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Q&A REVIEW

Insulin Resistance – Friend or Foe?

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Presenter: Dr. Ric Grummer

1. What does DA mean? Displaced abomasum.

2. Is insulin resistance (IR) more important in early lactation than during late gestation? This is almost a philosophical question. It is "easier" to meet the nutrient demands of pregnancy than early lactation. A nutrient deficit during late gestation is of shorter duration and lesser magnitude than that experienced during early lactation. So on that basis, one could say that it is more important during early lactation. Of course the duration and magnitude of nutrient deficiency in early lactation cows had been exacerbated by genetic selection of dairy cows. Fortunately, it appears that the genetic selection has been accompanied by greater IR.

3. How can I control IR during late gestation and early lactation by diet? As indicated in the presentation, feeding a controlled energy diet during the dry period may be an effective way to lower insulin resistance. Niacin is an antilipolytic compound. In other words, it reduces fat mobilization and may be used to mitigate insulin resistance. Provision of propylene glycol or other glucogenic precursors may also increase insulin concentrations and suppress lipolysis. However, glucogenic precursors must be provided in a slug dose to be effective. If mixed as part of a TMR, the cow will probably not consume enough precursor at any one time to cause an effective insulin response.

4. Is there any correlation between higher milk production and higher IR? Yes, the New Zealand study I showed indicated that cows with higher genetic potential for milk production have greater IR.

5. Is it just the liver that is the bottleneck of adipose tissue lipolysis/lipid mobilization? Where does the mammary gland come into the conversation? Many tissues in the body can utilize NEFA from lipid mobilization for energy and/or triglyceride synthesis, including the mammary gland. The liver does in effect become a bottleneck because NEFA uptake is so great. Uptake is high because NEFA concentration is high but also because blood flow to the liver is extremely high. Most of the cow's life the liver can "handle" the NEFA load. But around the time of calving it cannot, so the liver takes on an unusual role as a tissue of fat deposition because ruminants have an inherently low capacity to export fat. In contrast to adipose tissue, the liver is not intended to be a site of fat deposition.

6. Does Rumen Protected Choline help transition cows with de novo fatty acid synthesis in early lactation? Gene expression studies indicate that choline has no effect on fatty acid synthesis. Choline's role is to facilitate fat export from the liver as an essential constituent of very low density lipoprotein formation and secretion.

7. Are Goldilocks diets linked to low colostrum volumes from cows, quantity of colostrum and how about quality of IgG levels? Recent research from the University of Florida suggests that Goldilocks diets do not affect colostrum quality or quantity.

8. What is the reason behind higher genetic animals having higher insulin resistance? Is there a way to improve/lessen IR in high genetic cattle? To my knowledge, the details of why genetically superior animals have higher IR as not been delineated. Please see question 3 for potential strategies to alter IR in genetically superior cows.

9. Is one of the reasons the high genetic cows are able to produce more milk because they were treated (i.e. Glycol) when tested for high NEFAs or could they do this without treatment and without other negative impacts? This is a good question that I think refers to the University of Wisconsin research showing that ketogenic cows produced more milk. During the webinar I failed to address the fact that ketogenic cows had greater milk production but it was confounded since they were treated with propylene glycol. However, prior research indicates that three doses of 300 ml/d propylene glycol would be unlikely to account for the large difference in milk production between the ketogenic vs nonketogenic cows.

10. Is there information about whole lactation/lifetime milk production in regard to post-calving NEFA/BHBA levels? Some of the epidemiological studies showing relationships between milk production and NEFA/BHBA level have utilized whole lactation data. I am not aware of data using lifetime milk production.

11. Would reducing NEFA/BHBA level between one week and four weeks post-calving therefore be a better measure? Studies indicate that blood NEFA/BHBA at time points beyond 1-2 weeks postpartum become less reliable as an indicator of ketosis. This makes sense, since ketosis becomes less likely as the cow's dry matter intake increases and she is in less severe negative energy balance.

12. How many days in early lactation do cows stay insulin resistant? Most cows will be IR for two to three weeks postpartum and in some cows it may last longer if they are struggling to improve energy balance.

13. What are the indications if only one of either NEFA or BHBA is elevated? i.e. high NEFA but normal BHBA, and vice versa? NEFA is the better indicator of fat mobilization. BHBA is less indicative because it is a NEFA metabolite in the liver and hence its production is controlled by other factors than just extent of lipolysis. BHBA also can be formed when butyrate is absorbed by the rumen. Hence, feeds that have a high butyric acid content (e.g., poorly preserved forages) or result in high butyrate formation in the rumen (e.g., molasses or whey) will contribute to blood BHBA. I believe dietary factors are one of the reasons that Cornell research indicates that NEFA and BHBA are not as highly correlated as some might expect.

14. Do you think the systemic effects of lipolysis, and how NEFAs interact with the liver are important to consider when studying NEFA effects in *in vitro* studies? It is very hard to study the effects of NEFA in the live animal because there are so many other changes that occur during lipolysis. Therefore, it is very important to study the effects of NEFA on tissues *in vitro*. For example, *in vitro* studies have been conducted to study the adverse effects on oocytes, embryos, and liver tissue.

15. Does Dr Grummer think there may be nutritional choices affecting BHBA levels that are then falsely marked as 'showing ketosis'? There are certainly nutritional factors beyond negative energy balance that affect blood BHBA. As mentioned, in question 14, feeds and fermentation end products can influence BHBA entry into blood. But I would not say that elevations in BHBA due to diet "falsely" marks ketosis, as elevated BHBA may be detrimental regardless of source from which it is derived (diet or lipolysis).

16. Our conversations tend to focus on energy/fat mobilization. Are their also effects of insulin resistance on protein mobilization for the fresh cows that we should consider? Or for that matter, effects of low energy "Goldilocks" rations on protein mobilization? Great question and I do not know of studies in dairy cows. Insulin typically inhibits proteolysis and there is some data to suggest with type 2 diabetes, this inhibition is reduced. Greater insulin resistance is a characteristic of people with type 2 diabetes as it is with overfed dry cows.

17. There are herds using BHBA meters on-farm; what are your suggestions regarding how farms use those for either cow, group, or herd indicators? This question is good but really needs a discussion beyond what I can provide here. Briefly, I have no problem with routine testing of cows and using the results to decide on treatment of the cow. However, there are caveats, the major one being that cows may be classified as ketotic and may be treated when no treatment is really needed. I think use at the group or herd level also has a similar caveat. If cut-off values are used to determine an alarm level (e.g., more than 10% of cows testing above 1.2 mmol/L) and subsequent management changes, the cut-off level may not be appropriate for a particular herd (e.g. high genetic cows) and hence management changes may be made that are not necessary. In my opinion, routine monitoring of group or herd BHBA is best used to flag potential problems early on. But the criteria should not be a cut-off value. Instead, relative changes in herd average BHBA should be used. If BHBA values are drifting higher in herd, does this reflect a problem that needs addressing sooner than later? For example, does it suggest that pens are becoming overcrowded? Does it suggest that forage quality may be declining or forage quality is below what lab analysis suggests.

18. Niacin – you suggested to use in dire need. Is feeding niacin to appropriately conditioned/well managed transition cows under heat stress going to help us or hurt us? That is a very good question and is best answered through further research. I think the potential antilipolytic effects of niacin occur for a relatively short time after parturition (for first few weeks) and probably are of less consequence as feed intake increases and energy balance improves. The benefits during heat stress presumably occur for a greater proportion of the lactation. Consequently, if I had a post-fresh group of cows, e.g., for cows during the first 10-21 days postpartum, I would probably leave it out of the diet. However, if I had a one group situation or a high group that had cows in it for a longer period of time postpartum, I would probably include it in a heat stress situation.

19. In the case of over conditioned cows, what is the best second line of defense - propylene glycol or NiaShure? I do not know of any research that has addressed this question directly. Research indicates that both work but they have never been compared to each other. One advantage of NiaShure is that it can be effective when incorporated into the diet, whereas propylene glycol needs to be given as a slug dose. So, management preferences may be a major factor deciding which to use. I should mention that NiaShure could also be given as a bolus.

20. Physiologically, how do low energy rations, such as Goldilocks, make cows less insulin resistant? I do not know of research that has delineated this specifically, but possibilities include altered insulin receptor numbers, altered insulin receptor function, or alterations in the post-receptor signaling cascade.

21. Do you think the immune system plays a role in the normal insulin regulation at the transition? I do not know the answer to this, but we know that blood glucose and NEFA levels are associated with immune function, so it certainly seems plausible that there could be a link.

22. Is there an effect of dietary protein levels during the transition period on BHBA and NEFA concentrations? I have not seen a summary of the literature regarding dietary protein during the transition period and NEFA/BHBA. The 2001 NRC indicated that feeding excess dietary protein during the dry period may have a negative effect on feed intake postpartum. Hence, one could speculate that lower feed intake may be associated with greater negative energy balance and greater blood NEFA and BHBA. Immediately postpartum, cows are almost always in a deficit of metabolizable protein which does lead to break down of muscle protein. I am not sure if degree of catabolism of muscle protein (specifically ketogenic amino acids) would significantly influence BHBA but it is plausible.

23. How far down the stream was the milk production depressed? When I mentioned that it should not be surprising if reduced NEFA had a downstream effect on milk production, I meant that in a physiological sense and the response would be rapid. This was not meant to mean that it would happen in a later stage of lactation.

24. Could the source of energy fed to dry cows (particularly far off) make a difference in fat storage? Particularly out West, we used to feed a lot of grass silages (high lactic acid). We've moved to drier feeds and don't seem to have the same issues. We typically still have close up groups which are corn silage, a few pounds of straw and eight lbs of a close up grain and still would expect 100 lb of milk at 10 days. Can we influence the deposition of visceral vs adipose fat and can that be part of the picture? Unfortunately, we do not have a lot of data to answer this question because of the cost of sacrificing cows to get good data on visceral fat deposition. However, University of Illinois research has shown that controlled energy diets will reduce visceral fat deposition compared to diets that provide more calories than needed to meet requirements. However, this is likely a function of caloric intake. I have no information whether diets with different composition that provide similar caloric intake could influence fat deposition differentially.

25. How do you weight the contribution between glucose precursors as monensin and choline during the transition period? Choline is not a glucose precursor. Monensin will increase propionate production in the rumen, and propionate is a glucose precursor. But I view Monensin differently than glucose precursors such as propylene glycol or glycerol which are intended to purposely inhibit lipolysis. Through greater propionate production in the rumen, Monensin enhances the amount of energy the cow derives from each mouthful of feed which is a positive. If propylene glycol or glycerol were used as an energy source rather than specifically to manipulate lipolysis, they would be a very expensive source.

26. Is insulin resistance harmful to reproductive tissues? Remember, IR is not an all on or all off principle. There are varying degrees of IR. Yes, if IR is too great and NEFA mobilization is too excessive, reproductive function could be affected. As I stated in the presentation, the key to strike a balance in which NEFA mobilization is great enough to maximize milk production but not too great as to have adverse effects on milk production and reproduction.

27. Can high levels of BHBA affect embryonic implantation? *In vitro* studies indicate that BHBA can affect embryo development, but I don't have information specific to *in vivo* implantation or what levels may affect implantation.

28. Dr. Heather White's study around fermented ammoniated whey indicated feeding post fresh for the first 45 days helps a cow liver manage NEFA. Your comments on that study please? The data certainly suggests greater propionate formation in the rumen resulting in blood glucose and insulin responses that can depress NEFA. Interesting that milk yield was not altered but an intake suppression was seen starting at three weeks postpartum. I would like to see more data with this product before reaching conclusions.

29. In close-up prepartum cows on a controlled energy diet, is it preferable for the insulin level to be maintained or depressed? The idea behind a controlled energy diet is to reduce lipolysis (NEFA mobilization from fat tissue), therefore, it would be preferable to maintain insulin levels because depressing them may enhance lipolysis.

30. We are in the tropics here in Veracruz Mexico but we also milk cows. My question is: If cows stay in negative energy balance longer, for example 8 or even more 10 to 12 weeks, would the insulin resistance continue this long? I do not know the answer to your question, and it is difficult to speculate. Normally, I would speculate that may be the case, but research by Lance Baumgard suggests that heat stressed cows exhibiting depressed feed intake are actually hyper sensitive to insulin and do not experience increases in NEFA that are typical of early postpartum transition cows that are in negative energy balance.

31. If negative energy balance continues for more than 2-3 weeks, will IR continue? Yes, IR would likely diminish at a slower rate.

32. Your discussion about higher NEFA/BHBA (above "current cutoffs") postpartum. Does it also apply to prepartum NEFA/BHBA? I have not seen data to formulate an opinion on this. However, I would much prefer to see NEFA and BHBA measured after parturition. Concentrations during the last week prepartum are greatly influenced by hormones associated with parturition and initiation of lactation and are changing dramatically within a short period of time. Additionally, there is considerable cow variation. Consequently, interpretation of results during this period are difficult and probably of little value. If you take the sample prior to a week before calving, the major factor influencing NEFA/BHBA is body condition score (as it influences feed intake), so why not just monitor pen intakes and/or body condition score? It is cheaper and easier.

33. Do you have a recommendation based on herd or individual milk production to base a safe BHBA level higher than current cutoffs? No. If I would have remained at the university longer, I would have tried to answer this through rigorous research. Based on casual observations while conducting research and consulting, I concluded that a BHBA level 2.0 mmol/L or lower was likely of little concern in a high producing dairy cow.

34. If I have heavier BCS cows, what do you recommend from a nutrition/management perspective prepartum to help get them through transition? I assume you are referring to management on an individual cow basis. If choline is not being supplemented in the diet, my first action would be to make sure that rumen-protected choline is in the diet to help the over-conditioned cows. There is also good evidence that all cows benefit from rumen-protected choline, so dietary inclusion is justified. As mentioned above, propylene glycol and niacin can be good additives to consider next if more action is needed. Niacin can be included in the diet (e.g., 12 g NiaShure/day/cow) or be provided to individual cows as a bolus but it must be given for at least four days to reach proper levels in blood. Propylene glycol (300 ml/day/cow) for three days can be provided as a drench. Niacin as a bolus or PG administration as a drench should be targeted for the first few days post-calving.