic receptor function distortion (Britt et al., 1992; Tsutsumi et al., 1988; Van der Vliet and Bast, 1992).

Measurement of antioxidants and oxidants may not individually picture the whole shoot of OS. Therefore evaluating total antioxidant status (TAS) and total oxidant status (TOS), which have excellent precision values, reflect OS more accurately (Erel, 2004, 2005). The oxidative stress index (OSI) and the ratio of TOS to TAS, are the parameter to evaluate the balance between antioxidants and oxidants (Harma et al., 2003).

Prolidase (Pro) is an intracellular enzyme necessary to release proline and hydroxyproline from the carboxyl terminus of imidodipeptides, taking part in collagen degradation, recycling proline for protein synthesis, matrix remodeling and cell growth (Myara et al., 1982; Palka and Phang, 1997; Phang et al., 2001). Exposure of proline in brain of rats decreases antioxidant potential, suggesting that proline induces OS (Delwing et al., 2003a, 2003b, 2005).

Serum Pro activity, associated with OS, has been studied in some neuropsychiatric disorders (Arikanoglu et al., 2013; Selek et al., 2011). However, to our knowledge, serum prolidase activity in generalized anxiety disorder (GAD) has not been documented yet. In this study, we aimed to evaluate OS and its relation with Pro activity in untreated patients diagnosed with GAD.

2. Materials and methods

2.1. Subjects

The case-control study was conducted in medical faculty hospital after approval of the institutional ethics committee. The study comprised thirty patients diagnosed with GAD who were consecutively recruited among the individuals who first admitted to the psychiatry out-patient unit of the hospital. The patients had no history of psychiatric treatment and had been psychotropic medication-naive. An equal number of healthy controls were also recruited from the community. The controls were matched for age and sex with the patient group and had no clinical psychiatric disorder history. All subjects were informed about the study and written consent was obtained from each participant.

All patients and controls were between the ages of 18 and 65. The individuals who had any history of cardiovascular, gastrointestinal, renal, liver, rheumatologic, endocrinal, infectious, neurological diseases and any cancer were not included. All of the individuals were non-smokers and none of them had any substance or alcohol dependence. None of the patients and controls were on any regular medication for at least two months prior to the study. None of the subjects had BMI scores lower than 18.5 and higher than 24.9.

2.2. Clinical assessments

All of the participants were evaluated by a psychiatrist for psychiatric disorders by clinical interviews and symptom ratings according to the Structered Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders criteria. The GAD patients with any Axis-I comorbidity were excluded. The controls were all free of Axis-I disorders. Hamilton Anxiety Rating Scale (HARS), which was adapted to Turkish patients with established validity and reliability, was used to determine the anxiety levels of subjects in both patient and control groups (Hamilton, 1959; Yazici et al., 1998).

2.3. Blood analysis

Fasting blood samples were collected from antecubital vein of all subjects to heparinized tubes. The samples were immediately centrifuged to separate plasma and stored at −20 °C for analysis.

Serum TAS and TOS were determined by an automated measurement method developed by Erel. TAS was calculated by measuring the antioxidative power of the sample against the hydroxyl radical initiated reactions. Oxidants, present in the sample oxidize ferrous ion—dianisidine complex to ferric ion which is colored with xylenol orange in the acidic medium to be measured by spectrophotometer to calculate TOS. TAS is expressed as 1 mol Trolox Equivalent/L where 1 mol H_2O_2 Equivalent/L is used to state TOS (Erel, 2004, 2005).

OSI was defined as the percentage rate of TAS values to TOS values. It is formulated as: OSI (Arbitrary Unit) = TOS (μmol H_2O_2 Equivalent/L)/TAS (μmol Trolox Equivalent/L).

A spectrophotometric method measuring proline levels was used to evaluate prolidase activity (Chinard, 1952; Myara et al., 1982).

2.4. Statistical analysis

IBM SPSS Statistics version 20.0 was used to evaluate the obtained data. Mean differences of HARS, TAS, TOS, OSI and Pro levels between groups were examined using independent samples *t*-test. Pearson's correlation analysis was performed to compare HARS scores with TAS, TOS, OSI and Pro values. Data were denoted as mean ± standard deviation (SD). The significance level was $P < 0.05$.

3. Results

30 patients (18 females, 12 males) with a mean age of 27.97 ± 4.27 years and thirty controls (20 females, 10 males) with a mean age of 27.20 ± 4.27 years showed homogeneity and there was no statistically significant age or sex differences between the groups ($p = 0.517$; $p = 0.599$ respectively). HARS scores were statistically significantly higher (28.90 ± 4.08 vs. 5.13 ± 1.41, $p < 0.001$) in GAD patients compared to the control group.

Table 1
Serum Marker Levels of Oxidative Status.

Mean ± SD	GAD	Control	p value
TAS (μmol Trolox Eqv./L)	1.31 ± 0.21	1.29 ± 0.20	p = 0.687
TOS (μmol H_2O_2 Eqv./L)	45.61 ± 65.34	10.35 ± 4.83	p = 0.005
OSI (Arbitrary Unit)	3.52 ± 5.14	0.81 ± 0.36	p = 0.006
Pro (U/L)	586.31 ± 21.13	364.08 ± 10.63	p < 0.001

TAS: Total Antioxidant Status.
TOS: Total Oxidant Status.
OSI: Oxidative Stress Index.
Pro: Prolidase.

Mean TAS level measured in GAD patients was not statistically significantly different from mean TAS level measured in controls ($t = 0.405$, $p = 0.687$). The GAD group demonstrated statistically significantly higher TOS, OSI and Pro levels, when compared with the control group ($t = 2.947$, $p = 0.005$; $t = 2.874$, $p = 0.006$; and $t = 9.396$, $p < 0.001$ respectively). Mean TAS, TOS, OSI and Pro levels of patient and control groups are given in Table 1.

HARS scores were found to be positively and statistically significantly correlated with TOS, OSI and Pro levels ($p = 0.008$, $r = 0.338$; $p = 0.008$, $r = 0.339$; and $p < 0.001$, $r = 0.751$ respectively). No statistically significant correlation was determined between HARS scores and TAS levels. The powerful statistically significant correlation of Pro with HARS was attention grabbing. Relations between HARS scores, TOS levels, Pro levels and OSI scores are shown in Fig. 1.

No statistically significant bivariate or multivariate relationships of the TAS, TOS, OSI and Pro levels to age and sex variables were determined.

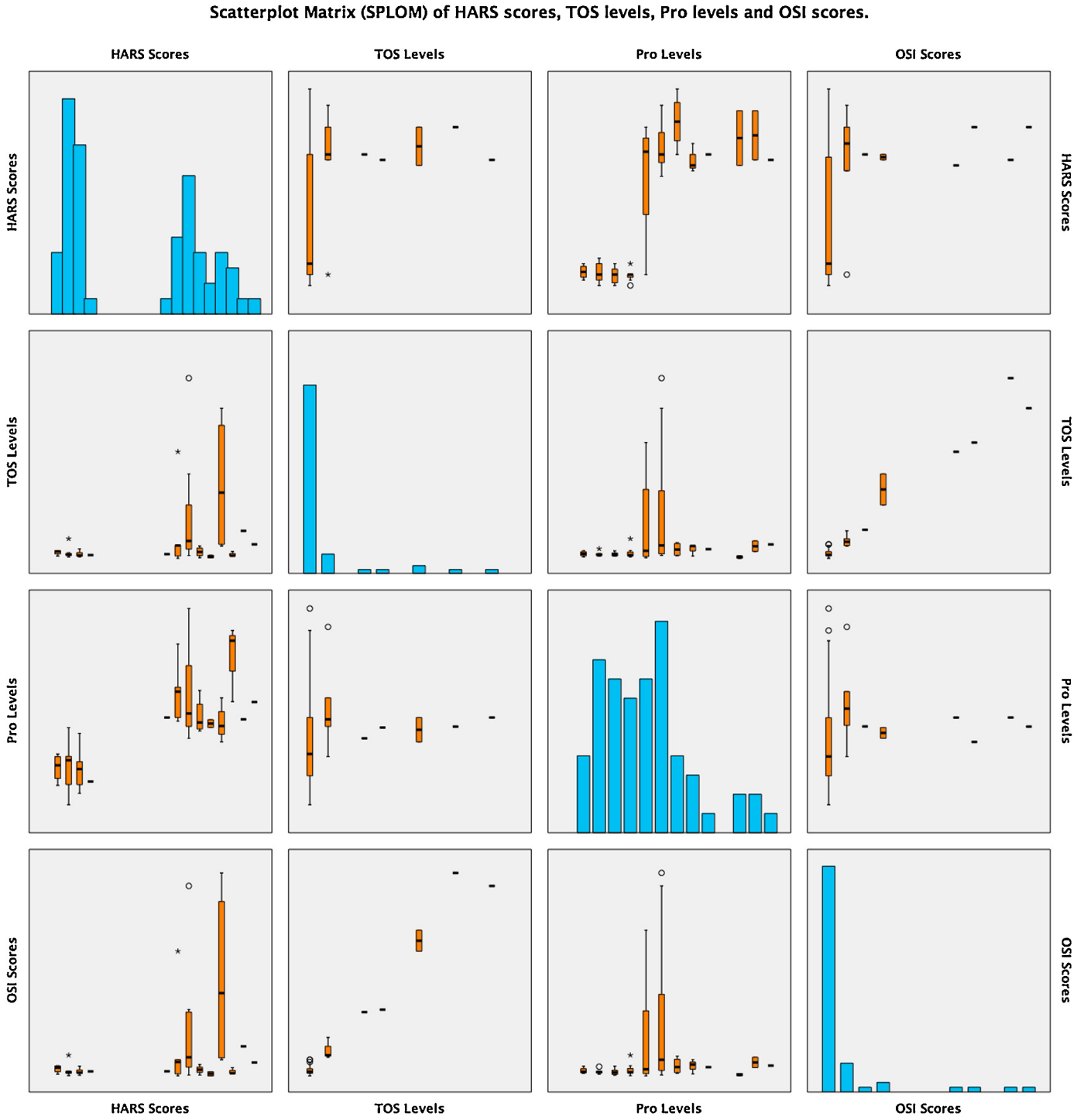


Fig. 1. Relations between Hamilton Anxiety Rating Scale (HARS) Scores, Total Oxidative Stress (TOS) levels, Prolidase (Pro) levels and Oxidative Stress Index (OSI) scores.

4. Discussion

In this study we hypothesized that there may be an association between serum prolidase activity, oxidative status and generalized anxiety disorder. A recent paper studying oxidant and antioxidant markers individually to point out OS in GAD has been published with results showing higher oxidant lipid hydroperoxide and lower antioxidant paraoxonase levels in treatment-free GAD patients (Bulut et al., 2013). On the other hand, the literature is deprived of studies measuring TAS, TOS and OSI to determine OS in GAD. Presence and role of Pro have been studied in many pathological conditions in concurrence with OS such as osteoarthritis, hypertension, erectile dysfunction and Alzheimer's disease (Altindag et al., 2007; Arikanoglu et al., 2013; Demirbag et al., 2007; Savas et al., 2010). However Pro activity still remains unclear in many psychiatric disorders. Main findings of this cross-sectional study are that patients with GAD have statisticallysignificantly higher levels of TOS, OSI and Pro compared to healthy controls.

TOS was found to be statistically significantly increased in patients with untreated GAD in this study, which was congruent with literature. In a study with child and adolescent OCD patients increased TOS levels accompanied by higher OSI scores have been reported. (Kandemir et al., 2013). Bipolar disorder patients had escalated TOS levels in a study done with bipolar disorder subtypes (Yumru et al., 2009).

Literature has inconsistent results about TAS in neuropsychiatric disorders. Some publications report increased superoxide dismutase, glutathione peroxidase scores and total antioxidant capacities in OCD (Behl et al., 2010; Kuloglu et al., 2002a; Selek et al., 2008). Elevated antioxidant enzyme degrees in major depression (Bilici et al., 2001), and escalated antioxidant superoxide dismutase levels in schizophrenia have also been found (Yao et al., 1998). On the other hand there are studies emphasizing decreased levels of antioxidants like paraoxonase, vitamin C and E in OCD (Ersan et al., 2006; Kandemir et al., 2013). Additionally studies on OCD, early-onset psychosis and Asperger's syndrome reported attenuated TAS scores (Kandemir et al., 2013; Micó et al., 2011; Parellada et al., 2012). In a study with post-traumatic stress disorder, antioxidant enzymes in patients did not differ from those in controls (Tezcan et al., 2003). Conformably, TAS was found to be unaltered in our study.

Consistency of TAS scores among patients and controls may point the compensation mechanisms of the organism. An increase in antioxidant enzyme levels caused by immune reaction mediated FR was shown before (Braga et al., 1995).

Although the TAS scores in GAD patients did not differ from those in control subjects, OSI was higher in patient group at a significance level of $p = 0.006$. OSI is valuable to assess both antioxidative and oxidative aspects of the oxidative metabolism. Elevated OSI levels indicate the alteration of oxidative equilibrium in favor of oxidants, underlying the incapability of the regulatory mechanisms of the organism to balance OS. Increased OSI in GAD patients in our study is congruent with OS found to be increased in psychiatric disorders such as schizophrenia, bipolar disorder, major depression, obsessive compulsive disorder and panic disorder in previous studies (Bilici et al., 2001; Herken et al., 2001; Kuloglu et al., 2002b, 2002c).

Whether the existence of increased oxidants causes psychiatric disorders or psychiatric disorders rise oxidant levels is still unclear. Catecholamines such as dopamine and norepineprine are found to provoke FR production and their metabolism may increase the FR burden (Graham, 1979). Overproduced FR rupture cell membranes changing the fluidity, plus ruin the catecholaminergic and serotonergic receptor functions and densities (Britt et al., 1992; Papas, 1996; Van der Vliet and Bast, 1992). Bearing in mind that dopamine and serotonin play a major role in all subtypes of anxiety disorders, GAD might be responsible for the OS produced by FR load (Nikolaus et al., 2010).

In recent studies FR were claimed to play an important role in the pathogenesis of panic disorder, which is associated with basal ganglia like GAD (Kuloglu et al., 2002b; Wu et al., 1991). The presence of OS markers in euthymic bipolar disorder patients suggests that OS takes part in the pathogenesis of psychiatric disorders (Savas et al., 2006). Therefore, a bidirectional relationship is expected to exist between GAD and OS. In any account, correction of the oxidative imbalance in psychiatric disorders might have therapeutic effects regardless of the underlying mechanisms (Berk et al., 2008).

The degree of severity of OS is related to the inhibition of collagen production and collagen degradation due to OS is mediated by Pro (Altindag et al., 2007; Sienkiewicz et al., 2004). In our study, HARS scores reflecting the severity of GAD were found to be positively correlated with Pro levels at a strong level statistical significancy. Thus, Pro might be the target enzyme of this course, promising to be a marker for the follow-up of GAD patients.

To the best of our knowledge, this study is the first to report statistically significantly higher levels of Pro, TOS and OSI in GAD patients compared to healthy controls. Regrettably, we have examined the blood measures and HARS scores only once. New studies with longitudinal follow-ups will be needed to overcome this limitation.

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