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Short communication: Associations between blood glucose concentration, onset of hyperketonemia, and milk production in early lactation dairy cows

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ABSTRACT

The objectives of this study were to describe the associations between hypoglycemia and the onset of hyperketonemia (HYK) within the first 6 wk of lactation, to evaluate the effects of body condition score at calving on glucose concentration, and to study the effects of hypoglycemia on milk production. A total of 621 dairy cows from 6 commercial dairy farms in Germany were enrolled between 1 and 4 d in milk (DIM). Cows were tested twice weekly using an electronic handheld meter for glucose and β-hydroxybutyrate (BHB), respectively, for a period of 42 d. Hypoglycemia was defined as glucose concentration ≤2.2 mmol/L. Hyperketonemia was defined as a BHB concentration ≥1.2 mmol/L. The onset of HYK was described as early onset (first HYK event within the first 2 wk postpartum) and late onset (first HYK event in wk 3 to 6 postpartum). The effect of ketosis status on blood glucose within 42 DIM was evaluated using a generalized linear mixed model. No effect was observed of HYK on glucose concentration in primiparous cows. Multiparous cows with early-onset HYK had a lower glucose concentration (−0.21 mmol/L) compared with nonketotic cows. Overall, primiparous cows had a lower prevalence and incidence of hypoglycemia than multiparous cows. Hypoglycemia in multiparous cows was associated with higher first test-day milk production and 100 DIM milk production. In conclusion, hypoglycemia mainly occurred in multiparous cows with early-onset HYK, whereas primiparous cows were at a lower risk for hypoglycemia.
Key words: glucose, β-hydroxybutyrate, body condition, transition

Short Communication

During early lactation, the energy requirements of a dairy cow exceed the available energy from feed intake (Jorritsma et al., 2003). Various metabolic and endocrine adaptations are necessary to provide the increased glucose needed to support milk production during lactation and to process nonesterified fatty acids taken up from mobilization of body stores (Herdt, 2000; Drackley et al., 2001). Those coordinated changes in metabolism of body tissues were described as homeorrhetic regulation and are necessary to support a physiologic state (Bauman and Currie, 1980; Bauman, 2000). During this process, a moderate increase in circulating ketone bodies is considered to be part of a normal metabolic response, whereas a poor adaptive response can lead to an excessive increase in BHB, which can be measured in blood (Duffield et al., 2009).

Two different types of hyperketonemia (**HYK**) differing in their onset and pathophysiology were hypothesized. Type I ketosis was described as HYK occurring 3 to 6 wk postpartum when milk secretion is so extensive that the demand for glucose exceeds the capacity for glucose production. The plasma levels of glucose and insulin are low, the levels of ketone bodies are high (Holtenius and Holtenius, 1996; Herdt, 2000). Type II was described as ketosis occurring earlier in lactation as a result of excessive body fat mobilization before or at calving. Insulin resistance and an impaired capacity to use glucose play a major role in the pathogenesis of type II ketosis. Blood insulin and glucose concentrations are high, whereas blood ketone concentrations are lower, in type II ketosis than in type I ketosis (Holtenius and Holtenius, 1996; Herdt, 2000).

There is a lack of science-based information that describes the association between hypoglycemia and HYK considering the ketosis classification. Therefore, the objectives of our study were (1) to describe the associations between hypoglycemia and HYK within the first 6 wk of lactation, (2) to evaluate the effects of BCS at calving on glucose concentration, and (3) to evaluate the effects of hypoglycemia on milk production.

The experimental procedures reported herein were conducted with the approval of the Institutional Animal Care and Use Committee of Freie Universität Berlin. Cows were managed according to the guidelines set by the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medical Products (Hellmann and Radeloff, 2000).

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A retrospective cohort study was performed as part of another field study evaluating the effect of HYK on reproductive performance. The sample size calculation was based on reproductive outcomes not analyzed here. Therefore, the sample size of this study can be considered as a convenience sample. A total of 621 dairy cows from 6 different commercial dairy farms in Germany were included in the trial. All farms kept at least 600 Holstein dairy cows in freestall barns with continuously feeding systems and recorded medical treatments using a computer-based farm management programs (HerdeW, version 5.8, dsp-Agrosoft Ltd., Ketzin, Germany). Annual milk production (ECM: 4.0% fat and 3.4% protein) ranged from 8,465 to 10,733 kg. During the transition period, all cows received a close-up and a fresh cow diet that was typical for the northeast region of Germany, using corn silage as the major forage and balanced by a professional nutritional consultant for protein, vitamins, and minerals. The TMR for close-up cows (n = 6; NE_L = 1.53 ± 0.04 Mcal/kg of DM) and for fresh cows (n = 6; NE_L = 1.68 ± 0.03 Mcal/kg of DM) consisted of corn silage and grass silage as forage with a corn-, soybean meal-, and canola meal-based concentrate. The TMR was balanced to meet or exceed minimum nutritional requirements for dairy cows (NRC, 2001). None of the herds used anionic salts in the close-up diet as a prevention strategy for milk fever.

Cows were enrolled between 1 and 4 DIM and were tested for BHB and glucose twice weekly (Monday and Thursday) until 42 DIM, resulting in 12 test results per cow. Therefore, the interval between 2 tests was either 3 or 4 d. At each test BCS was determined on a 5-point scale with 0.25-point increments (Edmonson et al., 1989) by a trained investigator. The term lactation week was used to describe the time of sample collection relative to calving (e.g., lactation wk 0.5 for the first measurement on DIM 1 to 4, lactation wk 1 for the second measurement on DIM 4 to 7, lactation wk 1.5 for the third measurement on DIM 8 to 11).

The collection of blood samples and the measurement of BHB by an evaluated electronic BHB meter (NovaVet, Nova Biomedical, Waltham, MA; Bach et al., 2016) were described in a study by Mahrt et al. (2015). Hyperketonemia was defined as BHB ≥1.2 mmol/L (Suthar et al., 2013). The measurement of glucose was conducted with a handheld electronic glucometer (Precision Xtra, Abbott Diabetes Care Inc., Mississauga, ON, Canada), which was evaluated for cow-side use in dairy cattle (Wittrock et al., 2013). A cut-point for blood glucose was determined by Gordon (2013) as blood glucose ≤2.2 mmol/L. In that study, animals that had blood glucose concentration ≤2.2 mmol/L at the time of ketosis diagnosis were more likely to cure and produced more milk after treatment. Treatment benefits did not extend to animals with blood glucose >2.2 mmol/L at the time of enrollment.

In total, 621 cows (195 primiparous; 426 multiparous) were used for the analysis. Of those, a total of 58 cows had 3 missing glucose or BHB test results (e.g., because they had not been detected on the test day). For the evaluation of prevalence, only cows with at least 10 test results for glucose and BHB, respectively, were considered for analysis (n = 563). For the evaluation of incidence, only cows with all 12 test results for glucose and BHB, respectively, were considered for analysis (n = 417) because incidence is determined relative to a risk period and therefore missing results could falsify the results. A total of 391 and 354 cows had sufficient milk production data available for the analysis of first test-day milk yield and cumulative 100 DIM milk yield, respectively.

Data from the cow-side evaluation of BHB and glucose and data from the on-farm computer system were exported to Excel (Microsoft Corp., Redmond, WA) spreadsheets and analyzed using SPSS for Windows (version 22.0, SPSS Inc., IBM, Ehningen, Germany).

To evaluate the effect of ketosis status (i.e., nonketotic = no HYK event within the first 6 wk of lactation; early onset = first HYK event within the first 2 wk; late onset = first HYK event within wk 3 to 6 postpartum) and BCS on blood glucose within 42 DIM, repeated measures ANOVA with first-order autoregressive covariance was performed using the GENLINMIXED procedure of SPSS. The outcome variable was blood glucose (mmol/L). Cow was the experimental unit and herd was considered as a random effect. According to the model-building strategies described by Dohoo et al. (2009), each parameter considered for the mixed model should be separately analyzed in a univariate model, including the parameter as a fixed factor (i.e., categorical parameter) or covariate (i.e., continuous parameter). Only parameters resulting in univariate models with $P \leq 0.2$ should be included in the final mixed model. The initial model contained the following explanatory variables as fixed effects: ketosis status (nonketotic, early onset, late onset), BCS (1.00 to 5.00) at the first and second BHB test, parity (primiparous vs. multiparous), and farm. Selection of the model that best fit the data was performed by testing each effect separately in a univariate model and finding the model with the lowest value for the Akaike information criterion (**AIC**) using a backward elimination procedure that removed all variables with $P > 0.10$ from the model. Regardless of the significance level, ketosis status was forced to remain in the model.