

Determination of dynamic thiol-disulfide levels in dairy cattle with foot disease

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ABSTRACT

Foot diseases are among the top three causes of economic loss in dairy cattle. Recent studies show that oxidative stress plays a critical role in the pathogenesis of foot diseases. There is no study determining the dynamic thiol-disulfide levels in dairy cattle with foot disease. This study aimed to determine dynamic thiol-disulfide levels in foot diseased and healthy dairy cattle. Demographic information about the animals, and clinical findings of foot diseases and lameness were presented. In the Foot Disease Group, native thiol ($P<0.01$), total thiol ($P<0.05$), disulfide ($P<0.01$), disulfide/native thiol ($P<0.01$) and disulfide/total thiol ($P<0.01$) results were found to be significantly higher than in the Control Group. Native thiol/total thiol ($P<0.01$) was found to be significantly higher in the Control Group than in the Foot Disease Group. As a result, statistically significant increases in thiol-disulfide levels were determined in foot diseased dairy cattle. It was shown that the thiol-disulfide balance was impaired. This study is the first to determine thiol-disulfide levels and thus changes in thiol-disulfide homeostasis in healthy and foot diseased dairy cattle. With further studies, oxidative stress changes that occur as a result of foot diseases can be better understood and the use of antioxidants as a part of treatment evaluated.

Key words: dairy cattle; foot disease; oxidative stress; thiol-disulfide

Introduction

Foot diseases and (ensuing) lameness are common clinical problems in dairy cattle. They are among the top three causes of economic loss in dairy cattle, as they significantly impair animal welfare and pave the way for infertility and a decrease in milk production. Intensive labor and expenses required for treatment represent additional losses (YALCIN et al., 2010; DEMIR et al., 2013).

In the pathophysiological process of foot diseases, events such as inflammation, bacterial contamination and pain should be treated in a timely manner. Otherwise, infected, lytic, erosive, ulcerative or necrotic lesions can reach from the nail to the bone, and even problems such as osteomyelitis may occur (KAMILOĞLU, 2014). As in many inflammatory disorders, an increase

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in oxidative stress mediators occurs with the stimulation of pro-inflammatory cytokines in foot diseases (TOTHOVA et al., 2014; PALMER and O'CONNELL, 2015; ERDOGAN et al., 2019). Oxidative stress parameters have been investigated in foot diseases and it has been shown that oxidative balance is impaired (MIRZAD et al., 2017; ERDOGAN et al., 2019).

Oxidative stress can be briefly defined as a change in the balance between free radicals and antioxidants in favor of free radicals (BETTERIDGE, 2000; LYKKESFELDT and SVENDSEN, 2007; DURGUT et al., 2016; CETINKAYA and CAMSARI, 2020). Past studies have shown that oxidative stress in animals plays a role in the pathophysiology of many diseases such as sepsis, mastitis, enteritis, and arthritis (LYKKESFELDT and SVENDSEN, 2007; CELI, 2011; TERZI, 2020). Recent studies show that oxidative stress plays a role in the pathogenesis of foot diseases and lameness in cattle (SEYREK et al., 2008; HEINECKE et al., 2010; OSORIO et al., 2012; ZHAO et al., 2015). The role of oxidative stress is critical in understanding the pathophysiology of foot diseases in cattle, and cannot be neglected (ZHAO et al., 2015) because many local and systemic inflammatory, infective, lytic, necrotic, and progressive events that occur in cattle foot diseases are associated with oxidative stress (AL-QUDAH and ISMAIL, 2012).

There are various enzymatic and non-enzymatic defense mechanisms against the harmful effects of Reactive Oxygen Species (ROS). One of these antioxidant mechanisms is thiol-disulfide homeostasis. It is known that these compounds containing sulfhydryl groups play an important role in the prevention of oxidative stress in cells. The primary target of intracellularly produced ROS are thiol groups in sulfur-containing amino acids in proteins. Thiol groups interact with ROS to form reversible disulfide bonds. After this, these disulfide bonds are reduced back to the thiol groups by antioxidant mechanisms. Thus, a dynamic thiol-disulfide balance is achieved (ATES et al., 2016). It has been shown that the dynamic thiol-disulfide balance has an important role in

antioxidant protection, detoxification, apoptosis, enzymatic activity regulation, transcription factors and cellular signaling mechanisms (BISWAS et al., 2006; CIRCU and AW, 2010). The association of abnormal thiol-disulfide balance with diseases such as diabetes mellitus, cardiovascular diseases, chronic kidney disease, and cancer has been reported (MATTEUCCI and GIAMPIETRO, 2010; GO and JONES, 2011; RODRIGUES et al., 2012; PRABHU et al., 2014). Veterinary studies on thiol-disulfide homeostasis are limited to endometritis in cattle, dehorning in calves, sarcoptic mange, and canine distemper in sheep (CAMKERTEN et al., 2019; ERDOGAN et al., 2019; DEGIRMENCAY et al., 2021; EMRE et al., 2021). To our knowledge, there is no study reporting the effects of foot diseases on dynamic thiol-disulfide balance in cattle. This study aimed to determine dynamic thiol-disulfide levels in foot diseased and healthy dairy cattle, and to note the changes in thiol/disulfide homeostasis.

Materials and methods

Animals and Experimental Design. The inclusion criteria were Holstein cows, over 1 year old, female, non-pregnant, used in intensive dairy farms. A total of 50 cattle, 20 of which were the Control Group (healthy) and 30 in the Foot Disease Group, were included in the study. Animals with diseases other than foot disease or which were pregnant were excluded from the study. Demographic information about all the animals included in the study were recorded. The clinical findings of the animals with foot disease and the diagnosis of the disease were recorded. The scoring system defined by SPRECHER et al. (1997) was used for clinical grading of lameness (SPRECHER et al., 1997).

Sample Collection. Immediately after the clinical examination procedures, peripheral blood samples were taken from the vena jugularis and delivered to the laboratory in a cold chain. After the samples were centrifuged at 1500 x g for 10 minutes, the sera were separated and transferred to Eppendorf tubes and stored in a deep freezer at -80°C until analyzed. Native thiol and total thiol levels of all serum samples were analyzed using

the spectrophotometric method newly developed by EREL and NESELIOGLU (2014). Disulfide levels were calculated using the formula [Disulfide levels ($\mu\text{mol/L}$) = (total thiol - native thiol)/2.] In addition, (disulfide/native thiol) x100, (disulfide/total thiol) x100 and (native thiol/total thiol) x100 rates were calculated (EREL and NESELIOGLU, 2014).

Statistical Analyses. All statistical analyses were performed using the IBM SPSS Statistics (Statistical Package for the Social Sciences version 22, Chicago, IL, USA) program. Mean and standard deviation values were given in descriptive statistics for quantitative data. An independent Sample T test (which is a parametric test) was used to compare groups, and $P < 0.05$ was considered significant.

Results

Demographics. The animals included in the study were determined to be 3-6 years old (mean 4.75 ± 0.94 , median 5) and 570-640 kg in body weight (mean 602.5 ± 16.99 , median 600) in the Control group (n=20). In the Foot Disease Group (n=30), their age was determined as 2-10 years old (mean 4.80 ± 1.8 , median 5), with 510-650 kg

body weight (mean 601.33 ± 41.53 , median 600). All cattle in the study were female, Holstein breed, and from the same intensive dairy farm (out of a population of 556 cattle).

Clinical Findings. The animals in the Control Group were cattle that showed neither clinical signs of foot disease nor signs of any other disease. Foot rot, solea ulcus, heel erosion, interdigital dermatitis, interdigital phlegmon, laminitis, white line disease, corium coronarium, hoof crack, hoof deformity lesions were recorded in the Foot Disease Group as a result of hoof examinations. By clinical examination it was determined that there were no other concurrent diseases in the Foot Disease Group. The foot disease lesions and the number of affected animals by each disease was recorded in the 30 cattle in the Foot Disease Group, as shown in Table 1. Foot disease pictures of three cattle from Foot Disease Group are presented in Fig. 1-3. The degree of lameness in the foot disease group was in the range of 1-4 (mean 2.73 ± 0.81 , median 3) according to Sprecher's lameness scoring system (SPRECHER et al., 1997). Since there was no lameness in the Control Group, the degree of lameness was scored as "0" in all healthy animals.

Table 1. The number of different foot disease lesions and Specher's Score (Mean \pm Standard Error of the Mean).

Foot Disease Lesions	Number	Specher's Score (Mean \pm SEM)
Foot rot	15	3.02 ± 0.18
Interdigital dermatitis	8	2 ± 0.19
Foot rot + Interdigital dermatitis	2	2.5 ± 0.5
Corium coronarium + Heel erosion	1	3 ± 0
White line disease + Hoof crack	1	2 ± 0
Foot rot + Claw deformity	1	4 ± 0
Solea ulcus + Interdigital flegmon	1	4 ± 0
Laminitis	1	2 ± 0



Fig. 1. Severe digital and interdigital dermatitis.



Fig. 2. Severe sole ulceration, hemorrhage and interdigital flegmon.



Fig. 3. Foot rot disease.

Biochemical Results. In the Foot Disease Group, native thiol ($P<0.01$), total thiol ($P<0.05$), disulfide ($P<0.01$), disulfide/native thiol (%) ($P<0.01$), and disulfide/total thiol (%) ($P<0.01$) results were found to be significantly higher than in the Control Group. In the Control Group, native thiol/total thiol (%) ($P<0.01$) was found to be significantly higher than in the Foot Disease Group. The analysis of the results of both groups are shown as values in Table 2 and as box plot charts in Fig. 4.

Table 2. A summary of thiol/disulfide homeostasis parameters in the healthy and foot diseased dairy cattle.

Parameters	Control (Healthy) (n=20) Mean±SD; Median (IQR) [Min-Max]	Foot Diseased (n=30) Mean±SD; Median (IQR) [Min-Max]	P
Native thiol (µmol / L)	265.10 ^a ±29.48; 317.5 (125.7) [201-548]	312.53 ^b ±45.04; 308.5 (66) [231-419]	0.000
Total thiol (µmol / L)	238.15 ^a ±32.58; 168.5 (74.7) [69-281]	267.30 ^b ±46.61; 266.5 (63.2) [168-365]	0.019
Disulfide (µmol / L)	13.47 ^a ±3.15; 79.2 (72.5) [6-184]	22.61 ^b ±7.39; 20.5 (8) [15-47]	0.000
Disulfide/Native thiol (%)	5.86 ^a ±1.99; 5.6 (3.4) [3.4- 10.1]	8.87 ^b ±3.86; 7.72 (4.3) [4.4-18.9]	0.001
Disulfide / Total thiol (%)	5.19 ^a ±1.57; 5.0 (2.7) [3.1-8.4]	7.37 ^b ±2.58; 6.69 (3.1) [4.0-13.7]	0.002
Native thiol / Total thiol (%)	89.60 ^a ±3.14; 89.9 (5.4) [83.1- 93.6]	85.24 ^b ±5.17; 86.6 (6.3) [72.4-91.9]	0.001

SD: standard deviation, IQR: interquartile range, Min: Minimum, Max: Maximum

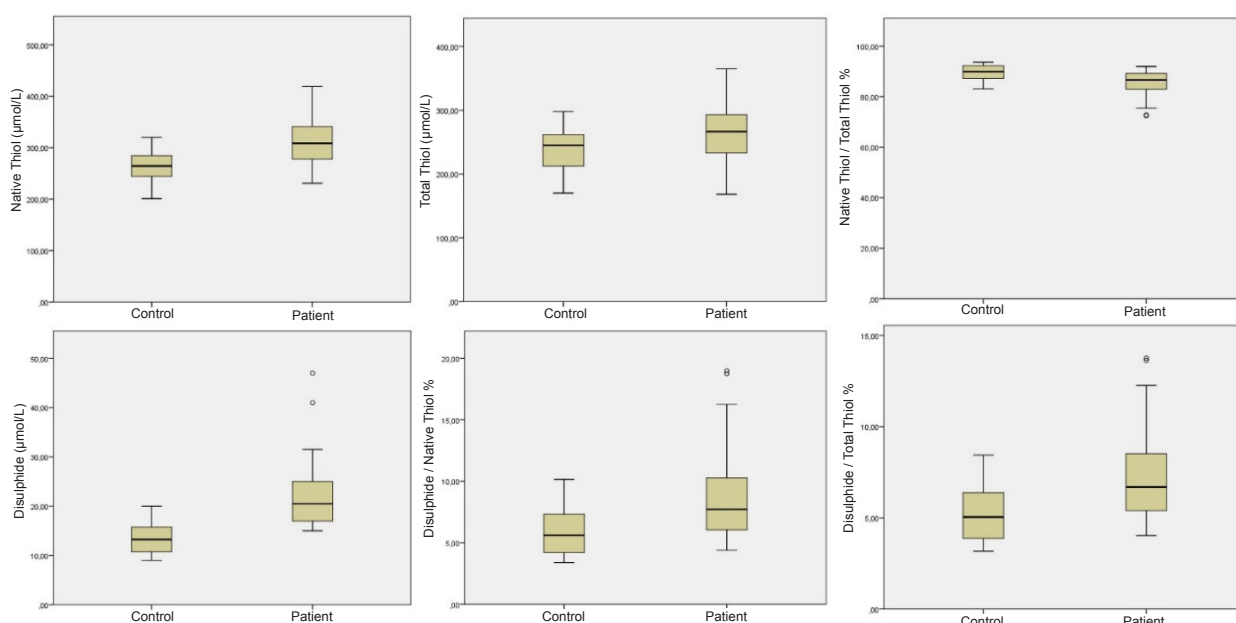


Fig. 4. Native thiol, total thiol, disulfide levels of healthy and foot diseased cattle, and thiols/disulfide comparison percentages (Box-Plot Charts: Upper whisker: Maximum, Lower whisker: Minimum, Upper box limit: Third quartile, Lower box limit: First quartile, The central line in the box: Median, Between lower and upper box limits: Interquartile range).

Discussion

Foot diseases and the related lameness in dairy cattle are among the most significant causes of economic losses, after infertility and mastitis. It has been reported that these diseases can cause annual losses of around \$200 million in the USA and UK. The release of histamine or endotoxins causes inflammatory reactions in cattle, locally affecting the foot area. The amount of histamine or endotoxins released depends on many factors, such as the underlying disease, malnutrition, environmental factors, weight, age, breed, pregnancy and trauma affecting the feet and nails (YALCIN et al., 2010; DEMIR et al., 2013; KAMILOGLU, 2014). In the absence of early diagnosis and proper treatment, inflammatory events may progress, and/or bacterial contamination may occur in the affected area. As a result, infected, lytic, erosive, ulcerative, and necrotic lesions in various parts of the foot, from the hoof to the bone, cause pain and lameness, which significantly affects animal welfare (KAMILOGLU, 2014).

During metabolic or inflammatory reactions reactive oxygen species (ROS) are produced in the cells, and their toxic effects are known (THANNICKAL and FANBURG, 2000; CHOI et al., 2004; CETINKAYA and CAMSARI, 2020; TERZI, 2020). ROS cause cell and tissue damage as a result of overproduction of oxidants or insufficiencies of the antioxidant defense system (PALIPOCH and KOOMHIN, 2015; CETINKAYA and CAMSARI, 2020). Infectious agents can increase the production of ROS in cells (TERZI, 2020). Under oxidative stress conditions, excessive ROS production predisposes to dyskeratosis in the hoof, apoptosis, and degeneration of chondrocytes (TOMLINSON et al., 2004; HEINECKE et al., 2010; ZHAO et al., 2015).

Thiols are non-enzymatic, low molecular weight antioxidants and are an important part of the antioxidative defense mechanisms of cells (OZOUGWU, 2016). Thiol-disulfide homeostasis plays important roles in antioxidant protection, detoxification, apoptosis, regulation of enzymatic activity, and signaling mechanisms (BISWAS et al., 2006; CIRCU and AW, 2010). Plasma thiols consist of cysteine, glutathione (GSH), homocysteine, and

albumin (ERKUS et al., 2015). Glutathione, one of the thiols, is a major intracellular antioxidant whose concentration is measured to estimate oxidative stress (MANDELKER, 2011). In cases of increased oxidative stress, thiol concentrations decrease due to the role of the sulfhydryl groups of thiols to compensate for ROS (ERKUS et al., 2015). Under oxidative stress conditions, thiol molecules regulate thiol/disulfide homeostasis (JONES and LIANG, 2009). In one study it was reported that serum glutathione peroxidase (GSH-Px) and reduced glutathione (GSH) levels were significantly lower in cattle with foot disease than in healthy cattle (AL-QUDAH and ISMAIL, 2012). In another study, it was shown that some foot diseases in sheep reduce serum glutathione peroxidase (GSH-Px) and glutathione (GSH) levels (YURDAKUL and YILDIRIM, 2018).

This study was planned using the hypothesis that the pathophysiological events taking place in foot diseases that cause lameness in dairy cattle disrupt the thiol/disulfide balance. For the first time, thiol/disulfide values were determined in healthy and foot diseased dairy cattle.

In our study, local findings and degrees of lameness in foot disease lesions, such as foot rot, solea ulcer, heel erosion, interdigital dermatitis, interdigital phlegmon, laminitis, white line disease, corium coronarium, hoof crack, hoof deformity diagnosed in dairy cattle, were found to be similar to various other studies (BECKER et al., 2014; YAKAN, 2018; YURDAKUL and ILKER, 2018; EROL et al., 2019; ISTEK and HAN, 2019). In addition, the demographic characteristics of the dairy cattle included in the study are similar, increasing the reliability of the study.

ERDOGAN et al. (2019) investigated thiol/disulfide homeostasis in the dehorning process in calves. Native thiol and total thiol results were found to be significantly higher in the groups using nonsteroidal anti-inflammatory drugs, while disulfide results were slightly lower. Reductions in native thiol and total thiol concentrations were associated with nutrition or pain management, not oxidative stress, due to no increase in disulfide levels (ERDOGAN et al., 2019). ÇAMKERTEN et al. (2019) showed that thiol/disulfide levels

increase in sarcoptic mange in sheep, and reported that antioxidants should be considered as one of the therapeutic options (ÇAMKERTEN et al., 2019). The results of our study show that significant increases in native thiol, total thiol and disulfide levels in dairy cattle with foot disease are associated with oxidative stress, as in the study by ÇAMKERTEN et al (2019) (ÇAMKERTEN et al., 2019). Therefore, oxidative stress-related thiol/disulfide homeostasis may need to be considered when selecting available treatment options. In another recent study, it was reported that there was a decrease in thiol/disulfide levels in canine distemper disease, but it was not statistically significant. It has been stated that the reason for the difference in thiol/disulfide homeostasis may be the decrease in plasma thiol concentration due to increased ROS as a result of oxidative stress (DEGIRMENCAY et al., 2021).

Furthermore, in a recent study changes were observed in thiol/disulfide homeostasis caused by acute and chronic endometritis in dairy cattle, and it was stated that endometritis-induced infertility may be associated with changes in thiol levels (EMRE et al., 2021). In the results obtained in that study, it was reported that there were increases in disulfide and disulfide/native thiol levels, similar to the foot diseased group in our study. However, unlike our study, they reported a decrease in native thiol and total thiol levels, and suggested that this decrease may have occurred due to the increase in oxidative stress (EMRE et al., 2021). Studies on this subject show that inflammatory processes in different species and diseases disrupt the thiol/disulfide balance in different ways (ÇAMKERTEN et al., 2019; ERDOGAN et al., 2019; KALKAN et al., 2019; DEGIRMENCAY et al., 2021; EMRE et al., 2021). In this context, there are other studies showing an increase in native thiol and total thiol in some diseases (KALKAN et al., 2019). In our study, native thiol and total thiol levels were found to be higher in the foot disease group than in the control group. The reason for this difference is that the balance point of thiol/disulfide homeostasis shifts to thiol formation as a result of the chronic inflammatory events of foot diseases in dairy cattle. On the basis of these reported studies, it

was understood that the changes in thiol/disulfide homeostasis in different species or different diseases are not always in the same direction. Therefore, it was considered necessary by the authors to determine the changes in thiol/disulfide levels in common domestic animals, such as cattle, sheep, dogs and cats, especially in common diseases. In addition, recent studies stated that thiol/disulfide levels can be a new marker in animals, and that more studies are needed on this subject (ÇAMKERTEN et al., 2019; ERDOGAN et al., 2019; DEGIRMENCAY et al., 2021; EMRE et al., 2021). The limitations of this study are the inability to perform more diverse biochemical analyzes, the inability to take samples from different dairy farms and from a larger number of healthy and foot diseased cattle.

As significant increases in thiol/disulfide levels were determined in foot diseased dairy cattle associated with lameness, this study has shown that thiol/disulfide balance was impaired in cattle with foot disease, and that thiol/disulfide levels were high with significant statistical differences. This study is the first to determine thiol/disulfide levels and thus changes in thiol/disulfide homeostasis in healthy and foot diseased dairy cattle. In further studies, thiol/disulfide changes should be determined in various foot diseases at different stages, and the role should be investigated of thiol/disulfide balance in the diagnosis, treatment, and prognosis process. In this way, oxidative stress changes that occur as a result of foot diseases can be better understood and the use of antioxidants in the treatment evaluated.

Ethics Committee Approval

The study was approved by the Ethics Committee of Hatay Mustafa Kemal University Animal Experiments (Decision no: E.11647 E.1072) and the fieldwork was done by the permission of Turkish Ministry of Food Agriculture and Livestock (Decision No: 76063909-325.04.02-E.563583).

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SAŽETAK

Bolesti papaka su među tri glavna uzroka ekonomskih gubitaka u mliječnom govedarstvu. Nedavna istraživanja pokazuju da oksidativni stres igra ključnu ulogu u patogenezi bolesti papaka. Nedostaje istraživanja o razinama tiol-disulfida u mliječnim goveda, stoga je cilj ovog rada bio je utvrditi dinamičke razine tiol-disulfida u zdravih goveda i goveda s bolesnim papcima. Prikazane su demografske informacije o životinjama te klinički nalazi bolesti papaka i hromosti. U skupini s bolestima papaka, utvrđeno je da su rezultati nativnog tiola ($P < 0,01$), ukupnog tiola ($P < 0,05$), disulfida ($P < 0,01$), disulfida/nativnog tiola ($P < 0,01$) i disulfida/ukupnog tiola ($P < 0,01$) znakovito viši nego u kontrolnoj skupini zdravih goveda. Nativni tiol/ukupni tiol ($P < 0,01$) bio je znakovito viši u kontrolnoj skupini nego u skupini goveda s bolesnim papcima. Kao rezultat navedenoga, utvrđena su statistički znakovita povećanja razina tiol-disulfida u mliječnim goveda s bolestima papaka što govori o njegovoj narušenoj ravnoteži. Ovo je istraživanje prvo koje je odredilo razine tiol-disulfida, a time i promjene homeostaze tiol-disulfida, u zdravih mliječnih goveda i goveda s bolestima papaka. Daljnjim istraživanjima moglo bi se doći do boljeg razumijevanja promjena zbog oksidativnog stresa kao posljedice bolesti papaka i procijeniti uporaba antioksidansa kao dijela liječenja.

Ključne riječi: mliječna goveda; bolesti papaka; oksidativni stres; tiol- disulfid