

# Nutritional interventions for prevention of metabolic disorders in transition cows

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## Abstract

The objective of this presentation is to overview the biology and hepatic metabolism that contributes to onset and progression of metabolic disorders. Nutritional interventions that decrease metabolic disorders will be discussed within the context of nutrient partitioning and hepatic metabolism in order to understand the mechanism of action. Although there are many nutritional interventions that can be considered to influence metabolic health, recent research on fermented ammoniated condensed whey, fatty acids, and choline are of interest here given their ability to influence nutrient partitioning, metabolic health, and production or feed efficiency in peripartum dairy cows.

**Key words:** dairy cows, peripartum, lipid metabolism, gluconeogenesis

## Introduction

The transition to lactation period for the dairy cow is characterized as 3 weeks prior to 3 weeks after calving.<sup>12,17</sup> While this peripartum period can be full of metabolic challenges, it also holds great opportunity for improvements in animal efficiency and health. Many of the challenges associated with the transition to lactation are rooted within energy balance. The voluntary feed intake reduction around the time of calving, coupled with increases in energy requirements to meet the needs of lactation, result in cows entering a state of negative energy balance (**NEB**) around calving. During periods of NEB, triglycerides (**TG**) are mobilized from fat stores and the resulting fatty acids and glycerol backbone are transported to the liver to help alleviate NEB. Glycerol can serve as a glucose precursor in the liver, and fatty acids provide milk fat precursors in the mammary gland or are oxidized for energy in the liver. Oxidation of nutrients, including fatty acids, is essential for liver cell functions, including fueling the energetically expensive pathway of gluconeogenesis (glucose synthesis), by which most of the glucose supply in ruminant animals is generated. The onset of NEB also creates a deficiency in glucose, amino acids, and other nutrients because of low dry-matter intake (**DMI**) during a time of elevated nutrient requirements. Given these nutrient demands, optimizing nutrient balance during the transition to

lactation period can potentially mitigate the onset or severity of metabolic disorders.

## Hepatic Metabolism and Metabolic Disorders

In order to target nutritional interventions to improve metabolic health during the transition to lactation period, it is important to understand nutrient partitioning and where disruptions or shortages may be occurring. Hepatic metabolism serves as a central hub for nutrient metabolism as recently reviewed,<sup>32</sup> and imbalance in these pathways can quickly lead to metabolic disorders. At the onset of NEB, TG are mobilized from adipose tissue and transported through the blood as NEFA and glycerol to provide precursors for energy or TG synthesis in other tissues. Within the liver, fatty acids are  $\beta$ -oxidized to acetyl-CoA units with 4 possible fates: complete oxidation through the TCA cycle, incomplete oxidation through ketogenesis, TG synthesis and packaging as very-low density lipoprotein for export from the liver, or TG synthesis for storage as liver lipids.<sup>17</sup> Fatty acids are proportionally taken up by the liver relative to concentration and blood flow<sup>14,27</sup> and can exceed TCA cycle capacity during peak adipose tissue mobilization, leading to increased production of ketone bodies and deposition of TG.<sup>31</sup> If flux of NEFA carbon through these alternative fates is excessive, cows may experience metabolic disorders such as hyperketonemia (**HYK**) or hepatic lipidosis<sup>31</sup> which contribute greatly to the cost of dairy production through treatment cost, lost milk, reduced reproductive efficiency, and involuntary culling.<sup>5,20</sup> Other hepatic functions such as gluconeogenesis and amino acid metabolism are closely intertwined with these pathways and are also impacted in cows with metabolic disorders.

While there are certainly negative impacts of metabolic disorders, it is also important to remember that the homeorhetic changes associated with the transition to lactation period are necessary for the animal to rapidly adapt to changing demands. Specifically, ketone bodies produced by ketogenesis can be used as an energy source by other tissues, including the mammary gland, central nervous system, heart, and muscle, allowing for export of energy from the liver.<sup>4</sup> It is only when production of ketone bodies exceeds peripheral tissue uptake that HYK occurs. This highlights the role of nutrition to support optimal metabolism and nutrient partitioning to both support the changing demands of the

peripartum period, and to avoid metabolic disorders that have negative impacts on animal health and productivity. Within the context of nutrient partitioning and preventing metabolic disorders, we can think of nutritional interventions in 3 categories: 1) increase glucose or energy precursors available to the liver; 2) increase capacity or efficiency of the liver to metabolize these precursors; or 3) export excess nutrients or energy-equivalents for use by other tissues. We have made progress across all 3 of these means of intervention and these proceedings will highlight a few recent areas of progress.

### Nutritional Interventions to Mitigate Metabolic Disorders

The amount of glucose required to support lactation combined with the necessity for nearly all of that glucose to be synthesized *de novo* in the ruminant animal has long highlighted increasing gluconeogenic precursors as a nutritional goal. Optimizing starch content within the ration and use of ionophores are well-established interventions that increase propionate production in the rumen and provide valuable gluconeogenic precursors to the liver that subsequently contributes to an increase in milk production.<sup>2,18,21,30</sup> Propionate is the greatest contributor to glucose carbon (60 to 74%) and is the primary contributor even when feed intake is reduced around with calving.<sup>2</sup> In addition to propionate, glycerol and lactate are valuable gluconeogenic precursors. Glycerol is available for hepatic uptake during triglyceride mobilization; however, the relative contribution to glucose carbon is considerably lower (0.5 to 3%).<sup>2</sup> Lactate contributes 16 to 26% of glucose carbon and the relative contribution is increased around the time of calving.<sup>2</sup>

Supplementation of lactate could be potentially advantageous if rumen acidosis is avoided. In an effort to provide lactate as a potential glucose precursor, cows were supplemented with fermented ammoniated condensed whey (FACW) which is a unique ammoniated lactate product (Glucoboost,<sup>a</sup> 72.7% lactate, 55.5% CP, pH = 6.5) from the day of calving to 45 days postpartum. Postpartum supplementation of FACW reduced  $\beta$ -hydroxybutyrate (BHB) and NEFA, and increased glucose concentrations in the immediate postpartum period and tended to reduce incidence of HYK from 60% to 37%.<sup>8</sup> Rumen fluid was analyzed in a subset of cows and supplementation resulted in increased propionate which may have reflected ruminal lactate fermentation to propionate. Potential increase in propionate availability could have supported increased hepatic gluconeogenesis, contributing to the improved feed efficiency observed. In order to better understand the mechanism of action, liver tissue was analyzed for gene expression and protein abundance, which supported both increased gluconeogenesis and greater oxidative capacity in FACW-supplemented cows. The mechanism of this intervention to both provide additional hepatic glucose precursors and increase oxidative capacity is thought to

explain the dual benefit of improved metabolic health with improved feed efficiency observed within the study.

While the intervention described above is centered on glucose metabolism, interventions that are primarily influencing lipid metabolism have also been successful. As described above, a hallmark of the peripartum period is a rapid increase in blood NEFA at the time of parturition. Although not all cows lose BCS across the transition to lactation period, those that do lose BCS are more likely to have negative impacts on metabolic health and fertility.<sup>3,26</sup> Despite the potential negative outcomes of metabolic disorders, mobilization of TG from adipose tissue serves a critical function during the transition to lactation period. Mobilized TG from adipose tissue provides valuable milk fat precursors for mammary gland utilization.<sup>24</sup> Additionally, complete oxidation (TCA cycle) and subsequent oxidative phosphorylation of energy equivalents is essential to fuel hepatic gluconeogenesis, ammonia detoxification via the urea cycle, and other hepatic functions. For these reasons, eliminating the NEFA mobilization in response to NEB is not advantageous. Interestingly, NEFA are not simply benign energy sources but rather many fatty acids that have regulatory effects. One example is prepartum supplementation with rumen protected conjugated linoleic acid (CLA; Lutrell Pure<sup>b</sup>) which increased milk energy output and decreased blood BHB and NEFA postpartum.<sup>23</sup> Other fatty acids may influence nutrient partitioning and influence relative flux of complete oxidation, ketogenesis, or lipid storage during the peripartum period;<sup>32</sup> however, much of this work is not yet ready for application and generally speaking, dietary fatty acid supplementation is focused on providing energy to mid- and late-lactation cows at this point.

Although liver lipid content increases peripartum in dairy cows, liver lipid content decreases as lactation progresses.<sup>16,28,29</sup> The mechanism of lipid export from the liver has been studied as a target of dietary intervention for several decades. Export of lipid from ruminant liver is primarily as very low density lipoprotein (VLDL), a lipid moiety that contains phosphatidylcholine, apolipoproteins, and lipids. In ruminants, export of VLDL is not sufficient to prevent lipid accumulation peripartum and may be limited by phosphatidylcholine availability. Synthesis of phosphatidylcholine can originate from dietary choline or from methylation of phosphatidylethanolamine. The classically described benefit of rumen-protected choline supplementation (RPC) is a reduction in liver fat accumulation across the transition to lactation. A decrease in liver fat has been observed with peripartum RPC supplementation (14.4 to 15 g/day choline) in several<sup>11,13,15,19,39</sup> but not all (14.4 to 19 g/day choline)<sup>25,35,37,38</sup> transition cow studies. When supplemented to dry, pregnant cows that were feed-restricted to mimic the NEB aspect of the transition period, RPC supplementation lessened fat accumulated within the liver.<sup>11,36</sup> When RPC was supplemented after fatty liver induction using the same model, supplementation reduced liver fat,<sup>11</sup> suggesting an ability of RPC to aid in recovery from fatty liver. The mechanism of choline to

reduce liver lipids is thought to be through increased VLDL export; however, it is very challenging to measure blood VLDL in ruminants because of the differences in lipid profile and because the mammary gland in dairy cows takes up more fat from the blood compared with other species due to greater milk fat synthesis. Markers of VLDL secretion were increased in transition cows supplemented with RPC that showed reduced liver TG accumulation.<sup>15</sup> Quantification of VLDL export from liver cells in culture by ELISA assay indicated an increase in VLDL export with increased choline supplementation.<sup>10</sup> In addition, recent advanced laboratory techniques have confirmed the ability of RPC supplementation to increase phosphatidylcholine concentrations in lipid-rich lipoproteins isolated from plasma of non-lactating cows.<sup>22</sup>

Just as mobilized NEFA can be used as a milk fat precursor, so can VLDL exported from the liver. Consistent with this, supplementation of RPC to peripartum dairy cows consistently increases milk or fat-corrected milk yield. A meta-analysis<sup>1</sup> examined RPC supplementation across 23 experiments (74 treatment means; 1,938 cows) demonstrated a significant increase in pre- and postpartum DMI (0.28 and 0.47 kg/d, respectively), increased energy-corrected milk (ECM; 1.61 kg/day weighted mean average), and increased fat and protein yield (0.08 and 0.06 kg/day, respectively). Within the meta-analysis, incidence of retained placenta and mastitis, but not displaced abomasum, ketosis, or metritis, were reduced by RPC supplementation.

Benefits of RPC supplementation do not appear to be dependent on prepartum dietary energy<sup>35</sup> or body condition score.<sup>6</sup> Despite a lack of interaction between prepartum dietary energy and RPC (ReaShure<sup>c</sup>) supplementation on production, treatment interactions on liver metabolism were evident that suggest overlapping mechanisms.<sup>7</sup> Interestingly, supplementation of RPC<sup>c</sup> may have benefits on production that persist beyond the supplementation period, as demonstrated by tendencies for improved milk yield at 15 and 40 weeks postpartum and improved milk components at 15 weeks postpartum after supplementation during the 3 weeks before and 3 weeks after parturition.<sup>35</sup> When supplementing prepartum, we also have the potential to influence the calf developing in utero, and improved average daily gain from calving or weaning to 50 weeks of age, and improved immune status and response to a bacterial challenge have been observed.<sup>33,34</sup>

Increases in milk fat yield may be reflective of increased VLDL export from the liver since the VLDL can subsequently be taken up and used by the mammary gland. Despite this, improvements in lipid metabolism may not fully explain production advantages observed with RPC supplementation because production responses have been seen without a decrease in liver fat.<sup>35</sup> Previously, it was noted that decreased liver fat may allow for increased liver gluconeogenesis.<sup>12,15</sup> Gluconeogenesis produces glucose for release into circulation for immediate use, or as glycogen that is stored in the liver for quick release when needed. Increased liver glycogen has been

observed with RPC supplementation in cows<sup>25,36</sup> and liver cell culture<sup>10</sup> and may reflect greater rates of gluconeogenesis. These findings reiterate the connection between the many metabolic pathways within the liver and support that many nutritional interventions have multi-faceted mechanisms.

## Conclusion

In conclusion, understanding hepatic metabolism and nutrient partitioning can highlight potential routes of nutritional intervention that can prevent metabolism disorders including HYK and fatty liver. Nutritional interventions that provide glucose or energy precursors, increase hepatic capacity for oxidation or metabolism, or export excess nutrients (ie, lipids) can be advantageous to prevent metabolic disorders. Additionally, some nutritional interventions may provide benefit through more than 1 of these mechanisms, which highlights the numerous intersection points of hepatic metabolic pathways. Application of this metabolic understanding can lead to nutritional interventions, such as prepartum supplementation of CLA, postpartum supplementation of FACW, or peripartum supplementation of rumen-protected choline, to improve postpartum metabolic health.

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## Endnotes

<sup>a</sup> GlucoBoost; Fermented Nutrition Corporation, Luxemburg, WI

<sup>b</sup> Lutrell Pure; BASF, Ludwigshafen, Germany

<sup>c</sup> ReaShure; Balchem Corporation, New Hampton, NY

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