Understanding the Impact of Subclinical Ketosis

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INTRODUCTION

Dairy cattle experience a remarkable shift in metabolism after calving, after which milk production typically increases so rapidly that feed intake alone cannot meet energy requirements (Bauman and Currie, 1980; Baird, 1982). Cows with a poor adaptive response to negative energy balance may develop hyperketonemia (ketosis) in early lactation. Cows that develop ketosis in early lactation lose milk yield and are at higher risk for other postpartum diseases and early removal from the herd.

DEFINING KETOSIS

Subclinical ketosis (SCK) is defined as an excess of circulating ketone bodies without clinical signs of ketosis (Andersson, 1988). The circulating ketone body most commonly used to diagnose SCK is blood β-hydroxybutyric acid (BHBA). The lower threshold concentration of BHBA for SCK is 1.2 mmol/L (or 1200 μmol/L or 12.4 mg/dl; note that multiplying by 10.3 converts BHBA concentrations from mmol/L to mg/dl). Other studies have reported lower thresholds for SCK ranging between 1.0 and 1.4 mmol/L. These different thresholds represent different outcomes and time periods; they will be explained in more detail later in this review.

The upper threshold of BHBA concentration for SCK should (by definition) be the onset of clinical signs. However, the detection of clinical signs of ketosis varies greatly from herd to herd. Therefore, ≥3.0 mmol/L blood BHBA has been used as the upper threshold for SCK (Oetzel, 2004; McArt et al., 2011). Cows above this threshold probably should have been detected as having clinical ketosis, although my clinical experience indicates that this is not always the case.

The clinical signs of ketosis in early lactation dairy cows are decreased appetite, weight loss, decreased milk production, and (perhaps) a positive cowside test result for ketosis. These clinical signs are mostly quite subjective in nature, and the cowside tests for ketosis commonly used by dairy producers have considerable variability in their sensitivity and specificity for detecting ketosis. Thus, the incidence of clinical ketosis in a herd (as determined by dairy producers) is of very limited value in assessing the true ketosis status of a herd. Producers in smaller herds tend to overestimate the incidence of clinical ketosis (Simensen et al., 1990), and producers in larger herds tend to underestimate the incidence of clinical ketosis (based on my own clinical observations). Using blood BHBA testing to measure the incidence or prevalence of SCK in a herd is a powerful and useful clinical tool.

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INCIDENCE VERSUS PREVALENCE OF SUBCLINICAL KETOSIS

Incidence of Subclinical Ketosis

The incidence of SCK in a herd is the number of new cases of SCK (blood BHBA between 1.2 and 2.9 mmol/L) that occurred during the risk period (early lactation) divided by the number of cows who completed the risk period. Most new cases of SCK occur within the first 2 to 3 weeks after calving in herds that manage cows in groups and feed a total mixed ration. Cows that are component-fed and housed in individual stalls appear to develop ketosis later (3 to 6 weeks after calving).

The time period over which the incidence of SCK is measured must be specified (e.g., a week, a month, or a year). Determining the incidence of SCK requires repeated testing of cows throughout this risk period. Testing must occur twice or more weekly in order to accurately assess the incidence of SCK. This is necessary because the median time for the resolution of SCK is about 5 days (McArt et al., 2011). If testing occurs only once a week, a cow could potentially develop and resolve her SCK between test intervals (McArt et al., 2012a). Because of the need for repeated testing, the incidence of SCK is usually determined only in research trials.

Published studies that did repeated testing of early lactation cows report early lactational incidence rates of ketosis between about 40% and 60% (Emery et al., 1964; Simensen et al., 1990; Duffield et al., 1998). These rates could have been even higher because some of these studies evaluated incidence based on once weekly blood BHBA testing. We (my Cornell coworkers and I) reported an overall SCK incidence rate of 43.2% for 1,717 cows in 4 large commercial herds (McArt et al., 2011). The SCK incidence ranged from 26.4% to 55.7% by herd. We also found that new cases of SCK occur remarkably soon after calving; peak incidence was at 5 days in milk (DIM; see Figure 1).

Figure 1. Histogram of the incidence of SCK (first blood BHBA test between 1.2 to 2.9 mmol/L) on any one of 5 or 6 tests between 3 and 16 DIM.
**Prevalence of Subclinical Ketosis**

Prevalence is a ‘snapshot’ measure of the current SCK status of a group of cows and is defined as the proportion of cows with blood BHBA concentrations between 1.2 and 2.9 mmol/L at a given point in time. Repeated testing of individual cows is not necessary for determining prevalence. It is usually done for a subset of the early lactation cows within a herd. Herds can be tested repeatedly for SCK and the results pooled into a cumulative prevalence; this increases the reliability of the estimate of the herd’s prevalence of SCK. For practical reasons, almost all herd-level evaluations for SCK are conducted as prevalence testing.

The peak prevalence of SCK occurred at 5 DIM in the large field study (McArt et al., 2012a; see Figure 2). At 5 DIM, 28.9% of cows were positive for SCK. This finding underscores the observation that SCK occurs very soon after calving.

![Histogram of prevalence of SCK in 1,717 Holstein dairy cows undergoing repeated testing for ketosis from 3 to 16 DIM. A positive test for SCK was defined as a blood BHBA concentration of 1.2 to 2.9 mmol/L.](image)

**Figure 2.** Histogram of prevalence of SCK in 1,717 Holstein dairy cows undergoing repeated testing for ketosis from 3 to 16 DIM. A positive test for SCK was defined as a blood BHBA concentration of 1.2 to 2.9 mmol/L.

**Estimating the Incidence of Subclinical Ketosis from its Prevalence**

Although the prevalence of SCK in a herd is much easier to determine than its incidence, the incidence of SCK must be known in order to estimate the overall negative impacts of SCK on herd performance. Knowledge of the herd’s prior incidence of SCK is also needed before determining the best ketosis testing strategy for a herd (McArt et al., 2012a).

The repeated testing necessary to determine the incidence of SCK within a herd is daunting and requires testing a large number of cows twice weekly for about the first two weeks of lactation. Fortunately, the incidence of SCK can be estimated from its prevalence. The incidence of ketosis has been reported to be 2.2 X the prevalence.
NEGATIVE IMPACTS OF SUBCLINICAL KETOSIS

Reduced Milk Yield

The negative impacts of SCK on milk yield are well-known. Estimates of milk yield loss due to ketosis represent the difference between ketotic and non-ketotic cows and do not fully account for how much milk the ketotic cow might have produced had she not developed ketosis. Thus, actual milk lost may be underestimated because cows with ketosis may have been higher producing cows prior to the onset of their ketosis.

Previous studies have reported milk yield losses in ketotic vs. non-ketotic cows of 2.2 to 3.1 lbs of daily milk (4.4 to 6.6%); a milk ketone test was used to diagnose ketosis in this study (Dohoo and Martin, 1984). Duffield et al. (2009) reported a 4.1 lb decrease (about 5.5%) in milk yield at first Dairy Herd Information Association (DHIA) test for cows with blood BHBA ≥ 1.4 mmol/L during the first week after calving. Ospina et al. (2010a) used a cutpoint of ≥ 1.0 mmol/L of blood BHBA to define SCK and reported that cows (≥ lactation 2) with SCK lost 865 lbs of 305-day ME milk (about 7.0%). Chapinal et al. (2012) reported a 5.3 lb reduction in milk yield (about 6.9%) at the first DHIA test for cows with blood BHBA ≥ 1.4 mmol/L during the first week after calving.

In our recent field study, cows (any parity) with SCK produced 2.6 lbs less daily milk (about 3.4%) for the first 30 DIM compared to non-ketotic cows (McArt et al., 2012a). Early detection and treatment of SCK with propylene glycol (300 ml orally once daily until the ketosis resolved) improved milk production by about 1.5 lbs of daily milk compared to cows whose SCK was left untreated (McArt et al., 2011).

The severity of the milk yield loss due to SCK was associated with magnitude of the elevation in BHBA at the first diagnosis of SCK (McArt et al., 2012a). Each additional 0.1 mmol/L increase in BHBA (beyond 1.2 mmol/L) was associated with 1.1 lbs more lost milk for the first 30 DIM. The difference between modest SCK (1.2 mmol/L BHBA) and more severe SCK (2.4 mmol/L) was 13.2 lbs of daily milk for the first 30 DIM (see Figure 3).

Days in milk at the first onset of SCK also affects the severity of the milk yield loss. Cows first diagnosed with SCK between 3 and 7 DIM produced 4.6 lbs less daily milk (about 6.0%) in the first 30 DIM compared to cows first diagnosed with SCK between 8 and 16 DIM (McArt et al., 2012a). This was the first study to report that earlier onset of SCK resulted in more detrimental effects to the cow. Other problems associated with SCK were more severe in cows that were first diagnosed between 3 and 7 DIM; these will be discussed later in this review.

Increased Risk for Early Lactation Removal
In our recent field study, we reported that cows with SCK were 3.0 times (95% CI 2.2 to 4.2) more likely to be removed from the herd (sold or died) in the first 30 DIM compared to non-ketotic cows (McArt et al., 2012a). No previous studies have reported the effect of SCK on herd removal.

Figure 3. Regression plot of mean predicted daily milk yield for the first 30 DIM by blood BHBA concentration of first positive BHBA test (1.2 to 2.9 mmol/L) for 369 Holstein dairy cows undergoing repeated testing for ketosis from 3 to 16 DIM. The solid line represents the best fit; 95% confidence intervals are shown for each predicted milk yield by BHBA concentration.

Increasing severity of ketonemia at the onset of SCK increased the risk for herd removal in the first 30 DIM (McArt et al., 2012a). Each 0.1 mmol/L increase in BHBA increased the risk for herd removal by 1.4-fold (95% confidence interval; CI = 1.1 to 1.8). For example, increasing blood BHBA at the onset of SCK from 1.2 to 2.4 mmol/L increased the risk for early lactation herd removal by 56.7 X (1.412). Note that this study only considered cows with blood BHBA < 3.0 mmol/L; cows with higher BHBA concentrations could have had an even greater risk for herd removal in the first 30 DIM.

Early detection and treatment of SCK with oral propylene glycol reduces the risk for early lactation removal. We reported that cows not treated for their SCK were 2.1 times (95% CI = 1.2 to 3.6) more likely to die or be sold by 30 DIM than cows treated with oral propylene glycol (McArt et al., 2012b).

Increased Risk for Displaced Abomasum

The association of SCK with increased risk for displaced abomasum (DA) is well-established. Duffield et al. (2009) reported that blood BHBA ≥ 1.2 mmol/L in the first week after calving increased the odds for DA by 2.6 (95% CI = 1.3 to 5.2). Ospina et al. (2010b) reported 6.9-fold higher risk for DA (95% CI = 3.7 to 12.9) for cows with postpartum BHBA ≥ 1.0 mmol/L. Interestingly, Chapinal et al. (2011) reported no effect
of postpartum BHBA on the risk for DA, although elevated blood non-esterified fat acid and low blood calcium were associated with increased odds for DA.

In our recent field study we found even more profound effects of SCK on the risk for subsequent DA. Cows with SCK were 19.3 times more likely to develop a subsequent DA (95% CI = 13.8 to 27.0). The very large risk ratio reported here reflects the very low rate of DA in non-ketotic cows in the study (0.3% in the non-ketotic cows vs. 6.5% in the cows with SCK).

We also reported that cows with more severe hyperketonemia at the onset of their SCK had increased risk for DA (McArt et al., 2012a). Each 0.1 mmol/L increase in BHBA at the first SCK-positive test increased the risk for developing a DA by a factor of 1.1 (95% CI = 1.0 to 1.2). A cow with an initial blood BHBA of 2.4 at the onset of her ketosis would have a 3.1-fold (1.112) increased risk for a subsequent DA compared to a cow with an initial BHBA concentration of 1.2 mmol/L at her first SCK diagnosis.

Days in milk at the first onset of SCK also affects the risk for subsequent DA (McArt et al., 2012a). Cows who first developed SCK between 3 and 5 DIM were 6.1 times more likely (95% CI = 2.3 to 16.0) to develop a DA compared to cows first testing positive for SCK between 6 and 16 DIM.

Early detection and treatment of SCK with oral propylene glycol reduces the risk for subsequent DA. We reported that cows not treated for their SCK were 1.6 times (95% CI = 1.3 to 2.0) more likely to develop a DA than cows treated with oral propylene glycol (McArt et al., 2012b).

**Increased Risk for Metritis**

Duffield et al. (2009) reported that blood BHBA ≥ 1.2 mmol/L in the first week after calving increased the odds for metritis 3.4-fold (95% CI = 1.6 to 7.2). The authors suggested that impaired immune function due to ketosis could explain the increased risk for metritis. Ospina et al. (2010b) reported a 2.3-fold higher risk for metritis (95% CI = 1.1 to 5.2) for cows with postpartum BHBA ≥ 0.7 mmol/L. We did not formally evaluate the association between metritis and SCK in our recent field study (McArt et al., 2012a), but instead offered it to the models as a potential confounding variable. Because metritis occurs very soon after calving and may not be diagnosed promptly, it is particularly difficult to infer whether the associations between SCK and metritis are cause or effect.

**Impaired Fertility**

Associations between SCK and fertility have been inconsistent. Walsh et al. (2007) evaluated cows from mostly small and medium-sized herds in Ontario in 1990’s and reported that ketosis (defined as blood BHBA ≥ 1.0 mmol/L) in the first week after calving reduced the risk for pregnancy at first service (odds ratio = 0.73, 95% CI = 0.54 to 0.99). In the second week after calving, ketosis (defined as blood BHBA ≥ 1.4
mmol/L) reduced the odds for pregnancy even more (odds ratio = 0.60, 95% CI = 0.40 to 0.88). Ospina et al. (2010a) studied larger herds (> 250 cows) in New York in the late 2000’s and found a less profound effect of ketosis on reproduction. They reported that the risk for pregnancy with 70 days of the voluntary waiting period tended to be lower (hazard ratio = 0.87, \( P = 0.10 \)) for cows with blood BHBA ≥ 1.0 mmol/L after calving.

Chapinal et al. (2012) followed cows from 55 herds (herd size >100 cows) from 2006 to 2007 and found no association between blood BHBA before or after calving on first service conception rates. In our recent field trial in 4 large commercial dairies, we found no overall effect of SCK on first service conception rates (McArt et al., 2012a). We did find that cows first diagnosed with SCK between 3 and 7 DIM were 0.7 times as likely to conceive at first service (95% CI = 0.6 to 0.8) compared to cows first testing positive between 8 and 16 DIM. We also reported reduced pregnancy rates by 150 DIM for cows that first developed their SCK earlier in lactation.

Early detection and treatment of SCK with oral propylene glycol increases first service conception. We reported that cows with SCK who were treated with oral propylene glycol were 1.3 times (95% CI = 1.1 to 1.5) more likely to conceive at first insemination than control cows (McArt et al., 2012b).

**Economic Impacts of Subclinical Ketosis**

The economic impact of SCK can be quantified, but is dynamic and dependent on the expected milk yield loss, feed costs, feed efficiency, expected increase in the occurrence of postpartum diseases, the background incidence of these diseases, expected costs of these diseases, expected increase in early lactation herd removals, slaughter value of sold cows, disposal costs of dead cows, treatment costs for sick cows, and the cost of herd replacements. Duffield (2000) estimated the cost of a case of SCK to be $50 CAD to $100 CAD, which is approximately US $46 to US $92 when adjusted for inflation and the exchange rate. Geishauser et al. (2001) derived a similar estimate of $78 CAD per case of SCK (approximately $68 USD after adjusting for inflation and the exchange rate). We are currently working on detailed models to estimate the cost of a case of SCK based on the results from our recent field trial.

The high incidence of SCK, in combination with even a moderate cost per case, results in very high overall costs to the dairy producer. We have seen large variations in herd-level incidence of SCK (from about 25 to 60%), which suggests that there are important economic opportunities in most dairy herds.

**COWSIDE BLOOD BHBA TESTING WITH A HAND-HELD KETOMETER**

Our understanding of SCK and the ability of veterinarians and dairy producers to diagnosis ketosis has been greatly enhanced by the availability of a rapid and accurate cowside test for blood BHBA. The Precision Xtra® meter (Abbott Laboratories) was developed to measure either whole blood BHBA or whole blood glucose in human patients. As far as we know, no other human glucometer can also function as a
ketometer (i.e., able to measure blood BHBA). The Precision Xtra® meter gives excellent results for measuring whole blood BHBA in cows. No additional calibration or adjustment from the human system is needed.

The Precision Xtra® ketone monitoring system is a simple and direct electrochemical test (which may explain why it works well for both human and bovine blood). The ketone test strip contains the enzyme β-hydroxybutyrate dehydrogenase, which oxidizes BHBA to acetoacetate. This reduces nicotinamide adenine dinucleotide (NAD+) to NADH. The NADH is then reoxidized to NAD+ by an electron transfer mediator molecule. The electrical current generated by this conversion is measured by the meter and is directly proportional to the BHBA concentration.

These meters retail in human pharmacies for about $80 USD. Veterinary suppliers carry the meters for about $50 each. The blood ketone test strips (which measure BHBA) are sold in boxes of 10 strips each. Veterinary suppliers sell these for about $13 to $15 for a box of 10 strips, or $1.30 to $1.50 per test. Human suppliers will typically sell them for about $4.00 to $5.00 per strip. Most pharmacies do not stock the blood ketone strips routinely but can order them for you.

The BHBA results on blood from cattle are surprisingly accurate using the Precision Xtra® system. Three initial studies (Burke et al., 2008; Oetzel and McGuirk, 2008; Iwersen et al., 2009) all gave very similar results. These studies involved a total of 622 cows with a 14.1% prevalence of ketosis. The average coefficient of determination (R²) between hand-held meter and laboratory BHBA results was 0.94. The hand-held meter was 91% sensitive and 94% specific for diagnosing ketosis (pooled results from all three trials). The positive predictive value for the meter was 73% and the pooled negative predictive value was 98%.

The most recent evaluation of the Precision Xtra® blood ketone system showed exceptionally high sensitivity and specificity (>98%) for ketosis diagnosis (Oetzel, 2010) using the threshold of ≥1.3 mmol/L. The R² between hand-held meter and laboratory BHBA results was 0.86, which was lower than for previous reports. This may have been the result of the cold conditions during this study. Although the meter and strips can be used as a cowside test year-round, it is important to keep the meter and strips as warm as possible (e.g., in an inside pocket) during cold weather.

The most rewarding use of cowside blood BHBA testing is for herd-based ketosis monitoring. Strategies for herd-based testing have been explained in detail (Oetzel, 2004). The cowside BHBA test with the hand-held meter can be used in place of submitting serum or plasma samples to a laboratory for BHBA testing. In summary, the protocol involves testing 12 or more cows in early lactation. If more than 10% of the cows tested have blood BHBA ≥1.2 mmol/L) the group is considered to have a ketosis problem.
CONCLUSIONS

Subclinical ketosis in dairy herds can be described by its incidence (the proportion of cows that develop SCK anytime in early lactation) and by its prevalence (the proportion of cows with SCK at any given point in time). Incidence is very difficult to determine because it requires repeated testing of individual cows. Prevalence is much easier to determine; the incidence can then be estimated from the prevalence.

The costs of SCK in affected cows are substantial and include lost milk yield (up to about 7%), increased risk for herd removal in early lactation, and increased risk for displaced abomasum. The effect of SCK on metritis is difficult to evaluate because both conditions occur at the same time. The effect of SCK on subsequent fertility is inconsistent and appears to be small. Cows affected with SCK earlier in lactation or with higher BHBA concentrations experience more negative effects. The total economic loss for a single case of SCK is between about $46 and $92 USD. Early detection of SCK using a cowside blood test followed by treatment of SCK with oral propylene glycol reduces the negative impacts of SCK.

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