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# Oxidative Stress in Transition Dairy Cattle: Current Knowledge and the Potential Impact of Supplementing Organic Trace Elements

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Authors MEA, MAY and SEK conceived and designed the study. Authors MEA and MY managed the literature searches and wrote the first draft of the manuscript. Author MEA edited the manuscript. Authors MEA, MAY, SEK and MY interpreted the data. All authors read and approved the final manuscript.*

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## ABSTRACT

The transition period in dairy cows entails three weeks around the time of calving and is considered a critical time for the entire lactation cycle. During that time, cows can demonstrate tremendous alterations of metabolic status and a dramatic change in cow`s immune system, as well as the pro-oxidant/antioxidant status. In this review, we present contemporary perspectives of the redox status in dairy cattle during the transition period and its effects on health and production with special reference to metabolic derangements, insulin resistance, assessment of redox status and the potential significance of supplementing non-organic and chelating trace elements to the transition cows.

*Keywords: Chelating trace elements; dairy cattle; insulin resistance; oxidative stress; transition period.*

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## 1. INTRODUCTION

The transition period is a demanding phase in the life of dairy cows and entails three weeks around the time of calving and is considered a critical time for the entire lactation cycle [1]. During that time, cows can demonstrate tremendous alterations of the metabolic status and even dramatic changes in cow`s immune system, as well as pro-oxidant/antioxidant status [2]. Such alterations are occurring due to the gap exist between the nutrient requirements and supply that results from variability in nutrient content of feeds and the decrease of dry matter intake (DMI) [3].

The ability of a dairy cow to cope these detrimental alterations is imperative in order to adapt herd management because the demands for milk production cannot be optimized solely by feed intake [4]. If cows are not able to transit the transition period safely, they are more likely to develop metabolic disorders and decrease milk production [4,5]. These metabolic derangements are of utmost clinical significance as they can favor the development of oxidative stress (OS) and alter the immunity of the animals and potentially decrease the animal's reproductive performance [1,6,7].

In the present review, we described the implication of oxidative status on dairy cattle health and production during the transition period and discussed the metabolic derangements, insulin resistance (IR), and the potential significance of supplementing non-organic and organic trace elements to the transition cows to augment the redox status of the transition cows.

### 1.1 Pro-Oxidants and Antioxidants and the Consequences of Oxidative Stress

#### 1.1.1 Pro-oxidants

Oxidants, are substances that can reduce themselves or oxidize others, include two main categories: reactive oxygen species (ROS) and reactive nitrogen species (RNS) [1]. The ROS are derived from molecular oxygen and superoxide anion by mitochondrial electron transport chain or from NADP oxidase; while RNS are derived from nitric oxide by nitric oxide synthase in mitochondria [8].

The most abundant free radicals in biological system are ROS [9]. The catabolic pathways, at the cellular level, has been reported to exaggerate the production of reactive oxygen metabolites (ROMs) [10]. The ROMs is a collective term that includes ROS, such as superoxide anion and hydroxyl radicals, and some non-radical derivatives as hydrogen peroxide and hypochlorous acid. The plasma level of ROMs is an indicator of free radical production [9]. The ROMs can be produced during the normal metabolic pathways and are essential for optimal cellular processes including proliferation, differentiation, and metabolic adaptations [11]. The generation of ATP in the mitochondria through the Krebs' cycle could generate the production of oxygen and $H_2O_2$ [12].

The plasma malondialdehyde has been found to increase immediately in healthy cows during the peripartum period (from one week before to one week after) [10,13], and can be generated in excessive levels as a consequence of lipid peroxidation and is considered as a biomarker of OS [1]. The excessive generation of ROMs has been reported to cause lipid peroxidation, DNA damage, cell membrane and protein damage although oxidative damage of proteins has been poorly elucidated in domestic animals [14].

Advanced Oxidation Protein Products (AOPPs) are novel markers of protein oxidative damage that has been first described in plasma of chronic uremic patients [15]. The authors stated that the AOPPs are generated by chlorinated oxidants by myeloperoxidase which are activated by neutrophils and are considered as mediators of pro-inflammatory responses and activate the immune reaction and the production of autoantibodies [14,16]. More information about the role of protein oxidation in ruminant health could be exaggerated by comparing the AOPPs with advanced glycation end products (AGE) which is considered an indicator of protein oxidation [9]. The correlation between the inflammatory parameter and AGE is weak and the induction of inflammatory activities caused by AOPP is more intense [9].

#### 1.1.2. Antioxidants

The antioxidants are substances that have the ability to delay, prevent, or remove the oxidative damage to the potential target molecules [2]. They can be traditionally classified as enzymatic, and non-enzymatic protein antioxidants, as well as non-enzymatic low molecular antioxidants [1]. The enzymatic antioxidants, includes glutathione

peroxidase (GPx) and superoxide dismutase (SOD), representing the main form of intracellular antioxidant defense [1]. Plasma GPx activity can protect cell membrane from the oxidative damage by catalyzing the reduction of hydrogen and lipid peroxide, thereby considering an indicator of OS [1,9].

The SOD catalyzes the dismutation of superoxide to hydrogen peroxide and is considered to be the first defense mechanism against prooxidants [9]. It is also considered a common indicator to evaluate OS and anti-oxidative system [17]. The SOD catalyzes the direct conversion of oxygen to $H_2O_2$. Both products participate in phosphorylation of various proteins that are a part of signaling networks including mitogen activated protein kinase phosphatases [12].

The non-enzymatic protein antioxidants are found in plasma and represent sulfhydryl (SH) groups of albumin which are valuable elements of extracellular antioxidant defense system against the OS [1]. The total thiol groups of plasma are the most chemically reactive sites and have a strong reducing properties and represent the SH groups of albumin, L-cysteine, and homocysteine under physiological condition [9].

The high susceptibility of protein to oxidative damage could be attributed to the complex nature of proteins and the presence of a variety of oxidizable functional groups in amino acids (e.g., the sulfur group in cysteine and methionine) [9]. Besides, the modification of the biological activity of the altered protein can likely cause an alteration of the tertiary structure of protein that results from a direct oxidation of a specific amino acid, or as a result of cleavage of the protein backbone [18]. The degree of protein damage has been shown to depend on many deferent factors and direct oxidation of cysteine and methionine residues in proteins are considered major consequences of OS-induced changes to protein activity [9,18].

The non-enzymatic low molecular-weight antioxidants, including glutathione, α-tocopherol, β-carotene, and uric acid, are found mainly in plasma and in other extracellular and intracellular fluid [1]. The glutathione, in particular, reacts directly with free radicals, lipid peroxides and protects the cells against oxidative damage and act as a substrate in enzymatic reaction [9].

Up to now, the endogenous regulation of antioxidants in dairy cattle is fully addressed although a few numbers of recent studies have suggested that these mechanisms could be the rationale for the controversial finding related to antioxidant supplementation during the transition period [19]. The nuclear factor E2- related factor 2 (Nrf2) is a redox sensitive transcription factor that controls the transcription of the genes encoding various antioxidant and cytoprotective protein, which is transcriptional regulation of Nrf2 dependent [20]. The ROS can activate Nrf2, which in turn counteract proinflammatory signaling pathways [1,19].

During the transition time, animals are typically in a state of inflammatory like-condition, especially in the liver [1]. During this period there is a strong up-regulation of Nrf2 target genes with antioxidant properties and the unfolded protein response is activated in the liver of dairy cows in this period leading to activation of Nrf2, and thereby increasing expression of antioxidant enzymes [21]. These mechanisms prevent tissue damage induced by ROS production and inflammation. Therefore, they represent an important target for assuring successful adaptation during the periparturient period, and that endogenous regulation of antioxidant molecule might explain the effect of high antioxidant supplementation as high amount of antioxidant might impair antioxidant capacity by suppressing the Nrf2 due to the lower level of ROS resulted in decreasing the expression of antioxidant enzymes [1].

### 1.2 Oxidative Stress during the Transition Period and the Associated Metabolic Derangements

The OS and its impact on dairy cattle health have received a particular attention from several researchers worldwide [9]. The oxidative damage depends on the stage of lactation, nutrition, disease, and seasonal variations [2]. It has also been reported that heat stress, depending on the climatic changes, generates free radicals and reduce plasma antioxidant activity [2,9].

Heat stress that occurs during the transition period of dairy cows could disturb the homeostasis of their physiology and ultimately their health as well as production of inflammatory cytokines (such as tumor necrosis factor alpha (TNF-α), interleukin 1, and interleukin 6) which

play key role in stimulating systemic inflammatory responses in the body [22].

The lactation stage could also play an important role in the OS progression [2]. As the energy reduced during the first weeks of parturition, the transition cow could likely associate with lipid and protein metabolic changes with a resultant increase fat mobilization, and generation of lipid peroxides and ROS [23].

On commercial farms, the estimated feed intake of highly producing dairy cows is not commonly correlated with the concentrate feeding. For example, high crude protein content in the ration of pregnant cows during the clops-up period could increase urea levels and is closely linked to the development of a nitroactive stress status with detrimental consequences on animal health [24]. The alterations of body condition scoring (BCS) around the time calving is also a determining factor for OS in transition cows; as cows with high BCS cows are more sensitive to OS and suffer greater loss of BCS after calving, whereas the median BCS animals had better milk yield performance [25]. Furthermore cows with high BCS are more prone to develop insulin resistance than are cows with medium and low BCS [26].

Under physiological conditions, the ROS are neutralized by the antioxidant system, and the OS occurs when excess production of ROS cannot be counteracted by antioxidant mechanism leading to oxidative damage, and a dysfunctional host immune and increase susceptibility of cows to health disorders [9]. Changes in the oxidative metabolism during the transition period could likely increase the incidence of diseases and might have a role in the progression of several reproductive disorders [1,16]. Hence, a coordinated shifting in nutrient partitioning should considered in order to cope the increased metabolic demands which is necessary for parturition and the onset of lactation [12].

The transition period is usually associated with increase the odds of production disease and the magnitude of such diseases on dairy cow health and productivity can extend far into next lactation, when cows fail to adapt to increasing demands of the transition period [1,2]. The hypermetabolic state that occur during the transition period can result in increased production of ROS and negatively affect the oxidative balance [12]. The generation of ROS can damage the tissues and disrupt metabolism and physiology and causing metabolic disorders and development of diseases in dairy cows [2].

If the energy requirements to the increasing milk yield are not met by the diet during the first few weeks of parturition, the cow will use its own energy reserve and mobilize lipid. When the release of non-esterified fatty acid (NEFA) is in limited concentration, the cow can adapt successfully to the negative energy balance (NEB) and the NEFA is metabolized fully [27]. Thereafter, when the concentration of NEFAs exceed the processing capacity of hepatocyte, the liver function is overwhelmed by triglyceride (TG) causing fatty liver and ketone bodies formation [8,28]. In contrast to increase plasma NEFA levels, the concentration of other plasma lipid fractions such as phospholipid and TG, decrease during the first week of parturition [1,8].

Following parturition, the concentration of palmate and stearate fatty chain within the plasma NEFA fractions are increase significantly and decrease the concentration of omega-3 long chain polyunsaturated fatty acid, these alternations in plasma fatty acid profiles encompass cellular membrane of blood cells including erythrocyte and peripheral blood mononuclear cells [8]. The content of saturated fatty acid such as palmitic acid and stearic acid is increased in the phospholipids and cholesterol esters fractions around the time parturitions, likewise omega-6 poly saturated fatty acids is increased in the cholesterol ester fractions [29,30].

The mobilization of lipids makes NEFA an alternative source of energy that is readily available to cells in different tissue. NEFAs are internalized by leukocyte and endothelial cells by free diffusion or by protein receptor mediation [1,8]. As being internalized in the cytoplasm, NEFAs can take different metabolic pathways in cellular organelles such as the endoplasmic reticulum, when used as an energy substrate, cell specific fatty acid acyl CoAs is formed by acyl-CoA synthetase in the leukocyte thereby facilitating the utilization of NEFAs with acyl-CoA binding protein [1,8]. The accumulation of NEFA has been reported to enhance the production of ROS during the β-oxidation [1]. High NEFA concentration and ROS production are characteristics of metabolic stress and risk factor for several diseases such as mastitis, retained fetal membrane, ketosis and fatty liver and abomasal displacement [31].

### 1.3 The Relationship between Oxidative Stress and Insulin Sensitivity

During the transition period, blood glucose is almost taken up by the udder for the synthesis of lactose, and therefore, a dysregulation in insulin response can be potentially develop in order to prioritize the use of glucose by the mammary gland which takes place insulin independently [32]. A transient state of IR is occurring in dairy cattle during the transition period which guarantees glucose supply to the fetus and to the udder by minimizing glucose uptake by peripheral insulin responsive tissues such as skeletal muscles and adipose tissue [26]. However IR can be exacerbated (because of the high milk production) which cause lipolysis of adipose tissue and accumulation of NEFA with subsequent greater IR, which is associated with several ailments such as fatty liver and a state of OS [7,11].

There has been an association between oxidative status and insulin sensitivity variables in dairy cattle around the time of calving [33]. The onset increase of milk synthesis and secretion are often accompanied by increase energy and oxygen requirement [34]. The increased oxygen demand augments the production of ROS [35], exacerbate inflammatory response and reduce insulin sensitivity [11,36].

### 1.4 The Relationship between the Immune-Inflammatory Reaction and Oxidative Stress

Physiological stress that occurs during the transition period can likely impact the effectiveness of the immune system making the lactating cow more vulnerable to infectious diseases such as mastitis and metritis, with a subsequent impairment of reproductive performance [37]. The development of OS is thought to be a significant factor that leads to dysfunctional inflammatory responses around the time of calving [38]. The intense lipid mobilization could increase the expression of TNF-*α* and exacerbate the production of acute phase proteins and the inflammatory response [11,36]. The resulting inflammatory mediators act locally on the vascular endothelium to increase blood flow and facilitate the migration of leukocyte from the blood to site of infections, and release the acute phase protein from the liver, which increase the heart rate and body temperature and decrease the feed intake [39]. The dysregulation of the inflammatory status is also a contributing factor to the metabolic disturbances of dairy cows [1,40].

In general, the dysfunctional inflammation resulting from ROS overproduction can activate the redox-sensitive transcription factors (NFκB) which increase the expression of pro inflammatory mediators (TNFα, IL-6 etc..) inducing tissue damage, decrease milk production, greater disease incidence and poor fertility, and metabolic stress [1]. It has been recently suggested that ROS could provoke the signaling activity of nuclear factor kappa B E2-related factor, which promotes inflammation and allows an adequate initiation of anti-oxidative defenses [11]. Taken together, the magnitude of acute systemic inflammation during the transition period include adipose tissue mobilization, breakdown of liver glycogen, and liver TG accumulation, impairment insulin sensitivity, and a direct stimulation of lipolysis and all of these condition are associated with ketosis and fatty liver [38]. Hence, the elevation of blood NEFA concentrations could impact the inflammatory response of transition cows and used as energy substrate at the peripheral tissue [1].

### 1.5 Impact of Oxidative Stress on Milk Constituents

The milk composition varies according to the health status of the cow, stage of lactation, feeding, and the genetic factors because several countries is using different breeds and feeding regimens and have had variable calving patterns and breeding practices [41]. Due to the fact that a close correlation exists between the oxidative status and mastitis in cows, a superiority of oxidizing processes can indicate a subclinical inflammation of the mammary gland, depending on the extent of inflammation one may observe a reduction in milk yield and unfavorable changes in the milk composition [42].

The oxidation processes occurring in milk, along with its low nutritive value could likely provoke a negative impact on organoleptic parameters principally taste, and might cause inactivation of many biologically active ingredients contained in it [43]. The same authors have mentioned that there are a negative correlation between the somatic cell count, milk yield and lactose and a positive correlation with fat and protein percentage, however, the elevated protein

concentration has been reported to be unfavorable because the amount of milk whey proteins rather than casein increased, making milk unfit for dairy production. On the other hand, elevated both somatic cells and bacteria in milk (accompanies the inflammation of the mammary gland) could have role in the assessment of milk quality [42].

The frequent milking of cows could also increase in the number of epithelium cells in the milk due to the local stimulation of the proliferation of cells and reduction of their destruction in the process of apoptosis. Likewise, the increased production of milk can increase the demand for energy, which in turn generates ROS [42]. Nevertheless, the high quality of milk is related to its content from antioxidants, owing to prolonging milk lifetime via reducing its oxidation [44].

## 1.6 Assessment of the Redox Status in Dairy Cows during the Transition Period

The role of OS in ruminant medicine has received a growing interests and great efforts to develop reliable methods for quantifying novel markers of OS [9]. In that context, it has been shown that the free radical analytical system technology is offering a quick, simple, precise and reliable method to assess oxidative status in dairy cattle [45]. The OS is still lacking the reference values of OS biomarkers which prevent the identification of individual cows that are liable to OS [9]. Among the factors that could likely cause difficulty in implementing reference values for antioxidants are (1) some degrees of ROS are essential for maintaining physiological process, (2) great influence of the diet, environmental temperature, milk yield, or BCS, although animals under identical housing and feeding show a great individual variation with regard to adaptation from pregnancy to onset of lactation [46].

The ROS are quantified using the d-ROM test as well as the total serum antioxidant capacity with the OXY- Adsorbent test, However, OS index (OSi) can be calculated as ROS/SAC [11]. The concentration of ROMs is relatively stable from 1 month -prior to- and after calving in healthy cows, except for a significant drop three days around the time of calving. The ROMs kit has been developed to assess oxidant levels in plasma and other biological fluids [10]. The ROMs test has been validated using spin resonances, which is considered the gold standard for measuring total oxidative status [9].

MDA is generated as a consequences of lipid peroxidation and is considered a biomarker of OS while, the AOPPs are considered markers of protein oxidation [9]. MDA is estimated by thiobarbutric acid reactive substance (TBARS), the most commonly encountered substance in veterinary medicine (by spectrophotometer) which give a red pigment but generally not specific because TBARS detect a wide range of lipid peroxidation products and not specific for MDA [1]. Using high pressure liquid chromatography or ELISA are highly specific and perhaps more accurate for detecting lipid peroxide compared to spectrophotometric procedure [1,9,39]. Alongside the measurable OS markers, several indicators of antioxidative markers could be estimated such as GPx and SOD, albumin, L-cysteine, and homocysteine, glutathione, α-tocopherol, and uric acid [1,11,14,16,17].

For more clarity, we tabulated a reference value of wide range of measurable variables during the transition period (Tables 1-6).

## 1.7 Implication of Antioxidant Supplementation during the Transition Period

Both trace elements and vitamins play a pivotal role in the health and production of dairy cows. Mineral matters like selenium(SE), zinc (Zn), copper (Cu), and cobalt (Co) have an important role in health, fertility, lactation and immune functions [47]. It has shown that vitamins and trace minerals are involved in the antioxidant defense system and deficiency of any of these elements could depress the immunity in transition cows [48]. Supplementing dairy cattle with trace minerals and vitamins has been reported to minimize stress and optimize animal production [49].

### 1.7.1 Selenium

SE is an important trace element and its deficiency is associated with poor growth, health and fertility in dairy animals [50]. It is a component of at least 25 different selenoproteins; in these proteins sulfur is replaced with SE allowing proteins to donate hydrogen and take apart of reduction reactions [51]. Selenoproteins include GPx and thioredoxin reductase which are important components of antioxidant and immune system to destroy

hydrogen peroxides and also lipid hydroperoxides [48,51,52]. SE is an essential micronutrient for ruminants, and has been demonstrated to be effective in counteracting OS and the severity of several ailments of dairy cattle, through direct antioxidant effect or via enhancing the immune function [53]. Similar to other essential micronutrients, it has been suggested that SE is needed for maintaining growth, pregnancy and lactation of dairy cow [53]. It is also essential for an optimum immune response through the key role regulation and antioxidant function [54]. The deficiency of SE deficiency is a more common clinical entity that is observed in adult transition dairy cattle and has been reported to be a significant risk factor for the development of mastitis, retained fetal membranes, and metritis [55]. Therefore, a prepartum supplementation of SE can reduce the incidence of retained placenta in dairy fed diet low in selenium [56].

### 1.7.2 Zinc

Zn is a component of antioxidant system "Cu-Zn SOD" and is needed to induce the synthesis of metallothionin, a metal binding protein, which may scavenge hydroxide radicals. Alongside its antioxidant efficacy, Zn can affect the immunity through its vital role in cell replication and proliferation [51], which hunts superoxide, one of the components of ROS in the immune cells [37]. Zinc plays a main role in the immune system and has a significant role in the repair and maintenance of the uterine covering following parturition [50].

### 1.7.3 Copper

Copper plays an important role in the immune system [50], and is a component of the antioxidant system "Cu-Zn SOD [37] and ceruloplasmin which is responsible for dismutation of superoxide radicals to hydrogen peroxide in the cytosol [48]. Cu is also involved in the metabolism of vitamin A&E [54] where the significance of these vitamins has been increased in heifers supplemented with mineral mixture containing Cu compared with non-supplemented group.

### 1.7.4 Cobalt

There has been limited published data about the systemic and tissue biological effect of supplementing Co during the transition period in dairy cows, although some researchers have observed that organic Co supplementation produces moderate alterations in glucose and fatty acids values and has beneficial effect on OS and inflammation [57]. The liver contains the highest concentration of Co within tissues and is considered the main storage site of this element. Some researchers have investigated the effect of supplemental dietary Co on milk production of cows [58]. The authors have found that the multiparous cows fed a diet with 1.26 mg of Co/kg of DM had greater milk and 3.5% FCM yields than multiparous cows fed diets with 0.37 or 0.68 mg of Co/kg of DM; however, no effect of dietary Co on milk yield was observed in primiparous cows. Limited research has determined the effect of Co source in dairy cattle diets on lactation performance and metabolism [52].

### 1.7.5 Manganese

As what has seen for Zn and Cu, Mn plays an important role in removing superoxide radicals produced by active immune cells [59] and is considered as a key mitochondrial element as Mn-dependent SOD protecting fragile mitochondrial membranes from attack of free radicals [60]. Although Mn is an essential component of a wide range of enzyme involving immune, and antioxidant protection and carbohydrate and lipid metabolism, there have been few studies that specially assessed the effect of immune function and metabolism in dairy cows [54]. In an earlier study, it has been found that Mn can increase antibody titers and other nonspecific resistance factors in dairy cattle [51].

### 1.7.6 Chromium (Cr)

The primary role of Cr appears to relate to its ability to enhance the action of insulin, and is essential for normal carbohydrate, lipid, and protein metabolism [61]. It has been demonstrated that Cr can affect energy metabolism through modulating tissue responses to insulin. The demand for Cr is typically increased during nutritional, metabolic, and physical stress [62]. The trophic effect of Cr is to enhance communication between insulin and its receptors located on the cell membrane of insulin sensitive tissues by increasing membrane fluidity and rate of insulin internalization [52,63].

**Table 1. Levels of cited pro-oxidant variables and redox status in dairy cattle during the transition period**

| Variables / Status/period | ROS (carr U) | SAC (µmol HClO/mL) | OSi | MDA (nmol/ml) | AOPP (ng/ml) | References |
|---|---|---|---|---|---|---|
| Close up | - | - | - | 31.87 | - | [74] |
| Early lactation | - | - | - | 33.17 | - | |
| Restricted production | 142 | 2219 | 0.064 | - | - | |
| High production | 134 | 2400 | 0.054 | - | - | [10] |
| Early lactation | 122.1 | - | - | - | 43.8 | [16] |
| Periparturient | 0.79 | - | - | 2.29±0.37 | - | [17] |
| 3w before | - | - | - | 0.57 ±0.0 8 | - | |
| 1w before | - | - | - | 0.54 ±0.13 | - | [23] |
| 1w after | - | - | - | 0.76 ± 0.21 | - | |
| 3 w after | - | - | - | 0.45 ± 0.16 | - | |
| -30d to-16 d | 140.6 | 528 | 0.28 | - | - | |
| -15d to-3d | 123.5 | 526 | 0.24 | - | - | [11] |
| 3d to15d | 142.6 | 510 | 0.30 | - | - | |
| 16d to30 d | 168.3 | 479 | 0.38 | - | - | |
| -21d | - | - | - | 3.21 ± 0.29 | - | |
| -14d | - | - | - | 3.19 ± 0.12 | - | |
| -7d | - | - | - | 3.31 ± 0.09 | - | |
| 0d | - | - | - | 3.69 ± 0.28 | - | [2] |
| 7d | - | - | - | 3.54 ± 0.21 | - | |
| 14d | - | - | - | 3.4 ± 0.13 | - | |
| 21d | - | - | - | 3.3 ± 0.17 | - | |
| -6 d | 148 | 159 | 0.93 | - | - | |
| 0 d | 194 | 187 | 1.03 | - | - | [40] |
| 1 d | 196 | 180 | 1.08 | - | - | |
| 2 d | 120 | 144 | 0.83 | - | - | |
| 6 d | 172 | 174 | 0.99 | - | - | |
| 12d | 175 | 135 | 1.3 | - | - | |
| Pre calving [a] | - | - | - | 8.75 ±2.37 | - | |
| Calving [a] | - | - | - | 9.13 ±1.19 | - | |
| Post calving [a] | - | - | - | 8.59 ±1.97 | - | |

| Variables / Status/period | ROS (carr U) | SAC (µmol HClO/mL) | OSi | MDA (nmol/ml) | AOPP (ng/ml) | References |
|---|---|---|---|---|---|---|
| Pre calving [b] | - | - | - | 8.84 ±1.49 | - | [25] |
| Calving [b] | - | - | - | 9.48 ±1.16 | - | |
| Post calving [b] | - | - | - | 6.93±1.96 | - | |
| Pre calving [c] | - | - | - | 9.05±1.28 | - | |
| Calving [c] | - | - | - | 9.54±2.1 | - | |
| Post calving [c] | - | - | - | 6.69±1.52 | - | |
| Pre calving [d] | - | - | - | 12.64±1.81 | - | |
| Calving [d] | - | - | - | 17.17±2.42 | - | |
| Post calving [d] | - | - | - | 10.03±1.23 | - | |
| BCS low | 134 | - | - | 7.40 | - | |
| BCS medium | 140 | - | - | 6.60 | - | [26] |
| BCS high | 127 | - | - | 7.13 | - | |

*** ROS: Reactive oxygen capacity, SAC: serum antioxidant capacity, OSi: OS index, MDA: Malondialdehyde; AOPPs: Advanced oxidation protein products, [a, b, c, and d]: indicted the BCS degree 3.25, 3.75, 4.25, and 5 respectively, BCS: body condition score*

**Table 2. Levels of cited antioxidants in dairy cattle during the transition period**

| Variables / Period/status | GPx (mu/ml) | SOD (U/ml) | Vitamin E (nmol/ml) | References |
|---|---|---|---|---|
| per parturient | - | 70.11 ± 7.86 | - | [17] |
| 3w before | 67.3 ± 5.7 | 510.3 ± 67.8 | 29.7±7.5 | |
| 1w before | 71.4 ± 6.2 | 546.3 ± 85 | 25.3±11.2 | [23] |
| 1w after | 69.7 ± 4.1 | 592.2 ± 67.1 | 24.5±5.6 | |
| 3 w after | 74.8 ± 4.8 | 624 ± 86 | 29.5±11.8 | |
| -21d | 31.6 ± 0.3 | - | - | |
| -14d | 31.9 ± 0.8 | - | - | |
| -7d | 27 ± 1.1 | - | - | [2] |
| 0d | 17 ± 1.12 | - | - | |
| 7d | 18.5 ± 0.4 | - | - | |
| 14d | 19.8 ± 1.6 | - | - | |
| 21d | 21 ± 0.21 | - | - | |
| Pre calving [a] | - | 177.40±27.52 | - | |
| Calving [a] | - | 191.46±32.91 | - | |
| Post calving [a] | - | 183.98±24.94 | - | |
| Pre calving [b] | - | 171.08±22.67 | - | |
| Calving [b] | - | 177.01±23.70 | - | |
| Post calving [b] | - | 125.09±19.07 | - | [25] |
| Pre calving [c] | - | 180.14±18.03 | - | |
| Calving [c] | - | 192.71±25.65 | - | |
| Post calving [c] | - | 131.74±20.74 | - | |
| Pre calving [d] | - | 256.79±25.84 | - | |
| Calving [d] | - | 348.58±23.43 | - | |
| Post calving [d] | - | 216.57±26.10 | - | |
| BCS low | 16.3 | 62.2 | | [26] |
| BCS medium | 15.9 | 65.0 | | |
| BCS high | 16.9 | 62.9 | | |

*** SOD: Superoxide dismutase; GPX: glutathione peroxidase, [a, b, c, and d]: indicted the BCS degree 3.25, 3.75, 4.25, and 5 respectively; BCS: body condition score*

**Table 3. Levels of cited metabolic variables in dairy cattle during the transition Period**

| Variable / Period/ status | NEFA (mmol/L) | Glucose (mmol/L) | Insulin (µlU/mL) | BHBA (mmol/L) | References |
|---|---|---|---|---|---|
| Pre parturient | 0.29 | 3.21 | 13.7 | - | [64] |
| Post parturient | 0.6 | 2.74 | 9.8 | 0.8 | |
| -21d $^{calving}$ | 0.47 | 3.99 | - | - | [75] |
| 7 d $^{calving}$ | 1.9 | 3.44 | - | - | |
| Close up | 0.39 | 4.12 | - | - | [74] |
| Early lactation | 0.53 | 3.93 | - | - | |
| Restricted production | 0.88 | 3.31 | - | - | [10] |
| High production | 0.65 | 3.64 | - | - | |
| 1w before $^{calving}$ | 0.79± 0.07 | 3.57 ± 0.15 | 5.63± 0.38 | - | [65] |
| 2w after $^{calving}$ | 0.61±0.05 | 3.19 ± 0.09 | 3.67± 1.42 | - | |
| 4w after $^{calving}$ | 0.54±0.05 | 3.05 ± 0.05 | 7.31± 1.05 | - | |
| Early lactation | 0.30±0.28 | 3.33 ± 0.49 | - | 0.82 ± 0.33 | [76] |
| Early lactation | 0.63 | 2.79 | - | - | [16] |
| -7d | 0.78 | 2.5 | 11.34 | - | [77] |
| At calving | 0.79 | 2.82 | 8.4 | - | |
| 21d | 0.79 | 2.57 | 6.1 | - | |
| Per parturient | 0.51±0.15 | 3.30 ± 0.16 | 14.01±2.01 | 0.62±0.11 | [16] |
| Pre parturient | 0.21 | 3.51 | 5.6 | 0.42 | [62] |
| Post parturient | 0.68 | 3.12 | 2.9 | 0.66 | |
| Day1$^{calving}$ | 0.55 | 3.79 | 4.5 | 0.8 | |
| Day7$^{calving}$ | 0.4 | 3.39 | 6 | 0.9 | [78] |
| Day14$^{calving}$ | 0.44 | 3.50 | 4 | 1 | |
| Day 21$^{calving}$ | 0.4 | 3.39 | 7 | 0.9 | |
| lactating cows | 0.176 | 3.50 | - | - | [79] |
| Healthy$^{st1}$ | 0.74 | 3.60 | - | 0.86 | |
| Ketotic$^{st1}$ | 0.69 | 3.60 | - | 1.2 | [80] |
| Healthy$^{st2}$ | 0.59 | 3.21 | - | 9.3 | |
| Ketotic$^{st2}$ | 0.88 | 3.11 | - | 9.2 | |
| -30d to-16 d | 0.38 | 3.35 | 8.4 | 0.55 | |
| -15d to-3d | 0.35 | 3.37 | 7.2 | 0.58 | [11] |
| 3d to15d | 0.52 | 3.13 | 5.2 | 0.54 | |
| 16d to30 d | 0.35 | 2.83 | 5.8 | 0.63 | |

| Variable / Period/ status | NEFA (mmol/L) | Glucose (mmol/L) | Insulin (µIU/mL) | BHBA (mmol/L) | References |
|---|---|---|---|---|---|
| 3w before | - | - | - | 0.44 ± 0.23 | |
| 1w before | - | - | - | 0.44 ± 0.33 | [81] |
| 1w after | - | - | - | 0.79 ± 0.50 | |
| 3 w after | - | - | - | 0.63 ± 0.91 | |
| -30 d | 0.119 ± 0.01 | 3.55 ± 0.07 | - | 0.072 ± 0.02 | |
| -15d | 0.123 ± 0.02 | 3.38 ± 0.06 | - | 0.271 ± 0.02 | [73] |
| -7 d | 0.169 ± 0.03 | 3.28 ± 0.71 | - | 0.309 ± 0.04 | |
| At calving | 0.463 ± 0.06 | 2.94 ± 0.06 | - | 0.573 ± 0.06 | |
| Postpartum $^{Day1}$ | 0.461 ± 0.06 | 2.74 ± 0.05 | - | 0.578 ± 0.03 | |
| Postpartum $^{Day2}$ | 0.447 ± 0.06 | 2.71 ± 0.04 | - | 0.573 ± 0.06 | |
| -6 d | 0.15 | - | - | 0.68 | |
| 0 d | 0.24 | - | - | 0.48 | [40] |
| 1 d | 0.59 | - | - | 0.67 | |
| 2 d | 0.33 | - | - | 0.72 | |
| 6 d | 0.22 | - | - | 0.51 | |
| 12d | 0.18 | - | - | 0.56 | |
| Pre calving $^{a}$ | 0.143±0.031 | - | - | 0.322±0.05 | |
| Calving $^{a}$ | 0.87 ±0.102 | - | - | 0.35±0.034 | |
| Post calving $^{a}$ | 0.151±0.03 | - | - | 0.37±0.05 | |
| Pre calving $^{b}$ | 0.14 ±0.03 | - | - | 0.35 ±0.064 | [25] |
| Calving $^{b}$ | 0.77 ±0.16 | - | - | 0.32 ±0.052 | |
| Post calving $^{b}$ | 0.9 ±0.15 | - | - | 0.34±0.047 | |
| Pre calving $^{c}$ | 1.53±0.35 | - | - | 0.41 ±0.06 | |
| Calving $^{c}$ | 0.83±0.13 | - | - | 0.35±0.06 | |
| Post calving $^{c}$ | 0.89±0.124 | - | - | 0.39±0.84 | |
| Pre calving $^{d}$ | 1.7±0.45 | - | - | 0.57±0.068 | |
| Calving $^{d}$ | 1.37±0.14 | - | - | 0.55±0.089 | |
| Post calving $^{d}$ | 1.6 ±0.15 | - | - | 0.56 ±0.066 | |
| BCS low | 119 | 3.19 | 1.97 | 0.56 | |
| BCS medium | 116 | 3.22 | 2.05 | 0.62 | [26] |
| BCS high | 134 | 3.27 | 2.41 | 0.57 | |

*** NEFA: Non stratified fatty acid; BHBA: Beta hydroxy butyric acid; $^{st:}$ study number, $^{a, b, c, and d}$: indicted the BCS degree 3.25, 3.75, 4.25, and 5 respectively; BCS: body condition score*

**Table 4. Levels of cited immune-inflammatory variables in dairy cattle during the transition period**

| Variable / Period/ status | SAA (µmg/L) | Haptoglobin (µmg/L) | IgG (mg/mL) | References |
|---|---|---|---|---|
| Early lactation | - | 27 | - | [16] |
| Pre parturient | - | 6.9 | - | [60] |
| Post parturient | - | 9.7 | - | |
| 21d before $^{calving}$ | - | - | 9.4 | [82] |
| 2d before $^{calving}$ | - | - | 3.1 | |
| 15d after $^{calving}$ | - | - | 10.8 | |
| 30d after $^{calving}$ | - | - | 10.3 | |
| Healthy$^{st1}$ | 17.2 | 13.9 | - | |
| Ketotic$^{st1}$ | 72.7 | 84.1 | - | [80] |
| Healthy$^{st2}$ | 58.1 | 4.7 | - | |
| Ketotic$^{st2}$ | 101.5 | 17.6 | - | |
| -30d to-16 d | 39.1 | 21 | - | |
| -15d to-3d | 52.1 | 39 | - | [11] |
| 3d to15d | 78.2 | 51 | - | |
| 16d to30 d | 66.4 | 66 | - | |
| -30 d | - | - | 31.13 ± 0.84 | |
| -15d | - | - | 32.67 ± 1.50 | [73] |
| -7 d | - | - | 31.57 ± 1.00 | |
| At calving | - | - | 28.42 ± 1.13 | |
| Postpartum $^{Day1}$ | - | - | 24.33 ± 1.05 | |
| Postpartum $^{Day2}$ | - | - | 22.72 ± 1.47 | |
| -6 d | - | 5 | - | |
| 0 d | - | 6 | - | [40] |
| 1 d | - | 6 | - | |
| 2 d | - | 7 | - | |
| 6 d | - | 4 | - | |
| 12d | - | 32 | - | |

***SAA: serum amyloid A; IgG: immunoglobulin G; $^{st:}$ study number*

**Table 5. Levels of cited hepato-renal and protein variables in dairy cattle during the transition period**

| Variables / Period/status | AST (U/L) | GGT (U/L) | Creatinine (µmo/L) | Albumin (g/dL) | Globulin (g/L) | TSP (g/L) | References |
|---|---|---|---|---|---|---|---|
| Close up | 29.08 | - | 122.9 | 42 | 30.1 | 72.1 | [74] |
| Early lactation | 34.31 | - | 107.8 | 42.7 | 34.5 | 77.2 | |
| Early lactation | 126.5±43.2 | | - | 28 ±3.7 | 52± 9 | 80.7± 8 | [76] |
| Per parturient | 93 ± 13 | 20.7±0.42 | - | 34 ± 2.2 | 41 ± 6 | 77 ± 5 | [17] |
| -30 d | 76.4 ± 1.37 | 22.86 ± 1.0 | - | - | - | - | |
| -15d | 80.7 ± 1.40 | 24.42 ± 0.9 | - | - | - | - | [73] |
| -7 d | 79.9 ± 1.11 | 22.7 ± 0.94 | - | - | - | - | |
| At calving | 85.47 ± 0.9 | 26.2 ± 0.62 | - | - | - | - | |
| Postpartum $^{Day1}$ | 86.5 ± 0.76 | 24.8 ± 0.76 | - | - | - | - | |
| Postpartum $^{Day2}$ | 84.5 ± 0.74 | 25.4 ± 0.68 | - | - | - | - | |
| -6 d | - | - | - | 35 | - | - | |
| 0 d | - | - | - | 34.9 | - | - | [40] |
| 1 d | - | - | - | 35.6 | - | - | |
| 2 d | - | - | - | 35.2 | - | - | |
| 6 d | - | - | - | 34.3 | - | - | |
| 12d | - | - | - | 32.5 | - | - | |
| BCS low | 67.6 | 26.5 | - | 30.9 | - | - | [26] |
| BCS medium | 62.9 | 30.1 | - | 31.5 | - | - | |
| BCS high | 68.0 | 30.4 | - | 32.3 | - | - | |

*** AST: aspartate amino transferase; GGT: gamma glutamyl transferase; TSP: total serum protein*

**Table 6. Levels of cited hematological variables in dairy cattle during the transition period**

| Variables<br>periods | RBC ($x10^{12}$/L) | Hb (g/L) | PCV (L/L) | MCV (fL) | MCH (pg) | MCHC (g/L) | PLT ($x10^9$/L) | WBC ($x10^9$/L) | Lymphocytes ($x10^9$/ L) | Eosinophil ($x10^9$/ L) | Monocytes ($x10^9$/L) | Neutrophils ($x10^9$/ L) | References |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Pre partum | 5.5 | - | - | - | - | - | - | 7.27 | 4.1 | - | 0.94 | 3.05 | [83] |
| Post-partum | 5.1 | - | - | - | - | - | - | 5.84 | 3.2 | - | 0.18 | 2.37 | |
| Pre calving | 6.49 | 111 | 0.31 | 43.8 | 16.02 | 364.2 | - | 13.80 | 5.30 | 0.99 | 0.14 | 7.30 | [84] |
| 0-21 fresh cow | 5.02 | 79 | 0.21 | 41.6 | 15.46 | 371.6 | - | 11.68 | 5.84 | 0.76 | 0.06 | 5.02 | |
| Pre partum | 5.36 | 81.1 | 0.28 | - | - | - | 286.354 | 13.46 | 8.92 | 1.52 | 7.2 | - | [85] |
| -30 d | - | - | - | - | - | - | - | 6.1 ± 0.2 | 2.53 ± 0.2 | - | 0.35 ± 0.02 | 2.8 ± 0.1 | |
| -15d | - | - | - | - | - | - | - | 6.1 ± 0.2 | 2.6 ± 0.1 | - | 0.36 ± 0.02 | 2.8± 0.1 | [73] |
| -7 d | - | - | - | - | - | - | - | 7.2 ± 0.3 | 3.2 ± 0.2 | - | 0.39 ± 0.02 | 3.2 ± 0.13 | |
| At calving | - | - | - | - | - | - | - | 8.7 ± 0.3 | 3.8 ± 0.2 | - | 0.47 ± 0.03 | 4.1 ± 0.2 | |
| Postpartum $_{d1}$ | - | - | - | - | - | - | - | 8.8 ± 0.4 | 3.8 ± 0.2 | - | 0.49 ± 0.04 | 4.03 ± 0.2 | |
| Postpartum $_{d2}$ | - | - | - | - | - | - | - | 9.4 ± 0.3 | 4.2 ± 0.16 | - | 0.48 ± 0.04 | 4.4 ± 0.2 | |
| -6 d | - | - | - | - | - | - | - | 10.0 | 4.85 | 0.07 | 0.27 | 4.79 | |
| 0 d | - | - | - | - | - | - | - | 9.46 | 4.68 | 0.06 | 0.25 | 4.43 | [40] |
| 1 d | - | - | - | - | - | - | - | 8.29 | 4.13 | 0.07 | 0.17 | 3.88 | |
| 2 d | - | - | - | - | - | - | - | 8.39 | 4.07 | 0.14 | 0.19 | 3.94 | |
| 6 d | - | - | - | - | - | - | - | 9.27 | 4.37 | 0.17 | 0.23 | 4.48 | |
| 12d | - | - | - | - | - | - | - | 8.69 | 4.08 | 0.24 | 0.19 | 4.13 | |
| BCS low | 6.30 | 91.8 | 0.30 | 48.5 | 14.4 | - | 453 | - | - | - | - | - | [26] |
| BCS medium | 6.36 | 91.4 | 0.31 | 49.2 | 14.6 | - | 447 | - | - | - | - | - | |
| BCS high | 6.44 | 95.2 | 0.31 | 48.5 | 14.6 | - | 463 | - | - | - | - | - | |

***RBCs: red blood cells; PLT: platelets; Hb: hemoglobin; PCV: packed cell volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; WBCs: white blood cells, $^{d1, d2}$: day1 and 2*

Supplementation of Cr might decrease lipolysis in the transition cows, from pregnancy to lactation, hence improving feed intake and milk yield [64]. Although some researchers have stated that Cr supplementation could increase the milk yield [63,65,66], other experiments stated that Cr supplementation did not affect the milk yield during the transition period [62,64]. In fact, Cr is believed to increase insulin action in insulin-sensitive tissues (i.e., adipose and muscles), resulting in increased farm animal production through the improvement of feed intake, growth rate, reproductive parameters and immune functions [67].

Several studies that have been conducted during the transition period and early lactation have demonstrated that cows supplemented with Cr have increased milk yield and improved energy metabolism, as measured by lower circulating concentrations of NEFA or β-hydroxyl butyric acid (BHBA), and had effect on nutritional metabolism [66]. Several studies have suggested that Cr supplementation may also have immunomodulatory effects in cattle [62].

#### 1.7.7 Chelated nutrients

Chelation refers to a bond formed between a metal ion (mineral) and ligand (protein and amino acid) as a mineral complex to be beneficial in dairy cattle, and present in the rumen stable form [68]. The trace minerals such as Cu, Mn, Zn have supplemented as inorganic form such as sulfate salts as it is associated with sulfate or oxide in a dry form, but dissociate from sulfate when hydrated in the digestive tract which interact with the components of digesta to form insoluble and indigestible compound that pass to the feces [69]. The same authors added that the organic forms, as metal amino acid chelates, metal complexes, methionine hydroxyl analog, metal proteinate and metal propionates, have been developed to increase the intestinal absorption and mineral bioavailability.

It has been hypothesized that bound to organic compound as Zn methionine is more available for absorption than inorganic form [68]. Zn proteinate might also enhance resistance to mammary infections by increasing the keratin synthesis in teat canal [48]. In an earlier study, supplementing cows with 360 mg Zn, 200 mg Mn, 125 mg Cu as amino acid complexes and 12 mg cobalt from Co glucoheptonate) could increase milk production, and improve milk constituent (such as milk energy, fat, crude protein yield, milk solids), and reduce mastitis cases [70]. In another study, it has shown that dietary supplementation of dairy cows with organic Zn, Cu and SE has led to decrease the number of new and total cases of subclinical mastitis when compared with cows that received inorganic sources [71].

In a recent study, it has shown that the post-partum supplementation of dairy cows by bioavailable Zn, Mn, Cu and Co glucoheptonate could improve polymorphonuclear cell function, elicit a greater capacity to control invading pathogen, improve liver function, and productive performance [72]. On the other side, the periparturient supplementation of dairy cows with chelated Cr did not affect the mammary gland health status but supplementation of Cr picolinate during the last 9 weeks of pregnancy has found to reduce the incidence of retained placenta in dairy cows [48]. Chromium chelated with propionate has led to increase feed intake before increasing milk yield [64]. The pre partum Cr methionine supplementation could help cows to enter earlier during the next lactation and can complete lactation with optimal DMI [73]. However, the prepartum supplementation of rumen protected choline to cattle with subclinical ketosis during the transition period has elicited a great effect on some energy metabolites including BHBA, triglyceride, and very low-density lipoprotein with minimal effect on insulin sensitivity. On the other side, supplementing rumen protected niacin exhibited a marked effect on serum cortisol and potentiated insulin sensitivity with minimal effect on BHBA concentration [86].

## 2. CONCLUSION

Oxidative stress is occurring in hypermetabolic dairy cattle during the transition time due to increase in ROS and/or impairment of antioxidant capacity. Accurate assessment of ROS is difficult due to their bewildering variety, low serum concentrations, high reactivity, and the extremely short half-life of ROS. The AOPPs are likely considered novels alternative marker of OS because it is stable and easy to detect. Despite being controversial, supplementing a transition dairy cow with organic trace elements is quite interesting that warrant an extensive investigation.

## CONSENT

It is not applicable.

## ETHICS APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

## REFERENCES


1. Abuelo A, Hernández J, Benedito JL, Castillo C. The importance of the oxidative status of dairy cattle in the periparturient period: revisiting antioxidant supplementation. J Anim Physiol Anim Nutr. 2015;99:1003-16. DOI:10.1111/jpn.12273
2. Hatice Esra C, Murat Onur Y, Ufuk K, Ekrem Cagatay C, Serdal K, Burcu O, et al. MDA and GSH-Px activity in transition dairy cows under seasonal variations and their relationship with reproductive performance. J Vet Res. 2017;61:497-502. DOI:https://doi.org/10.1515/jvetres-2017-0067
3. Sundrum A. Metabolic disorders in the transition period indicate that the dairy cows' ability to adapt is overstressed. Animals. 2015;5:978-1020.
4. Herdt T. Metabolic diseases of ruminants, an issue of veterinary clinics: food animal practice. E-Book: Elsevier Health Sciences. 2013;33-34.
5. Drackley JK. Biology of dairy cows during the transition period: the final frontier? J Dairy Sci. 1999;82:2259-73. DOI:https://doi.org/10.3168/jds.S0022-0302(99)75474-3
6. Barth K, Aulrich K, Haufe HC, Müller U, Schaub D, Schulz F. Metabolic status in early lactating dairy cows of two breeds kept under conditions of organic farming-a case study. Landbauforschung. 2011;61: 307-16.
7. Youssef MA, El-Ashker MR, Younis MS. The effect of subclinical ketosis on indices of insulin sensitivity and selected metabolic variables in transition dairy cattle. Comp Clin Path. 2017;26:329-34. DOI:10.1007/s00580-016-2377-z
8. Contreras GA, Sordillo LM. Lipid mobilization and inflammatory responses during the transition period of dairy cows. Comp Immunol Microbiol Infect Dis. 2011;34:281-9. DOI:https://doi.org/10.1016/j.cimid.2011.01.004
9. Celi P. Biomarkers of oxidative stress in ruminant medicine. Immunopharmacol Immunotoxicol 2011; 33:233-40. DOI:10.3109/08923973.2010.514917
10. Pedernera M, Celi P, García SC, Salvin HE, Barchia I, Fulkerson WJ. Effect of diet, energy balance and milk production on oxidative stress in early-lactating dairy cows grazing pasture. Vet J. 2010;186: 352-7. DOI:https://doi.org/10.1016/j.tvjl.2009.09.003
11. Abuelo A, Hernández J, Benedito JL, Castillo C. Association of oxidative status and insulin sensitivity in periparturient dairy cattle: an observational study. J Anim Physiol Anim Nutr. 2016;100:279-86. DOI:10.1111/jpn.12365
12. Mavangira V, Sordillo LM. Role of lipid mediators in the regulation of oxidative stress and inflammatory responses in dairy cattle. Res Vet Sci. 2018;116:4-14,
13. Begg CB, Mazumdar M. Operating Characteristics of a Rank Correlation Test for Publication Bias. Biometrics. 1994; 50:1088-101. DOI:10.2307/2533446
14. Celi P, Merlo M, Da Dalt L, Stefani A, Barbato O, Gabai G. Relationship between late embryonic mortality and the increase in plasma advanced oxidised protein products (AOPP) in dairy cows. Reprod Fertil Dev. 2011;23:527-33. DOI:https://doi.org/10.1071/RD10268
15. Wu Q, Zhong ZM, Pan Y, Zeng JH, Zheng S, Zhu SY, et al. Advanced oxidation protein products as a novel marker of oxidative stress in postmenopausal osteoporosis. Med Sci Mon Int Med J Exp Clin Res. 2015; 21:2428.
16. Celi P, Merlo M, Barbato O, Gabai G. Relationship between oxidative stress and the success of artificial insemination in dairy cows in a pasture-based system. Vet J. 2012;193:498-502. DOI:https://doi.org/10.1016/j.tvjl.2012.02.002
17. Xu C, Shu S, Xia C, Wang B, Zhang H, Jun B. Investigation on the relationship of insulin resistance and ketosis in dairy cows. J Vet Sci Technol. 2014;5:162.
18. Surai FP, Kochish II, Fisinin IV, Juniper TD. Revisiting Oxidative Stress and the Use of Organic Selenium in Dairy Cow Nutrition. Animals. 2019;9.

DOI :10.3390/ani9070462

19. Kim J, Cha YN, Surh YJ. A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders. Mutat Res Fundam Mol Mech Mutagen. 2010;690:12-23. DOI:https://doi.org/10.1016/j.mrfmmm.2009.09.007
20. Khan M. Effects of prepartum dietary energy and lipid supplementation on hepatic transcriptome profiles in dairy cows during the transition period: University of Illinois at Urbana-Champaign; 2013.
21. Gessner DK, Schlegel G, Keller J, Schwarz FJ, Ringseis R, Eder K. Expression of target genes of nuclear factor E2-related factor 2 in the liver of dairy cows in the transition period and at different stages of lactation. J. Dairy Sci. 2013;96:1038-43. DOI:https://doi.org/10.3168/jds.2012-5967
22. Grewal S, Aggarwal A, Alhussien MN. Seasonal alterations in the expression of inflammatory cytokines and cortisol concentrations in periparturient Sahiwal cows. Biol Rhythm Res. 2019;10. DOI:1080/09291016.2019.1670971:1-11.10.1080/09291016.2019.1670971
23. Konvičná J, Vargová M, Paulíková I, Kováč G, Kostecká Z. Oxidative stress and antioxidant status in dairy cows during prepartal and postpartal periods. Acta Vet Brno. 2015;84:133-40,
24. Abuelo A, Hernández J. Redox Biology in Transition Periods of Dairy Cattle: Role in the Health of Periparturient and Neonatal Animals. Antioxidants. 2019;8. DOI:10.3390/antiox8010020
25. Zhao W, Chen X, Xiao J, Chen XH, Zhang XF, Wang T, et al. Prepartum body condition score affects milk yield, lipid metabolism, and oxidation status of Holstein cows. Asian-Australas J Anim Sci. 2019; 32:1889-96. DOI:10.5713/ajas.18.0817
26. Wu J, Liu J, Wang D. Effects of body condition on the insulin resistance, lipid metabolism and oxidative stress of lactating dairy cows. Lipids Health Dis. 2020;19:1-7.
27. Sordillo LM, Raphael W. Significance of Metabolic Stress, Lipid Mobilization, and Inflammation on Transition Cow Disorders. Vet Clin Food Anim Pract. 2013;29:267-78. DOI:10.1016/j.cvfa.2013.03.002
28. Schuh K, Sadri H, Häussler S, Webb LA, Urh C, Wagner M, et al. Comparison of performance and metabolism from late pregnancy to early lactation in dairy cows with elevated v. normal body condition at dry-off. animal. 2019;13:1478-88. DOI:10.1017/S1751731118003385
29. Tyburczy C, Lock AL, Dwyer DA, Destaillats F, Mouloungui Z, Candy L, et al. Uptake and Utilization of Trans Octadecenoic Acids in Lactating Dairy Cows1. J Dairy Sci. 2008;91:3850-61. DOI:https://doi.org/10.3168/jds.2007-0893
30. Leroy JLMR, Vanholder T, Mateusen B, Christophe A, Opsomer G, Kruif Ad, et al. Non-esterified fatty acids in follicular fluid of dairy cows and their effect on developmental capacity of bovine oocytes in vitro. Reproduction. 2005;130:485-95. DOI:10.1530/rep.1.00735
31. Herdt TH. Variability characteristics and test selection in herdlevel nutritional and metabolic profile testing. Vet Clin Food Anim Pract. 2000;16:387-403. DOI:10.1016/S0749-0720(15)30111-0
32. De Koster JD, Opsomer G. Insulin resistance in dairy cows. Vet Clin Food Anim Pract. 2013; 29:299-322. DOI:10.1016/j.cvfa.2013.04.002
33. Abuelo Á, Hernández J, Benedito JL, Castillo C. Association of oxidative status and insulin sensitivity in periparturient dairy cattle: an observational study. J Anim Physiol Anim Nutr. 2016;100:279-86,
34. Gitto E, Reiter RJ, Karbownik M, Tan D, Gitto P, Barberi S, et al. causes of oxidative stress in the pre- and perinatal period. Neonatology. 2002;81:146-57. DOI:10.1159/000051527
35. Halliwell B, Gutteridge JM. Free radicals in biology and medicine: Oxford University Press, USA; 2015.
36. Smolensky MH, Siegel RA, Haus E, Hermida R, Portaluppi F. Biological rhythms, drug delivery, and chronotherapeutics. Fundamentals and applications of controlled release drug delivery: Springer. 2012;359-443.
37. Balamurugan B, Mehrotra S, Veligatla T, Jena D, Ramamoorthy M, Gopi M, et al. Effect of high-energy diet supplemented with additional copper and zinc during the transition period on oxidative stress and postpartum reproductive performance in the crossbred cows. Biol. Rhythm Res. 2019;50. DOI:https://doi.org/10.1080/09291016.2019.1628399

38. Sordillo LM, Aitken SL. Impact of oxidative stress on the health and immune function of dairy cattle. Vet Immunol Immunopathol. 2009;128:104-9. DOI:https://doi.org/10.1016/j.vetimm.2008.10.305
39. Aitken SL, Corl CM, Sordillo LM. Immunopathology of mastitis: insights into disease recognition and resolution. J. Mammary Gland Biol Neoplasia. 2011; 16:291-304. DOI:10.1007/s10911-011-9230-4
40. Putman AK, Brown JL, Gandy JC, Wisnieski L, Sordillo LM. Changes in biomarkers of nutrient metabolism, inflammation, and oxidative stress in dairy cows during the transition into the early dry period. J Dairy Sci. 2018;101:9350-9. DOI:10.3168/jds.2018-14591
41. Heck JML, van Valenberg HJF, Dijkstra J, van Hooijdonk ACM. Seasonal variation in the Dutch bovine raw milk composition. J Dairy Sci. 2009;92:4745-55. DOI:https://doi.org/10.3168/jds.2009-2146
42. Poławska E, Bagnicka AW, Niemczuk K, Lipinska J. Relations between the oxidative status, mastitis, milk quality and disorders of reproductive functions in dairy cows-a review. Anim Sci Pap Rep. 2012;30:297-307.
43. Sawa A, Neja W, Bogucki M. Relationships between cytological quality and composition of milk and the effect of some environmental factors on the frequency of recurrent mastitis in cows. J Cent Eur Agric. 2007;8:295-300.
44. Castillo C, Pereira V, Abuelo Á, Hernández J. Effect of supplementation with antioxidants on the quality of bovine milk and meat production. Sci World J; 2013.
45. Conference Proceedings MerloB M, CeliA P, BarbatoC O, GabaiB G. Relationships between oxidative status and pregnancy outcome in dairy cows. Proc Aust Soc Anim Prod; 2008.
46. Abuelo A, Hernández J, Benedito JL, Castillo C. Oxidative stress index (OSi) as a new tool to assess redox status in dairy cattle during the transition period. Animal. 2013;7:1374-8. DOI:10.1017/S1751731113000396
47. Todorović MJ, Davidović V, Rašović MB. The effects of some microelements supplementation-selenium, zinc and copper into dairy cows feeds on their health and reproductive performances. J Anim Sci Biotechnol. 2016;32.
48. Spears JW, Weiss WP. Role of antioxidants and trace elements in health and immunity of transition dairy cows. Vet J. 2008;176:70-6. DOI:https://doi.org/10.1016/j.tvjl.2007.12.015
49. McDowell LR. Recent advances in minerals and vitamins on nutrition of lactating cows. Pak J Nutr. 2002;1:8-19,
50. Balamurugan B, Ramamoorthy M, Mandal RSK, Keerthana J, Gopalakrishnan G, Kavya K, et al. Mineral an important nutrient for efficient reproductive health in dairy cattle. Int. J. Environ. Sci. Technol. 2017;6:694-701.
51. Conference Proceedings Gressley TF. Zinc, copper, manganese, and selenium in dairy cattle rations. Proceedings of the 7th annual mid-Atlantic nutrition conference. 2009;56-71.
52. Generic Council NR. Nutrient requirements of dairy cattle. seventh revised. National Academic Press. Washington, DC; 2001.
53. Gong J, Xiao M. Effect of organic selenium supplementation on selenium status, oxidative stress, and antioxidant status in selenium-adequate dairy cows during the periparturient period. J Anim Sci Biotechnol. 2018;186:430-40.
54. Overton TR, Yasui T. Practical applications of trace minerals for dairy cattle1,2. Anim. Sci. J. 2014;92:416-26. DOI:10.2527/jas.2013-7145
55. Sordillo LM. Selenium-dependent regulation of oxidative stress and immunity in periparturient dairy cattle. Vet Med. Int.; 2013.
56. Allison RD, Laven RA. Effect of vitamin E supplementation on the health and fertility of dairy cows: a review. Vet Rec. 2000;147:703. DOI:10.1136/vr.147.25.703
57. Osorio JS, Trevisi E, Li C, Drackley JK, Socha MT, Loor JJ. Supplementing Zn, Mn, and Cu from amino acid complexes and Co from cobalt glucoheptonate during the peripartal period benefits postpartal cow performance and blood neutrophil function. J Dairy Sci. 2016;99:1868-83. DOI:https://doi.org/10.3168/jds.2015-10040
58. Akins MS, Bertics SJ, Socha MT, Shaver RD. Effects of cobalt supplementation and vitamin B12 injections on lactation performance and metabolism of Holstein dairy cows. J Dairy Sci. 2013;96:1755-68. DOI:https://doi.org/10.3168/jds.2012-5979

59. Ghanem MM, Abdel-Hamid OM. Clinical, haematological and biochemical alterations in heat intolerance (panting) syndrome in Egyptian cattle following natural foot-and-mouth disease (FMD). Trop Anim Health Prod. 2010;42:1167-73,
60. Conference Proceedings Tomlinson D, Socha M, DeFrain J. Role of trace minerals in the immune system. Proc. Penn State Dairy Cattle Nutrition Workshop. Grantville, PA. 2008;39-52.
61. Al-Saiady MY, Al-Shaikh MA, Al-Mufarrej SI, Al-Showeimi TA, Mogawer HH, Dirrar A. Effect of chelated chromium supplementation on lactation performance and blood parameters of Holstein cows under heat stress. Anim. Feed Sci Technol 2004;117:223-33.
DOI:https://doi.org/10.1016/j.anifeedsci.2004.07.008
62. Yasui T, McArt JAA, Ryan CM, Gilbert RO, Nydam DV, Valdez F, et al. Effects of chromium propionate supplementation during the periparturient period and early lactation on metabolism, performance, and cytological endometritis in dairy cows. J. Dairy Sci. 2014;97:6400-10.
DOI:https://doi.org/10.3168/jds.2013-7796
63. Hayirli A, Bremmer DR, Bertics SJ, Socha MT, Grummer RR. Effect of chromium supplementation on production and metabolic parameters in periparturient dairy cows1. J. Dairy Sci. 2001;84:1218-30.
DOI:https://doi.org/10.3168/jds.S0022-0302(01)74583-3
64. Rockwell RJ, Allen MS. Chromium propionate supplementation during the peripartum period interacts with starch source fed postpartum: Production responses during the immediate postpartum and carryover periods. J. Dairy Sci. 2016;99:4453-63.
DOI:https://doi.org/10.3168/jds.2015-10344
65. Soltan MA. Effect of dietary chromium supplementation on productive and reproductive performance of early lactating dairy cows under heat stress. J Anim Physiol Anim Nutr. 2010;94:264-72.
DOI:10.1111/j.1439-0396.2008.00913.x
66. Sadri H, Ghorbani GR, Rahmani HR, Samie AH, Khorvash M, Bruckmaier RM. Chromium supplementation and substitution of barley grain with corn: Effects on performance and lactation in periparturient dairy cows. J Dairy Sci. 2009;92:5411-8.
DOI:https://doi.org/10.3168/jds.2008-1877
67. Bin-Jumah M, Abd El-Hack ME, Abdelnour SA, Hendy YA, Ghanem HA, Alsafy SA, et al. Potential use of chromium to combat thermal stress in animals: A review. Sci Total Environ. 2020;707:135996.
DOI:https://doi.org/10.1016/j.scitotenv.2019.135996
68. Hassan AA, El Ashry GM, Soliman SM. Effect of supplementation of chelated zinc on milk production in ewes. Food Sci Nutr. 2011;2:706,
69. Nemec LM, Richards JD, Atwell CA, Diaz DE, Zanton GI, Gressley TF. Immune responses in lactating Holstein cows supplemented with Cu, Mn, and Zn as sulfates or methionine hydroxy analogue chelates. J. Dairy Sci. 2012;95:4568-77.
DOI:https://doi.org/10.3168/jds.2012-5404
70. Griffiths LM, Loeffler SH, Socha MT, Tomlinson DJ, Johnson AB. Effects of supplementing complexed zinc, manganese, copper and cobalt on lactation and reproductive performance of intensively grazed lactating dairy cattle on the South Island of New Zealand. Anim Feed Sci Technol. 2007;137:69-83.
DOI:https://doi.org/10.1016/j.anifeedsci.2006.10.006
71. Cortinhas CS, Botaro BG, Sucupira MCA, Renno FP, Santos MV. Antioxidant enzymes and somatic cell count in dairy cows fed with organic source of zinc, copper and selenium. Livest Sci. 2010;127:84-7.
DOI:https://doi.org/10.1016/j.livsci.2009.09.001
72. Batistel F, Osorio JS, Tariq MR, Li C, Caputo J, Socha MT, et al. Peripheral leukocyte and endometrium molecular biomarkers of inflammation and oxidative stress are altered in peripartal dairy cows supplemented with Zn, Mn, and Cu from amino acid complexes and Co from Co glucoheptonate. J Anim Sci Biotechnol. 2017;8:33.
DOI:10.1186/s40104-017-0163-7
73. Gultepe EE, Uyarlar C, Bayram İ. Supplementation of Cr Methionine During Dry Period of Dairy Cows and Its Effect on Some Production and Biochemical Parameters During Early Lactation and on Immunity of Their Offspring. Biol Trace Elem Res. 2018;186:143-53.

74. Castillo C, Hernandez J, Bravo A, Lopez-Alonso M, Pereira V, Benedito JL. Oxidative status during late pregnancy and early lactation in dairy cows. Vet J. 2005;169:286-92. DOI:https://doi.org/10.1016/j.tvjl.2004.02.001
75. Kincaid RL, Lefebvre LE, Cronrath JD, Socha MT , and Johnson AB . Effect of Dietary Cobalt Supplementation on Cobalt Metabolism and Performance of Dairy Cattle. J. Dairy Sci. 2003;86:1405-1414. DOI:https://doi.org/10.3168/jds.S0022-0302(03)73724-2
76. García A, Cardoso FC, Campos R, Thedy DX, González FH. Metabolic evaluation of dairy cows submitted to three different strategies to decrease the effects of negative energy balance in early postpartum. Pesqui Vet Bras. 2011;31:11-17. DOI:https://doi.org/10.1590/S0100-736X2011001300003
77. Kafilzadeh F, shabankareh HK, Targhibi MR. Effect of Chromium Supplementation on Productive and Reproductive Performances and Some Metabolic Parameters in Late Gestation and Early Lactation of Dairy Cows. Biol. Trace Elem. Res. 2012;149:42-49. DOI:https://doi.org/10.1007/s12011-012-9390-0
78. Elischer MF, Sordillo LM, Siegford JM, Karcher EL. Short communication: Characterizing metabolic and oxidant status of pastured dairy cows postpartum in an automatic milking system. J. Dairy Sci. 2015; 98:7083-7089. DOI:https://doi.org/10.3168/jds.2014-8941
79. Leiva T, Cooke R, Brandão A, Aboin A, Ranches J, Vasconcelos J. Effects of excessive energy intake and supplementation with chromium propionate on insulin resistance parameters, milk production, and reproductive outcomes of lactating dairy cows. Livest Sci. 2015;180:121-128. DOI:https://doi.org/10.1016/j.livsci.2015.08.007
80. Abuajamieh M, Kvidera SK, Fernandez M VS, Nayeri A, Upah NC, Nolan EA, Lei SM, DeFrain JM, Green HB, Schoenberg KM. Inflammatory biomarkers are associated with ketosis in periparturient Holstein cows. Res. Vet Sci. 2016;109:81-85. DOI:https://doi.org/10.1016/j.rvsc.2016.09.015
81. Karimi N, Mohri M, Azizzadeh M, Seifi HA, Heidarpour M. Relationships between trace elements, oxidative stress and subclinical ketosis during transition period in dairy cows. Iran J. Vet Sci Technol. 2016; 7:46-56. DOI:https://doi.org/10.22067/veterinary.v7i2.45798
82. Toghyani E, Moharrery A. Effect of various levels of dietary protein in transition period on colostrum quality and serum immunoglobulin concentration in Holstein cows and their newborn calves. Ann Anim Sci. 2015;15:493-504. DOI:https://doi.org/10.2478/aoas-2014-0085
83. Moussavi AH, Mesgaran MD, Soleimani A, and Vafa T. Effect of supplemental fish meal on reproduction and immunology responses in early lactating Holstein dairy cows. J Anim Vet Adv. 2008; 7:520-525.
84. Gǎvan, C, Retea C, Motorga V. Changes in the hematological profile of Holstein primiparous in periparturient period and in early to mid lactation. J Anim Sci Biotechnol. 2010;43:244-246.
85. Soleimani A, Moussavi AH, Mesgaran MD, and Golian A. Effects of dry period length on, milk production and composition, blood metabolites and complete blood count in subsequent lactation of Holstein dairy cows. World Acad Sci Eng Technol. 2010; 68:597-602.
86. Youssef M, El-Ashker M, Younis M. Effect of prepartum supplementation with niacin, choline, and cod liver oil on postpartum insulin sensitivity and the redox status in cows with clinical ketosis. Anima Prod Sci. 2018;58:1847-1853.



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