

# **The Role of Liver Metabolism During Transition on Postpartum Health and Performance**

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## **Introduction**

Liver occupies a unique role in nutritional physiology. A considerable portion (90%) of the blood flow to the liver in lactating dairy cows comes directly from the abdominal cavity that drains the gastrointestinal tract and spleen. Consequently most nutrients, lipids being a notable exception, are absorbed across the gut and encounter liver before any other organ or tissue in the body. Therefore liver is uniquely positioned to both respond to the nutrients absorbed across the gastrointestinal tract (including rumen) and to modify the profile of nutrients available to the rest of the body. The fact that the liver also receives arterial blood serves to coordinate the metabolism of absorbed nutrients under the influence of metabolites and hormones released from other tissues. During the transition to lactation and other physiological states these activities are coordinated as part of the homeorrhetic and homeostatic controls of metabolism.

Although liver comprises only 1.3 to 1.6% of body weight of ruminants it demands a considerable amount of the energy available to the animal due to the multitude of metabolic processes that are orchestrated in this tissue (Baldwin, 1995). Liver plays a key role in glucose, lipid, and protein metabolism, ketogenesis, immune function, ammonia detoxification, steroid hormone catabolism, vitamin and mineral metabolism and several other processes. It is widely recognized that transition cow health is closely tied to the capacity of liver to coordinate these processes and to cope with the changes in nutrient supply, endocrinology, and shifting metabolic demands that accompany the transition to lactation. Likewise transition cow problems are often linked with inadequate metabolic capacity in liver. Enhanced knowledge of the processes that regulate liver function and factors that potentiate the capacity of liver to coordinate shifts in nutrient supply and demands by other tissues has led to significant improvements in transition cow management and health. This review will explore some of the recent developments in transition cow management with particular emphasis on glucose and lipid metabolism and their impact on cow health and productivity.

## **Nutritional Status at Calving and Impact on Liver Function and Potential Issues**

The term 'transition dairy cow' first appeared in the early 1990's and is used in reference to the nutritional, management and metabolic needs of the dairy cow during the last 3 weeks of gestation and first 3 weeks of lactation. It is now recognized that

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defining and meeting the nutritional requirements of the transition dairy cow can greatly impact animal health, production in the ensuing lactation, overall longevity, and animal well-being.

Much of the effort in managing transition cows has focused on avoiding the voluntary reduction in feed intake at calving or compensating for changes in intake by manipulating the nutrient profile of the transition diet. Seminal studies performed at the University of Wisconsin-Madison (Bertics et al, 1992) served to highlight the problems associated with the reduction in feed intake at calving, negative energy balance and mobilization of adipose tissue. Several strategies have been explored since that time to alter the timing and severity of the onset of negative energy balance and associated negative consequences on liver. One strategy that has been implemented is to increase the nutrient density of the transition diet to compensate for reduced feed intake. Although increased fermentable energy of the diet has been successful in some cases, there is an associated risk of rumen acidosis and abomasal displacements (Penner et al, 2007). In some instances rations composed of high fiber byproduct feeds and bulky feeds have been evaluated and tend to promote high levels of intake during the dry period and into the transition phase, however, transition problems are still evident (Karcher et al., 2007).

The past 2 decades of research on transition cow nutrition and management has illuminated the complexities of the nutritional physiology of the dairy cow. During this interval the widely held concept that overall prepartum DM intake is the driver for transition cow success (Grummer, 1995; Hayirli et al., 2003) has given way to alternatives that suggest that the rate and extent of decrease in DM intake before calving is a more meaningful predictor of overall transition health and performance. Controlled studies have evaluated the necessity for high caloric intake during the prepartum period. Cows restricted to 17.6 lb/d of DM in the late prepartum period showed no difference in postpartum milk production and health compared with cows that ate 27.3 lb/d of DM (Holcomb, et al., 2001). Other data indicated that the relative degree of change in DM intake the final 21 days prepartum is more important in regulating postpartum nonesterified fatty acids (**NEFA**) and liver triacylglycerol (**TG**) concentrations than the overall DM intake during the same period (Mashek and Grummer, 2003). Recent reports indicate that when feeding is manipulated to promote overconsumption of energy relative to NRC requirements a metabolic profile results that has characteristics similar to those of diabetes and obesity. Underfeeding cows relative to their caloric requirements, however, does not appear to have negative consequences providing the level of underfeeding is not severe or the drop in DM intake is not sudden (Janovick et al., 2011; Townsend and Donkin, 2004).

One of the salient findings from two decades of research on transition cow nutrition and metabolism is recognition of the tremendous capacity of the dairy cow to adapt metabolically to the transition to lactation. It appears that the magnitude and timing of these reductions in voluntary feed intake appear to play a greater role in transition cow health than a lower but consistent energy intake level (Janovick et al., 2011). Sudden reductions in energy intake may occur as a consequence of social

disruptions in pens, errors in feed mixing, inconsistencies in feed delivery or bunk space availability. It appears that a key element in determining the adaptive capacity of the dairy cow to the transition to lactation is a metabolic flexibility and capacity of liver and the time needed to respond to altered demands. The capacity of liver to coordinate lipid and glucose metabolism is at the center of a successful transition to lactation. Our laboratory has focused on determining the signals that control the molecular events that coordinate these responses and using this knowledge to identify feeding strategies that will adjust the metabolic set point of the transition cow towards greater health and productivity. Our work has identified pyruvate carboxylase, an enzyme in both the synthesis of glucose and activity of the TCA cycle, as a key regulated step in determining transition cow health. This work demonstrates the importance of this process in liver in adapting transition cows to the nutritional and physiological demands at calving when energy supply is limiting.

### **The Need for Efficient Glucose Production in Transition Cows**

By virtue of the extensive fermentation of carbohydrates in the rumen, the dairy cow absorbs very little dietary glucose. Almost all the glucose needs for normal tissue function and milk lactose synthesis are met through glucose synthesis in liver in a process known as gluconeogenesis (new glucose synthesis). The transition to lactation serves to underscore the importance of control of gluconeogenesis in dairy cows as hypoglycemia, ketosis, and related metabolic disorders are often observed when gluconeogenic capacity fails to adapt to the increased demands for glucose that accompany the onset of lactation.

The main substrates for glucose synthesis in fed ruminants are propionate, lactate, and amino acids. Glycerol, from adipose tissue, can also contribute carbon for glucose synthesis during feed restriction and energy deficiency. Propionate contributes approximately 50% of the carbon for gluconeogenesis, whereas lactate or amino acids contribute 10 to 15% each (Huntington, 1990). The use of amino acids in the synthesis of glucose may be of considerable importance when intake is depressed in late gestation (Bell et al., 2000). Because the primary source of propionate for gluconeogenesis is from rumen fermentation the transition to lactation further increases the dependence on lactate, glycerol and amino acids to support tissue glucose demands (Danfaer et al., 1995). The transition to lactation is marked by adaptations in the gluconeogenic machinery in liver that enable greater use of lactate to support whole body glucose needs.

It is estimated that 10 to 15% of all dairy cows experience clinical ketosis (Dohoo and Martin, 1984; Melendez et al., 2006) at a cost per cow of approximately \$200 per case and an annual cost to the US dairy industry in excess of \$184,000,000 per year in lost production and veterinary costs. Additional losses are likely due to secondary disease symptoms and subclinical ketosis. Therefore successful transition cow nutrition and management strategies are closely linked to appropriate adaptation of the ability of liver to meet the demands for glucose production.

Glucose production in liver is controlled by the availability of substrates for glucose, the metabolic capacity of the primary cells of the liver (hepatocytes) that synthesize glucose and hormonal status of the animal particularly insulin and glucagon. Controlled studies have demonstrated that fat infiltration in liver cells impairs their ability to synthesize glucose (Cadórniga-Valiño et al., 1997; Armentano et al., 1991) and to detoxify ammonia (Zhu et al., 2000). Likewise fatty liver and ketosis are closely linked. Because there is limited capacity for bovine liver to export triglycerides three strategies exist for managing liver metabolism in transition cows 1) limit mobilization of adipose tissue and fatty acid load on liver 2) enhance fatty acid oxidation by liver or 3) increase the capacity for triglyceride packaging and export (Figure 1).

### **Prevention and Amelioration of Fatty Liver**

Fat accumulation in liver of dairy cows can be classified using a needle biopsy sample as mild, moderate and severe fatty liver corresponding to < 5, 5 to 10 and >10 TG as a % of wet weight of the liver. Ketosis is preceded by fatty liver and is the best recognized consequence of the condition. Triglyceride content in liver above 8 to 10% TG (% wet weight) leads to histological and functional differences including impaired capacity to synthesize glucose and ketosis. Healthy, mildly ketotic, and severely ketotic cows have a liver lipid content of 5, 8, and 17 % respectively. approximately 50% of multiparous cows in three trials at the University of Wisconsin had liver lipid contents > 15% at calving and 30% had lipid content of > 20%. Classification of liver TG as moderate to severe based on TG content per  $\mu\text{g}$  DNA corresponds to values greater than 14  $\mu\text{g}$  TG per  $\mu\text{g}$  liver DNA. Studies at Purdue University indicate that between 26% and 70% of transition cows had moderate to severe fatty liver based on a TG content of greater than 14  $\mu\text{g}$  TG per  $\mu\text{g}$  DNA in liver or 15% liver lipid by weight.

Feeding practices that limit the rate and degree of fatty acid mobilization from adipose tissue, reduce the esterification of NEFA as TG in liver, increase the export of TG from liver, and increase the oxidation of fatty acids all act to decrease fatty liver in dairy cows. However, most strategies to reduce lipid accumulation in liver must be implemented before calving in order to reduce the severity and incidence of liver lipid accumulation. The capacity to overcome the hypophagic effects of ketosis and additional adipose tissue mobilization are difficult to overcome once this process has been engaged. Glucose infusion and propylene glycol administration have been used to treat clinical ketosis but prevention requires attention to many management factors including transition cow rations, feeding behaviors, social interactions in groups of cows.

Reducing the severity of feed intake depression at calving decreases the severity of fatty liver and tends to increase milk production. There has been a concerted effort towards improved feeding management strategies for transition dairy cows. Supplying adequate energy by increasing the energy density of transition cow diet may act to counter the effects of intake depression at calving however the level of energy in the diet may also lead to other diabetogenic signals. For example increased circulating NEFA during late pregnancy may diminish responsiveness to insulin and lead to subsequent enhanced mobilization of adipose tissue.

Increasing the energy density of the prepartum diets is beneficial in increasing liver glycogen content but not in reducing liver lipid. The ratio of TG to glycogen in liver appears to be a predisposing factor for ketosis; therefore, increasing glycogen indirectly reduces the effects of fatty liver. Feeding and management programs that minimize the reductions in energy intake particularly during the last 3 to 5 days before calving appear to be most successful in minimizing adipose tissue mobilization.

Several compounds have been investigated for their ability to diminish the incidence and severity of fatty liver. Increasing the supply of precursors for glucose synthesis in liver using propylene glycol reduces liver TG. A portion of the response to propylene glycol may be a consequence of increased blood insulin, reduce circulating NEFA, and increased liver glycogen. Overfeeding energy during the dry period may induce insulin resistance temporarily resulting in adipose tissue mobilization that would mimic overconditioning of dry cows. Feeding additional protein to transition cows does not appear to be advantageous and may lead to increases in adipose tissue mobilization despite the potential use of amino acids as glucose precursors (Greenfield et al. 2000, Hartwell et al. 2000). Ionophores, which act to alter rumen metabolism in favor of propionate production, reduce the plasma ketones and subclinical ketosis. The addition of ionophores, such as rumensin, to transition cow diets alters the metabolic set point of the transition cow to better handle the increased propionate available from the rumen (Karcher et al., 2007).

Phosphatidylcholine, the major lipid component of the very low density lipoprotein (VLDL) surface, may be limiting for VLDL assembly under some conditions in ruminants. A shortage of dietary choline has been linked to accelerated ApoB degradation, a component of VLDL, and a reduction in VLDL synthesis. Because choline is extensively degraded in the rumen and because choline and other methyl donors are critical to VLDL synthesis the addition of rumen protected choline has proved beneficial for transition dairy cows. Rumen-protected choline acts to reduce circulating NEFA concentrations reduce the severity of liver lipid accumulation. Likewise, rumen-protected choline appears to enhance the rate of lipid clearance in cows that have been experimentally induced to express fatty liver (Cooke et al., 2007) and in overconditioned transition cows that are more susceptible to fatty liver (Hartwell et al., 2000).

### **A Role for Supplemental Fat?**

Supplemental fat is often used to increase the energy density of lactating cow rations. However, evaluation of added fat for transition cows has resulted in inconsistent and often contradicting results. These inconsistencies may be related to the level of fat feeding relative to body condition and therefore propensity for adipose tissue mobilization, palatability of the fat source, form of fat including calcium salts and whole seed forms, timing of fat introduction relative to calving and profile of fatty acids. Mixed responses feeding fat to transition cows has led to the generalized recommendation of delaying the addition of fat in rations for dairy cattle until 30 days postpartum and to limit total dietary fat to 5-6% of the ration DM.

Recently the profile of fatty acids has emerged as a potential factor in regulating the metabolic capacity of liver. Fatty acids released from adipose tissue and the dietary profile of fatty acids appears to play a role in this response. Diet and feeding level during the far off dry period appears to alter the concentration and profile of fatty acids in plasma at calving. Cows that are overfed to induce fatty liver at calving had plasma NEFA and liver triglycerides that were approximately twice control values. In addition the fatty acids profiles of the control and fatty liver cows differed considerably. At calving, the greatest differences in fatty acid profile were predominately C16:0, C18:0, and C18:1cis9 (Rukkwamsuk et al., 2000).

We have extensively characterized molecular changes in liver that are linked to the transition interval. One of the most striking changes that correspond with the transition to lactation is increased expression and activity of pyruvate carboxylase. As described above this enzyme is a key component of gluconeogenesis from lactate and amino acids and is tied to the capacity of liver to oxidize fatty acids in the TCA cycle. The activity of this enzyme is directly tied to the abundance of pyruvate carboxylase in liver cells and linked to the rate of transcription of the pyruvate carboxylase gene.

The change in pyruvate carboxylase at calving is linked to increased concentrations of NEFA in plasma. This is not surprising as several metabolic reactions are regulated by fatty acids at the level of the activation of genes that encode key regulatory enzymes (Jump et al., 2005), including gluconeogenesis and fatty acid metabolism. Studies using rats and human cells have demonstrated that these changes are linked to peroxisome proliferator-activated receptors (**PPARs**) and in particular PPAR- $\alpha$  (reviewed by Jump et al., 2005; Sugden et al., 2010). These PPARs are activated in response to elevated fatty acids and bind to DNA in specific locations to activate genes.

We cloned the gene for bovine pyruvate carboxylase and tested the response to fatty acid and mediators of fatty acid action including peroxisome proliferator activated receptors or PPARs. We discovered that the pyruvate carboxylase gene is upregulated by fatty acids and PPAR- $\alpha$  agonists (White et al., 2011). We also discovered that activation of pyruvate carboxylase is down regulated by certain fatty acids, namely stearic acid. It is interesting to note that these fatty acids are also elevated in cows that experience fatty liver at calving. If stearic acid levels predominate at calving this would act to reduce the capacity of the dairy cow to cope with adipose tissue mobilization is impaired. Conversely if fatty acids, such as linoleic acid are elevated at calving the pyruvate carboxylase gene is activated and the capacity for fatty acid oxidation and glucose synthesis enhanced. It is noteworthy that cows that are over conditioned and more likely to experience fatty liver at calving have elevated saturated fatty acids (Rukkwamsuk et al., 2000). Therefore, it would appear that under some conditions the profile of fatty acids released into plasma from adipose may suppress pyruvate carboxylase expression at a critical time when it is needed for increased gluconeogenesis from lactate and increase oxidation of fatty acids from adipose tissue. Conversely feeding and management strategies that enhance long chain polyunsaturated fatty acids including C18:3 may be effective stimulators for pyruvate

carboxylase expression and the capacity to coordinate gluconeogenesis and lipid metabolism.

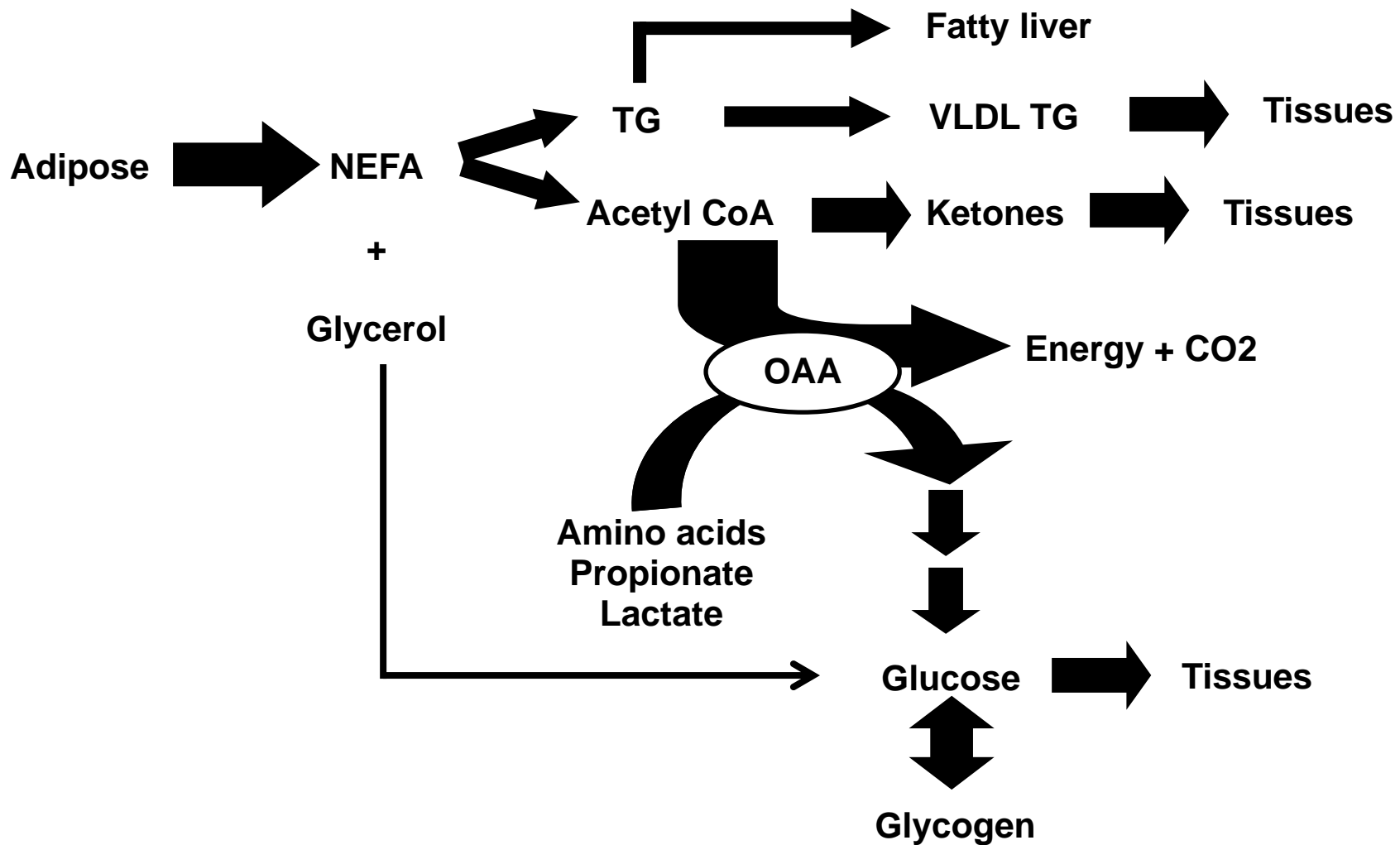
A summary of some of the recent studies that have evaluated fat feeding during the transition to lactation I provided in Table 1. The approach to feeding fat has not been consistent and several studies examine the impact of fat feeding in diet that re fed at restricted intake. In the diets outlined in Table 1 fat source was included in the diet and offered for ad libitum intake. Notable differences exist in the level of fat fed, form of fat, and the profile of fatty acids. Although it is difficult to generalize across these studies the inclusion of palm oil containing primarily C16:0 was either without effect or was detrimental to cow performance and health indicators. Feeding flaxseed oil, which contains less C16:0 and a greater proportion of C18:3 appears to be beneficial in reducing liver lipid and is without negative consequences on intake or milk production (Petit et al., 2007). Our research, which indicates activation of pyruvate carboxylase with PPAR agonists, is consistent with the increased capacity for fatty acid oxidation in transition cows fed fat sources, such as flaxseed, that contain higher concentrations of polyunsaturated fatty acids. Additional work is needed to determine the minimal level and profile of polyunsaturated fatty acid feeding that will enhance hepatic capacity and successful transition to lactation.

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**Figure 1.** Fates of nonesterified fatty acid (NEFA) metabolism in liver and relationship to gluconeogenesis. The NEFA and glycerol released from adipose tissue are taken up by liver. Glycerol is used for glucose synthesis. The NEFA can be reesterified to triglycerides (TG) and packaged in very low density lipoproteins (VLDL) and exported from liver or deposited in TG droplets and stored in liver. The NEFA can also be metabolized to acetyl CoA in the hepatocyte. Acetyl CoA can be completely oxidized to CO<sub>2</sub> and water to release energy in the form of ATP or can be partially oxidized to ketones and released from liver. The formation of glucose from propionate, lactate and the carbon skeletons of amino acids are metabolized to glucose. Propionate and lactate can both be used to form oxaloacetate (OAA). The production of OAA impacts the capacity for NEFA oxidation and gluconeogenesis. NOTE: The arrows depict reactions that are subject to regulation, the relative flow to any reaction may impact the follow of other reactions to promote or reduce fatty liver, ketosis, or gluconeogenesis.

**Table 1.** Effect of fat feeding on selected characteristics in transition cows

Reference	Level of fat	Fat source and primary fatty acids	Effects
Douglas et al. (2004)	6.4 to 6.7% DM	Choice white grease  24.2% C16:0 13.8% C18:0 46.2% cis-C18:1	↔ DM intake ↔ Liver TG ↔ NEFA ↔ BHBA ↔ Milk
Knegsel et al. (2007)	5% of DM  0.83 Mcal/lb	Palm oil  (16:0)	↔ DM intake ↑ Liver TG ↑ NEFA ↑ BHBA ↔ Milk
Duske et al. (2009)	Far off and transition 5.1 and 6.2% DM 0.64 and 0.78 Mcal/lb	Ca salts  44% palmitic (C16:0) 40% oleic (C18:1) 9.5% linoleic (C18:2)	↓ DM intake ↓ Milk ↔ FCM ↑ NEFA ↑↔ Liver TG
Petit et al. (2007)	Control, Flax, ERG  2.7, 4.2, 4.1% DM  0.67, 0.67, 0.69 Mcal/lb	Control    Flaxseed    ERG C12:0    0.5    0    0.8 C14:0    0.7    0.1    2.7 C16:0    16.7    11.5    27.3 C16:1    0.1    0    0.7 C18:0    2.5    2.8    23.4 C18:1c11    1.3    0.7    1 C18:1c9    19.3    17.8    11.3 C18:1t9    0    0    1 C18:2    46.6    35.1    21.5 C18:3    12.3    32.0    10.3	Flaxseed    EB DM intake    ↔    ↔ Liver TG    ↔    ↔ NEFA    ↔    ↔ BHBA    ↔    ↔
Zachut et al. (2010)	5.8% of DM 0.80 Mcal/lb	Flaxseed  C18:3	↔ DM intake ↑ Milk ? Liver TG

# **SESSION NOTES**