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Review Article
Metabolic, Inflammatory and Immune Adaptation in Periparturient Dairy Cows and their Predictive Tools

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Abstract
Transition period is associated with important metabolic, nutritional and immune system changes. The combined effects of all these changes reduce production and increase culling rate that ultimately reduces profitability of farms. Therefore, the aim of this study was to know the potential interaction of these changes along with different predictive tools to evaluate these problems for the development of management strategy. In this review, metabolic, inflammatory and immune system changes in transition cow and its effect on health during the later postpartum period in dairy animals were discussed along with the integrative approaches at animal, cellular and molecular level using some predictive tools to unravel these complex interactions that predispose cows to periparturient diseases. This review is important as it showed that disregulatory immune function plays a key role for the incidence of several transition problems. Yet, reliable modern predictive tools can solve this issue to a huge extent as they have the ability to examine the immune and inflammatory status of individual transition dairy cows to clarify the intrinsic mechanism of peripartal disorders.

Key words: Transition period, periparturient diseases, inflammation, immune function, predictive tools

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INTRODUCTION

Transition period, from 3 weeks pre-calving to 3 weeks post-calving[1] is considered as the most difficult time of the lactation cycle[2]. Thus, this period has become the most challenging areas for both producers and scientists to address the issues of herd health. The importance of the transition period has been highlighted in several review articles[3,4], mainly presenting the physiological changes occurring in periparturient dairy cows and their relationship to the development of typical metabolic diseases of this phase. Recently, immune functionality is also considered as an important factor[2,5,6] that may favour the development of different infectious and metabolic diseases during transition period.

Interestingly, clear signs of immunosuppression[7] and reduced immune functions in late pregnancy[8] may be observed in correlation with an inflammatory response and a metabolic stress-related condition in early lactation[9,10]. Furthermore, the interplay between the immune, endocrine and metabolic systems[11] diminished immune competence at calving and increases host susceptibility to infections[5]. The etiology of periparturient immunosuppression is multifactorial and not well understood, but seems to be due to physiological changes associated with induction of parturition and the initiation of lactation and to metabolic factors related to these events[2,12]. Nevertheless, some studies have noted contradictory data regarding the function of polymorphonuclear neutrophilic leukocytes[13] and maternal lymphocytes[14] in the transition period. There exist an important individual components for the susceptibility to the immune-suppression and inflammatory phenomena occurring in the transition period[10].

An improved understanding of the complex interaction of immunity, metabolism and inflammation along with evaluation of immune response capacity of individual cows can help to select better herd with high immune response potentiality which will allow a broad array of potential treatments or management to prevent transition disorders. Thus, the aim of this paper was to review the potential interaction of immune, metabolism and inflammatory status along with different predictive tools to evaluate these problems with the emphasis of recent investigations.

CHANGES IN METABOLIC STATUS AND ITS EFFECT

Reduction of dry matter intake: Regarding metabolic changes, the most important aspect of transition period is the insufficient dry matter intake (DMI) compared to the energy requirements for lactation and maintenance[15], resulting in a period of negative energy balance (NEB)[3]. A reduction of DMI in the last 3 weeks of gestation is considered physiologic[16], but this reduction in DMI does not occurs always and about 90% of cows decrease their intake only 5-7 days before calving[17]. Interestingly, the low DMI at the end of pregnancy (last 10-14 days) seems responsible for a lower intake after calving[17,18]. The reasons behind the radical decrease in feed intake in late pregnancy include a decrease in rumen volume and the hormonal actions that accompany the periparturient period[19] and also the occurrence of some inflammatory phenomena[20]. Besides the metabolic reasons, the clinical or subclinical health problems play a role for the reduction of DMI[20]. The mechanism that exerts this effect is partly due to the release of cytokines (e.g., TNF-α, IL-1, IL-6), which occurs during the inflammatory response and that is characterized by an anorectic effect[21]. As previously described the pro-inflammatory cytokines (e.g., IL1 and IL6) showed higher concentrations in cows with more severe health problems[5, 20] around calving.

In turn, the reduction in DMI in the peripartum increases the body fat mobilization, resulting in elevated NEFA concentrations and increased hepatic lipid accumulation[22]. As the concentration of NEFA in blood increases around calving or in early lactation, more NEFA are taken up by the liver[23]. If NEFA uptake by the liver becomes excessive, fatty liver may develop[24]. Negative energy balance and carbohydrate insufficiency in the liver after calving also leads towards increased production of ketone bodies, which can result in clinical or subclinical ketosis[25]. This pathology has important implications on the liver functionality and on the overall health status. The mobilization of body fat reserves is measured through Body Condition Score (BCS) and used to study the impact of negative energy balance on stress symptoms by correlating it to high milk yield[26]. Increased concentrations of NEFA before calving and BHBA after calving were strongly related to development of displaced abomasums[27]. Negative energy balance, intense mobilization of adipose TG and ketogenesis are highly associated with periparturient disorders and diseases[24].

Adaptations in carbohydrate and protein metabolism also occur around calving[22]. The low insulin concentrations of this time result in decreased oxidative use of glucose by peripheral tissues, thereby sparing glucose for milk synthesis. In the liver, the efficiency of gluconeogenesis from propionate increases after parturition. Glucose synthesis from glycerol and glucogenic amino acids such as alanine increases around parturition to meet the glucose demand that cannot be supplied by propionate due to low DMI (or at least inadequate in comparison to the demand for milk synthesis). As consequences, body protein mobilization also increases during the first 3 weeks postpartum to supply amino acids for both milk protein synthesis and glucose synthesis[22,25].

Calcium metabolism: The onset of milk synthesis creates a large drain of calcium from blood, sometimes resulting in a marked decrease in blood calcium concentration when the mobilization from bone tissue and gut absorption is inadequate. Subclinical hypocalcemia is a common nutrition-related issue that occurs in most of transition cows. Calcium is an important signal transducer in many other cell types, including immune cells[28] low blood Ca around the time of calving could contribute to periparturient immunosuppression[7]. Additionally, the low plasma Ca concentration has been observed in lactating cows as a consequence of the inflammatory condition[29,30]. Hypocalcemia has some widespread effects that predispose cows to other periparturient diseases like dystocia, retained fetal placenta, metritis, displaced abomasum, foot problems, ketosis, mastitis and coliform mastitis[31,32].

CHANGES IN IMMUNE SYSTEM AND ITS EFFECT

The transition from gestation to lactation in dairy cows is not only characterized by metabolic stress, but also an altered immune functions[9,10]. The response of the immune system (innate and adaptive type) determines the modification on both cell-mediate and humoral components. The week prior to and immediately following parturition is associated with neutrophilia, eosinopenia, lymphocytopenia and monocytosis. Even with the increase in some white blood cells, cows showed a decrease in phagocytosis and oxidative burst activity[33,34]. Neutrophil and lymphocyte functions as measured by iodination and blastogenesis are impaired during the weeks immediately before and after parturition[7].

The control and eradication of an infection is associated with rapid migration and recruitment of neutrophils to the site of septicity[35]. Down-regulation and shedding of CD62L molecules from neutrophils have been reported around calving; consequently less numbers of cell are able to migrate into peripheral tissues[36].

During the transition period, inflammatory cytokines play a key role in stimulating systemic inflammatory responses, including increased body temperature and heart rate and decreased feed intake[9,37]. For example, coliform mastitis releases endotoxin into the bloodstream and increased plasma concentrations of cytokines as well as of acute phase proteins[38]. The stage of lactation influences the response of the peripheral leukocytes, in fact when the isolated mononuclear cells are stimulated with lipopolysaccharide (LPS), periparturient dairy cows produce significantly higher levels of TNF-α than mid to late lactating dairy cows regardless of the location of the tissue[39]. The serum TNF-α concentration in healthy periparturient dairy cows decreased linearly from 1 week prepartum to 4 weeks postpartum[40].

Recent findings observed that the concentrations of IL-1β and IL-6 pre-partum are higher than in postpartum and the cows with the highest concentrations of IL-1β in late pregnancy showed the worst condition in term of health status, metabolic and inflammatory conditions and performances in early lactation[9,41]. Another study also noted the higher IL-6 concentration in dry period than lactation period. More interestingly, cows with good health condition showed a marked reduction of IL-6 after calving in comparison with cows with unsatisfactory transition period[20]. Instead the low concentration of IL-1 at 15 days prior or at calving may be used to identify the cows susceptible to develop post-partum reproductive diseases[42]. In addition, the same authors in another experiment[43] claimed that the increased concentration of the IL-10 an anti-inflammatory cytokine, 15 days pre-partum can also be a good predictor of retained placenta and metritis. Another author found a higher concentration of IL-6 pre-partum than postpartum and associated the high concentrations of IL-6 pre-partum with some post-partum reproductive disorders (retained placenta, endometritis, follicular cyst)[14]. In case of humans, many works have already been performed in cytokine profiling during different stage of pregnancy and also after delivery to know the immune activities of these periods[44,45]. In dairy cows, researches in this area are very limited[9-10,41] and more studies are needed to know the physiological changes of cytokine profile during the transition period, for the better understanding of the role of the immune system with occurrence and severity of the metabolic disorders.

Large changes occur during this period also in the adaptive immune response. As parturition approach, the proportion of blood lymphocytes and their functional activities, such as cloning expansion and antibody production decrease, reaching a nadir during the days around parturition[46,47]. The decrease in lymphocyte numbers is due to a net depression in CD^{4+}, CD^{8+} and γδ+T lymphocytes[47,48]. In addition, the functions of certain sub-populations are modified. It has been observed that blood CD^{4+} T-cells preferentially produce IL-4 and IL-10 around parturition (e.g., prevail Th2 cells), while they shift to IFN-γ production during mid to late lactation (e.g., prevail Th1 cells;)[49]. Moreover, CD^{8+} lymphocytes of the suppressor type predominate at this time, which may also contribute to higher levels of IL-4 and IL-10, setting a Th2 or humoral immune response. The changes of leukocytes and cytokine production are observed around calving which result in a suppression of the cellular immune response. It is necessary to deal with intracellular bacteria and viruses, thereby making the animal more susceptible to infections. Despite the changes detected as parturition approach in the different T-cells subsets, the percentage of B-lymphocytes seems to remain fairly constant[50]. In contrast, a higher proportion of B-cells in blood occurs before and at calving than after parturition[48]. Anyway, a diminished antibody production during the time of parturition, suggested a reduced functional activity of B-cells[46].

RELATIONSHIP OF METABOLISM AND IMMUNE SYSTEM IN PERIPARTURIENT DAIRY COWS

Dietary factors during the periparturient period have been associated with metabolic and/or immunological dysfunctions. For example, the inadequate supply of metabolizable protein is correlated with an impaired function of the immune system[51]. Interestingly, retained placenta-commonly associated with dystocia, milk fever (metabolic diseases) and twin births have been linked to a malfunction of the immune system[52]. This suggested that nutrition (protein, Se, vitamin E)[53,54] have a marked impact on the incidence of retained placenta as well as of the other common diseases of the transition period. A recent finding showed that the plasma markers of the energy metabolism during peripartum express a relationship with the transcriptome of the circulating leucocytes[55].

RELATIONSHIPS OF METABOLISM AND INFLAMMATION IN PERIPARTURIENT DAIRY COWS

Several findings have documented the relationships between inflammatory mediators and metabolic disorders. Plasma concentrations of haptoglobin and serum amyloid A, markers of inflammatory status were increased in cows that developed fatty liver[56]. An increased serum TNF-α activity is found in cows with moderate to severe fatty liver[57]. Increased circulating concentrations of NEFA and oxidative stress are significant contributing factors to systemic inflammation and to the development of inflammatory-based diseases[58]. Nevertheless, it is known that inflammation commonly starts before important metabolic changes and oxidative stress[5]. Thus, the increase of lipo-mobilization (raise of NEFA) and oxidative stress (raise of ROM) can be important consequences of the inflammatory events and could be important phenomena able to reiterate the inflammatory process. Strong evidences from some studies suggested that inflammatory mediators directly induce metabolic problems. Interferon-α (usually considered as an anti-inflammatory cytokine) was administered daily per os, during the final 2 weeks of gestation, but observed an increase of the release of pos-APP and more severe consequences of the inflammation in early lactation in comparison with the control cows (i.e., significantly higher plasma ketone concentrations in the first 2 weeks after calving)[59]. A sub-cutaneous injection of TNF-α for 7 days was found to double the liver triglyceride content in dairy cows in their late-lactation. Moreover, the changes in mRNA abundance into the liver were consistent with transcriptionally-mediated increases in fatty acid (FA) uptake, esterification and reduction of the FA oxidation. Several study observed the higher accumulation of the liver TG in early lactating cows after the inflammation caused by the treatment with endotoxin[60]. These results strongly supported the hypothesis that inflammation disrupts normal metabolism in the peripartum, because both treatments, despites were considered at low-dose and with a short term effect, promoted ketosis and fatty liver. Figure 1 shows the metabolic condition during transition period and their effects of on immune suppression, inflammation and health status.

PREDICTIVE TOOLS TO EVALUATE INDIVIDUAL IMMUNE AND INFLAMMATORY RESPONSIVENESS OF DAIRY COWS

Previous researches[3,20] demonstrated that cows belonging to the same herd and receiving the same diet and management can be able to cope with the metabolic, inflammatory and immune challenges occurring in transition time or can get into trouble with severe consequences for performance and survival. These results suggested the existence of important individual components for the susceptibility to the immune-suppression and inflammatory phenomena occurring in the transition period. In general, there is an acceptable accuracy on the diagnosis of diseased cows but little is known about the identification of cows with (or without) the ability to adapt to a new lactation[12,20]. Early identification of the susceptibility of adaptation would make it possible to apply a cow-specific management strategy[12,29] for this reason predictive tools are of great interest which recognize changes in the immune and inflammatory status during the transition period, before the appearance of symptoms of diseases.

Existing tools: In order to assess the different response of each cow to inflammatory status in the early lactation, two multiple indexes (Liver Functionality Index (LFI)[61] and Liver Activity Index (LAI)[62]) have been developed in the last years, based on the concentrations and the changes of some neg-APP in the first month of lactation. The aim

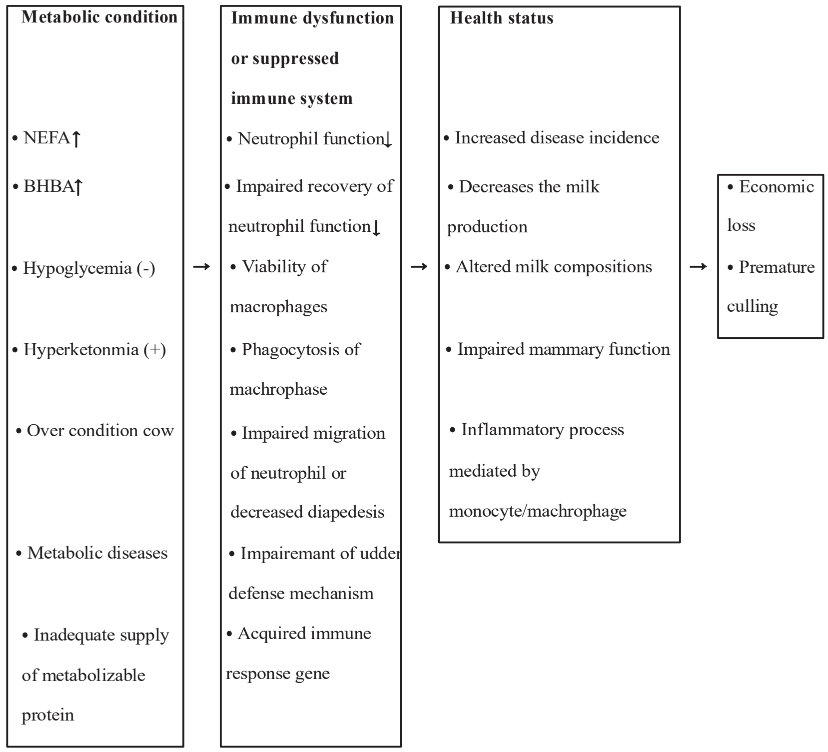

Fig. 1: Metabolic condition during transition period and their effects on immune suppression, inflammation and health status

was to monitor the changes on the liver activity induced by inflammatory events occurred around calving as recently reviewed[5,12,29]. Post-calving Inflammatory Response Index (PIRI) is another useful tool to identify cows affected by inflammatory problems in the first days after calving[63]. In particular its structure takes into account the inflammatory status (pos-APP) and its consequences (neg-APP) allowing a better assessment of the whole inflammatory event in respect to the previous indices LFI and LAI which only considered neg-APP. The fairly good correlation with LFI and LAI considered the differences in the composition of the indices suggested that also PIRI could be a good index to describe inflammation in post-calving of dairy cows[63].

Possible tools

Carrageenan challenge: When injected sub-cutaneously, carrageenan induces an aseptic footpad edema by the activation of macrophages. This treatment is widely used for the evaluation of prospective anti-inflammatory drugs[64,65]. The inflammatory response is quantified by measuring the increase in paw size (edema)[64,66]. However, some authors stated the immunological property of carrageenan as well as its effect or interference in immune system[67,68]. Another study has used carrageenan as inducers to cause non-specific inflammatory reactions (aseptic) toward the goal of developing protocols of preventing immune disorders via dietary supplements[69]. Lacetera *et al.*[70] and Agazzi *et al.*[71] used phytohaemagglutinin (plant lectin used to stimulate lymphocyte and thus to assess immune function) instead the carrageenan. They evaluated the effects of the immune system by the changes in skin thickness after intradermal injection. Lacetera *et al.*[70] and Agazzi *et al.*[71] interpreted the skin thickness increase as an index associated with a greater cell mediated immune response of animals or kids. In transition dairy cows carrageenan skin test is used as first attempt to better describe the changes of the innate immune response at a local level[10] around calving but the possibility to assess the immunosuppressive and immunogenic properties by this approach is still debated.

***Ex vivo* whole blood stimulation assay (WBA):** *Ex vivo* whole blood stimulation assay (WBA) with LPS has proved to be a useful tool for the evaluation of pro-inflammatory cytokines secretory capacity of circulating leukocytes in several species[72-75]. The blood pro inflammatory cytokines secretory ability is associated with different type of infectious diseases[76-77] and different physiological states[39,76,78-79], which can also reflect the immune activation of an individual[80].

The ability of mononuclear cells to produce TNF-α *in vitro* is examined during periparturient period in dairy cows. High blood plasma concentrations of TNF-α have been associated with severe clinical mastitis and septic shock[39]. As mentioned above, WBA with LPS is limitedly utilized previously by Sordillo *et al.*[39] and Rontved *et al.*[75] but researches in transition dairy cows are very limited except[10] who used WBA to confirm changes in immunocompetence around calving. So research in this area should be encouraged for a better understanding of the immune and inflammatory status.

Omics tools: New technologies like, genomics, proteomics, lipidomics and metabolomics are currently used to detect changes at molecular levels[12,81-83]. The gene expression profiling in tissues (e.g., liver, immune system, mammary gland and blood) is the widely investigated and has already produced interesting progress in the understanding of several biological processes[84-86]. The RNA-sequencing (RNA-seq) approach allows the analysis of the whole transcriptome furnishing a comprehensive annotation and quantification of the genome in a given sample[87]. This technique opened a new era of applying genomic information to better understand the physiological state, immune and metabolism of cattle[12,88]. Few papers[55,89,90] have been published which used RNA-seq to study nutrition, physiological state, immune status and reproduction of dairy cows. However, more research is warranted in this new area for the better understanding of the changes in physiology of transition cows and to find out novel approaches to minimize transition disorders.

CONCLUSION AND FURTHER RECOMMENDATION

This study revealed that disregulatory immune function plays an important role for the incidence of several transition problems. However, reliable modern predictive tools can be used to assess the immune and inflammatory status of individual transition dairy cows to elucidate the intrinsic mechanism of peripartal disorders which can complement the measures of classic biomarkers in biological fluids. Moreover, it will open a new area for future researches to manage critical transition period.

SIGNIFICANCE STATEMENT

Available literature discusses association among metabolic, inflammatory and immune system changes and its consequences during transition period but no effective management is developed yet. This study discovered a new avenue to assess the individual cow's immune and inflammatory response capacity during transition period to separate them for the development of management tools. Thus this study will helps to add new knowledge in existing literature as well as it will open a new area for future research to solve the problems and a new theory on managing critical transition period may be arrived at.

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