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# Transition Period, Negative Energy Balance and Oxidative Stress

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**Abstract**

The transition period, lasting three weeks before and three weeks following parturition, is critical for high-yielding dairy cows. Hormonal and metabolic changes occur during this period. The energy requirements increase significantly with the onset of lactation. However, if dry matter intake is insufficient, the energy need cannot be met. In this case, the cow attempts to compensate for this by mobilizing its body fat reserves. This leads to the production of free radicals and oxidative stress. Nutritional diseases such as abomasum displacement, hypocalcemia, ketosis, fatty liver, mastitis, metritis, retained placenta, acidosis, and laminitis are particularly common during the transition period in high-yielding cattle. They are all interrelated, and oxidative stress often accompanies or exacerbates many of these diseases. Furthermore, the emergence of one of these diseases triggers the development of others.



**Keywords:** Cow, Nutritional Diseases, Oxidation

## INTRODUCTION

Oxidative stress emerges when an animal's ability to create antioxidants is exceeded by the amount of free radicals it produces. As a result, the animal's defense system is compromised, increasing the risk of infectious disease (Singh, 2015). Increased levels of non-esterified fatty acids (NEFA) in the blood cause the production of lipid peroxides. Immune system cells become inactive when lipid peroxide levels increase. Oxidative stress is brought on by an imbalance in the cell between oxidants and antioxidants. The synthesis of nicotinamide adenine dinucleotide phosphate (NADPH) depends on glucose. NADPH oxidase is an enzyme that generates free radicals and converts oxygen into superoxide anions. The superoxide anions can then be converted into toxic hydrogen peroxide ($H_2O_2$) by the enzyme superoxide dismutase. H2O2 is converted into water and oxygen by glutathione peroxidase (GSH-Px) and catalases. Glutathione enzymatically protects cell membranes from lipid peroxidation. Glutathione peroxidase and glutathione are both cellular antioxidants. The glutathione peroxidase enzyme transforms glutathione's reduced form into its oxidized form. This process is managed by NADPH (Hayırlı et al., 2012; Lean et al., 2013; Koca & Karadeniz, 2003).

Dry matter consumption (DMC) decreases during the transition phase due to rumen volume reduction, calf growth, and hormonal imbalances. This situation causes the animal to enter Negative Energy Balance (NED), weakening its immune system. The antioxidant selenium (Se) enters the structure of the GSH-Px enzyme system. These enzymes degrade H2O2 and lipid hydroxides (Hayırlı et al., 2016; LeBlance et al., 2004). Due to the excretion of minerals and fat-soluble vitamins in milk during lactation, the immune system may be suppressed, leading to immune dysfunction (Curtis et al., 1983). Negative energy balance causes the immune system to be suppressed, which leads to diseases, including retained placenta, mastitis, and metritis (Hayırlı et al., 2016).



**Transition period and negative energy balance in dairy cows**

The transition period in dairy cattle refers to the three weeks before parturition (prepartum period) and the three weeks after parturition (postpartum period). The term "periparturient period" refers to the few days leading up to and following parturition (Büyükoğlu and Aslan, 2018). Dairy cattle go through physiological, endocrinological, and metabolic changes throughout this time. Due to the growing calf and increased milk production, there are significant rises in energy and nutritional needs, especially during the transition period. However, during these times, there are severe decreases in DMC, which prevent the necessary energy from being supplied, leading to NED (Píšťková et al., 2018; Song et al., 2014; Sordillo, 2013). The transition period is defined by complex interactions between NED-induced metabolic and inflammatory changes as well as diseases (Ma et al., 2024). NED, commonly seen in high-yielding dairy cattle, causes increased fat mobilization and a subsequent increase in NEFA concentrations in the blood (Song et al., 2014). This is attributed to the increased energy and nutritional requirements at the onset of lactation and the intensive mobilization of fat reserves (Bezdíček et al., 2024). Negative energy balance typically peaks during the second and third weeks of lactation (Bezdíček et al., 2024; Folnožić et al., 2015).

The liver is the main organ responsible for fat metabolism. Adipose tissue is mostly composed of palmitic acid (C16:0), stearic acid (C18:0), oleic acid (C18:1), and NEFA. The concentration of fatty acids in the blood increases throughout the transition period due to NED (Vanholder et al., 2005). The liver's ability to esterify NEFAs may be exceeded when increased blood NEFA release from NED occurs, leading to NEFAs being oxidized in hepatocytes to produce ketone bodies, primarily β-hydroxybutyric acid (BHBA), acetoacetate, and acetone. These ketone bodies enter the bloodstream, urine, and milk. These bodies serve as an alternate ATP source when glucose levels are low. Ketone bodies support an organism's energy needs, allowing it to cope and even survive during challenging periods (Bezdíček et al., 2024; Zahrazadeh et al. 2018). Increased fatty acids in the blood are dangerous since significant levels of NEFA are converted to ketones or synthesized to triglycerides in hepatocytes, causing ketosis or fatty liver. NEFA concentrations are higher in dairy cattle with high body condition score (BCS) (Bezdíček et al., 2024; Folnožić et al., 2015; Song et al., 2014). Ketone bodies have been found to provide energy for the neurological system, intestinal cells, and heart in several mammals (Bezdíček et al., 2024; Zahrazadeh et al., 2018). Zhang and Ametaj (2020) found a link between ketosis and the susceptibility of cattle to infectious diseases and immune responses. Zarrin et al.(2014b) found that BHBA might be used as an alternative energy source. Zarrin et al. (2014a) further found that an increase in plasma ketone body concentrations is associated with an increased susceptibility to mastitis in dairy cows during early lactation. Ketosis has also been linked to decreased reproduction (Beran et al., 2013), with cattle with subclinical ketosis being 4.3 times less likely to succeed at first insemination than healthy cattle (Rutherford et al., 2016).



NED in cows during the transition period is a highly complex issue and can be examined from multiple perspectives, including external analysis, blood analysis, and a comparison of the components of milk, particularly fat and protein ratios (Ducháček et al., 2020; Stádník et al., 2017). NEFA and BHBA concentrations are reported as indirect markers of NED (Folnožić et al., 2015). The cut-off value for BHBA in cow blood serum is 1.2 mmol/L, while the cut-off value for NEFA in healthy cattle is approximately 0.6 mmol/L (Bezdíček et al., 2024). In recent years, NED in cattle has been focused on the identification of stress signals such as immune changes, oxidative stress, and heat shock proteins. Moreover, many researchers studied changes in immunological response and oxidative status together (Catalani et al., 2010; Shen et al., 2019; Sun et al., 2021). Some authors (Karimi et al., 2021; Shen et al., 2019; Sun et al., 2021) have focused on proinflammatory (e.g., IL1, IL6, IL12, IL19, TNF-α [tumor necrosis factor alpha], IFNY [interferon gamma]) and anti-inflammatory cytokines (e.g., IL-4, IL-10, IL-11, IL-13, TGF-β). Shen et al. (2019) found that in ketosis-affected cattle, the concentration of the anti-inflammatory cytokine IL-10 was reduced, while blood levels of proinflammatory cytokines (IL18, IL1B, and TNF-α) were elevated. According to Sun et al. (2021), cattle with ketosis exhibited decreased activity of GSH-Px, catalase, and superoxide dismutase (SOD), elevated levels of TNF-α, IL6, and IL1B, and elevated levels of H2O2 and malondialdehyde (MDA). Karimi et al. (2021) also found that cows with subclinical ketosis had significantly greater levels of IL-4, IL-10, TNF-α, and haptoglobin throughout the

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transition period than the control group. Furthermore, Petrovic et al. (2022) showed a link between NED and high levels of extracellular HSP70, TNF-α, BHBA, and NEFA.

**Stress and its effects**

Dairy cattle are exposed to various stress factors during the transition period. Stress has a direct impact on nutrition, well-being, and disease. Cattle may experience oxidative stress and diseases during the transition period due to metabolic changes (Bezdíček et al., 2024; Büyükoğlu and Aslan, 2018).

**Free radicals**

Free radicals are molecules or molecule fragments that contain one or more unpaired electrons. These structures are naturally formed during cellular respiration, electron transport, enzymatic processes, and the killing methods used by macrophages, neutrophils, and other phagocytic leukocytes. Free radicals are constantly produced in the active regions of enzymes as intermediate products of enzymatic processes that occur during cellular metabolism (Büyükoğlu and Aslan, 2018; Lean et al., 2013). However, free radicals are unstable and interact with the environment. They produce toxic lipids, reactive proteins, and other free radicals, causing further tissue, DNA, and RNA damage (Lean et al. 2013).



The conversion of nutrients into the energy required to support normal physiological functions occurs through a series of metabolic reactions known as cellular respiration. Aerobic cellular respiration requires oxygen, and reactive oxygen species (ROS) are metabolites produced by the electron transport chain reaction in mitochondria (Büyükoğlu and Aslan, 2018; Sordillo, 2013). ROS are powerful metabolites that can boost the oxygenation of molecules involved in regulating critical cellular functions like differentiation and proliferation. ROS generation at low or moderate levels is critical for a variety of typical immunological responses, both innate and adaptive. There is also evidence that some ROS participate in signal transduction pathways that cause the release of cytokines, eicosanoids, and other immune regulatory factors required for host defence during infection. By changing the way vascular endothelial cells operate, ROS can regulate both the duration and magnitude of the inflammatory response. ROS have a crucial role in enhancing inflammatory responses, particularly during the initial phases of disease (Bezdíček et al., 2024; Sordillo, 2013). Reactive oxygen species acquire electrons by reacting with carbohydrates, lipids, proteins, and DNA. When the number of reactions increases, lipids in the membrane peroxidize and vascular permeability is reduced. This leads to an imbalance of intracellular ions (Büyükoğlu and Aslan, 2018; Ma et al., 2024). Lipids are the molecules that are most damaged by free radicals. Stress-induced lipid peroxidation can lead to an increase in the amount of MDA, a peroxidation product. 8-hydroxy 2'-deoxyguanosine (8-OHdG) is known as a direct indicator of oxidative DNA damage (Büyükoğlu and Aslan, 2018).

**Oxidative stress**

Energy demand leads to increased ROS generation. The antioxidant defense system regulates ROS concentrations (Píšťková et al., 2018). Oxidative stress leads to oxidative damage to the cell membrane and other components. Necrosis and death occur in the cell. Overproduction of ROS leads to stress throughout the organism. This is also seen during NED in cattle. Since oxidative stress plays a critical role in the pathogenesis of many diseases, it can increase their severity. However, ROS does not always lead to negative results. For instance, it contributes to apoptosis activation and influences physiological processes like ovulation, angiogenesis, and corpus luteum activation and regression (Bezdíček et al., 2024; Büyükoğlu and Aslan, 2018). Intermediates like MDA and 4-hydroxyalkenals are indicators of oxidative stress (Píšťková et al., 2018).

Metabolic stress occurs mostly during the periparturient period, when physiological homeostasis is disrupted by abnormal food metabolism, chronic inflammation, and oxidative stress. Metabolic stress in cattle can lead to health problems such ketosis, metritis, and mastitis (Bezdíček et al., 2024; Putman et al., 2018). Metabolic stress in periparturient cattle is similar to the metabolic syndrome in humans. It is caused by oxidative stress, chronic inflammation, and dyslipidemia, all of which are interconnected and influenced by abnormal nutrient metabolism. While lipid mobilization is a typical physiological reaction that helps the cow adjust to these conditions, excessive fat mobilization might be problematic (Putman et al., 2018). Tissues consume more oxygen during periods of high metabolic demand to supply the energy needed for lactation to begin through normal cellular respiration. Increased plasma NEFA levels can cause an increase in ROS (Putman et al., 2018; Sordillo, 2013). This increase in metabolic activity leads to an accumulation of ROS and a depletion of antioxidant defenses (Sordillo, 2013). Concentrations of oxidative stress biomarkers such reactive oxygen metabolites and ferric reductant antioxidant power have been linked to the onset of ketosis in dairy cattle (Mezzetti et al., 2019). Several studies (Cattaneo et al., 2021; De Koster et al., 2019; Tremblay et al., 2018; Vossebeld et al., 2022) assessed metabolic status by analyzing blood variables, including plasma glucose, NEFA and BHBA concentrations, insulin-like growth factor-I (IGF-1), and insulin levels.

There have been also studies that link NEFAs to apoptosis. In a study to determine the molecular mechanism of oxidative stress caused by NEFAs and whether NEFAs cause hepatocyte apoptosis, it was reported that high concentrations of NEFAs promoted apoptosis of bovine hepatocytes, and NEFAs activated the ROS-p38-p53/Nrf2 signaling pathway to induce apoptotic damage in bovine hepatocytes (Song et al., 2014). Additionally, NEFAs activated the ROS-p38-p53/Nrf2 signaling pathway, leading to apoptotic damage in these cells (Song et al., 2014). In addition to changes in metabolic status and NED, inflammation is involved in the etiology of health issues in early lactation as well as cow adaptation to a new lactation. Acute phase proteins (APP), including albumin and haptoglobin, are involved in both the acute and systemic responses to inflammation.

Furthermore, the mobilization of body fat during NED and the subsequent elevation in plasma NEFA levels may contribute to the inflammatory response in dairy cows in early lactation. Inflammation during NED has been linked to increased positive APP synthesis (haptoglobin and ceruloplasmin) and decreased negative APP synthesis (albumin). Studies have shown that cattle with fatty liver had higher haptoglobin and ceruloplasmin concentrations and lower albumin and paraoxonase concentrations in their serum (Ametaj, 2005; Janovick et al., 2023). Ceruloplasmin and haptoglobin concentrations in the plasma of cattle with ketosis were shown to be higher than in healthy cattle (El-Deeb and El-Bahr, 2017; Mezzetti et al., 2019).

**Oxidative stress during the transition period**

The third trimester of pregnancy is when the fetus gains most of its birthweight. Pregnant cows have higher dietary needs during this time. After calving, nutritional requirements rise due to milk production (Folnožić et al., 2015). During the transition period, dairy cows require more energy, which leads to higher oxygen demand and ROS production (Büyükoğlu and Aslan, 2018; Folnožić et al., 2015; Sordillo, 2013). DMC decreases by up to 30%, particularly during the periparturient period. The return or increase in energy is slow, which does not meet the cow's needs, and negative energy balance (NEB) leads to oxidative stress that can continue for four to eight weeks after calving (Collet et al., 2019; Folnožić et al., 2015). A balance of oxidants and antioxidants is required during the transition period to increase dairy cattle productivity (Zahrazadeh et al., 2018). However, an imbalance in the antioxidant defense mechanisms, which are necessary to limit the increased production and buildup of ROS, typically leads to cell damage through peroxidation reactions and, subsequently, to increased oxidative stress in cattle (Büyükoğlu and Aslan, 2018, Folnožić et al., 2015). Calving and lactation are pro-inflammatory processes. Inflammation is an essential component of the innate immune response and is only a negative response when uncontrolled. Controlling inflammation requires an appropriate balance between pathogen exposure and cattle's ability to build effective innate and humoral immune responses (Lean et al., 2013). Oxidative damage can impact cell membranes, enzymes, proteins, nucleic acids, and lipids (Büyükoğlu and Aslan, 2018; Folnožić et al., 2015). The calving and lactation processes are pro-inflammatory. Inflammation is an essential component of the innate immune response and is only a negative response when uncontrolled. Controlling inflammation is achieved by maintaining a balance between exposure to pathogens and the capacity of cattle to activate innate and humoral immune responses (Lean et al., 2013). Oxidative damage can affect the structure and function of cell membranes, enzymes, proteins, nucleic acids (DNA and RNA), and lipids (Büyükoğlu and Aslan, 2018; Folnožić et al., 2015). It has been stated that cattle with a high body condition score (BCS) before calving tend to lose more BCS after calving, which increases plasma reactive oxygen species (ROS), active thiobarbituric acid precursors, and thiol groups, while decreasing plasma superoxide dismutase (SOD) levels in periparturient dairy cattle. Furthermore, it has been established that obese cattle have compromised antioxidant defence systems. Studies revealed that the concentrations of some antioxidant system enzymes, including SOD and GSH-Px enzyme, as well as vitamins and minerals that function as cofactors of non-enzymatic immune systems, decrease during this time (Collet et al., 2019; Píšťková et al., 2018; Zahrazadeh et al., 2018). Song et al., 2014 found that elevated levels of NEFAs caused oxidative damage and apoptosis in bovine hepatocytes. It has also been shown that NEFAs may regulate the ROS-p38-p53/Nrf2 signalling pathway, causing apoptotic damage to bovine hepatocytes.

## Conclusion

The transition period is a critical physiological phase in dairy cattle. The transition period results in NED, which is characterized by decreased dry matter consumption and higher energy demands. This period results in increased NEFA levels, excessive ROS production, and an increase in ketone bodies, particularly in cattle with a high body condition score (BCS), due to excessive lipid mobilization. Oxidative and metabolic stress conditions consequently lead to nutritional diseases such fatty liver, metritis, mastitis, ketosis, and retained placenta. These issues may not occur if endogenous or exogenous antioxidant defence systems are effective. Due to selenium (Se) deficiencies in soil across many regions, it is necessary to supplement cattle with Se. Furthermore, oxidative stress during the transition period can be avoided by applying antioxidants like vitamin A and E as soon as the dry period begins. Periparturient cattle still experience oxidative stress and related health issues, despite the widespread acceptance of including selenium (Se) and other trace minerals in their diets. More studies are needed to better understand how to prevent immune disorders and oxidative stress, as well as to protect against diseases during the transition period through research on the use of antioxidants.



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