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MECHANISMS OF MASTITIS IN DAIRY CATTLE: INVOLVEMENT OF OXIDATIVE STRESS AND INFLAMMATORY RESPONSE

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Abstract

The transition period, spanning late gestation to early lactation, is a critical window for high-producing dairy cows due to markedly increased energy requirements. During this phase, cows undergo profound physiological and endocrine adaptations, often resulting in negative energy balance. Elevated metabolic activity drives higher oxygen consumption, leading to excessive *generation of reactive oxygen species (ROS) and free radicals, which trigger oxidative stress. At the same time, endogenous antioxidant defenses are frequently weakened, rendering biological macromolecules vulnerable to damage and disrupting normal metabolic and physiological functions. Consequently, cows are at heightened risk of metabolic and infectious disorders, including ketosis, retained placenta, metritis, and particularly mastitis. Despite its often subclinical nature, oxidative stress has emerged as a major factor influencing animal health and productivity, making it a growing area of interest in veterinary research. This review consolidates current insights into the mechanisms and consequences of oxidative stress in dairy cattle, with a focus on its pathophysiological contribution to mastitis development. Furthermore, it highlights the broader implications of oxidative imbalance on lactation performance and overall herd wellbeing, underscoring the importance of targeted strategies to mitigate oxidative damage and optimize health outcomes in high-yielding dairy cows.*

Key words: *Oxidative Stress; Inflammatory Response; Mastitis; Dairy Cows*

INTRODUCTION

Over the last two decades, the modernization of dairy farms and ongoing innovation in the dairy industry have introduced new challenges for both farmers and dairy processors. Environmental factors such as housing conditions, nutritional management, and the implementation of advanced technologies in modern cattle breeding exert a profound influence on milk production. Earlier, during the calving period of dairy cows and the onset of lactation, the primary focus was on preventing infectious diseases and providing adequate dietary energy. Today, herd health prevention strategies emphasize not only the control of infectious disease but also the effective management of stress, regulation of energy balance, and limitation of animal exposure to endotoxins and oxidative stress (Barkema et al. 2015).

Diseases of the mammary gland are among the most common worldwide and cause substantial economic losses as milk is the fundamental raw material for the dairy industry. Despite advances in the diagnosis and control of mastitis, this disease continues to be regarded as the most significant health problem in dairy cattle production. According to European Union legislation and national regulations on raw milk quality, farmers are obliged to produce hygienic milk that does not pose a risk to public health. Milk obtained from diseased animals or milk characterized by elevated bacterial load and high somatic cell counts must not be used for human consumption. Early detection of mastitis enables proactive management to mitigate its adverse effects and improve therapeutic outcomes (Tommasoni et al. 2023).

Disturbance of the redox balance, that is, oxidative stress, has a negative impact on the health and functionality of physiological systems. Some disorders arise as a direct consequence of oxidative stress, while in other cases, oxidative stress appears as a secondary phenomenon associated with specific pathological processes. Free radicals are molecules or atoms that, at low concentrations, play beneficial roles in the organism by activating biological pathways and participating in physiological processes. However, at elevated concentrations, they exert harmful effects. Any udder anomaly typically increases in somatic cells in the milk, thereby reducing milk yield and quality (Andrei et al. 2016).

Mastitis is important from the perspective of public health, milk processing, and animal welfare. The occurrence of both clinical and subclinical mastitis also affects key productive parameters in dairy cows. Specifically, mastitis is associated with a prolonged calving interval, an extended period to first *post-partum estrus*, an increased insemination index, and a higher risk of early pregnancy loss within the first 45 days of gestation (Egyedy and Ametaj 2022).

MASTITIS

Mastitis is an inflammatory process of the mammary gland parenchyma, characterized by pathological changes in udder tissue and physical, chemical, and microbiological alterations of milk. Although the mammary gland is generally considered a closed, sterile system, its sterility may be disrupted by several factors that facilitate microbial invasion. Pathogens can penetrate the gland through three main routes: galactogenic (via the teat canal), lymphogenic (through skin injuries and lymphatic vessels), and hematogenic (through the bloodstream) (Nee and Cheng Wei 2020).

The disease results primarily from the host's immune response aimed at neutralizing and destroying invading pathogens. This process leads to a marked increase in the number of somatic cells in milk, which represent the first line of defense. The risk of mastitis is highest during the transition period from pregnancy to lactation, when dairy cows are particularly susceptible to oxidative stress (Kibebew 2017). Although mastitis is most commonly of bacterial origin, cases associated with viruses, yeasts, and even algae have been reported. More than 150 Gram-positive and Gram-negative bacterial species are recognized as etiological agents, with *Staphylococcus aureus*, *Streptococcus uberis*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, and *Escherichia coli* being the most frequent (Morales-Ubaldo 2023). In addition to microbiological agents, mastitis may also be triggered by physical trauma or chemical irritants.

Depending on the mode of transmission, mastitis is classified as either contagious or environmental. Contagious mastitis is typically associated with pathogens such as *Streptococcus agalactiae*, *Staphylococcus aureus*, and *Mycoplasma* spp., which spread primarily during milking. In contrast, environmental mastitis arises from exposure to bacteria present in bedding, manure, or contaminated surroundings, and is most frequently caused by *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Citrobacter* spp., *S. dysgalactiae*, *S. uberis*, enterococci, yeasts, and unicellular algae (Nee and Cheng Wei 2020).

Clinical and subclinical mastitis are the two primary forms of the disease. Clinical mastitis is manifested by visible alterations in milk (such as clots and flakes), reduced milk yield, and signs of inflammation, including swelling, redness, pain, and sometimes fever. By contrast, subclinical mastitis is more challenging to detect, as it lacks visible symptoms in the udder or milk. Yet, it is often associated with systemic health disturbances and long-term reductions in productivity (Stanek et al. 2024).

Epidemiological studies suggest that mastitis can occur year-round, although a higher incidence is often observed in winter than in summer. Seasonal variation also appears to influence the dominance of specific causative agents. The highest risk period is the first month of lactation, during which early-onset mastitis negatively affects subsequent productivity, predisposes cows to recurrent infections, and contributes to persistently elevated somatic cell counts (Kibebew 2017). Treatment strategies depend on the causative pathogen. Antibiotic therapy remains the most widely accepted and effective approach; however, outcomes are frequently unsatisfactory, particularly in infections caused by *S. aureus*. Moreover, inappropriate or excessive use of antimicrobials contributes to the emergence of resistant strains and to the presence of antibiotic residues in milk, posing significant public health concerns (De Souza et al. 2024).

While these clinical and epidemiological aspects provide an overview of mastitis in dairy cattle, a deeper understanding of its underlying mechanisms requires closer examination of the oxidative stress and inflammatory pathways involved in its pathogenesis, which will be discussed in the following section.

PATHOGENESIS OF MASTITIS

Mastitis is a complex inflammatory disorder of the mammary gland that progresses through three stages: invasion, infection, and inflammation. During the invasion stage, pathogens penetrate the teat canal (ductus papillaris), which functions as the first anatomical and biochemical barrier. The canal is lined with keratin, containing antimicrobial fatty acids and keratin-associated proteins that adsorb bacteria and inhibit their survival. However, during the periparturient period, increased intramammary pressure and keratin loss during milking compromise this defense, facilitating bacterial entry (Kerro Dego and Vidlund 2024).

Once pathogens breach this barrier, they colonize and proliferate within the mammary parenchyma- the infection stage. This is followed by an inflammatory response mediated by immune and mammary epithelial cells. Macrophages and neutrophils phagocytose invading bacteria using hydrolytic enzymes, peroxidases, and reactive oxygen species (ROS). Bacterial toxins stimulate leukocytes and epithelial cells to release cytokines such as TNF-α, IL-1, and IL-8, as well as eicosanoids, oxygen radicals, and acute-phase proteins, which amplify the inflammatory cascade and recruit polymorphonuclear neutrophils (PMNs) to the site of infection (Stanek et al. 2024). While this immune response is crucial for pathogen elimination, it often causes collateral tissue damage, reduced milk synthesis, and leakage of enzymes such as N-acetyl-β-D-glucosaminidase and lactate dehydrogenase (LDH) (KerroDego and Vidlund 2024; Stanek et al. 2024).

After bacterial clearance, most PMNs undergo apoptosis and are subsequently phagocytosed by macrophages. The remnants of immune and epithelial cells are excreted into the milk, contributing to an elevated somatic cell count (SCC). Moreover, immune cell function is impaired in milk due to limited glucose availability and reduced opsonin concentration, further delaying infection resolution (Stanek et al. 2024).

Recent studies also highlight the role of oxidative stress in mastitis pathogenesis. In transition dairy cows, negative energy balance promotes ROS overproduction, depletes antioxidant defenses such as SOD, GPx, and catalase, and triggers NF-κB–mediated pro-inflammatory signaling, while simultaneously downregulating antioxidant gene expression such as Nrf2 and NQO1 (Ayemele et al. 2021). This oxidative imbalance exacerbates inflammation and increases susceptibility to intramammary infections. In summary, mastitis results from a breakdown of physical barriers, uncontrolled microbial invasion, and an immune-inflammatory response that, while protective, frequently causes mammary tissue injury and reduced milk yield. Metabolic and oxidative stress further intensify this pathogenic process.

QUALITATIVE AND QUANTITATIVE CHANGES IN MILK

All nutrients that render milk and dairy products essential components of the human diet simultaneously provide a favorable medium for the growth of pathogenic microorganisms. Milk obtained from cows with subclinical mastitis, which shows no visible alterations, when mixed into bulk tank milk, enters the food chain and poses a potential risk to human health.

Consequently, milk and dairy products may serve as vehicles for pathogen transmission. Mastitis not only reduces milk yield but also markedly compromises its quality (Schadt and Iris 2023).

Qualitative and quantitative alterations in milk are strongly correlated with the severity of mammary gland inflammation. These changes are characterized by an increased number of somatic cells, higher concentrations of serum-derived proteins, increased permeability of cellular membranes, cellular disruption with release of cytosolic components, elevated enzymatic activity, and reduced secretion of key milk constituents (lactose, casein, fat), ultimately resulting in a decreased overall milk yield (Alhussien et al. 2018). Lactose synthesis, which occurs in the Golgi apparatus of mammary secretory cells under the action of galactosyltransferase and *α*-lactalbumin enzymes with blood glucose as a precursor, is significantly impaired during inflammation, as the glucose supply to the mammary gland diminishes. (Sadovnikova et al. 2021). Consequently, the lactose concentration in milk is reduced. Similarly, the fat content decreases as bacterial infection of the mammary gland damages the secretory epithelium, induces the formation of intercellular gaps, and enhances blood capillary permeability. This process facilitates the influx of Na^+ and Cl^- ions into the alveolar lumen in order to maintain osmotic balance, while K^+ concentration decreases proportionally. Proteins synthesized in secretory cells (*α*-casein, *β*-casein, *α*-lactalbumin, *β*-lactoglobulin) decline, whereas serum-derived proteins such as albumin and immunoglobulins increase. Given that calcium in milk is predominantly casein-bound, impaired casein synthesis contributes to reduced calcium content. Moreover, enhanced capillary permeability enables bicarbonate ions to enter the milk, leading to an increase in pH (Rainard et al. 2022).

Pasteurization effectively reduces viable microbial populations but does not inactivate preformed bacterial toxins. A common mastitis-causing pathogen, *S. aureus*, is frequently isolated from milk, and enterotoxins produced by toxigenic strains are major contributors to foodborne illness. Additionally, antibiotic residues present in milk can elicit severe hypersensitivity reactions in individuals allergic to these compounds (Almurawif et al. 2019).

PRODUCTION OF FREE RADICALS AND OXIDATIVE STRESS

Redox processes represent one of the fundamental biochemical mechanisms in living organisms, as they involve the transfer of electrons in metabolic reactions. Disturbance of redox homeostasis arises when an imbalance occurs between reducing agents (electron donors) and oxidants (electron acceptors), resulting in either reductive or oxidative stress. When the production of oxidizing chemical agents exceeds the reducing capacity of the cell, oxidative stress develops- an imbalance in favor of prooxidants. In general terms, oxidative stress is defined as a disruption of the equilibrium between the production of reactive oxygen species (ROS) and the antioxidant defense mechanisms at the cellular or systemic level. Numerous studies have confirmed that impairment of this balance has detrimental effects on organismal health and biological functionality (Turk et al. 2017).

Oxidants are molecules or molecular fragments capable of independent existence, characterized by one or more unpaired electrons in their outer orbital, which makes them highly reactive. Free radicals may arise through several mechanisms: hemolytic cleavage of covalent bonds, loss of an electron from a stable molecule, or gain of an electron by a stable molecule. The latter two mechanisms, both involving electron transfer, are more common in biological systems than hemolytic fission. Although oxygen free radicals are constantly generated as by-products of aerobic metabolism, their biological impact depends on concentration. At high levels, ROS exhibit cytotoxic effects, whereas at controlled physiological levels they participate in essential processes, including cell differentiation, proliferation, and redox-sensitive signaling pathways (Konvičná et al. 2015).

Based on the most widely accepted classification, oxidants are divided into free radicals and non-radical reactive species, depending on the presence of an unpaired electron in the outer orbital. Common free radicals include the hydroxyl radical, nitric oxide, and superoxide anion. Non-radical reactive molecules include peroxynitrites, hydrogen peroxide, and hypochlorous acid. Among these, the hydroxyl radical is considered the most reactive and short-lived species, capable of inducing severe localized damage due to its inability to diffuse away from the site of formation (Kleczkowski et al. 2017).

Oxidative products are generated during aerobic processes such as physical or metabolic stress, inflammatory reactions, infections, and tissue injuries. Infections and autoimmune responses further contribute to the accumulation of oxidants. Dairy cows in the early post-partum period are particularly prone to disrupted redox homeostasis, which is reflected in reduced activity of antioxidant enzymes in erythrocytes and plasma. Stress associated with calving and the initiation of lactation is frequently accompanied by immunosuppression and oxidative stress. The onset of lactation increases the oxygen demand of mammary epithelial cells, thereby enhancing the generation of free radicals as metabolic end-products. Consequently, reactive oxidative metabolites accumulate in peripheral circulation, impair immune responses, and increase susceptibility to both metabolic and infectious diseases during this critical period (Tufarelli et al. 2023).

Nevertheless, the incidence of disease cannot be attributed exclusively to oxidative stress. Genetic predisposition, physiological status, and environmental factors also play a significant role. Importantly, nutritional interventions aimed at strengthening antioxidant defenses have been shown to mitigate these risks. Diets enriched with trace elements such as zinc, copper, and selenium improve the activity of key antioxidant enzymes, thereby increasing the organism's overall antioxidant capacity (Turk et al. 2017).

ANTIOXIDATIVE MECHANISMS

In order to preserve the balance in the body and thereby prevent the possible occurrence of side effects, in response to the creation of free radicals, the creation of protective antioxidant defense mechanisms occurs at the same time (Kleczkowski et al. 2017).

With those mechanisms, the body defends itself from the harmful influence and uncontrolled creation of oxygen radicals during metabolic processes and maintains them in low concentrations. When reactive oxidative metabolites exceed the body's antioxidant capacity, a state of oxidative stress occurs. Antioxidative systems found in cells or other biological fluids protect biologically important macromolecules from peroxidative damage. The protective role results in an improvement of the immune response, which reduces the incidence of infectious diseases, including mastitis (Chandimali et al. 2025).

Antioxidant protection is a system responsible for neutralizing reactive oxygen radicals and can be divided into the following units: - enzymatic antioxidant protection, which refers to enzymes that neutralize free radicals (superoxide dismutase, catalase, glutathione reductase and glutathione peroxidase); - non- enzymatic antioxidant protection consisting of proteins that bind potentially dangerous iron and copper ions in their inactive form and thus prevent the formation of free radicals and numerous low-molecular compounds such as L-ascorbic acid, alpha-tocopherol, carotenoids, glutathione, uric acid, etc. (Sharma et al. 2011).

Enzyme activity is closely related to the mineral status of the animal body. Microelements are an important part of enzymes. Superoxide dismutase is a metalloenzyme present in all eukaryotic cells. It is an enzyme that catalyzes the transformation of superoxide anion into H_2O_2 and oxygen radicals and represents the first line of defense against free radicals. Then, neutralization of the formed hydrogen peroxide is carried out by the activity of catalase or glutathione peroxidase. Superoxide dismutase is an enzyme that helps break down potentially harmful oxygen molecules in cells, which can prevent tissue damage (Konvičná et al. 2015).

Copper (Cu) is considered an important part of this enzyme. It facilitates the absorption and transport of iron. Catalase is among the most widespread enzymes in nature. The main biological role is the breakdown of toxic hydrogen peroxide. It contains a heme part at the active site and can convert two molecules of hydrogen peroxide into oxygen and water. Catalases are present in aerobic organisms, including almost all mammalian tissues, but catalases show the highest enzymatic activity in the liver and in erythrocytes. In eukaryotic cells, catalase is predominantly found in peroxisomes, cytosol and mitochondria (Yang et al. 2015).

Glutathione peroxidase-GPx has a major biological role in defending the body against oxidative damage. The biochemical function of GPx is to reduce lipid hydroperoxides to their alcohol compounds and to reduce free hydrogen peroxide to water. The GPx system has a strong defense power at a low degree of oxidative stress. Selenium (Se) is an important component of this enzyme and plays a significant role in protecting intra- and extracellular lipid membranes from oxidative damage.

Glutathione reductase-GR catalyzes the reduction of glutathione disulfide to glutathione, thus maintaining the intracellular level and its ratio, thereby protecting SH-groups from intracellular proteins and preventing irreversible changes in cell structure (Zigo et al. 2019).

Zinc (Zn) has been found to be a component of over 300 metabolic enzymes. It is necessary to maintain the integrity of the keratin in the milk duct, and zinc deficiency is also associated with reduced formation of T and B lymphocytes and phagocytes. Low Zn level leads to increased incidence of mastitis, low-quality milk and increased somatic cell count. (Omur et al. 2016).

Tocopherol, β-carotene, vitamin A and vitamin C belong to the group of non-enzymatic antioxidant substances. Ascorbic acid is the most abundant and important water-soluble antioxidant for all mammals. Cows suffering from mastitis have lower concentrations of vitamin C in milk and plasma. Vitamin E or tocopherol is the most important lipid-soluble membrane antioxidant and improves the functional efficiency of neutrophils thus protecting against oxidative damage. It acts as a lipid-soluble cellular antioxidant, free radical cleaner and protects against lipid peroxidation. The richest source of vitamin E is fresh green animal food, while concentrates and stored animal food have generally low levels of vitamin E. Plasma concentrations of alpha-tocopherol are low in parturition, so immunosuppression occurs. Antioxidant vitamin supplementation may reduce the inflammatory response and oxidative stress during mastitis. Vitamin A and its precursor β-carotene are important in the maintenance of epithelial tissues and play a vital role in the integrity and stability of the mucosal surface, which can affect the resistance to the entry of pathogenic microorganisms into the mammary gland. Vitamin A is an important factor in improving immune function and reducing oxidative stress.

In addition, β-carotene appears to function as an antioxidant, reducing the formation of superoxide in the phagocyte and playing a significant role in protecting udder tissue and milk from the damaging effects of free radicals. Beta-carotene is also thought to have stimulating effects on immune cells.

Cows with mastitis have significantly lower plasma levels of vitamin A and beta-carotene (Miazek et al. 2022)

More recently, vitamins and minerals have been recognized as antioxidants in animal health and reproduction. Cows fed with high-energy food with added antioxidants in the period from 3 days before to 10 days after calving showed higher activity of antioxidant enzymes in plasma during the same period, compared to cows whose food was not supplemented with antioxidants. Adding antioxidant enzymes and non-enzymatic antioxidants to food, such as vitamin C and E, reduced glutathione, alpha-lipoic acid, flavonoids and minerals, helps prevent oxidative stress (Sharma et al. 2011).

CONCLUSION

The development of mastitis in dairy cows is influenced by multiple interacting factors, including host defense mechanisms, environmental conditions, and the biological nature of the pathogen. High-producing cows are particularly vulnerable, as the metabolic and physiological changes that occur after calving often induce oxidative stress, compromising overall health and welfare. Oxidative imbalance not only predisposes animals to infection but also impairs reproductive performance, shortens the productive lifespan, and increases disease incidence. Both clinical and subclinical mastitis are closely associated with elevated free radical production, reduced antioxidant activity, and altered redox status of milk. Antioxidant enzymes, supported by adequate levels of minerals and vitamins, represent the first line of defense against oxidative damage. Dietary supplementation with antioxidants such as vitamin E and selenium has been shown to mitigate oxidative stress, reduce tissue injury, support immune function, and improve reproductive and productive outcomes.

Therefore, preventive strategies should combine optimal nutrition with proper herd management and hygiene practices to minimize oxidative stress, enhance disease resistance, and safeguard the health and performance of dairy cows.

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