Minimizing Subclinical Metabolic Diseases in Dairy Cows

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■ Take Home Message

- Subclinical metabolic diseases are common periparturient conditions marked by low calcium, high ketones, and possibly low rumen pH.
- Subclinical ketosis causes losses through reduced milk, reduced fertility, increased clinical disease risk, impaired immune function, and increased risk of culling.
- Subclinical hypocalcemia significantly increases the risk of early lactation culling.
- Maximizing and ensuring consistent dry matter intake is critical through the transition period for prevention of these diseases.
- Feed additives such as ionophores for ketosis and anionic products for hypocalcemia are important and helpful aids in prevention.

■ Introduction

Most periparturient abnormalities have some metabolic element as a component of the cause of clinical disease. The metabolic disturbance of milk fever can be measured through low serum calcium concentrations. Negative energy balance, fat mobilization and subsequent elevations in ketone body concentrations play a contributing role in the expression of fatty liver syndrome, clinical ketosis, and abomasal displacement. A negative energy balance may also increase the risk of retained placenta, metritis, and mastitis through impaired immune function. A third category of metabolic disease in early lactation might include rumen acidosis, which is marked by low rumen pH. Thus, calcium homeostasis, energy balance, and rumen pH are important considerations for disease prevention in transition dairy cows (Goff and Horst, 1997).
In general, subclinical disease incidence is more common than clinical disease. Frequently it goes unnoticed and is associated with significant economic losses that include increased clinical disease risks, impaired milk production and reduced reproductive performance, and culling losses. Of the three major subclinical metabolic diseases, the most published information currently exists for subclinical ketosis, which is common and associated with significant economic loss. Prevention depends on several factors including proper transition cow nutrition and management and optimal body condition. The use of certain feed additives such as propylene glycol, and ionophores may also aid in the prevention of ketosis. It is commonly accepted that subclinical hypocalcemia is an important disease, but very little is published on the impact of this problem on subsequent risk of disease or production loss. Subacute rumen acidosis (SARA) is also thought to be a major problem on many dairies but is difficult to measure and very little controlled research exists for this syndrome. In addition, SARA is more likely to be a problem in component-fed rather than in TMR-fed transition cows. This article will focus primarily on the importance and prevention aspects of subclinical ketosis.

### Disease Frequency

The reported prevalence of subclinical ketosis ranges widely. Reported prevalences for hyperketonemia in the first two months of lactation have ranged from 8.9 to 34% in various studies (Dohoo and Martin, 1984; Duffield et al, 1997). Duffield et al (1998) reported the cumulative incidence of subclinical ketosis over the first 9 weeks of lactation in 507 untreated cows from 25 Holstein dairy farms was 59% and 43% using cutoff threshold beta-hydroxybutyrate (BHBA) concentrations of 1200 and 1400 µmol/L respectively. It is difficult to compare these numbers across studies since numerous factors beyond cow and herd level risk influence the rates. The test characteristics (sensitivity and specificity) influence prevalence, as does the timing and intensity of sampling. Generally studies that measured rates with less sensitive milk tests report much lower prevalences than those using serum or urine.

Dohoo and Martin (1984) found more positive milk ketone tests in the first versus the second month of lactation, and observed that the peak prevalence of hyperketonemia occurred in the third and fourth week of lactation. However, recent work suggests that there is an earlier peak that occurs in the first two weeks postcalving (Duffield et al, 1997). It may be that advances in genetics and feeding management have pushed the metabolic challenge closer to calving. Alternatively, differences in peak occurrence for subclinical ketosis may reflect differences in etiology, with early lactation occurrence reflecting suboptimal dry cow management and expression of fatty liver, while later occurrences may indicate deficiencies in lactating cow management (Cook et al, 2001).
Subclinical hypocalcemia ranges in prevalence depending on the cutpoint chosen for defining it. Ranges of 20 to 40% subclinical hypocalcemia have been reported.

### Association With Periparturient Disease

Several investigations have evaluated the relationship between clinical ketosis and other health parameters, but few studies have attempted to assess the associations between subclinical ketosis and periparturient disease. Although subclinical and clinical ketosis are both part of the same continuum, we can only assume the associations found for clinical ketosis would be the same for the subclinical condition. Subclinical ketosis as a risk factor for subsequent disease occurrence has been linked with clinical ketosis, abomasal displacement, metritis, mastitis, and cystic ovarian disease. The most consistent associations have been between subclinical ketosis, clinical ketosis and displaced abomasum. Impaired immune function either through reduced energy or by direct effects of ketones on white blood cells, are likely the reason for effects on infectious disease such as metritis and mastitis. Dohoo and Martin (1984) found that cows with subclinical ketosis had an increased risk of metritis or clinical ketosis four days later. However, the authors argued that since metritis is a condition which normally develops at calving, subclinical ketosis is more likely a result rather than a cause of metritis.

The relationship between displaced abomasum and ketosis has been identified as bi-directional. That is, ketosis may be a cause of displacement and abomasal displacement may lead to ketosis. Correa et al (1993) found that ketosis increased the risk of abomasal displacement, but not the reverse. Dohoo & Martin (1984) could find no direct association between the two conditions. However, ketosis as an inciting or predisposing cause of abomasal displacement can be further supported by several recent papers. Elevated BHBA concentrations above 1000 μmol/L increased the likelihood of abomasal displacement (Duffield, 1997; Geishauser et al, 1997, LeBlanc et al, 2005). Cows with concentrations of BHBA at or above1400 μmol/L in the first two weeks post calving were three times more likely to subsequently develop either clinical ketosis or abomasal displacement (Duffield, 1997).

Few disease associations with subclinical hypocalcemia have been reported. One study (Massey et al, 1993) reported a nearly 5 fold increase in the risk of abomasal displacement (1997). However, this has not been observed in Canadian studies when other serum constituents, including ketones, have been evaluated (Geishauser et al, 1997; LeBlanc et al, 2005).
Impact On Milk Production And Milk Components

In general there is consensus that a negative association between hyperketonemia and milk production exists, however there are conflicting reports. In one study, the loss of production associated with a positive milk ketone test was 1.0 to 1.4 kg of milk per day (Dohoo and Martin, 1984). This represented 4.4 to 6.0% of the mean test day milk production. In this study, both the milk samples and the milk weights were obtained on the same day, and thus milk ketone levels and milk production were evaluated concurrently. Test day milk production was negatively correlated with milk acetone levels in several Scandinavian projects. By contrast, Kauppinen (1984) showed a significant positive correlation between both the BHBA and acetoacetate concentrations in blood and milk yield. Kauppinen subsequently reported that subclinically ketotic cows had significantly higher annual milk yields than nonketotic cows. It is possible that higher milk yields put cows at increased risk of developing subclinical ketosis. Increased levels of milk production may be associated with increased fat mobilization and a greater risk of hyperketonemia. However, without objective measures for ketosis, the definition might vary widely in observational studies such as this. Regardless of the threshold chosen for hyperketonemia, the incidence of subclinical ketosis should be considerably higher than that of clinical ketosis. Assuming that higher producing cows are more likely to be hyperketonemic, a larger proportion of subclinically ketotic cows combined with misclassification bias of clinical ketosis cases could mute any association between clinical ketosis and previous lactation milk yield. Inverted milk curves in hyperketonemic cows were noted in a large Swedish study (Gustafsson et al, 1993). Most of the loss in milk production occurred in the first 100 days of lactation and amounted to 328 kg loss in fat corrected milk yield over 200 days. Recent studies support both the subclinical ketosis, clinical ketosis temporal association and the negative impact on milk production. Milk yield was lower 2 to 4 weeks in one study (Rajala-Schultz et al, 1999) and 8 to 9 days in another study (Edwards and Tozer, 2004) prior to the diagnosis of clinical ketosis. Noticeable milk yield losses weeks prior to actual diagnosis is strong support for the negative and unrealised impact of subclinical ketosis on milk production.

Milk fat and milk protein are significantly altered in hyperketonemia. Milk fat percentage was increased in subclinically ketotic cows (Miettenen, 1994). Mean annual milk fat yield was significantly higher in both subclinically ketotic and clinically ketotic cows compared to normal cows (Kauppinen, 1984). The association between milk fat and hyperketonemia is, presumably, because of increased availability of BHBA and fatty acids for milk fat synthesis. It is unclear whether increased levels of circulating ketones cause increased milk fat, or if cows that are prone to higher milk fat yields are more susceptible to subclinical ketosis. Milk protein percent has been reported to be lower in cows with subclinical ketosis (Miettenan and Setala, 1993). This may be the
result of a reduced energy supply, since milk protein percent is positively associated with net energy balance.

Negative associations between subclinical hypocalcemia and milk production have not been reported, perhaps because higher previous lactation milk yield is a risk factor for the occurrence of milk fever.

Impact On Reproductive Performance

There has been conflicting research findings on the impact of subclinical ketosis on reproductive performance. However recent work seems to be building a consensus that there is a negative impact. Significant correlations between the herd prevalence of hyperketonemia and herd mean intervals from both calving to first service and calving to last service have been noted but this is herd level data and doesn't necessarily imply a cow-level association (Andersson, 1988). A link between subclinical ketosis and the increased incidence of cystic ovaries has been reported suggesting an impact on ovarian function (Dohoo and Martin, 1984). A significant inverse relationship between milk fat percentage and first insemination pregnancy rates has also been identified (Kristula et al, 1995). Miettenen and Setala (1993) found an increased interval from calving to conception in cows with high milk yield and high fat yield. Whitaker et al (1993) found cows with a better energy status at 14 days postpartum had a reduced interval from calving to the onset of cyclicity and fewer services per conception. No effect was observed when energy status was evaluated at 21 days postpartum or at first service. This study was only conducted on 24 cows within one herd. More recently, however, studies with larger numbers of cows have also identified some negative impacts of subclinical ketosis on fertility. Walsh et al (2004) have reported that 1st service conception rate was decreased by 50% in cows with serum BHBA concentrations \( \geq 1400 \) umol/L in the 2nd week post-calving, based on 869 cows having at least one breeding postcalving. In addition, the odds ratio decreased from 0.7 at 1100 umol/L BHBA to 0.31 at 1900 umol/L BHBA, implying in a sense a dose effect of ketone concentration. Koller et al (2003) found increased concentrations of ketone bodies in the first 6 weeks post calving delayed conception.

Culling

The influence of subclinical ketosis on the risk of culling has not been well described. Culling may be more likely because of impaired health, reduced production and potentially impaired reproductive performance. Clinical ketosis increased the risk of culling both early in lactation and late in lactation (Grohn et al, 1998). Presumably the early lactation risk was associated with reduced
production and increased disease risk, while the later culling association might be related to reduced reproductive performance. Cook et al (2001) reported an increased culling risk for ketotic cows measured through milk acetone in a 410 cow study. Both subclinical ketosis and subclinical hypocalcemia appear to increase the risk of culling. Cows with serum calcium concentrations less than or equal to 1.8 mmol/L and not diagnosed with milk fever were approximately 3.0 times and cows with serum BHBA concentrations above 1400 umol/L were 1.4 times more likely to be culled in the first 60 days of lactation, after controlling for the risk of clinical disease on culling and the random effect of herd (Duffield et al, 2005).

- Thresholds For Defining Subclinical Disease

Most thresholds in the literature for defining subclinical disease are arbitrary. Many thresholds used for subclinical hypocalcemia and ketosis are based on reference values where the limit is set at above or below a 95% confidence interval. Since higher concentrations of ketone bodies and lower calcium concentrations are expected at calving and postpartum, arbitrarily assigning a threshold based on a best guess or data distribution runs the risk of just being on the higher or lower end of normal. Few studies have actually reported threshold concentrations based on either negative impacts on health, production, reproduction or culling. There is a lack of published studies that have established cutpoints in this way for subclinical hypocalcemia. Duffield et al (2005) recently reported a cutpoint of serum calcium ≤ 1.8 mmol/L in the week following calving was associated with a significant threefold increase in early lactation culling risk.

Some research does exist for more defendable cutpoints for subclinical ketosis. Reist et al (2003) used milk acetone at 0.4 mmol/L and serum BHBA at 2300 umol/L and found significantly reduced milk yield at both cutpoints and increased the risk of endometritis at the milk acetone threshold. Duffield and Geishauser have both reported a three-fold increased risk of clinical ketosis and displaced abomasums at serum concentrations of BHBA at or above 1400 umol/L. Duffield (1997) also found a significant reduction in milk yield at first DHI test at 1800 umol/L BHBA, with a non-significant (P=0.13) reduction at 1600 umol/L. However, the increasing thresholds were associated with increasing reductions in milk yield. Leblanc et al (2005) reported cows with 1200 umol/L BHBA in the first week postcalving were 8 times more likely to develop an abomasal displacement. Walsh et al (2004) have identified reductions in fertility starting at a cutpoint of 1100 umol/L and Duffield et al (2005) have identified increased culling risk at 1400 umol/L BHBA. Based on the above data, it would appear that a threshold for defining subclinical ketosis with serum BHBA should start at about 1400 umol/L.
Key Strategies For Prevention

General Guidelines

Since ketosis occurs in early lactation, recommendations for prevention have focused on the nutritional management of the dry and transition cow. Detailed recommendations for nutrition during the dry period can be found elsewhere (Oetzel, 1998). It is a common recommendation to divide the dry period into two feeding groups: far-off and close-up (Radostits et al, 1994). Typically, far-off diets follow NRC guidelines for dry cows. The close-up diet is usually balanced according to recommendations that are halfway between the dry cow and early lactation cow and should be fed starting at least three weeks before expected calving (Oetzel, 1998). The goals of the transition diet (specifically designed to prevent subclinical ketosis) are to maximize dry matter intake and to provide adequate energy density (Oetzel, 1998). Avoidance of ketogenic feedstuffs and increased frequency of feeding concentrates have been advocated as preventive measures against subclinical ketosis. The reduction of overconditioning cows in late lactation and the early dry period, as well as lead feeding with concentrates about three weeks prior to calving have also been suggested as aids in prophylaxis (Andersson, 1988). Maximizing dry matter intake (DMI) and maintenance of a consistent intake through the last three weeks prior to calving is likely the hallmark of a successful transition cow program. Recent work at Guelph (Osborne, 2003) indicates that a DMI of less than 12 kg per cow per day in the last 3 weeks prior to calving substantially increases the subsequent risk of subclinical ketosis (Odds Ratio 5.7, p < 0.05). Achieving group DMI targets above an average of 12 kg per cow per day are possible and based on the above finding should be a goal for the close-up group. More important than ration formulation and ration ingredients, close attention should be paid to cow comfort and environmental issues. These factors include but are not limited to adequate pen space or stall space per cow, adequate feed bunk space, sufficient and comfortable bedding, adequate water supply and minimization of heat stress.

Role of Feed Additives

In addition to good nutrition, certain feed additives have been found beneficial in reducing subclinical ketosis when administered prophylactically. Niacin fed prior to calving at the rate of 3 to 6 grams per day may be helpful in reducing blood levels of BHBA (Fronk and Schultz, 1979; Dufva et al, 1983). However, the first citation (Fronk and Schultz) contained no control group and the impact identified in the second study (Dufva) was only marginal. Propylene glycol has been used successfully for the prevention of subclinical ketosis (Emery et al, 1964; Sauer et al, 1973). Treatment of cows for 8 weeks starting at calving with either 3% or 6% propylene glycol in a concentrate
mixture significantly reduced the incidence of positive milk ketone tests (Fisher et al, 1973). Precalving oral treatment with 300 g of propylene glycol per day for 10 days lowered serum non-esterified fatty acid (NEFA) concentrations and improved some measures of reproductive performance in one study (Formigoni et al, 1996). A dose of propylene glycol of 1L per day as an oral drench for 9 days prior to calving decreased BHBA, and NEFA and increased glucose concentrations (Studer et al, 1993). It appears that a bolus of propylene glycol is necessary for maximum effect, since mixing in a total mixed ration is not as efficacious as either an oral drench or when mixed with a small quantity of grain (Christenson et al, 1995). Propylene glycol requires repeated daily oral administration and sodium propionate may reduce feed intake (Sauer et al, 1989). Ionophores have been proposed as potential prophylactic agents for reducing hyperketonemia. In contrast to propylene glycol, ionophores are relatively inexpensive and much easier to administer.

The gluconeogenic potential of monensin has attracted researchers to investigate its possible role as an antiketogenic agent in dairy cattle. Rogers and Hope-Cawdery (1980) first described the beneficial effects of monensin for reducing the incidence of ketosis in a herd with a clinical ketosis problem. The antiketogenic properties of monensin were later investigated in a Canadian trial involving two levels of monensin and three groups of 12 Holstein cows (Sauer et al, 1989). Monensin included at 30 grams per ton of total ration (high group), decreased the incidence of subclinical ketosis and significantly reduced blood BHBA levels in the first three weeks postpartum (Sauer et al, 1989). The incidence of subclinical ketosis, defined as total blood ketones > 9 mg/100 ml (900 µmol/L), was reduced by 50% and blood BHBA levels were reduced by 40% for the high monensin group. Based on the average feed intakes observed in this trial, the low monensin group received approximately 208 mg of monensin per day and the high group 399 mg per day. Green (1997) reported that administration 3 wk prior to expected calving of a monensin controlled release capsule (CRC), which delivers 335 mg per day, significantly reduced the concentrations of BHBA and increased those of glucose. Monensin treatment in this study was also reported to reduce both the onset and severity of subclinical ketosis when cows where restricted to 90% of ad libitum feed intake commencing at 2 wk postcalving. Duffield et al (1998b) reported that monensin CRC administration at 3 wk prior to calving reduced the incidence, prevalence, and duration of subclinical ketosis in a 1010-cow multi herd field study. Monensin treatment also significantly reduced the concentrations of serum BHBA and aspartate aminotransferase, and increased the concentrations of serum glucose and urea (Duffield et al, 1998a).

Stephenson et al (1997) conducted a small study involving 24 cows from 2 farms where monensin CRCs were administered 50 d precalving. A significant decrease in NEFA, BHBA and glucose was noted in the precalving period. No significant effects on these energy indicators were observed post
calving. Duffield et al. (2003) also observed a significant precalving reduction in NEFA. Cows from the Stephenson study were also evaluated for their neutrophil function. Monensin significantly improved the chemotactic function of neutrophils (Stephenson et al., 1996), indicating that monensin may improve immune function indirectly via an improvement in energy status.

Reductions in liver enzymes and improvements in energy indicators such increased glucose and lower NEFA and BHBA suggest a possible impact on liver function and health. Recently, monensin CRC treatment 3 wk prior to calving was found to significantly increase liver glycogen 3 wk postcalving (Zahra, 2004).

The negative associations between subclinical ketosis, health and production impairment are supported by the impact of monensin on reduction of subclinical ketosis and the observed improvement in health and production. Administration of a monensin controlled release capsule precalving reduced the incidence of clinical ketosis by 50%, abomasal displacement by 40% and multiple illness by 40% (more than one disease) (Duffield et al., 1999b). The milk production response depended on body condition and was 0.85 kg/day at peak lactation in cows with a precalving BCS of 3.25 to 3.75, and was 1.2 kg/day for the first 90 days of lactation in fat cows (BCS 4.0) (Duffield et al., 1999a). No milk production response was noted in thin cows presumably because they had the lowest BHBA concentrations and were at decreased risk of subclinical ketosis. A subsequent Canadian study conducted in 45 dairy herds confirmed that monensin CRC reduces the incidence of displaced abomasum (Duffield et al., 2002). A pooled summary of the two Canadian projects showed that monensin CRC reduced the incidence of displaced abomasum and clinical ketosis by 40% each. In addition, the incidence of retained placenta tended to be lowered by 25% in monensin treated cows (P=0.09).

Rumen protected choline has been shown to influence liver glycogen and triglyceride (Pipenbrink and Overton, 2003), but not in all studies (Zahra, 2004). A topdress of 56 g per day of rumen protected choline during the transition period did not affect BHBA, NEFA, liver glycogen or liver triglyceride. However, milk production was significantly increased in choline treated cows and this effect was more pronounced in cows that were over-conditioned.

Approaches to reducing the prevalence of low serum calcium include reducing potassium in feedstuffs precalving and adding chlorinated supplements to the close-up diet. Although the latter is efficacious it needs to be closely monitored for efficacy through regular urine pH checking. If DMI is reduced through approaches to achieve a negative dietary cation anion difference, metabolic problems may get worse rather than better.
Conclusions

Subclinical ketosis is an important disease of dairy cattle that is associated with increased risk of clinical diseases, lost milk production, reduced reproductive performance and increased culling risk. Estimates indicate it costs at least $78 US (Geishauser et al, 2001) (and probably closer to $350 CDN), which considered at the herd level, is considerably more than most clinical diseases, since subclinical disease is far more frequent. Cow-level risk factors are parity, body condition score and season of calving. Herd variation for this disease is wide and herd level risk factors are poorly described. However, herd level risk factors most likely involve combinations of management, feed quality and nutritional programs, cow comfort, environment, and other variables that influence dry matter intake. Prevention should therefore focus on removing factors that might limit dry matter intake. Consideration should be given to the strategic use of proven ancillary aids such as propylene glycol and monensin.

References


