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Review: Metabolic challenges in lactating dairy cows and their assessment via established and novel indicators in milk

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The increasing lactational performance of dairy cows over the last few decades is closely related to higher nutritional requirements. The decrease in dry matter intake during the peripartal period results in a considerable mobilisation of body tissues (mainly fat reserves and muscle mass) to compensate for the prevailing lack of energy and nutrients. Despite the activation of adaptive mechanisms to mobilise nutrients from body tissues for maintenance and milk production, the increased metabolic load is still a risk factor for animal health. The prevalence of production diseases, particularly subclinical ketosis is high in the early lactation period. Increased β-hydroxybutyrate (BHB) concentrations further depress gluconeogenesis, feed intake and the immune system. Despite a variety of adaptation responses to nutrient and energy deficit that exists among dairy cows, an early and non-invasive detection of developing metabolic disorders in milk samples would be useful. The frequent and regular milking process of dairy cows creates the ability to obtain samples at any stage of lactation. Routine identification of biomarkers accurately characterising the physiological status of an animal is crucial for decisive strategies. The present overview recapitulates established markers measured in milk that are associated with metabolic health of dairy cows. Specifically, measurements of milk fat, protein, lactose and urea concentrations are evaluated. Changes in the ratio of milk fat to protein may indicate an increased risk for rumen acidosis and ketosis. The costly determination of individual fatty acids in milk creates barriers for grouping of fatty acids into saturated, mono- and polyunsaturated fatty acids. Novel approaches include the potential of mid-IR (MIR) based predictions of BHB and acetone in milk, although the latter are not directly measured, but only estimated via indirect associations of concomitantly altered milk composition during (sub)clinical ketosis. Although MIR-based ketone body concentrations in milk are not suitable to monitor the metabolic status of the individual cow, they provide an estimate of the overall herd or specific groups of animals earlier in a particular stage of lactation. Management decisions can be made earlier and animal health status improved by adjusting diet composition.

Keywords: biomarker, milk, ketosis, metabolic status, mid-IR spectra

Implications

At the onset of lactation, dairy cows experience an increased metabolic load as seen by increased circulating ketone body concentrations. This is attributed to the prevailing negative energy balance (NEB), making them more susceptible to infectious and metabolic diseases. In particular, ketosis negatively affects performance and health of dairy cows. Milk composition is related to the metabolic status. The present review will give an overview on recent developments in milk analysis in terms of assessing the metabolic status in dairy cows. Established and novel indicators in milk likely reflecting the animal's health status are revisited and their suitability evaluated.

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Introduction

Dairy cows' health and metabolic status have profound effects on performance and milk quality. Metabolic status and milk composition are subject to profound changes during the course of lactation (Bruckmaier and Gross, 2017). Deviations from a dairy cow's metabolic homeostasis are manifested by respective alterations in body fluids such as blood, urine, saliva and milk (Overton *et al.*, 2017). The commonly accepted gold standard for diagnosing health disorders (in particular metabolic diseases) is the analysis of key factors in the blood circulation (Oetzel, 2004). However, isolation, fixation (even for a short time) of the animal and the inevitable procedure of obtaining blood by venous puncture must be considered as a target of public perception in terms of animal handling and animal welfare (Solano *et al.*, 2004). Furthermore, only experienced veterinarians or

trained staff may guarantee a fast and unstressful sampling. Furthermore, interaction with dairy cows can expose humans to risk of injury. Although blood samples enable the precise analysis of multiple factors (e.g. metabolites, endocrine factors, inflammatory markers, vitamins and minerals), a frequent sampling schedule (i.e. daily samples) for early detection and following the development of metabolic diseases is neither feasible at an individual cow nor at a herd level. Alternatively, non-invasively obtained media such as milk may provide hints to the animal's metabolic and health status. This implies that alterations in blood must be closely mirrored by the composition of milk. The analysis of milk constituents is advantageous for following individual dairy cows daily, and routine methods have been established for collection of milk, making this a low-cost and high-throughput analysis. The present review will give an overview on recent developments in milk analysis for assessment of the metabolic status of dairy cows. Established and novel indicators in milk likely reflecting the animal's health status are revisited and their suitability evaluated.

Metabolic status in early lactating dairy cows

Compared with non-lactating stages, milk production beginning at parturition requires an increase in the energy and nutrients supply. Feed intake is moderate during non-lactating periods before parturition, and decreases further just before parturition (Gross *et al*., 2011a). Energy requirements for milk production and maintenance increase faster than concomitant energy intake via feed. Temporarily a deficiency of energy and nutrients commonly termed 'NEB' emerges, which lasts for the first 6 to 8 weeks of lactation and sometimes even beyond (Gross *et al*., 2011a; Bruckmaier and Gross, 2017). Serving the respective needs for today's daily milk yields above 30 to 40 kg, lipolysis of adipose tissue compensates the prevailing NEB with detectable metabolic changes already during the periparturient period (Duffield *et al*., 2009). Thus, susceptibility towards metabolic disorders depends on the metabolic adaptation at a very early stage of lactation. In addition, over-conditioned cows at parturition have a higher lipolysis and consequently a greater risk to develop infectious and metabolic diseases (Roche *et al*., 2005). Despite the presence of a NEB, milk production further increases during early lactation. Contrary, an experimentally induced similar energy deficiency at a later lactational stage was immediately followed by a reduction in milk production to compensate for the main part of the lack of energy and nutrients (Gross *et al*., 2011a).

The typical metabolic situation in early lactating dairy cows is characterised by low plasma concentrations of glucose with concomitantly elevated concentrations of non-esterified fatty acids (NEFA) and β-hydroxybutyrate (BHB) (Bruckmaier and Gross, 2017). Fatty acids (FA) released from adipose tissue are oxidised in the liver. An excess of NEFA that cannot be oxidised is re-esterified to triglycerides. As the capacity of hepatic lipoproteins is limited, not all triglycerides can be exported and remain in the liver, consequently leading to the development of fatty liver (Bobe *et al*., 2004; Gross *et al*., 2013). Fatty liver can develop quickly within the 1st week of lactation even before elevated concentrations of ketone bodies are detected in blood (Gross *et al*., 2013). The accumulation of triglycerides in the liver negatively impacts other essential hepatic functions (e.g. gluconeogenesis) (Bobe *et al*., 2004). In parallel, abundant NEFA are converted to the ketone acetoacetate which is predominantly metabolised to BHB and to a lower extent to acetone (Bruckmaier and Gross, 2017). Hence an increase of circulating concentrations of BHB occurs to be delayed compared with plasma concentrations of NEFA (Gross *et al*., 2011a).

Elevated concentrations of blood ketone bodies and primarily those of BHB without concomitant clinical signs of ketosis are considered as subclinical ketosis (SCK). Thresholds for SCK diagnosis based on blood BHB concentrations range from 1.2 to 1.4 mmol/l (Brunner *et al*., 2019). Prevalence of SCK ranges between 10% and 40% in early lactation with highest values reported within the first 3 weeks after parturition (Oetzel, 2004; Brunner *et al*., 2019). Manifest signs of clinical ketosis such as reduced milk production, lethargy and loss of appetite are commonly observed at higher concentrations of BHB (e.g. $>$3.0 mmol/l) (Chapinal *et al*., 2011). However, an elevated metabolic load does not automatically equate with poor animal health status. Individual cows may be exposed to high BHB concentrations without expressing typical clinical signs of ketosis, whereas others show symptoms already at only slightly elevated plasma BHB concentrations (Bruckmaier and Gross, 2017; Zbinden *et al*., 2017).

Nevertheless an early detection of SCK in dairy cows is crucial. Ketones have been shown to depress feed intake (Laeger *et al*., 2010), reduce fertility (Raboisson *et al*., 2014) and to impair immune function (Sordillo *et al*., 2009; Zarrin *et al*., 2014). Thus, excessive lipolysis of adipose tissue and consequent formation of ketone bodies are detrimental, when cows' immune competence is low and animals in early lactation are highly susceptible to metabolic and infectious diseases anyway (Bradford *et al*., 2015). Subclinical ketosis was shown to negatively affect milk production (Duffield *et al*., 2009; Zbinden *et al*., 2017) and is evidently related to a greater risk of further production-related diseases such as clinical ketosis, retained placenta, displaced abomasum and mastitis (Duffield *et al*., 2009; Brunner *et al*., 2019). Considerable economic losses due to lower milk production, poor fertility and increased culling rates are attributed to the negative effects of elevated blood ketone body concentrations (McArt *et al*., 2015). For instance, blood BHB concentrations $\geqslant$1.2 mmol/l in the 1st week after parturition were a harbinger for a considerably greater risk of displaced abomasum and metritis (Duffield *et al*., 2009). Ospina *et al*. (2010) reported increased risk ratios of 4.9 for clinical ketosis, 2.3 for metritis and 6.9 for displaced abomasum in cows with plasma BHB concentrations above 1.0 mmol/l during the first 2 weeks of lactation. The economic impact of SCK is therefore indisputable, although exact figures quantifying

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costs of SCK are scarce. Based on an earlier study on Canadian dairy farms including more than 2600 cows, McLaren *et al*. (2006) estimated that a reduction of 1% in SCK incidence could save up to 584 USD per year. Recently, McArt *et al*. (2015) calculated average total costs of 289 USD per case of diagnosed hyperketonaemia (blood BHB concentrations $\geqslant$ 1.2 mmol/l).

Established parameters in milk analysis

This chapter summarises parameters measureable in milk that are established since many years and allow conclusions regarding the metabolic status of lactating dairy cows.

Milk solubles, in particular milk fat and protein, are targets for breeding in dairy cows and basis for raw milk payment in many countries since decades. Consequently, gravimetric and further wet-chemical analytical methods have been early established. The introduction of IR spectroscopy starting in the 1960s (Goulden, 1964), and the Fourier transform IR (FTIR) analysis established in the late 1990s (Tsenkova *et al*., 1999) enabled a rapid high throughput and non-destructive determination of milk composition (fat, protein, lactose, urea) at a rather low-cost level per sample. Moreover, this widely standardised technology has been established in many laboratories and organisations involved in the official milk control of dairy cows all over the globe.

Milk fat and protein content, and fat-to-protein ratio

Milk fat and protein content are affected by various factors such as breed, feeding, lactational, metabolic and health status. Jersey cows are known to have a higher milk fat content compared with Holstein dairy cows (Jensen *et al*., 2012). Moreover, the cow strain may affect milk composition. North American Holsteins' milk obviously contains less fat and protein compared with Holsteins in Western Europe (Miglior *et al*., 2006). Brown Swiss cows tend to have a higher milk protein content compared with Holstein cows (De Marchi *et al*., 2008). Feeding of hay, oilseeds or other dietary fat sources increases milk fat content, whereas feeding of starch rich diets based on corn silage and grain may reduce milk fat content (Palmquist and Jenkins, 2017). Likewise, providing fresh herbage with a high content of linoleic acids or feeding of technically produced CLA (*trans*-10, *cis*-12 isomer) reduce the *de novo* synthesis of milk fat as well (Griinari *et al*., 1998).

Immediately after parturition, the contents of fat and protein in milk are highest, and decline concomitantly with the increase of milk production until peak lactation (Gross *et al*., 2011a). After the period of highest milk yields the milk fat and protein contents increase gradually with decreasing milk production. Both fat and protein contents are indicative for the animals' energy status. During energy deficient stages like in early lactation but also in later lactation milk fat content is increased (Gross *et al*., 2011a). Concomitantly milk protein tends to be reduced indicating insufficient energy supply for the rumen microbes and consequently less ruminal synthesis of protein provided for intestinal absorption (Nousiainen *et al*., 2004). The respective elevation of milk fat-to-protein ratio (FPR) clearly coincides with periods of a NEB and adipose tissue mobilisation. Milk FPR above 1.35 to 1.50 can be considered to identify cows exposed to an energy deficiency (Heuer *et al*., 1999; Gross *et al*., 2011a). On the other side, a reduced FPR could be indicative of (subacute) rumen acidosis due to less rumen volatile FA production (acetate and butyrate) serving as precursors for mammary FA synthesis (Kleen *et al*., 2003).

Lactose and urea content in milk

Milk lactose is considered the main osmole determining milk yield via the water uptake in the secretory vesicles of the lactocytes. Milk lactose content is reduced during the colostral period and up to two weeks after parturition, when other osmotically active milk constituents like proteins and electrolytes are elevated. Thereafter, lactose content in milk remains widely constant throughout lactation, and remains almost unaffected by energy shortages (Gross *et al*., 2011a). Milk urea shows a very close correlation with urea in blood (Broderick and Clayton, 1997). The interpretation of milk urea concentration must be conducted along with the concomitant milk protein content. Low urea concentrations in the first weeks of lactation along with low milk protein concentrations are indicative for low energy and protein intake via feed and thus limiting for amino acid supply after duodenal absorption (Nousiainen *et al*., 2004). Elevated milk urea concentrations at simultaneously low and normal milk protein contents suggest the presence of excessive dietary CP and concomitantly lack of energy supply, which emphasise the importance of synchronous energy and nitrogen delivery for the rumen microbes (Nousiainen *et al*., 2004).

Milk fatty acid profile

Milk fat represents the major component causative for energy expenditure in terms of milk production. Not only the quantification of milk fat content but also of changes in single milk FA allows conclusions about the metabolic status of dairy cows (Kay *et al*., 2005; Stoop *et al*., 2009). More than 95% of milk fat consists of triglycerides and more than 400 individual FA are documented in milk fat (Jensen *et al*., 1991). The comprehensive analysis of FA via gas chromatography is costly and labourious. However, the FTIR technology provides a reliable estimate of FA groups: saturated fatty acid (SFA), monounsaturated fatty acid (MUFA) and polyunsaturated FA (Gottardo *et al*., 2017). In the past milk FA composition attracted manufacturers' and consumers' interest as it significantly influences nutritional, flavour and other physical–chemical properties such as oxidative stability during milk processing (Kay *et al*., 2005). Milk FA can originate from four major sources: diet, *de novo* synthesis in the mammary gland, rumen (biohydrogenation, bacterial degradation and synthesis) and body fat mobilisation (Stoop *et al*., 2009).

Nutrition of dairy cows is one of the main factors influencing milk FA composition. Dietary FA (in plants mainly

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long-chain unsaturated FA > C18) are incorporated into milk fat after absorption. Besides diet, the lactational stage associated with the degree FA derived from lipolysis of the adipose tissue clearly determines the FA profile in milk (Kay *et al*., 2005; Stoop *et al*., 2009). The *de novo* synthesis of FA in the mammary gland ends up in FA with maximum C16 (short- and medium-chain length FA), whereas adipose tissue lipolysis during the NEB releases particularly long-chain FA (SFA in form of palmitic and stearic acid C16:0 and C18:0, and unsaturated oleic acid C18:1,9*c*) (Kay *et al*., 2005). Mobilised C18:1,9*c* is transferred to a high extent from plasma into milk fat (Tyburczy *et al*., 2008), which was confirmed by an elevated proportion of C18:1,9*c* in milk fat during the NEB *post partum* by Gross *et al*. (2011b). Consequently, the proportion of short and medium chain FA in milk fat is lowest in early lactation (Palmquist *et al*., 1993; Kay *et al*., 2005) and increases later on (Stoop *et al*., 2009), whereas the content of MUFA, in particular oleic acid, decreases concomitantly with improving energy balance after parturition (Gross *et al*., 2011b). Considerable milk FA profile changes, especially in SFA and MUFA, were observed only during the NEB in early lactation (Gross *et al*., 2011b). Long-chain FA derived from the plasma and incorporated into milk fat were shown to inhibit the *de novo* synthesis of short chain FA in the mammary gland (Palmquist *et al*., 1993).

During an energy deficiency induced by feed restriction in mid-lactation, similar changes (although lower in their extent) in milk FA pattern were observed as during the NEB in early lactation (Gross *et al*., 2011b). Again, the classes of SFA and MUFA were able to indicate an energy deficit (Gross *et al*., 2011b). Changes in milk FA profile occurred rapidly within only a few days after the initiation of the nutrient shortage. A study by van Haelst *et al*. (2008) determined whether concentrations of specific FA in milk fat are suitable for the early detection of SCK as lipolysis of adipose tissue precedes ketosis development. Hence, an elevated proportion of C18:1,9*c* was identified suitable for prediction of SCK, particularly since oleic acid was elevated in milk fat before ketosis detection (van Haelst *et al*., 2008). The close correlation between energy balance and categories of milk FA (Gross *et al*., 2011b; 0.92 to 0.98 for SFA, MUFA (predominantly C18:1,9*c*), *de novo* synthesised and preformed FA) confirms that milk FA groups detectable by FTIR are suitable to reflect energy balance and thus metabolic status in dairy cows. Of course, diet composition affects milk FA composition as well. Supplementation of fat to improve energy supply increases milk fat content and the content of FA like oleic acid. Hence, feeding contributes to milk oleic acid content as well. Therefore, changes in milk FA composition must be interpreted carefully under consideration of the diet.

Summarising the validation of established milk biomarkers so far, milk fat and protein content (and therefrom derived the milk FPR) as well as the gross classification of FA (SFA and MUFA) are suitable for estimating the metabolic status of dairy cows. All of them can be determined via FTIR, which is routinely used in the official milk control. However, the common monthly intervals (or 11 times per year) of milk sampling do not necessarily cover all animals at risk for ketosis. Metabolic status in blood may rapidly change within days or a few weeks. A more frequent sampling density would be required to ensure an early detection of health disorders at an individual animal level. However, already the few above mentioned parameters in milk can give valuable hints about the health status of dairy cows. Although monthly milk control reports are not appropriate for early diagnosis of metabolic disorders like ketosis at an individual cow level, management interventions (e.g. changes in feeding) are possible for groups of animals in large dairy herds (i.e. with a considerable number of animals in different lactational stages) when thresholds for detection of SCK as indicated by, for example, the milk FPR are exceeded at herd level.

Novel indicators in milk for assessing metabolic status

Besides blood, elevated concentrations of ketone bodies can be detected also in urine and, most importantly, in milk. Cow-side tests based on dip sticks for the measurement of ketones in milk revealed a good specificity, but only a poor sensitivity (Geishauser *et al*., 2000). Recent analytical methods of metabolomics along with bioinformatics are able to precisely detect a wide range of factors related to metabolic status (Huber *et al*., 2016). However, these approaches are cost-intensive and currently not suitable for routine analysis and implementation in the dairy business.

So far, only part of mid-IR (MIR) spectra data were used in milk analysis for determination of milk composition (fat, protein, lactose, urea, FA). The progress in computing capacities, machine learning-based algorithms, digitisation, big data analysis and data exchange during the last few years pushed the further exploitation of potential biomarkers and various traits estimated from MIR spectra (de Roos *et al*., 2007; Grelet *et al*., 2016). The electronic storage of milk spectral data of repeated milk control during and across lactations allows additionally a retrospective data analysis (De Marchi *et al*., 2014). It seems reasonable to calculate associations of milk spectral data with traits included in the estimation of breeding values (Koeck *et al*., 2014). Furthermore, phenotypic data (e.g. methane emissions, feed efficiency) determined in animal experiments are correlated with respective data in milk (McParland and Berry, 2016).

However, it must be clearly emphasised that many of the 'novel' indicators predicted from MIR spectra are only indirect estimates. For instance, methane emission indicated by MIR spectra are only estimates based on associations with other traits in milk, but methane itself is not present and therefore not measurable in milk (Vanlierde *et al*., 2018). Likewise, prediction of ketone bodies like BHB and acetone in milk based on MIR data does not represent true concentrations in milk (De Marchi *et al*., 2014). Instead, algorithms for estimating ketone body concentration include associations

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with several spectral regions of milk components that are changed during energy deficient stages in cows with a concomitant high metabolic load (i.e. milk fat, protein, FA profile) (de Roos *et al*., 2007; Schwarz, 2018). Unfortunately, defined chemical compounds cannot be assigned to detection peaks at certain wavelengths of the milk MIR spectrum and require specific calibration equations (Grelet *et al*., 2016). This indirect method of estimating milk BHB and acetone via MIR data has therefore only a limited suitability to indicate the metabolic status of a cow. The gold standard for detection of (subclinical) ketosis is currently the measurement of blood BHB (Oetzel, 2004). When ketone bodies are elevated in blood and exceed thresholds for SCK diagnosis, likely more ketone bodies are detectable in milk as well. The enzymatic-colorimetric analysis of milk BHB and acetone directly determines respective concentrations of these compounds and correlates reasonably well with MIR-based predicted values if the concentrations are considerably elevated (Grelet *et al*., 2016). Furthermore, milk BHB predicted by MIR spectra highly correlated with blood BHB in studies with many animals actually having subclinical or clinical ketosis (Koeck *et al*., 2014). However, the number of false-positive results can be high when predicting BHB and acetone by MIR spectra, and at lower BHB concentrations in blood corresponding correlations with BHB in milk are poor and frequently provide results below the detection limit (de Roos *et al*., 2007; Grelet *et al*., 2016). Nevertheless it is crucial to early identify cows at risk for developing ketosis and thus alerts based on milk MIR spectra might be too late. The combination of classical, established and novel MIR-based biomarkers is promising in improving the diagnostic value in terms of ketosis detection compared with the sole consideration of each of the factors alone (Denis-Robichaud *et al*., 2014). Besides the analytical limitations, spectral data need a standardisation as individual machines, though calibrated, may generate a different output on the same milk sample. Similarly to the established milk parameters discussed above, using MIR-predicted BHB and acetone values from the monthly milk control intervals is not suitable for monitoring individual cows. Reasonably, MIR-based parameters like BHB and acetone can give an estimation of the general metabolic status at a large herd level supporting the interpretation of milk gross composition compounds (Santschi *et al*., 2016). Therefore, the use of milk MIR spectral data for ketosis screening purposes is undoubtedly justified, but accuracy of data can be considerably improved by the combination with further biomarkers directly measured in milk (Overton *et al*., 2017).

Again, a more frequent sampling density would be required to ensure an early detection of evolving metabolic disorders like ketosis. Recent commercially available precision livestock farming tools allow a dense sampling schedule and automatic inline enzymatic analysis of BHB in milk (Overton *et al*., 2017). Especially during the critical early lactation stage, where cows are most susceptible to develop ketosis, an earlier treatment of animals at risk is possible, when accuracy of ketosis detection is improved.

Conclusions

The surveillance of the metabolic status of dairy cows in milk presupposes causal relationships of the selected parameters with respective changes in blood. Milk has a great potential to serve as diagnostic medium as it is non-invasively and regularly obtained by milking and routine analytical procedures are established since years. However, the impact of breed and feeding on milk composition must be kept in mind, when defining thresholds for parameters indicating metabolic disorders. Established biomarkers in milk like fat, protein and FA give already a basic estimate on the metabolic situation of dairy cows. Classical enzymatic analyses and chromatographic analyses of single FA, BHB and acetone in milk enable a more precise and in-depth interpretation of cows' energy status, but is not suitable for high-throughput analysis at low cost level. The use of milk MIR spectra predicting BHB and acetone provides only estimates that need to be interpreted with caution as they are not directly measured. Algorithms based on milk traits altered during energy deficient stages seem to reliably predict BHB and acetone in milk only when ketone bodies in blood are above thresholds for diagnosing SCK. Currently, it cannot be advised to apply MIR-based prediction of ketone bodies to accurately detect individual cows at risk for ketosis. However, at herd or population level its implementation can improve management decisions.

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Declaration of interest

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Ethics statement

None.

Software and data repository resources

None.

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