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Evaluation of Oxidative Stress in Sheep with *Toxoplasma gondii* by Malondialdehyde, Glutathione Levels, Total Oxidant Status, Total Antioxidant Capacity and Oxidative Stress Index Markers

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Abstract: This study was conducted to evaluate oxidative stress using markers such as malondialdehyde (MDA), glutathione (GSH), total oxidant status (TOS), total antioxidant capacity (TAC) and oxidative stress index (OSI) in sheep naturally infected with *Toxoplasma gondii (T. gondii)*. A total of 30 Morkaraman breed sheep were used in this study. Blood samples were obtained from 10 healthy control sheep and 20 sheep naturally infected with *T. gondii.* malondialdehyde, GSH, TOS and TAC levels were determined in serum samples. The ratio of serum TOS to TAC levels was assessed as OSI. While the serum MDA level increased significantly (P<0.01), the serum TAC and TOS levels decreased significantly (P<0.01) in naturally infected with *T. gondii* sheep. There were no different for serum GSH and OSI in between the groups (P>0.05). Negative correlation (P<0.01) between TAC and OSI and a positive correlation (P<0.01) between TOS and MDA were determined in naturally infected with *T. gondii* sheep. In conclusion, the results of study suggested that OSI, TAC and MDA could be used as indicator of oxidative stress for sheep naturally infected with *T. gondii*.
Keywords: Oxidative stress, sheep, *T. gondii*

Toxoplasma gondii'li koyunlarda Oksidatif Stresin Glutatyon, Malondialdehit Düzeyi, Oksidatif Stres İndeksi, Toplam Oksidan Durumu ve Toplam Antioksidan Kapasitesi Kullanılarak Değerlendirilmesi

Öz: Bu çalışma, *Toxoplasma gondii (T. gondii)* ile doğal olarak enfekte olmuş koyunlarda malondialdehit (MDA), glutatyon (GSH), toplam oksidan durumu (TOS), toplam antioksidan kapasite (TAK) ve oksidatif stres indeksi (OSI) gibi belirteçler kullanılarak oksidatif stresi değerlendirmek amacıyla yapıldı. Bu çalışmada toplam 30 baş Morkaraman ırkı koyun kullanıldı. Kontrol için 10 sağlıklı koyundan ve *T. gondii*ile doğal olarak enfekte olmuş 20 koyundan kan örnekleri alındı. Serum örneklerinde MDA, GSH, TOS ve TAK seviyeleri belirlendi. Serum TOS' un TAK seviyelerine oranı OSI olarak değerlendirildi. *T. gondii* ile doğal olarak enfekte olan koyunlarda serum MDA düzeyi önemli ölçüde artarken (P<0.01), serum TAK ve TOS düzeyleri önemli ölçüde azaldı (P<0.01). Serum GSH ve OSI düzeyleri yönünden gruplar arasında farklılık bulunamadı (P>0.05). *T. gondii*ile doğal enfekte koyunlarda TAK ile OSI arasında negatif (P<0.01), TOS ile MDA arasında ise pozitif (P<0.01) korelasyon saptandı. Sonuç olarak *T. gondii*ile doğal enfekte koyunlarda OSI, MDA ve TAK değerlerinin oksidatif stres göstergesi olarak kullanılabileceği tespit edildi.
Anahtar kelimeler: Koyun, oksidatif stres, *T. gondii*

Introduction

Toxoplasmosis is a widespread zoonotic disease caused by intracellular protozoan parasite *Toxoplasma gondii* (*T. gondii)* (Oncel and Vural, 2006). It causes serious economic loss by causing neonatal losses, stillbirths and aborts in all livestock species, especially sheep (Van der Puije et al., 2000). It can affect all warm-blooded animals, including humans (Ragozo et al*.,* 2008). There are three mechanism of transmission of *T. gondii*; ingestion of oocysts of definitive host's (cats) via shed in the feces, congenital transmission from mother to the fetus and ingestion of tissue cysts in half-cooked meat (Gao et al., 2018; Duncanson et al., 2001). Infected cats, which are definitive hosts, can shed oocysts in their feces, and this is a major source of infection for sheep (Innes et al*.,* 2009).

Infectious agents and phagocytosed cells of the immune system lead to respiratory burst, which is the basic resource of free radicals by consuming very fast oxygen (Sezer and Keskin, 2014). The shifting of the equalize between body's antioxidant defense system and the free radicals in favour of oxidants is named oxidative stress. Although oxidants occur as a

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physiological product of aerobic metabolism, they can be generated at high rates under abnormal conditions (Sies, 1997). Oxidants cause oxidative stress by production of free radicals or by inhibiting antioxidant system. Free radicals are generated in tissues can directly damage macromolecules such as lipids, proteins and nucleic acids (Neelam et al., 2017). The roles of antioxidants include inactivating excess free radicals, protecting cells against the toxic influences of free radicals and contributing to the prevention of diseases (Karabulut and Gülay, 2016). It involves enzymatic and non-enzymatic molecules. Enzymatic molecules include glutathione transferase (GST), catalase, superoxide dismutase (SOD), glutathione peroxidase (GTPx), and thioredoxin; non-enzymatic antioxidants include such asvitamin E, vitamin C, glutathione (GSH), and carotenoids (Birben et al., 2012).

Glutathione is synthesized in the liver and made up ofcysteine, glycine and glutamic acid amino acids and it protects the cells from oxidative damage. Most antioxidants have been investigated in protozoa and helminth-borne diseases (Karaman et al., 2008). It is necessary to protect cells from toxoplasma infestation (Ali et al., 2006). It has been suggested that the oxidative stress index (OSI), which was developed to define oxidative/antioxidant imbalances more clearly, may be a suitable parameter for determining oxidative stress (Baltacıoğlu et al., 2014).

T. gondii induces IFN-gamma and other proinflammatory cytokines and that causes host tissue damage and death (Engin et al., 2012). To detection of oxidative stress in ruminants the last product of lipid peroxidation, malondialdehyde (MDA), enzymatic and non-enzymatic antioxidants, total antioxidant capacity (TAC) and total oxidant status (TOS) are used (Aktas et al., 2017). Parasitic infections can cause defense mechanisms that involve the generation of enhanced reactive oxygen species (ROS) (Sanchez-Campos et al., 1999; Bahrami et al., 2016). Antioxidants in oxidative tissue damage are thought to be a powerful treatment in preventing oxidative stress (Süleyman et al., 2018). This study was performed to investigate possibility of usage ofMDA, GSH,TOS,TAC as well as OSI markers for determination of the oxidative stressin *T. gondii* in naturally infected sheep.

Material and Method

Animals and protocol design

The present study was approved by the Ethics Committee of Veterinary Faculty, Atatürk University, Erzurum, Turkey (approval number 2022/13). A total of 30 female Morkaraman breed sheep, between 2 and 3 years old were used in this study. The sheep were divided into two groups: 10 healthy control sheep and 20 sheep naturally infected with *T. gondii* (n=20). Animal welfare and ethical principles were followed at all stages of the study. Blood samples were collected from sheep in accordance with animal welfare.

Blood sampling

10 ml blood collected from the vena jugularis of sheep were transferred to sterile tubes (BD Vacutainer System, Becton, Dickinson & Co. UK). After the samples were kept at room temperature for 30 minutes, and they were centrifuged at 3000 rpm for 15 minutes. Serum samples obtained were kept in a deep freezer at –20° C until analysis were done.

Serological investigations

An enzyme linked immune assay (ELISA) test kit was used to detect antibodies of *T. gondii* in sheep serum samples. The ELISA test was conducted via a commercially available enzyme immunoassay kit in accordance with manufacturer’s directives (CHEKIT TOXOTEST, IDEXX Laboratory, USA).

Biochemical assay

To measure levels in MDA spectrophotometrically, Ohkawa et al. (1979) method was used. The measurement of serum GSH level was enforced based on the method developed by Sedlak and Lindsay (1968). The TOS and TAC values in the blood were measured with a commercial kit (Rel Assay Kit Diagnostics, Turkey). As a calibrator, Trolox was used for TAC tests and the results were evaluated in mmol Trolox equiv/L (Erel, 2004). As a calibrator, hydrogen peroxide was used for TOS tests and the results were expressed in mmol H2O2 equiv/L (Erel, 2005). OSI was determined by the ratio of TOS to TAC level. The calculation of the OSI value was made with respect to the OSI (arbitrary unit) = TOS (μmol H_2O_2 Eq/L)/TAC (μmol Trolox Eq/L) (Kosecik et al., 2005; Mutlu et al., 2011).

Statistical analysis

Shapiro-Wilks test was used to determine whether the data were suitable for normal distribution and Levene homogeneity test was used to determine whether the variances were homogeneous. Data were statistically analyzed by using Student's t-test. The relationship among GSH, MDA, TOS, TAC, and OSI in *T. gondii* positive sheep was determined by Pearson’s correlation coefficient. Data are summarized with arithmetic mean and standard error values. Significance levels were taken as 5% (P<0.05) in all analyzes. All statistical analysis was conducted in SPSS for Windows Ver. 10.0 (IBM, USA, 1999).

Results

Serological findings

In the analyzes performed using the ELISA test kit, it was determined that *T. gondii* antibodies were positive for all sheep in the *T. gondii* group while sheep in the control group were negative.

Biochemical findings

Table-1 shows the serum MDA, GSH, TOS, TAC as well as OSI levels. A significant increase in serum MDA levels (P<0.01) and a significant decrease in TOS (P<0.05) and TAC levels (P<0.01) in the naturally infected with *T.gondii* group compared to the control group was determined. Although differences between control and naturally infected with *T.gondii* groups concerning GSH and OSI levels were not statistically significant (P>0.05), numerical increases of the GSH and OSI levels in naturally.

Table 1. Serum concentrations MDA, GSH levels, TOS, TAC, and OSI of sheep in groups (mean±SE)

Parameters	Control group (n=10)	Naturally infected with *T. gondii* group (n=20)
MDA (nmol/ml)	15.26±1.18	24.8±1.03**
GSH (mmol/ml)	1.545±0.45	1.663±0.06
TOS (µmol H_2O_2Eq/L)	33.75±2.10	27.92±1.60*
TAC (mmol Trolox Eq/L)	1.42±0.03	1.10±0.03**
OSI (arbitrary unit)	24.44±1.37	26.24±1.95

*MDA: malondialdehyde, TOS: total oxidant status, TAC: total antioxidant capacity, GSH: glutathione, OSI: oxidative stress index. The data are presented as mean ±SE. *P<0.05 and ** P<0.01 compared with control group.*

The correlation analysis conclusions between MDA, GSH, TOS, TAC and OSI of sheep in the naturally infected with *T.gondii* group are given in Table 2. It was determined that there was a negative significant correlation (P<0.01) between OSI and TAC, and a positive significant correlation (P<0.01) between OSI and TOS.

Table 2. Correlations among MDA, GSH levels, TOS, TAC and OSI of sheep in naturally infected with *T. gondii* group

Parameters	MDA	GSH	TAC	TOS	OSI
MDA	-	0.368	0.115	0.144	0.024
GSH		-	0.280	-0.160	0.321
TAC			-	-0,346	-0.695**
TOS				-	0.902**
OSI					-

*MDA: malondialdehyde,GSH: glutathione, TOS: total oxidant status, TAC: total antioxidant capacity, OSI: oxidative stress index. ** P<0.01*

Discussion and Conclusion

Toxoplasmosis is a common parasitic disease in Turkey as well as in other countries. It is most important factor of abortion in sheep. Therefore, it causes great economic losses in sheep breeding. Toxoplasmosis effects both human medicine and veterinary science because of its zoonotic property (Mor and Arslan, 2007). Many parasitic infections are caused by oxidant production, which can suppress the antioxidant defense system and damage host cells (Heidarpour et al., 2013a). Oxidative stress and antioxidants were examined in different parasitic diseases of people and animals (Sanchez-Campos et al*.,* 1999; Heidarpour et al*.,* 2013a; Jafari et al*.,* 2014; Heidarpour et al*.,* 2013b; Saleh, 2008; Saleh et al*.,* 2009). No studies were found on the measurement of serum, MDA, GSH, TOS, TAC and OSI and levels in sheep which was infected naturally with *T. gondii*. Therefore, this study was performed in sheep infected naturally with *T. gondii* to determine serum MDA, GSH, TOS, TAC and OSI levels and to assess oxidative stress status.

Malondialdehyde, the final product of lipid peroxidation, is used as a biomarker of oxidative stress (Aktas et al*.,* 2017; Sanchez-Campos et al*.,* 1999). Most researchers reported elevation of MDA in diseases such as theileriosis, psoroptic mange, Bluetongue disease, naturally infected with *Dicrocoelium dentriticum* (*D. dentriticum*), naturally infected with Pox Virus, Schmallenberg virusin sheep and coccidiosis in cattle (Baghshani et al*.,* 2011; Aktas et al*.,* 2017; Aytekin et al*.,* 2015; Şimşek et al*.,* 2006; Kirmizigulet al*.,* 2016; Macun et al*.,* 2018; Yılmaz et al*.,* 2014).

Atmaca et al. (2015) found that the MDA level in gerbils infected with *T. gondii* increased significantly compared to the control group in their experimental research. Also Karaman et al. (2008) reported that serum MDA levels were increased significantly in *Toxoplasma* seropositive people. Increase in the level of MDA was found parallel with other studies in our study. This increase in MDA level can be considered as an indicator of increased free radical production in *T. gondii* positive sheep. Although it is not statistically significant, the positive correlation between MDA and TOS in *T. gondii* group supports this information.

Reactive oxygen species have harmful effect on cells. The imbalance between oxidants and antioxidants causes damage to cells by leading to oxidative stress (Celi and Gabani, 2015). GSH is synthesized in the liver and made up of glycine, glutamic acid, and cysteine amino acids and it protects the cells from oxidative damage (Karaman et al*.,* 2008). It was reported that GSH levels were decreased in hosts infected with *Fasciola hepatica, Schistosoma mansoni, D. dentriticum* compared to healthy controls (Sanchez-Campos et al*.,* 1999; El-Sokkary et al*.,* 2002; Kolodziejczyk et al*.,* 2005). Antioxidant defense capability consists of enzymatic and non-enzymatic systems, the latter mainly represented by glutathione (Luberda, 2005). In our study, although the TAC level was significantly lower in the *T. gondii* group compared to the control group, there was no significant difference between GSH levels, suggesting that the enzymatic antioxidant defense may have been affected more. It is known that the nonenzymatic antioxidant defense does not consist only of GSH. Therefore, studies need to be conducted on more samples and evaluating more enzymatic and nonenzymatic antioxidants together with GSH.

The measure of TAC reflects all antioxidants. It is a reliable marker used to detect oxidative changes not only single specific antioxidants (Celi, 2010).This method can be used for interpreting the result of different treatments on plasma redox status in healthy subjects (Ghiselli et al*.,* 2000). Significant decrease of TAC level was reported in cows with mastitis, coccidiosis and *Babesiosis* in sheep (Atakisi et al*.,* 2010; Yılmaz et al*.,* 2014; Esmaeilnejad et al*.,* 2014). Kirmizigul et al. (2016) found that the TAC level was significantly lower in infected sheep compared to healthy sheep in their study which was carried out on sheep with Pox virus. In this study, it was found that serum TAC level was significantly decreased in sheep infected with toxoplasmosis compared to the control group. Reduction of TAC level in the infected sheep may possibly mean that antioxidant enzymes are consumed as free radical scavengers during oxidative process in natural toxoplasmosis. The negative correlation of OSI with TAC in the group of sheep infected naturally with *T. gondii* supports this information.

Since measuring oxidant substances one by one is not a very simple process in the evaluation of oxidant status, knowing TOS level is used as another parameter in determining / evaluating oxidative stress (Erel, 2004). Studies using TOS in determining oxidative stress have been conducted and different results have been obtained. Aktaş et al. (2017) in sheep with *Psoroptes ovis*, Kükürt et al. (2018) in sheep with pneumonia, and Kirmizigul et al. (2016) in naturally infected sheep with pox virus reported significant increases in TOS levels compared to healthy sheep. Durgut et al. (2013) noted that there was insignificant difference in TOS levels between bovine herpes virus -1 positive cattle and healthy cattle, but there was a negative correlation between TOS and TAC. Contrary to these reports, serum TOS levels in sheep infected with *T. gondii* group were significantly lower than in control group in this study. In addition, similar to the data of Durgut et al. (2013), it was determined that there was a negative correlation between total antioxidant capacity (TAC) levels and total oxidant status (TOS), although it was not statistically significant. These data obtained from the study can be interpreted as that antioxidant mechanisms are very active to combat oxidative stress.

Although there are doubts about its interpretation; OSI is a parameter used in the determination of oxidative stress such as MDA, hydroperoxides, DNA damage, IMA, protein carbonyls, thiols, prolidase, paraoxonase, antioxidant enzymes, antioxidant vitamins and other markers. Overall, the increase of OSI indicates the severity of oxidative stress (Martha et al*.,* 2019). Aktaş et al. (2017) in sheep infected with *Psoroptes ovis*, Kükürt et al. (2018) in sheep with pneumonia found that the OSI level was significantly higher than the healthy sheep. Baptistiolli et al. (2018) determined that the OSI level in sheep experimentally infected with *Haemonchus contortus* was much higher than the control group on the 28th and 34th days of inoculation. According to Durgut et al. (2016) in cattle with abomasum displacement, they found that OSI level was significantly greater in cattle with right displacement compared to with left displacement and healthy cattle. Invernizzi et al. (2019) found in a study they conducted that the OSI level at the calving time was higher than the dry period and the 30th day after calving. Durgut et al. (2013) did not find any difference between the OSI levels of bovine herpes virus-1 infected cattle and healthy cattle. In this study, it was determined that the OSI levels of sheep naturally infected with *T. gondii* group were numerically higher, although not statistically significant. In addition, a significant negative correlation was found between TAC and OSI, and a significant positive correlation between OSI and TOS in the group of sheep naturally infected with *T. gondii.*

As a result, the data obtained from this study, which was the first to evaluate oxidative stress in sheep naturally infected with *T. gondii*, show that oxidative stress develops in sheep which was naturally infected with *T. gondii*, and OSI, TAC as well as MDA could be used as markers in determination of oxidative stress in these animals.

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