Insulin Resistance in Transition Dairy Cows: Friend or Foe?

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Introduction

An alternative title for this presentation could be: Fat Reserves- How to Manage a Valuable Resource? Most transition dairy cows experience periods of intense fat mobilization. Mobilized fat supports lactation, but if not managed properly it may lead to metabolic disorders such as fatty liver and ketosis. At calving and in early lactation, hormonal changes are important in governing fat mobilization. Discussing all the endocrine changes in this presentation is not possible; therefore, the focus will be on Insulin. Insulin is a key hormone that regulates nutrient metabolism in dairy cows. It is known as an anabolic hormone because it signals to tissues that the nutritional state is favorable and nutrients can be stored. Results from these signals include increasing glucose storage in the liver (as glycogen) and stimulation of fat synthesis and storage in adipose tissue and inhibition of fat mobilization from adipose tissue.

During the transition period, cows become "insulin resistant". Simply defined, this means that insulin has less of an affect than normal. If insulin is less effective, it means that liver glucose storage is decreased and fat mobilization from adipose tissue is increased. It is important to note that insulin resistance is not an all or nothing proposition. The magnitude of resistance is a sliding scale, so the degree of fat mobilization can vary and does not only occur at a maximum rate or not at all. Mobilization of fat helps support lactation. If mobilization of fat is too extensive, metabolic disorders such as fatty liver and ketosis can result. This begs the question, is insulin resistance a friend or a foe?

Insulin resistance: A Friend

In one very important respect, insulin resistance is a "friend". Cows purposely undergo insulin resistance as a means to support pregnancy and lactation. It is a normal biological process and a classic example of homeorhesis. Homeorhesis is a term coined by Dale Bauman, Cornell University (Bauman and Currie, 1980), and is defined as: the orchestrated or coordinated control in metabolism of body tissues to support a physiological state. In the case of the transition cow, glucose uptake by insulin sensitive tissues (muscle, adipose tissue) is decreased. Therefore, extra glucose is available to be channeled to the fetus or mammary gland, which are insulin insensitive (not affected) tissues. Additionally, fatty acid mobilization is increased when the cow becomes more insulin resistant. Once lipolysis takes place and the nonesterified fatty acids (NEFA) enter the blood, they can be diverted to the growing fetus or mammary gland to serve as an energy source or as a precursor for milk fat synthesis. The process of becoming insulin resistant is very important, especially to just fresh cows because they typically can't consume enough feed to meet the nutrient needs of lactation. The coordinated shift of nutrients from reserves to the mammary gland is instrumental in getting the cow through the

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transition period and to a period of time when feed intake can provide sufficient nutrients to support lactation.

Insulin Resistance: A Foe

It is my impression that for most people, insulin resistance has a negative connotation and is perceived as a deleterious event. Can it be a foe? A potential negative aspect of insulin resistance is *excessive* NEFA mobilization from adipose tissue. About one third of the NEFA mobilized from adipose tissue is taken up by the liver (Emery et al., 1992). Liver uptake of NEFA is influenced primarily by NEFA concentration in blood and blood flow to the liver. NEFA concentration in blood may increase 5-7 fold at calving and blood flow to the liver is increased two-fold (Reynolds et al., 2003). NEFA daily uptake by the liver can increase by as much as 10-15-fold as the cow transitions from the dry period to lactation (Overton, unpublished). This dramatic increase presents a tremendous challenge to the liver. Ideally, these extra fatty acids will either be completely oxidize to CO_2 to provide energy to the liver or they will be exported as part of a very low density lipoprotein and be available to the mammary gland as an energy source or precursor for milk fat synthesis. If the capacity to utilize the fatty acid for those purposes is exceeded, then the fatty acids may be stored in the liver as triglyceride or be converted to ketones. In other words, the cow may experience fatty liver and subclinical or clinical ketosis. Additionally, elevated NEFA concentrations have been linked to depressed feed intake, suppressed immune function, and decreased risk of pregnancy and other maladies of transition cows. So yes, insulin resistance can be a foe.

At what point does insulin resistance become a foe? Unfortunately, this is a very difficult question to answer. Researchers have tried to measure blood NEFA or beta-hydroxybutyrate (BHBA, a ketone) or liver triglyceride and correlate it to production, health or reproduction (e.g. Chapinal et al., 2012). The goal of this research is to find "cut-off levels" or concentrations that are predictive of when herd performance or health is at risk of being impaired. Liver triglyceride is not a practical measure because it requires a liver biopsy, which is too invasive. However, blood measures such as NEFA or BHBA can be useful tools. Suffice it to say, interpretation of these tests can be very tricky. For example, do "one size fits all" cut offs from large epidemiological studies apply to all herds?

Is Reducing NEFA (Reducing Insulin Resistance) Always Good?

The following are three examples that argue that reducing NEFA (reducing insulin resistance) may not always be beneficial. Example 1. Genetically superior cows for milk production have higher blood NEFA and BHBA concentrations during the first 3 weeks postpartum (Harrison et al., 1990). This occurs because milk production increases faster relative to feed intake in genetically superior cows compared to cows with lower genetic potential to produce milk. Evidence also indicates that genetically superior cows my experience greater insulin resistance (Chagas et al., 2009). Example 2. There is compelling evidence that overfeeding energy to cows during the dry period leads to lower liver triglyceride and blood NEFA and BHBA concentrations (Janovick et al., 2011, Richards, 2011, Mann et al., 2015). This evidence has resulted in the promotion of feeding "controlled energy" diets in which dry cows are fed to meet energy requirements during the dry period. It has been hypothesized that overfeeding energy creates cows that are similar to human type 2 diabetics and have increased insulin resistance.

However, in some but not all studies, feeding a controlled energy diet led to a reduction in milk production, milk fat percentage, or energy corrected milk production compared to cows overfed energy (e.g. Janovick et al., 2011). This probably occurs because these cows mobilize less fat to support lactation. Example 3. Niacin, if fed in a form that protects it from degradation in the rumen, affects adipose tissue directly and suppresses fat mobilization. Consequently, blood NEFA and liver triglyceride is reduced (Yuan et al., 2012). Once again, the reduction in NEFA corresponded to nearly a 20 lb/d reduction in energy-corrected milk during the first week postpartum.

Strategies for Managing Insulin Resistance and Fat Mobilization

On one hand, we desire insulin resistance and fat mobilization to support lactation; on the other hand it may potentially compromise liver health and function. How can nutritionists balance the act?? Historically, the main strategy has been to reduce lipid mobilization during the transition period (Figure 1). Options include feeding controlled energy diets during the dry period (Janovick et al., 2011), feeding protected niacin (Yuan et al., 2012), shortening the dry period (Rastani et al., 2005), and drenching with propylene glycol (Studer et al. 1993). As previously discussed these strategies risk a loss of milk or milk fat yield. John Newbold stated it very nicely in the proceedings from the Nottingham Nutrition Conference (2005): *"Nutritional restriction to adipose tissue mobilisation might be necessary, but there is a philosophical problem. We have selected cows that have increased reliance on mobilised body reserves as a source of nutrients for milk production. The farmer has paid the geneticist for this- are we now going to ask him to pay the nutritionist to work in the opposite direction? We have our priorities wrong. We should explore what can be done to help the liver deal with mobilised fatty acids before considering whether we need to try to reduce the amount of fatty acid supplied to the liver."* Feeding rumen-protected choline is the only proven strategy to assist the liver during times of elevated NEFA. Choline in feedstuffs is degraded in the rumen, therefore insufficient quantities are absorbed from the intestine. Fatty liver is a symptom of choline deficiency. Choline is required for phosphatidylcholine synthesis, which in turn is required for VLDL assembly and fat export from the liver. Feeding rumen protected choline to transition cows reduces severity of fatty liver and ketosis (Lima et al., 2012) and increases milk production and energy-corrected milk production (Grummer et al., 2012).

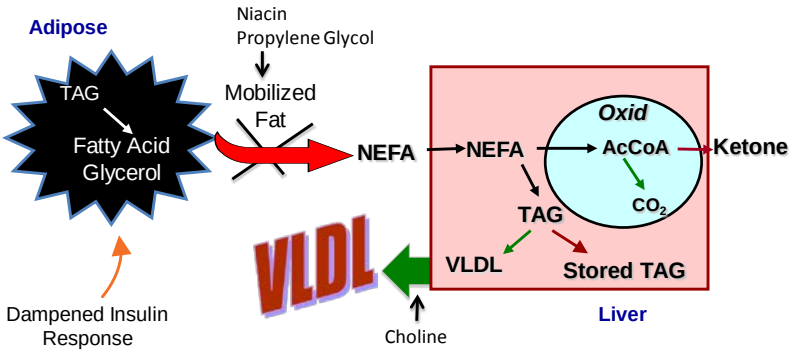

Figure 1. Strategies to manage insulin resistance: Agents such as niacin and propylene glycol reduce fat mobilization; choline enhances triglyceride (TAG) export from the liver as part of very low density lipoproteins (VLDL). NEFA= nonesterified fatty acids, AcCoA=acetylCoA.

This article should raise many questions. Are elevated NEFA or BHBA always bad and do one size fits all "cut off" values for alarm levels in blood serve us well? May alarm levels vary depending on the herd's genetic potential for milk production? What do you tell a dairy producer if "too many" cows are testing above cut-offs for blood NEFA or BHBA but the cows are milking like crazy? How will you manage fat mobilization? Perhaps a combination of antilipolytic compounds prepartum (e.g. feeding rumen-protected niacin or drenching propylene glycol) and rumen-protected choline pre- and postpartum to enhance liver fat export to the mammary gland may be most effective? By feeding antilipolytic compounds prepartum, the surge in blood NEFA that occurs at calving may be reduced (Yuan et al., 2012). By feeding rumen-protected choline prepartum, the liver will be able to process the fatty acids mobilized during the surge at calving. By feeding postpartum, choline will facilitate transfer of fatty acids from adipose tissue to the mammary gland during negative energy balance.

Bottom line: Insulin resistance and mobilization of fat reserves as NEFA are essential for cows to successfully transition from the dry period to lactation. Nutritional tools are available to manage insulin resistance so that there is a greater chance that it is a friend rather than a foe.

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