

Dairy cow physiology and production limits

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Implications

- Milk production in dairy cows increased worldwide for many decades and continues to increase.
- The early lactation period in particular imposes a considerable metabolic stress that is accompanied by an increased occurrence of health disorders.
- Major limitations for milk production are set by the availability of glucose and amino acids, for which the mammary gland and the immune system compete.
- High milk production is often associated with health problems and reduced welfare, but this is not an obligatory outcome because high performance is only possible in healthy cows.

Key words: dairy cow, high milk yield, limits, metabolism, milk production

Introduction

Global milk production of dairy cows has increased steadily for many decades. In the United States, the average annual milk production per cow has doubled within the last 40 years and is nowadays approximately six times greater than 100 years ago (Figure 1; USDA NASS, 2023). Whereas the secretory capacity of the mammary gland currently seems not to be compromised, a significant number of health disorders and reduced reproductive performance related to the high milk production are observed. In particular, the first weeks of lactation are characterized by a greater incidence of so-called production diseases (e.g., hypocalcemia, ketosis, hepatic lipidosis, displacement of the abomasum, and mastitis) and problems with reproduction (Fleischer et al., 2001; Ingvartsen et al., 2003).

Concomitantly with increasing milk yields, energy and nutrient requirements for lactation increase. After parturition,

energy demands suddenly increase and may be more than 5-fold greater during peak lactation in a cow producing 60 kg of milk per day compared with those of a nonlactating dairy cow (Figure 2). Nowadays, daily milk production of individual high-yielding cows can achieve more than 100 kg. There is a disagreement on whether limits of milk production are already reached. However, in view of the current increased prevalence of health disorders that continuously increased during the last decades, it seems obvious that physiological limits are clearly exceeded in many individuals. In the early 1980s, researchers assumed that the genetic capacity for milk production was reached at that time and any further increase in milk yield would harm animal health (Kennedy, 1984). Although there may be no relationship between health disorders and performance level in dairy cows in many studies (Fleischer et al., 2001), dairy farmers experience limitations on a daily basis. As a consequence, an improvement in overall lifetime performance and longevity to achieve more efficiency and sustainability in milk production is obviously imperative.

The scope of the present review is to provide a short overview on metabolic stress situations in dairy cows, their interactions with animal health, and wherefrom limitations for milk production may arise. Physiological and nutritional boundaries for milk production are described with respect to consequences for animal health, reproductive performance, and environment. In addition, selected environmental and management-related factors affecting dairy cow performance are discussed. The awareness and knowledge of physiological limits, however, shall not pursue the aim of further pushing milk production. As only healthy animals are feeling comfortable and can use their genetic capacity to produce greater amounts of milk, any improvements in animal health and welfare will benefit sustainable milk production.

Metabolism of Dairy Cows During Early Lactation

Metabolic load, risk of disease, and longevity

Undoubtedly, the most challenging period for dairy cows is the transition from gestation to lactation, where numerous orchestrated adaptation responses towards a new physiological status (i.e., homeorhesis) take place (Bauman and Currie, 1980). In the light of homeorhetic adaptation, the increased metabolic priority of the mammary gland at the onset of lactation in dairy cows preferentially directs nutrients to the mammary

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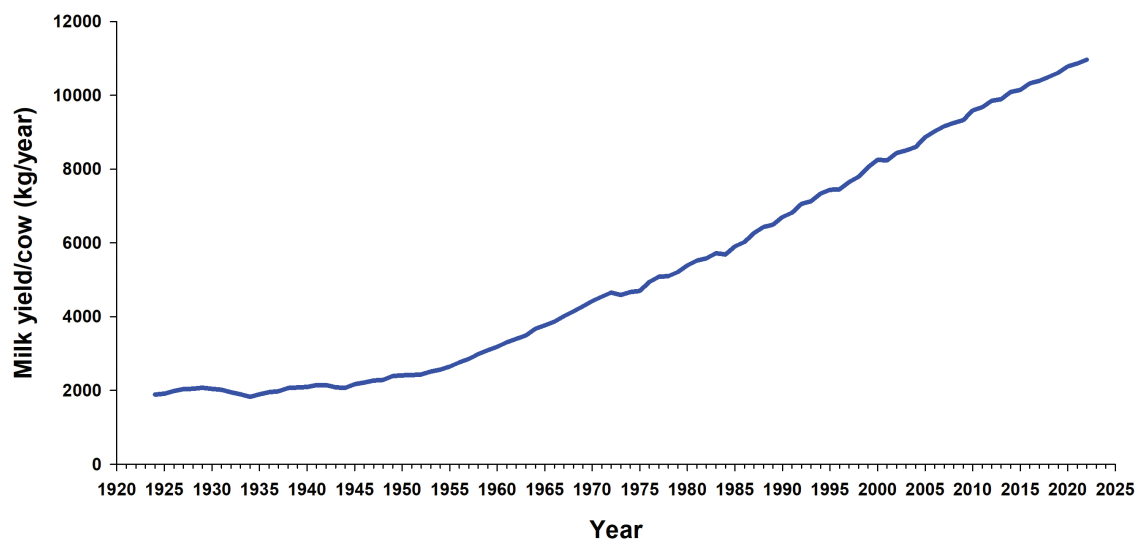


Figure 1. Development of the average annual milk production per cow in the United States since 1924. Data from <https://quickstats.nass.usda.gov/> (USDA NASS, 2023, assessed January 09, 2023).

gland (Bauman and Currie, 1980). Although cows experience a considerable negative energy balance (NEB) after parturition, milk production is further increased until peak lactation. From an evolutionarily point of view, the inherited maternal care allows lactation to support survival of the milk-dependent offspring, but also enables selection of high-yielding dairy cows.

Increasing milk production after parturition results in greater energy and nutrient requirements. However, dry matter intake (DMI) declines during the periparturient period, and increases slower and later compared with the increase of milk production. As a consequence, DMI cannot cover the

nutrient needs, resulting in a NEB with loss of body weight (Figures 3 and 4), and possibly to protein, calcium and other deficiencies. Catabolic stages, like NEB, are compensated by mobilization of body tissue reserves, predominantly adipose tissue (Figure 5). Already at the time of calving a high lipolysis rate expresses high-yielding dairy cows to metabolic stress (Ingvarsen et al., 2003). Consequently, the susceptibility towards metabolic and infectious diseases commences at the very beginning of lactation. Inadequate feeding and overconditioning during the dry period may further predispose cows for periparturient health disorders (Ingvarsen et al.,



Figure 2. The high metabolic priority of the mammary gland during early lactation imposes metabolic stress on the dairy cow.



Figure 3. Maximizing feed intake is of major importance in early lactation.

2003). The periparturient period in dairy cows is characterized by an acute systemic inflammatory state due to events related to parturition (e.g., stress, tissue damages of uterus, altered epithelial permeability) (Trevisi et al., 2012). Inflammatory responses occur after the release of signaling molecules following activation of immune cells by stressors, toxins, or invading pathogens. Proinflammatory cytokines like tumor-necrosis factor alpha (TNF- α), interleukin (IL)-1 β , and IL-6 play a key role in stimulating systemic inflammatory responses, including increased body temperature, increased heart rate, or reduced DMI. The acute phase response is one example for effects induced by pro-inflammatory cytokines, where the liver produces positive acute phase proteins (APP) such as haptoglobin, ceruloplasmin, and C-reactive protein

(Bertoni et al., 2008). Furthermore, function of polymorphonuclear (PMN) cells is impaired around parturition, which negatively affects their viability, survival, and sensitivity to proinflammatory mediators as well as chemotaxis, phagocytosis, and respiratory burst (Mehrzaad et al., 2001).

However, there is a considerable biological variation and plasticity in adaptation success to NEB in early lactation within dairy cow populations characterized by a high genetic homogeneity, and a high number of cows adopt successfully to the metabolic stress. Therefore, an increased metabolic load is not necessarily accompanied with poor animal health status indicating metabolic robustness. The extent of metabolic stress of early lactating dairy cows is not related to the overall lifetime performance (Gross et al., 2016). Highest yielding Swiss dairy cows did not have more metabolic problems than cows with average milk yield (Aeberhard et al., 2001).

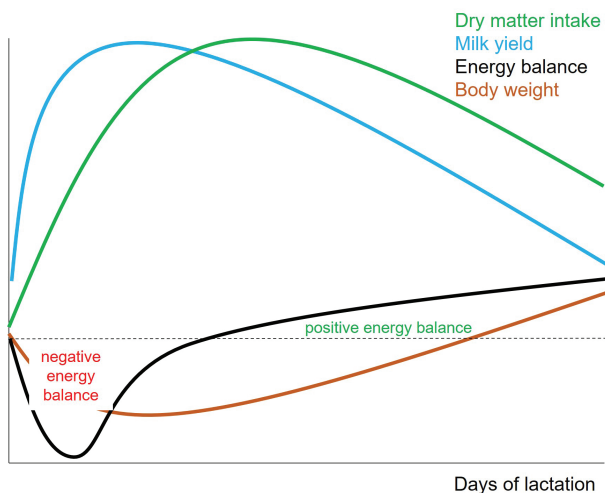


Figure 4. Patterns of dry matter intake, milk production, energy balance, and body weight in dairy cows during lactation.

Glucose as essential substrate for milk synthesis and immune system

Approximately 85% of glucose turnover during lactation accounts primarily for lactose synthesis and therefore milk production because the production of lactose mainly determines the amount of milk production (Bauman and Currie, 1980). However, blood glucose concentrations show a nadir in early lactation, and gluconeogenesis starts only at a low rate immediately after parturition, because of low activation of the extra-mitochondrial non-constititional phosphoenol-pyruvate-kinase (PEPCK). Because glucose is not only used by the mammary gland (for lactose synthesis), but also by the immune system, the central nervous system (especially the brain), and the kidneys, glucose is one of the most limiting factors especially during early lactation in dairy cows. Especially an enhanced glucose utilization is observed during activation of the immune

system (glucose is used e.g., by activated NK cells, T cells, B cells, dendritic cells, macrophages, and granulocytes) (Kvidera et al., 2017). Most of the glucose is taken up into the mammary gland in early stages of lactation via insulin-independent glucose-transporter-1 (GLUT-1), whereas at later lactational stages, the importance of insulin-dependent glucose uptake increases (Mattmiller et al., 2011). Consequently, the mammary gland has a lower metabolic priority during established energy and nutrient homeostasis in later lactational stages.

Endocrine control of tissue mobilization and energy homeostasis

The mammary gland is controlled by a large number of hormones and tissue factors. Endocrine control of anabolic mammary gland metabolism and catabolic extramammary metabolism is essential. Once lactation is established after parturition (stage of galactopoiesis), in cows growth hormone (GH) is known as the most important hormone stimulating milk yield, as shown by parenteral administration of GH (Bauman et al., 1985). Effects of GH are in part mediated by insulin-like growth factor (IGF)-1. The somatotrophic axis with GH, IGF-1, IGF binding proteins, and receptors for GH and IGF have a crucial role in nutrient partitioning towards milk synthesis. In this regard, differences in lactational performance of genetically divergent Holstein cow strains can be explained by different IGF-1 and GH concentrations (Hart et al., 1978). It is obvious that IGF-1 is a marker for resilience and metabolic robustness in dairy cows. In early lactation, hepatic IGF-1 production and plasma concentrations are reduced despite elevated plasma GH concentrations, due to loss of feedback control of GH by IGF-1 and GH resistance in association with NEB (Ronge et al., 1988). Together with low insulin secretion, plasma levels and sensitivity, fat mobilization is enhanced and (re-)uptake of circulating nutrients, such as AA, by peripheral (nonmammary) tissues inhibited, whereas flow of substrates for milk synthesis to and uptake by the mammary gland is insulin-independent and thus enhanced (De Koster and Opsomer, 2013). Low insulin concentrations are therefore essential for lipomobilization. In terms of gluconeogenesis (see previous section), glucagon plays an important role in glucose supply. Furthermore, adipocytokines like adiponectin and leptin are also involved in nutrient uptake to peripheral tissues (De Koster et al., 2017). And with decreasing insulin sensitivity, decreased adiponectin and leptin concentrations further support direction of glucose toward the mammary gland.

In terms of regulation of metabolism and synthetic capacity of the mammary gland, thyroid hormones (i.e., thyroxine (T_4) and triiodothyronine (T_3)) are substantially involved. Although their concentrations are reduced after parturition in dairy cows (Blum et al., 1983), especially concentrations of T_3 were shown to be associated with metabolic rate (Blum et al., 1980), NEB in dairy cows (Reist et al., 2002), and stimulatory effects on milk production (Blum et al., 1983). T_3 levels are primarily the result of the reduced extrathyroidal, mainly hepatic, conversion of T_4 to T_3 by the enzyme 5'-deiodinase. Interestingly, the

conversion of T_4 to T_3 in the mammary gland (in contrast to the extramammary/hepatic) is enhanced despite catabolic stages in dairy cows (Capuco et al., 2001). Because the metabolic activity of cells and organs is generally greatly influenced by T_3 , this mechanism is thought to allow the high metabolic activity of mammary gland despite NEB. Among other effects, prolactin and GH exert galactopoietic effects through the stimulation of 5'-deiodinase activity during NEB (Capuco et al., 2001). During established lactation, however, the galactopoietic effects of prolactin seem to be of minor importance.

Competition between gluconeogenesis and lipid metabolism

Especially in early lactation and in association with NEB, NEFA are released from adipose tissues and are primarily metabolized in the liver in the presence of the citric acid component oxaloacetate after being activated by binding to acetyl-coenzyme A (acetyl-CoA). However, gluconeogenesis relies on oxaloacetate as well. Cows in early lactation therefore face a problem if oxaloacetate, used in connection with gluconeogenesis as well as NEFA oxidation, is depleted because of overconsumption. Because amounts other components of the citric acid cycle are also in part decreased, its function is additionally disturbed. Therefore, oxaloacetate can be considered as a primary limiting substrate in early lactation, especially in high-yielding dairy cows.

Fatty acids that are not completely oxidized are re-esterified to TAG, bound to apolipoprotein, and released into the bloodstream as very low density lipoprotein (VLDL). However, the ability of the liver to export triglycerides is limited. Concomitantly, cholesterol concentrations are decreased in early lactation likely despite an upregulation of hepatic cholesterol biosynthesis (Kessler et al., 2014). Consequently, TAG accumulate in hepatocytes, possibly resulting in fatty liver disease (steatosis). A further metabolic pathway to relieve the TCA cycle is the formation of ketone bodies (acetone, acetoacetate, and BHB) in the presence of abundant NEFA. Because ketone bodies are energy-yielding substances, their loss through milk and urine (especially BHB) and exhalation (acetone) exaggerates NEB.

Consequences of metabolic load for performance, reproduction, and animal health

The detrimental effects of ketone bodies are due to their depressing effects on milk yield, feed intake, fertility, and impairment of immune function (McArt et al., 2012; Zarrin et al., 2017). In part, these effects are in part due to critical metabolic acidosis during massive accumulation of these two acids. Thus, an excessive lipolysis and ketogenesis in early lactation, combined with reduced immune competence and hence elevated infection rates, health disorders are further enhanced (Trevisi et al., 2012). However, ketone bodies serve also as a valuable energy source for certain tissues (e.g., skeletal muscle, heart, and brain). As a consequence, loss of ketone bodies through milk and urine (especially BHB) and exhalation (acetone) exaggerates

NEB. The preferential use of BHB instead of glucose by the immune system indicates the ability of dairy cows to spare glucose (Gross et al., 2018). On the other hand, increased BHB concentrations depress gluconeogenesis and further reduced plasma glucose concentrations (Zarrin et al., 2017). Today, the majority of higher yielding dairy cows experiences hyperketonemia in early lactation (McArt et al., 2012). Plasma BHB concentrations above 1.2 to 1.4 mmol/L indicate subclinical ketosis (McArt et al., 2012). Moreover, the risk of developing metabolic and infectious health disorders increases several-fold when ketone bodies are elevated (McArt et al., 2012).

Production Limits in Dairy Cows

Limitations imposed by diet and digestion

Typically for the digestive system of dairy cows is the rumen fermentation of plant fiber by microbes. Depending on dietary composition, decreased passage rate through the rumen and the overall gastrointestinal tract can limit DMI (Figure 3). From a nutritive perspective, roughages used in dairy cow diets provide much fiber, but low amounts of energy. Therefore, exclusive herbage feeding supports milk production only up to 30 kg/d (Kolver, 2003). Beyond this production level, more mobilization of body fat stores and feeding of supplementary concentrates are required to cover the energy needs. Therefore, maximizing of DMI is of central importance for achieving high milk yields. Because, maintenance of rumen activity requires a minimum amount of dietary fiber content, feeding excessive amounts of starch-based concentrates is problematic because this may result in (subclinical) rumen acidosis (SARA) due to retarded rumination activity and insufficient production of salivary buffers (Neubauer et al., 2020). The possibility to feed (non-rumen-protected) fat, too, is restricted to approximately 5 to 6% in the diet to avoid depression of fiber degradation. Therefore, compensating the NEB in early lactation by the

addition of more energy dense concentrates is limited by rumen physiology. Only in rumen-protected form, various sources of protein, fat, and starch are indispensable for the formulation of balanced diets to support high milk production. However, we can assume that post-ruminal digestive and absorptive capacity are limited at some point as well.

Limitations imposed by tissue turnover, intermediary metabolism, and the mammary gland

The amount of energy and nutrients stored in body tissues seems not to be a limiting factor for milk production per se. It is rather the turnover that temporarily reaches physiological boundaries. As an example, skeletal stores of calcium in a cow are in the order of several kilograms, whereas the circulating calcium pool in plasma consists of only a few grams (Goff, 2014). With the start of lactation, calcium requirements abruptly increase. The delayed endocrine effects (especially parathyroid hormone, vitamin D) to sufficiently mobilize calcium may result in hypocalcemia that is associated with reduced peak milk yield, DMI, and an increased risk for the development of further production diseases like displaced abomasum, enhanced lipolysis, ketosis, and mastitis (Reinhardt et al., 2011).

Over-conditioning of cows during the dry period is problematic because it is associated with reduced DMI and substantially increased rate of lipolysis compared with lean cows (Schuh et al., 2019). This further aggravates metabolic load in obese cows with an increased likelihood to develop ketosis and fatty liver.

In high-yielding dairy cows, NEFA are excessively released from body fat, leading to thin cows and low body condition scores after parturition (Figure 5). However, the capacity of the liver to completely oxidize NEFA during the early lactation period is limited. To be more specific, availability of carnitine, capacity of the carnitine shuttle system, and capacity for



Figure 5. Body reserves are essential to support lactation. However, excessive mobilization of body fat may cause a massive body weight loss and a skinny appearance, expressing a poor body condition. This situation is often associated with health disorders like ketosis and fatty liver.

β -oxidation of fatty acids are restricting factors. In the liver, carnitine is required for the transfer of fatty acids across the inner mitochondrial membrane for subsequent beta-oxidation. Moreover, TCA cycle activity depends on oxaloacetate that is simultaneously obliged for gluconeogenesis.

Due to limited glucose availability, gluconeogenesis is of major importance in dairy cows. Despite upregulation of gluconeogenesis rate between late pregnancy and early lactation, glucose concentrations are at reduced concentrations, when demand for milk production and immune system are greatest (Hötger et al., 2013).

Cardiac output and mammary blood flow are associated with supply to, and substrate turnover of the mammary gland synthesis rate (Davis and Collier, 1985). Substrate availability and entry rate of nutrients into mammary epithelial cells besides regulation of transporters depending on the physiological status of the cow can be limiting for milk production (Davis and Collier, 1985). As described above, for example, the metabolic priority of the lactating mammary gland is closely related to the expression pattern of insulin-independent and insulin-dependent GLUTs in an attempt to maintain milk production irrespective of the systemic glucose shortage. Of course, number and activity of mammary gland alveolar cells determine capacity for milk production (Akers, 2017). Persistence of lactation and maintenance of milk production closely interact with the galactopoietic response to thyroid hormones and GH (Capuco et al., 2001).

Limitations imposed by genetics, epigenetics, management, and environment

It is not still possible to define the maximum capacity for milk production in dairy cows. The genetic potential is certainly higher than the performance level currently observed in practice. The reasons for this discrepancy are manifold and involve inadequate feeding, housing, environment, and management. Dairy breeds intensively selected for milk yield (e.g., Holstein Friesian) tend to produce more milk than other breeds within the same environment.

Moreover, a considerable variation of physiological adaptation under conditions of identical feeding and management exists among animals. Although there is no negative relationship between high animal performance, disease occurrence, and culling (Fleischer et al., 2001; Ingvarsten et al., 2003), a greater milk production implies a greater metabolic load particularly in early lactation. Consequently, risk and susceptibility for different production diseases are increased.

From environmental perspectives, heat stress must be considered a major threat imposing limits to milk production as it decreases milk yield, DMI, animal health, and reproductive performance and is associated with marked metabolic and endocrine changes (Wheelock et al., 2010). Besides cooling devices or adjusted feeding (e.g., by increasing dietary energy content via supplementary fat) to alleviate thermal stress, cattle breeds with a greater heat tolerance, such as Jersey's or by breeding dairy cows with *Bos indicus* genetics, will expectedly gain in importance in the future.

Singh et al. (2010) investigated epigenetic regulation of milk production and addressed the importance of early fetal and metabolic programming on later production outcome. Even after birth, rearing intensity of calves until weaning and feeding of heifers during puberty affects their future milk production (Soberon et al., 2012; Korst et al., 2017). For example, even when lactation is established, the dry period length can affect health and milk yield in the subsequent lactation (van Kneegsel et al., 2013). Shortening or even omitting the dry-period does not only allow to benefit from milking of still high producing cows before parturition, but also decreases metabolic stress after parturition in previously overconditioned individuals. Likewise, extension of the lactation period is a strategy to optimally use genetic capacity when combined with delayed insemination.

Conclusions

Average milk production in dairy cows will most likely continue to increase. Currently known limitations originate from the physiology and effects of adverse environmental factors restrict maximal exploitation of genetic capacity. In particular a sufficient provision especially of glucose and amino acids are the major limiting factors for milk production. Concomitantly with the high demands for milk precursors of the lactating mammary gland, the immune system competes for energy and nutrients. Rumen physiology and intermediary metabolism in many individual cows are close to or above their functional limits, resulting in increased health disorders. However, a great number of high-yielding dairy cows is able to manage lactational challenges and remain healthy. Further selection targets will need to address fitness traits in changing environmental conditions. Dairy farmers are advised to implement preventive strategies in their dry cow management (e.g., hypocalcemia prophylaxis, avoidance of overconditioning), avoid heat stress, and to maximize feed intake in early lactating cows. Research needs to address issues of efficiency traits of digestion, intermediary metabolism, and nutrient utilization by the mammary gland under different environmental conditions in future.

Conflict of interest statement. None declared.

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