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Metabolic Reprogramming of Hepatic Gluconeogenesis in Transition Dairy Cows: Integrative Strategies from Nutritional Precursors to Epigenetic Modulation

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ABSTRACT

This review focusses on metabolic changes in early lactation dairy cows with respect to hepatic gluconeogenesis and potential avenues to optimize metabolic adaptation. During transition, there is a negative energy balance, decreased dry matter intake, significant amounts of lipid mobilization and greater demands for glucose is required for lactose synthesis, all these activites put a lot of stress on the liver. Therefore, hepatic gluconeogenesis is critical to ensure glucose homeostasis and productive performance. Propionate, lactate, glycerol and glucogenic amino acids are important glucogenic precursors that, together regulates the enzymatic activity and play a significant role in hepatic glucose production. The review also covers nutritional interventions to enhance metabolic resilience and minimize transition associated disorders, including propylene glycol, rumen-protected nutrients, probiotics and precision feeding strategies. Furthermore, the regulation of hormonal mechanisms, pathways involved in sensing nutrients and epigenetic modifications of gluconeogenic genes are dscussed. Nutrigenomics and the use of metabolomics markers combined with the advent of AI-driven precision nutrition could offer future possibilities for health and sustainability in dairy production during transition.

Keywords: Transition period, Negetive Energy Balalnce, Hepatic Gluconeogenesis, Nutritional interventions, Epigenetic modulation of gluconeogenic genes

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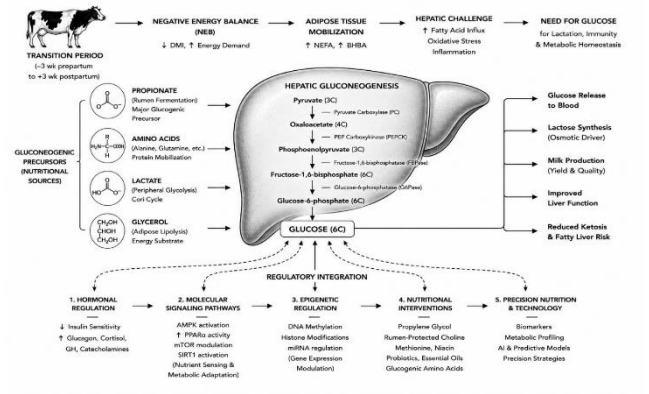

Graphical Abstract

Introduction

The transition period, from three weeks before to three weeks after parturition, is considered the most metabolically challenging stage in dairy cows. During this phase, cows undergo major physiological, endocrine and metabolic adaptations to support fetal growth, colostrum synthesis and lactation. However, dry matter intake (DMI) declines during late gestation while nutrient and energy demands increase after calving, resulting in negative energy balance (NEB) [1]. This imbalance leads to mobilization of adipose reserves, causing an increase in the levels of non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHBA) in the blood, which impose an enormous metabolic load on the liver [2].

Glucose metabolism is central to transition adaptation because lactose synthesis regulates milk secretion and yield. Unlike monogastrics, ruminants absorb little direct dietary glucose due to ruminal fermentation of carbohydrates into volatile fatty acids (VFAs). Therefore, hepatic gluconeogenesis becomes the primary pathway maintaining glucose homeostasis. Propionate is the major glucogenic precursor, while lactate, glycerol and glucogenic amino acids also contribute to hepatic glucose synthesis. Efficient activation of gluconeogenic pathways is essential for lactation performance, metabolic stability and postpartum health. Recent studies further indicate that transition adaptation involves alterations in hepatic transcriptomic activity, gluconeogenic enzyme expression, mitochondrial function and nutrient-sensing pathways [3]

Failure of proper metabolic adaptation exposes dairy ruminants to ketosis, fatty liver syndrome, oxidative stress, inflammation, impaired immunity and reproductive dysfunction. Excessive hepatic uptake of NEFA often exceeds the liver's oxidative and very-low-density lipoprotein (VLDL) export capacity, leading to triglyceride accumulation and ketone body formation. Oxidative stress and inflammation further impair insulin sensitivity, mitochondrial efficiency and cellular metabolism [4]. Impaired gluconeogenesis additionally limits glucose availability for lactation and immune function, thereby reducing productive efficiency [5]. Although conventional nutritional strategies such as glucogenic supplementation and transition feeding programs have shown beneficial effects, their outcomes often remain inconsistent because hepatic metabolism is regulated through complex interactions among nutrients, hormones and signaling pathways [4].

Recent research has therefore focused on integrative approaches combining nutritional interventions with molecular and epigenetic regulation of hepatic metabolism. Nutritional precursors can enhance hepatic glucose production and metabolic resilience during early lactation [4], while advances in nutrigenomics and epigenetics demonstrate that nutrients regulate hepatic gene expression and metabolic adaptation [6]. Therefore, this review aims to critically discuss the metabolic reprogramming of hepatic gluconeogenesis in transition dairy cows, with particular emphasis on the integrated roles of nutritional precursors, molecular signaling pathways and epigenetic modulation as emerging strategies to improve metabolic health, lactational efficiency and transition success.

Hepatic Gluconeogenesis Pathways

Glucose production from non-carbohydrate metabolic precursors, mostly in hepatic tissues, is an important metabolic pathway (hepatic gluconeogenesis). This is of importance in ruminants since only small percentages of dietary glucose are able to pass the rumen and be absorbed in the small intestine. Ruminal microbes, however, transform most dietary carbohydrates to volatile fatty acids (VFAs) leaving endogenous glucose synthesis necessary to maintain metabolic homeostasis. This means that the glucose requirements with lactose synthesis, milk production and immune competence and physiological adaptation in early lactation are also significantly dependent on hepatic gluconeogenesis in transition dairy cows [3, 7].

Propionate is regarded as the most important gluconeogenic substrate in ruminants. It is synthesized in the rumen from starch and soluble carbohydrates during the fermentation process and then carried by portal blood to the liver where it is converted to succinyl-CoA and oxaloacetate, entering the gluconeogenic pathway. Enhanced glucose availability, as well as improved energy balance and lactational performance, are hence closely linked to increased ruminal production of propionate in transition dairy cows [7]. Other amino acids that can be converted to glucose are also important for hepatic glucose synthesis, for example, glucogenic amino acids like alanine and glutamine. During negative energy balance, peripheral tissues will generate lactate, which is transformed to glucose in the Cori cycle; in addition, adipose tissues will release glycerol, which is used as another source of substrate [8].

Glucose production is strictly controlled by a number of important hepatic enzymes that regulate it and influence metabolic efficiency in early lactation. Pyruvate carboxylase (PC) is a mitochondrial enzyme that converts pyruvate to oxaloacetate, thereby providing the first step in the gluconeogenic pathway and replenishing intermediates in the tricarboxylic

acid (TCA) cycle. The oxaloacetate is then converted to phosphoenolpyruvate (PEP) by the enzyme phosphoenolpyruvate carboxykinase (PEPCK), which is one of the key rate-limiting enzymes for hepatic glucose production.

Oxaloacetate + GTP → Phosphoenolpyruvate + GDP + CO_2

The reaction involves decarboxylation and phosphorylation of oxaloacetate to produce phosphoenolpyruvate that then enters a chain of enzyme-catalyzed reactions to produce glucose. This bypass pathway is metabolically important as it bypasses the irreversible step of glycolysis, pyruvate kinase, allowing the continual production of glucose from endogenous stores during conditions of increased glucose requirement. In addition, fructose-1,6-bisphosphatase and glucose-6-phosphatase are enzymes that catalyze the dephosphorylation of fructose-1,6-bisphosphate and glucose-6-phosphate, respectively, and thus play a role in the final steps of gluconeogenesis. These enzymes are highly regulated by hormones and metabolism during the transition period [3].

This is why it is crucial for the liver to be able to efficiently mobilize glucose, ensure milk is produced, ensure lactose production is maintained and ensure a supply of glucose for early lactation. Dysregulation of the gluconeogenic pathways, however, reduces the production of glucose and worsens metabolic disorders like ketosis and fatty liver syndrome [2, 9].

Table 1: Major Gluconeogenic Precursors and Their Metabolic Roles in Transition Dairy Cows

Gluconeogenic Precursor	Primary Source	Hepatic Conversion Pathway	Functional Role During Transition
Propionate	Ruminal fermentation of starch and soluble carbohydrates	Propionate → Succinyl-CoA → Oxaloacetate → Glucose	Major glucogenic precursor supporting lactose synthesis and energy balance
Alanine	Skeletal muscle protein mobilization	Alanine → Pyruvate → Oxaloacetate → Glucose	Maintains glucose supply during protein catabolism and NEB
Glutamine	Tissue amino acid turnover	Glutamine → α-ketoglutarate → TCA cycle intermediates	Supports hepatic glucose production under metabolic stress
Lactate	Peripheral glycolysis and Cori cycle	Lactate → Pyruvate → Glucose	Recycles carbon substrates to maintain glucose homeostasis
Glycerol	Adipose tissue lipolysis	Glycerol → Dihydroxyacetone phosphate → Glucose	Alternative substrate during excessive fat mobilization

Nutritional Precursors and Feeding Strategies

Nutritional management of the transition period is key to control hepatic gluconeogenesis, energy balance and to reduce the risk of developing metabolic disorders in dairy cows. The importance of glucose demand during early lactation has made the nutritional strategies to increase the delivery of glucogenic substrates to the rumen and to optimize ruminal fermentation significant topics of discussion as potential ways of improving the metabolic adaptation and lactational performance of early lactation cows [7].

One of the main nutrition strategies is to manipulate the rumen fermentation to increase propionate production by using high-glucogenic diets and carefully managing starch supplementation. The fermentation of fibrous carbohydrates in ruminants primarily yields acetate, and the increased production of propionate in the rumen with starch-rich diets. Propionate is the major glucogenic precursor in dairy cows, so increasing the propionate-to-acetate ratio will benefit hepatic glucose production and energy efficiency in early lactation. However, too high a proportion of starch fermentation can also reduce rumen pH and the risk of subacute ruminal acidosis (SARA), which indicates the need of an appropriate balance between acetate and propionate production in order to maintain rumen health and metabolic stability [7, 10].

Propylene glycol is a common glucogenic supplement used during the transition period, as a quick glucose source. Propylene glycol is metabolized in the rumen and liver and convert into propionate and glucose precursors, increasing blood glucose levl and decreasing ketone body production. The supplementation of propylene glycol has been shown to significantly reduce circulating β-hydroxybutyrate (BHBA) level and the prevalence of ketosis in transition dairy cows in several studies [11]. However, its supplementation can cause a decrease in feed intake and a detrimental effect on rumen fermentation, especially when using excessive amounts in negative energy balance.

Rumen-protected nutrients such as methionine, choline and niacin are also seen to be beneficial in promoting hepatic metabolism and transition cow health. The methionine is used as a methyl donor in one-carbon metabolism and antioxidant production, and in hepatic lipid transport. Likewise, rumen-protected choline is important for the synthesis of very-low-density lipoprotein (VLDL) and triglycerides export from the hepatic tissues, thereby decreasing the degree of hepatic lipid accumulation and development of fatty liver. In addition, niacin has also been reported to modulate lipid mobilization, and enhance energy metabolism, by decreasing excessive lipolysis of adipose tissue during early lactation. Together, these nutrients provide enhanced liver function, metabolic resilience and gluconeogenic efficiency in transition dairy cows.

The amino acids supplementation is another significant approach to promoting glucose production in liver during transition phase. Alanine and glutamine are a class of amino acids referred to as glucogenic that directly contribute to gluconeogenesis, particularly important during periods of protein mobilization and nutrient deficiency. Furthermore, the synchronization of dietary protein and energy suppl optimizes the rumen microbial efficiency and nutrient utilization, which helps in overall metabolic adaptation and productive performance [3].

The functional feed additives that are gaining greater scientific interest in their effects on rumen fermentation and metabolic stability include yeast cultures, probiotics, plant bio actives and essential oils. Probiotics and yeast cultures help maintain a balanced rumen pH and improve fiber digestion and microbial balance, while plant-based bioactive compounds have antioxidant and anti-inflammatory activity that can reduce oxidative stress during the transition period [12]. Indirectly, these additives can help improve hepatic gluconeogenesis by improving rumen efficiency and decreasing metabolic stress. Better precision nutrition that takes into account metabolic biomarkers, automated sensors, artificial intelligence (AI) and real-time monitoring systems is also supporting tailored feeding strategies and early detection of metabolic issues in transition dairy cows [8].

Table 2: Nutritional Interventions for Improving Hepatic Glucose Metabolism in Transition Dairy Cows

Nutritional Intervention	Primary Mechanism	Metabolic Benefit	Potential Limitation
High-glucogenic diets	Increase ruminal propionate production	Enhances hepatic gluconeogenesis and energy balance	Excess starch may induce SARA
Propylene glycol	Rapid glucogenic precursor	Reduces ketosis and elevates blood glucose	Excessive supplementation may depress feed intake
Rumen-protected methionine	Methyl donor and antioxidant support	Improves hepatic metabolism and VLDL synthesis	High supplementation cost
Rumen-protected choline	Promotes triglyceride export from liver	Reduces fatty liver and improves liver function	Variable responses among cows
Niacin	Regulates adipose tissue lipolysis	Reduces excessive NEFA mobilization	Limited efficacy in severe ketosis
Yeast culture and probiotics	Stabilize rumen microbial activity	Improve nutrient utilization and metabolic stability	Response depends on diet composition

Plant bio actives and essential oils	Antioxidant and anti-inflammatory effects	Reduce oxidative stress and improve rumen health	Inconsistent dose-response relationships

Hormonal and Molecular Regulation

During the transition period in dairy cows, extensive hormonal and molecular changes occur that influence partitioning of nutrients, hepatic metabolism and energy homeostasis. Physiological insulin resistance is one of these adaptations and is considered to be an essential mechanism to survive during early lactation. Lower insulin sensitivity results in lower uptake of glucose by peripheral tissues like muscle and adipose and it allows glucose to be spared for the mammary gland, which requires a great amount of glucose for lactose production and milk yield [2]. However, excessive insulin resistance may aggravate adipose tissue lipolysis and increase circulating non-esterified fatty acids (NEFA) and hence exacerbate the metabolic stress during negative energy balance (NEB) [11].

Other important hormones that regulate hepatic gluconeogenesis during the transition period are glucagon and cortisol. The increase in glucagon leads to an increase in the expression and activity of gluconeogenic enzymes like pyruvate carboxylase (PC) and phosphoenolpyruvate carboxykinase (PEPCK) in the liver, which increases glucose production. Similarly, cortisol facilitates gluconeogenesis and mobilization of amino acids and fatty acids to meet energy requirements at early lactation and during NEB conditions [7].

The hepatic adaptation in early lactation involves several nutrient sensing and metabolic signaling pathways at the molecular level. AMP-activated protein kinase (AMPK) stimulates fatty acid oxidation and prevents excessive accumulation of lipids in the liver. Peroxisome proliferator-activated receptor alpha (PPARα) and mammalian target of rapamycin (mTOR) are involved in the regulation of genes related to β-oxidation and ketogenesis and protein synthesis and nutrient signaling, respectively. In addition, under metabolic stress, sirtuin-1 (SIRT1) regulates mitochondrial biogenesis, oxidative metabolism and hepatic gluconeogenesis [3, 8].

During transition, oxidative stress and inflammation also impact hepatic metabolic regulation. Overproduction of reactive oxygen species (ROS) leads to dysfunction of the mitochondria, a decrease in ATP production, and a decrease in metabolic efficiency in the liver. On the other hand, inflammatory cytokines increase insulin resistance and disrupt the nutrient-sensing pathways leading to the development of ketosis, fatty liver disease and decreased productive performance in transition dairy cows [9].

Epigenetic Modulation of Hepatic Gluconeogenesis

Recent progress in molecular biology highlights the significance of epigenetic regulation in controlling hepatic metabolism and metabolic adaptation during transition period in dairy cows. Epigenetics is the study of heritable changes in gene expression without changes to the base sequence of DNA. Epigenetic regulation can take many forms, but includes DNA methylation, histone modification and regulation by microRNA (miRNA) regulation. DNA methylation tends to inhibit gene transcription by modifying cytosine bases to become methylated, while histone modification affects chromatin structure, and thus the accessibility of transcriptional machinery to target genes. Unlike, miRNAs can modulate the expression of genes after transcription through mRNA degradation or by inhibiting protein synthesis [7, 8]

These epigenetic mechanisms are regulated by nutritional status, and are directly involved in hepatic metabolic adaptation. Folate, choline and methionine are all nutrients involved in one-carbon metabolism and DNA methylation reactions. Rumen protected methionine and choline supplementation has been linked to improved hepatic function, increased antioxidant status and changes in the expression of genes associated with lipid metabolism and gluconeogenesis in transition dairy cows. The results indicate that nutrition can also affect hepatic metabolic efficiency beyond simply providing substrates for metabolism, and by modifying the epigenetic regulation of metabolic pathways. The enzymes in gluconeogenesis such as phosphoenolpyruvate carboxykinase (PEPCK), pyruvate carboxylase (PC) and glucose-6-phosphatase (G6Pase) are potential target genes that may be epigenetically regulated during the transition period. Transcriptional activity of these genes might be negatively controlled by altered DNA methylation and histone acetylation under NEB, which in turn may affect gluconeogenic efficiency [8]. MicroRNAs have been identified as important regulators of lipid metabolism, response to oxidative stress, mitochondrial function and gluconeogenesis in metabolic stress conditions. [10]. In transition dairy cows with ketosis and fatty liver syndrome, altered miRNA expression profiles have been reported, highlighting a role for miRNAs in metabolic dysfunction and hepatic adaptation. Precision metabolic programming and individual nutrition are anticipated to be the future of dairy nutrition, given the integration of nutrigenomics and epigenetics [7].

Table 3. Epigenetic Mechanisms Influencing Hepatic Gluconeogenic Genes in Transition Dairy Cows

Epigenetic Mechanism	Target Genes/Pathways	Regulatory Effect	Metabolic Consequence
DNA methylation	PEPCK, G6Pase	Alters transcriptional activity	Modulates hepatic glucose synthesis during NEB
Histone acetylation/deacetylation	PC, PEPCK	Changes chromatin accessibility	Influences gluconeogenic enzyme expression
microRNA (miRNA) regulation	Lipid metabolism and oxidative stress genes	Post-transcriptional suppression of mRNA	Regulates hepatic adaptation and metabolic stress response
Methionine-mediated methylation	One-carbon metabolism pathways	Provides methyl groups for DNA methylation	Supports metabolic gene regulation and antioxidant defense
Choline-associated epigenetic modulation	Hepatic lipid transport genes	Regulates VLDL synthesis and lipid export	Reduces hepatic triglyceride accumulation

Conclusion and Future Directions

In transition period dairy cows suffer from metabolic stress due to negative energy balance and increased glucose demand during early lactation. So, Hepatic gluconeogenesis is very important in this phase to physiologically support the dairy cows. Nutritional interventions such as glucogenic diets, propylene glycol, rumen-protected nutrients and functional feed additives have improved the hepatic metabolism and reduced metabolic disorders. Meanwhile, hormonal regulation, nutrient-sensing pathways and epigenetic mechanisms in metabolic adaptation, gained more attention during recent years. Bovine-specific epigenetic studies and integrated omics research are limited, and development of universal feeding strategies are complicated due to variation among cows. Future research should focus on precision feeding technologies, biomarker-guided nutrition, AI-integrated metabolic monitoring, and epigenetic studies to develop individualized nutritional interventions to improve metabolic resilience in transition dairy cows.

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