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# Typical Metabolic Characteristics of Peripartum Dairy Cows and Technical Approaches for Nutritional Regulation (Postprint)

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## Abstract

The perinatal period is a critical stage in the lactation cycle of dairy cows, characterized by negative balance of multiple nutrients, impaired physiological and metabolic functions, and susceptibility to various metabolic and other diseases, which seriously threaten cow health and production efficiency. Consequently, nutritional regulation during the perinatal period has become a research priority and hotspot. Based on our group' s recent research achievements, this review takes the nutritional and physiological processes of perinatal dairy cows as the theoretical foundation, with the precise and efficient supply of glucose for systemic metabolism as the core objective, and discusses advances and technical strategies for nutritional regulation from three hierarchical levels: rumen metabolic regulation, efficient utilization of small intestinal starch, and liver function modulation, aiming to provide references for related research and formulation of nutritional strategies in the dairy industry.

## Full Text

## Preamble

### Typical Metabolic Characteristics and Technical Approaches for Nutritional Regulation in Transition Dairy Cows: A Review

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**Abstract:** The transition period represents a critical stage in the lactation cycle of dairy cows. During this phase, cows experience negative balance of multiple nutrients, develop partial physiological metabolic dysfunction, and become prone to various metabolic and infectious diseases, which seriously threaten both cow health and productive efficiency. Consequently, nutritional regulation during the transition period has emerged as a major research focus and priority. Building upon our research group' s recent work and grounded in the theoretical framework of nutritional physiological processes, this review discusses advances and technical strategies for nutritional regulation in transition dairy cows across three hierarchical levels: rumen metabolism regulation, efficient small intestinal starch utilization, and liver function modulation. The core objective is achieving precise and efficient supply of metabolizable glucose, aiming to provide scientific and technical references for related research and dairy industry nutrition strategies.

**Keywords:** nutritional regulation; metabolizable protein; metabolizable glucose; AMPK signaling pathway; transition dairy cow

## 1 Typical Metabolism: Theoretical Basis

The transition period encompasses three weeks prepartum and three weeks postpartum. During this stage, dairy cows exhibit distinctive nutritional physiology and metabolic patterns, including altered neuroendocrine function [1], insufficient nutrient intake with low utilization efficiency, significantly enhanced mobilization of body reserves for major nutrients (lipids, proteins, calcium, phosphorus, etc.) [2-3], diminished metabolic and immune function across organs, and increased exposure to stressors (parturition, dietary transition, metabolic stress, oxidative stress, and environmental stress) [4]. These changes weaken the barrier function against harmful microbial invasion [4-5], rendering cows highly susceptible to metabolic diseases (fatty liver, ketosis, milk fever) and microbial infections (bacterial mastitis, bacterial metritis), thereby causing substantial economic losses to the dairy industry [6-8]. Therefore, investigating the physiological and biochemical mechanisms underlying nutritional processes and developing effective nutritional regulation technologies and feeding management protocols are essential for safeguarding cow health, sustaining efficient lactation performance, and promoting sustainable dairy industry development.

Elucidating the mechanistic network governing key nutrients from intake through digestion, absorption, transport, metabolism, transformation, utilization, and excretion, and clarifying the pathogenesis of major metabolic stresses and diseases, constitute the theoretical foundation for regulating efficient nutrient utilization and health in transition dairy cows. Using fatty liver and ketosis as examples, negative energy balance (NEB) triggers body fat mobilization, flooding the liver with non-esterified fatty acids (NEFA) for energy metabolism via three primary pathways [9-11]: 1) complete oxidation to CO and H O, releasing substantial ATP for efficient energy supply; 2) incomplete oxidation producing ketone bodies, mainly -hydroxybutyric acid (BHBA), with low energy efficiency, where ketone accumulation readily induces ketosis; and 3) esterification to triglycerides (TG), which if not exported from the liver as very low density lipoprotein (VLDL), cause hepatic fat infiltration and fatty liver [12-16]. Accordingly, the risk of fatty liver and ketosis can be mitigated through: 1) promoting complete NEFA oxidation by increasing hepatic carnitine content and enhancing expression of the rate-limiting enzyme CPT1 [10-11]; 2) reducing BHBA synthesis by modulating expression and secretion of key enzymes -hydroxy- -methylglutaryl-CoA (HMG-CoA) and HMG-CoA reductase [17]; and 3) promoting VLDL synthesis to export excess TG from the liver [18-22].

Supplementation with specific nutritional regulators (e.g., choline, glycerol, and vitamin E) can enhance antioxidant and immune functions, reduce metabolic disease incidence, and improve postpartum lactation and reproductive performance [1,5,23-26]. Lean et al. [27] systematically reviewed research advances and technical principles of nutritional requirements and regulation in transition dairy cows, proposing alarm incidence rates and regulatory targets for metabolic diseases (Table 1 ) to guide nutritional and technical management on dairy farms.

**Table 1 Alarm incidence rates of main metabolic diseases and regulatory targets in transition dairy cows**

| Item | Alarm levels | Regulatory targets |
|---|---|---|
| Milk fever[2] | Clinical ketosis | Subclinical ketosis[3] |
| Retained placenta (>6 h) | Lameness (Locomotion score >2, five-grade system) | Clinical mastitis |
| Hypomagnesemia | Calvings requiring assistance | Displaced abomasums |
| Clinical acidosis | | |

[1] Except for special instructions, percentages represent the proportion of cows developing diseases within 14 days postpartum relative to the total herd.
[2] For older cows (>8 years), the alarm level remains unchanged while the regulatory target is 2%.
[3] Blood BHBA concentration is measured using enzymatic assay; subclinical ketosis is defined as blood BHBA concentration >1 mmol/L.
Number of affected cows per 100 cows within 30 days postpartum.

## 2 Technical Approaches

Dairy cows undergo complex physiological and biochemical adaptations and metabolic regulatory mechanisms from dry-off to lactation initiation. This transition period represents the integrated outcome of neuroendocrine regulation, metabolic signaling, digestive tract microorganisms and their metabolites, internal and external stressors, and various pathogens [6,28-30]. Several classic reviews have addressed herd monitoring, nutritional requirements, metabolic regulation, and health intervention in transition dairy cows [23,27,31-34]. Building upon our group' s research foundation, we outline technical approaches for energy and protein metabolism regulation in transition dairy cows, focusing on energy metabolism while considering protein metabolism.

Our research group aims to improve overall dietary energy utilization efficiency, with the core objective of enhancing metabolizable glucose (MG) supply. The main research components include (Figure 1 [Figure 1: see original paper]): 1) physiological mechanisms and comprehensive regulation of rumen health and efficient fermentation; 2) scientific basis and regulatory technologies for efficient small intestinal nutrient utilization (primarily starch); 3) pathway analysis and nutritional regulation of hepatic energy metabolism and efficient conversion; and 4) development of feed databases, nutritional evaluation systems, and related software. To balance rational carbohydrate allocation between rumen and small intestine and achieve efficient energy conversion, our group integrated research findings to propose the Carbohydrate Balance Index (CBI), calculated as: CBI = peNDF/RDS, where peNDF represents physically effective neutral detergent fiber (currently recommended as peNDF . ), and RDS represents rumen degradable starch. The contribution of different peNDF lengths to CBI and cow physiology requires further quantification [35-37].

**Figure 1** A research network of carbohydrate nutrition and regulation of energy metabolism in ruminants [37]

*CBI: carbohydrate balance index; NDF: neutral detergent fiber; NFC: non-fibrous carbohydrate; G: glucose; MG: metabolizable glucose; mTOR: mammalian target of rapamycin; peNDF: physically effective neutral detergent fiber; RDNFC: rumen degradable non-fibrous carbohydrate; RES: rumen escape starch; RDS: rumen degradable starch.*

### 2.1 Regulating Rumen Microecology to Promote Efficient Conversion and Utilization of Rumen Nutrients

Rumen homeostasis is essential for supplying energy, protein, and other nutrients to dairy cows. Acetate serves as a crucial substrate and regulatory factor for milk fat synthesis; propionate is the primary substrate for hepatic gluconeogenesis, while glucose is not only the main energy source for vital activities but also a precursor for lactose synthesis. Microbial crude protein (MCP) constitutes an important component of small intestinal protein, together with rumen undegraded protein (RUP) and endogenous crude protein (ECP) forming metabolizable protein (MP) sources for dairy cows. The rumen microbiota shifts during the transition period, accompanied by declining rumen function. Pitta et al. [38] compared dynamic changes in the rumen microbiome of primiparous and multiparous cows, revealing that Bacteroidetes and Firmicutes were the most abundant phyla, with the Bacteroidetes:Firmicutes ratio increasing from 6:1 to 12:1 around parturition, potentially related to metabolic physiology and dietary transition. With lactation initiation, cows transition from dry cow diet (high forage) to lactation diet (high concentrate), markedly increasing lactic acid-producing bacteria such as *Streptococcus bovis* and *Lactobacillus* while decreasing *Selenomonas ruminantium* and *Megasphaera elsdenii* [39]. These shifts may lead to: 1) reduced propionate production and insufficient substrates for hepatic gluconeogenesis, forcing extensive use of glucogenic amino acids for gluconeogenesis and causing amino acid "waste" that exacerbates energy and protein negative balance; 2) increased lactic acid production, decreased rumen pH, acidosis induction, rumen epithelium damage, and reduced MCP synthesis; 3) decreased rumen energy and protein conversion efficiency, stimulating body fat and protein mobilization, increasing hepatic metabolic burden, and elevating risks of ketosis and fatty liver; and 4) insufficient energy and substrates for mammary lactation, reducing postpartum performance. Therefore, maintaining rumen health and efficient energy output during the transition period (especially postpartum) is critical for cow health and lactation performance.

Achieving optimal carbohydrate allocation between rumen and small intestine while improving rumen nutrient conversion efficiency and ensuring rumen health represents an important technical approach for rumen metabolism regulation in transition cows, with the CBI system providing valuable reference. Research progress and applications of CBI are documented in our group's publications [36-37,40-46]. The regulatability of rumen environment and nutrient metabolism is well-established, with numerous regulatory measures available (Figure 1). However, research on rumen metabolism regulation specifically in transition cows remains notably limited. Wang Xiaoxu [47] demonstrated using in vitro co-culture technology that the combination of *Saccharomyces cerevisiae* + *Candida utilis* + *Burton pichia pastoris* most effectively utilized lactic acid for propionate production and promoted propionate synthesis by *Selenomonas ruminantium* and *Megasphaera elsdenii*. Feeding this compound probiotic to healthy and ketotic transition cows regulated rumen microbiota, increased rumen short-chain fatty acids (SCFA) and blood glucose, decreased blood BHBA, and showed no adverse effects.

### 2.2 Enhancing Small Intestinal Digestion and Absorption to Increase Exogenous Glucose and MP Supply

Nutrients entering the small intestine are degraded into small molecules by digestive enzymes, absorbed via free diffusion or transporter assistance, and utilized by various tissues through blood circulation and metabolic transformation. The pancreas secretes multiple digestive enzymes including -amylase, trypsin, and pancreatic lipase, playing vital roles in small intestinal nutrient digestion. The energy supply efficiency of dietary starch digested and absorbed in the small intestine significantly exceeds that in the rumen, yet the small intestinal digestibility of rumen escape starch (RES) does not exceed 70%, with insufficient pancreatic -amylase secretion being one limiting factor [48-51].

Addressing this key scientific question, our group systematically investigated the effects of functional amino acids including leucine (Leu) and phenylalanine (Phe) on pancreatic digestive enzyme expression, secretion, and signaling networks in ruminants, using dairy goats and young cows as models combined with pancreatic tissue incubation and primary cell culture techniques [35,37]. Yu Hongxia [49] found that duodenal infusion of 3 or 6 g Leu increased pancreatic -amylase secretion in dairy goats independently of insulin. Further research demonstrated that Phe could also regulate pancreatic exocrine function, enhance small intestinal digestive enzyme activity, and improve starch and other nutrient digestibility. Leu and Phe primarily regulate pancreatic protein synthesis in goats through hormones and the mammalian target of rapamycin (mTOR) signaling pathway [51-53]. Building on these findings, we employed multi-cannulated Holstein heifers, pancreatic tissue incubation, and primary pancreatic acinar cell culture to preliminarily elucidate the mechanisms by which Phe, Leu, isoleucine (Ile), and valine (Val) regulate pancreatic enzyme expression and secretion, constructing regulatory networks [48,54-56], and are currently investigating the specific sensing and response networks of the cow pancreas to functional amino acids.

Integrating the CBI system with comprehensive regulation of pancreatic exocrine function in dairy animals can ensure rumen health and efficient fermentation while improving small intestinal digestibility of RES and other nutrients. We preliminarily established a technical approach to optimize overall dietary nutrient utilization in ruminants, though its effects on small intestinal nutrient absorption require further investigation. High-intensity lipid metabolism during the transition period causes free radical accumulation, readily inducing oxidative stress, making dietary fat supplementation to alleviate NEB inappropriate. Under balanced dietary nutrition and small intestinal amino acid balance, appropriately increasing RES and RUP content through feed processing or other measures, supplemented with rumen-protected amino acids (e.g., Leu, Phe), may offer a novel approach to alleviate NEB and negative protein balance (NPB) in transition cows. However, whether these functional amino acids can regulate pancreatic exocrine function in transition cows requires further research.

### 2.3 Ensuring Liver Health to Improve Hepatic Energy Metabolism and Nutrient Output

The liver serves as the energy metabolism hub and a major site for synthesis of important proteins such as albumin and VLDL in dairy cows. Approximately 70% of glucose originates from hepatic gluconeogenesis, with ATP produced from glucose and lipid oxidation in hepatocytes providing crucial energy for growth, reproduction, lactation, and other vital activities. Therefore, ensuring liver health and improving its energy metabolism and nutrient output efficiency are key research priorities in transition cow nutrition.

Liver health and metabolism in transition cows face several major challenges [5,57-58]: 1) limited capacity for complete lipid oxidation, insufficient VLDL synthesis, and hepatic TG accumulation causing hepatocyte fat infiltration or fatty liver; 2) excessively active lipid metabolism producing radicals beyond clearance capacity, causing oxidative stress and hepatocellular damage; 3) insufficient gluconeogenic precursors and decreased hepatocyte gluconeogenic capacity, resulting in MG negative balance; 4) decreased synthesis of metabolic enzymes and active substances in hepatocytes under neuroendocrine and multifactorial regulation; and 5) hepatocyte inflammatory responses where acute-phase proteins (e.g., tumor necrosis factor- ) inhibit hepatocyte function. The root cause is negative balance of major nutrients, particularly energy and protein. Therefore, liver health can be regulated through two approaches: 1) promoting nutrient intake, improving overall dietary nutrient utilization, and alleviating NEB and NPB to indirectly enhance liver health; 2) regulating core hepatic energy and lipid metabolic pathways, reducing hepatic lipid deposition, decreasing oxidative stress and inflammatory responses, and enhancing liver function [10,59].

Research demonstrates that adenosine 5' -monophosphate-activated protein kinase (AMPK) functions as a cellular energy metabolism switch, playing a central role in hepatocyte energy and lipid metabolism [17]. AMPK is a highly conserved serine (Ser)/threonine (Thr) protein kinase comprising one catalytic subunit and two regulatory subunits ( and ), regulated by AMP/ATP ratio, upstream kinases [e.g., liver kinase B1 (LKB1)], and hormones such as leptin [60-62]. When hepatic AMPK is activated, downstream target proteins are phosphorylated at Ser or Thr residues, subsequently modulating their expression to inhibit hepatic lipid synthesis while promoting lipid and carbohydrate oxidation for energy (Figure 2 [Figure 2: see original paper]). Studies have shown that leptin and adiponectin can activate hypothalamic AMPK to increase feed intake in rodents [63-65], whereas ghrelin injection activates rat hypothalamic AMPK, impairing feed intake [66-67]. However, whether leptin and ghrelin regulate transition cow dry matter intake (DMI) through hypothalamic AMPK activation/inhibition remains unreported. AMPK research in dairy cows has primarily focused on energy and lipid metabolism in mammary and adipose tissues [68-70], with limited investigation of hepatic AMPK. Deng et al. [71] found that BHBA could activate AMPK in bovine primary hepatocytes, promoting lipid oxidation while inhibiting lipid synthesis. This suggests AMPK plays an important role in hepatic carbohydrate and lipid metabolism in dairy cows, though its regulatory network requires further elucidation, and whether existing nutritional interventions exert effects through AMPK remains unclear.

Therefore, clarifying the role and mechanisms of AMPK in hypothalamic feed intake regulation and hepatic glucose-lipid metabolism during the transition period, screening feed additives and/or bioactive compounds that activate hepatic AMPK and modulate hormone secretion, and promoting hepatic nutrient metabolism and transformation could theoretically alleviate nutrient negative balance, ensure fetal and maternal health, and improve postpartum lactation performance.

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## 3 Summary

Nutrient negative balance during the transition period seriously threatens cow health and efficient production throughout the lactation cycle, while direct regulation of DMI proves relatively difficult. Therefore, ensuring rumen health and efficient nutrient conversion, appropriately increasing RES supply, simultaneously promoting pancreatic -amylase synthesis and secretion, and regulating liver health and nutrient metabolism constitute important technical approaches for nutritional regulation in transition dairy cows.

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