The purpose of this article is to review body condition scoring and the role of body fat reserves in relation to insulin sensitivity and metabolic phenotyping. This article summarizes body condition scoring assessment methods and the differences between subcutaneous and visceral fat depots in dairy cows. The mass of subcutaneous and visceral adipose tissue (AT) changes significantly during the transition period; however, metabolism and intensity of lipolysis differ between subcutaneous and visceral AT depots of dairy cows. The majority of studies on AT have focused on subcutaneous AT, and few have explored visceral AT using noninvasive methods. In this systematic review, we summarize the relationship between body fat reserves and insulin sensitivity and integrate omics research (e.g., metabolomics, proteomics, lipidomics) for metabolic phenotyping of cows, particularly overconditioned cows. Several studies have shown that AT insulin resistance develops during the prepartum period, especially in overconditioned cows. Nonoptimal body conditions (under- or overconditioned cows) exhibit marked abnormalities in metabolic and endocrine function. Overall, reducing the number of cows with nonoptimal body conditions in herds seems to be the most practical solution to improve profitability, and dairy farmers should adjust their management practices accordingly.

Key words: body fat depots, metabolic status, omics, review

The BCS system is a noninvasive, rapid, and inexpensive estimate of energy reserves in dairy cows (Edmonson et al., 1989). However, the subjective nature of visual scoring may result in the same cow receiving different BCS scores, and it may also be influenced by previously scored cows. Differences in how the BCS is assessed (i.e., visually and through tactile contact or visually only), as well as the level of training and experience of the evaluator, contribute to underlying variations in the BCS in the visual assessment of body condition (Berry and Kelleher, 2021). According to Kristensen et al. (2006), the quality of visual BCS depends on the experience of the evaluator, with a trained observer achieving 58% to 67% accuracy and an untrained observer achieving 27% accuracy (Ferguson et al., 1994). This can lead to inaccuracies, especially if the barn is crowded.

Measurement of adipose tissue (AT) and muscle thickness can be performed using either ultrasound (Scholz et al., 2015; Wagner et al., 2019). The sacral region is the most appropriate site to assess backfat thickness (BFT) in dairy cows because the region contains the largest amount of AT in the back and there is a high correlation ($r = 0.9$) between body fat content and BFT (Klawuhn, 1992; Staufenbiel, 1992). For consecutive ultrasonic measurements of BFT, the overall accuracy ranged from 1 to 2 mm, and the deviations increased with increasing BFT (Brethour, 1992; Robinson et al., 1992; Schröder and Staufenbiel, 2006). This greater error can be explained by variations in body posture, subjectivity in measurement site selection, and variations in respiration in overconditioned cows (Brethour, 1992). Despite the high accuracy of ultrasonography in evaluating the body reserves of cows (Schröder and Staufenbiel, 2006), the procedure is still labor intensive, and cows must be restrained individually to obtain ultrasound images, making it difficult to use this technique for extended periods. In addition, the training and time required for accurate and repeatable body fat assessment with ultrasound were significantly
higher than for visual and tactile body condition assessment (Mizrah et al., 1999).

With advances in machine vision technology, both a single 3-dimensional (3D) camera and multiple 3D cameras have recently been introduced to assess the BCS from multiple angles (Zin et al., 2020). There are different commercialized automatic BCS systems based on 3D image processing, which include DeLaval BCS (DeLaval International AB), Protrack BCS (LIC Automation), BodyMat F (Ingenera SA), and Biondi 4DRT-A (Biondi Engineering SA; Silva et al., 2021). Although 2-dimensional and 3D cameras can be used to monitor BCS more frequently, the use of automated cameras is still limited by factors such as reduced accuracy under inconsistent lighting conditions. The realistic BCS estimation system should adapt to the farm environment and run stably over a long period. There is a need to improve automated BCS technology to increase the efficiency and accuracy of herd-level BCS assessments while minimizing costs.

**ASSOCIATIONS OF SUBCUTANEOUS AND VISCERAL FAT WITH BCS**

Adipose tissue is distributed throughout the body (Bjørndal et al., 2011). In cattle, the subcutaneous fat depot lies underneath the skin, with larger depots located around the tailhead (Clark, 2014). Intermuscular fat has been demonstrated to contribute most to the changing of body fat content (Butler-Hogg et al., 1985), but this depot was not addressed in later studies due to the difficulty in assessing it quantitatively (Butler-Hogg et al., 1985). The visceral fat depot consists of retroperitoneal, mesenteric, and omental fat, and the intrapelvic fat depot is all the fat in the pelvic cavity (Clark, 2014; De Koster et al., 2017). The thoracic fat depot consists of the AT located on the inside of the ribs, in the mediastinum, and around the heart (De Koster et al., 2017). There are differences in adipocyte size (Akter et al., 2011) and metabolic activity (Locher et al., 2011; Saremi et al., 2014) between different fat depots in the body. In the subcutaneous and retroperitoneal AT, adipocyte cell areas vary from 4,521 to 8,000 µm², with large cells being predominant in the retroperitoneal AT (Akter et al., 2011; Kenéz et al., 2015). During the early lactation period, adipocyte size decreases, while adipocyte numbers remain stable (Smith and McNamara, 1990). The intensity of lipolysis in postpartum (p.p.) cows is influenced by the size of adipocytes, and when lipolysis is induced, the larger adipocytes release more glycerol and fatty acids (FA) than the smaller adipocytes (De Koster et al., 2016; Contreras et al., 2017). According to Kenéz et al. (2015), retroperitoneal AT undergoes more time-related changes in cell size, DNA, and protein content, indicating greater metabolic flexibility compared with subcutaneous AT. In line with this notion is the finding that the mass of the retroperitoneal fat depot is also more readily decreased than subcutaneous fat and other visceral depots during the first 42 d of lactation, as demonstrated in primiparous heifers (Akter et al., 2011; von Soosten et al., 2011). Molecular studies at both the mRNA and the protein levels have shown differences in metabolism and immune response between subcutaneous and visceral AT depots of dairy cows (Ji et al., 2014; Contreras et al., 2015; Kenéz et al., 2019).

Subcutaneous and visceral AT mass change significantly but disproportionately during the transition period (Gibb et al., 1992; von Soosten et al., 2011; Szura et al., 2020; Knob et al., 2021). For overcoming the limitations of post mortem assessments of the visceral fat share, Raschka et al. (2016) developed an ultrasonographic technique to estimate the mass of subcutaneous, retroperitoneal, omental, mesenteric, and total AT in vivo in German Holstein dairy cows and validated it by post mortem assessments. Using this ultrasonographic technique, Ruda et al. (2019) showed that the estimated abdominal depot mass was about 2.5 times greater than that of the subcutaneous depot, and was also mobilized faster p.p. than the subcutaneous fat. Further studies with this ultrasonographic method are needed. Estimating the depot mass of the subcutaneous and visceral AT depots of 31 pluriparous Holstein cows by ultrasound revealed fat gain (subcutaneous AT) during the dry period (from d −42 to 7 relative to calving) when energy balance was positive, and fat mobilization during the fresh cow period (d 7 to 28) and early lactation period (d 28 to 70 relative to calving) when energy balance was negative (Szura et al., 2020). In their study, the mobilized visceral AT mass in the overconditioned cows compared with the underconditioned cows originated mainly from retroperitoneal and omental AT, because mesenteric AT revealed no differences between the treatment (Szura et al., 2020).

Drackley et al. (2014) showed that overfeeding for 8 wk to nonpregnant, nonlactating cows increased AT mass in nonlactating dairy cows, with omental, mesenteric, and perirenal fat masses about twice as high; however, BCS at the end of the feeding period was not affected. Thus, cows with excessive energy intake may have accumulated more AT in visceral depots, but this was not reflected in higher BCS. There can be a nearly 2-fold difference in visceral AT weight between cows with the same subcutaneous mass and BCS (Drackley et al., 2014). This is reflected in the wide range of the ratio of subcutaneous to total abdominal fat mass (from 0.38 to 0.83) during early lactation (≤100 DIM, n = 6; Raschka et al., 2016) and from 0.23 to 0.31 in late
gestation (10 to 13 d before calving, n = 10; De Koster et al., 2015). If cattle with the same BCS have different internal AT depots, the effects on production may be different because visceral AT is more readily mobilized than subcutaneous AT (Ruda et al., 2019).

**RELATIONSHIP OF INSULIN SENSITIVITY AND METABOLIC PHENOTYPING WITH BCS**

**Insulin Sensitivity**

The transition from pregnancy to lactation and establishing high milk production is challenging and has the potential to compromise immune function and increase the risk of metabolic and reproductive disorders in dairy cows (Thatcher, 2017). The regulation and coordination of energy intake and postabsorptive nutrient partitioning, particularly glucose and lipid metabolism, are key elements of the homeorhetic adaptation to lactation in periparturient dairy cows (Roche et al., 2009). Insulin is the most potent anabolic hormone and plays a key role in the partitioning of nutrients in periparturient dairy cows, whereby insulin secretion, the circulating insulin levels, insulin responsiveness, and insulin sensitivity of peripheral tissues are the main determinants (Drackley et al., 2001; De Koster and Opsomer, 2013). As part of the homeorhetic adaptation, decreased insulin secretion and insulin sensitivity in insulin-dependent peripheral tissues support the transfer of glucose to the tissues that need it most—that is, as the growing fetus, fetal membranes, and the mammary gland just before and during early lactation (Bell, 1995; Drackley et al., 2001; De Koster and Opsomer, 2013). Insulin signaling and metabolic status differ between dry and lactating cows. The main contribution to glucose uptake in periparturient cows occurs independently of insulin due to massive glucose withdrawal by the gravid uterus and later by the lactating mammary gland (De Koster and Opsomer, 2013). Also, hepatic gluconeogenesis is increased during late gestation and early lactation to meet the demands of the gravid uterus or lactating mammary gland (Bell and Bauman, 1997). As a result of the higher glucose uptake by the mammary gland compared with the gravid uterus, lactating cows have a higher glucose uptake than dry cows. Therefore, when comparing insulin sensitivity between dry and lactating cows or lactating cows with different milk yields, it is important to consider the differences in basal (non-insulin-stimulated) glucose disappearance, otherwise lactating cows may have an overestimated insulin sensitivity (for detailed information, see De Koster and Opsomer, 2013).

Insulin resistance can manifest itself as a decrease in insulin sensitivity (the insulin concentration that elicits a half-maximal response), a decrease in insulin responsiveness (the maximal effect of insulin on insulin-sensitive tissues), or as both simultaneously (Kahn, 1978). Over the past decade, several studies have been conducted in periparturient dairy cows using the hyperinsulinemic-euglycemic clamp (HEC) as the gold standard and the intravenous glucose tolerance test (IVGTT) to assess insulin sensitivity (Bossaert et al., 2008; Schoenberg et al., 2012; De Koster et al., 2016; Mann et al., 2016; Weber et al., 2016; Bogaert et al., 2018; Jaakson et al., 2018; Saed Samii et al., 2019; Karis et al., 2020). Nevertheless, it has been proposed that the IVGTT for assessing peripheral insulin sensitivity in dairy cows may be biased by the massive glucose uptake of the lactating mammary gland caused by its insulin-independent glucose consumption (Bossaert et al., 2008). Insulin resistance can be assessed by evaluating insulin responsiveness or insulin sensitivity at the receptor and postreceptor levels (Hayirli, 2006). The binding of insulin to the insulin receptor (INSR) on the cell membrane of insulin-sensitive tissues triggers a cascade of events and coordinates anabolic responses to nutrients (Saltiel and Kahn, 2001).

At the postreceptor level, insulin signaling is mainly influenced by adaptive mechanisms that activate PI3K (phosphatidylinositol 3-kinase), which in turn activate mTOR (mammalian target of rapamycin), PKC-zeta (protein kinase C zeta), and Akt (protein kinase B) through phosphorylation (Sasaki, 2002). When the cellular energy is adequate, PKC-zeta stimulates lipogenesis by activating FAS (fatty acid synthase). Also, Akt phosphorylation promotes the translocation of insulin-dependent GLUT4 (glucose transporter 4) into the cell membrane and thus stimulates glucose uptake (Sasaki, 2002). In addition, Akt activates PDE3B (phosphodiesterase 3B), which inhibits lipolysis by decreasing phosphorylation of HSL (hormone-sensitive lipase) (Sasaki, 2002). When cellular energy is depleted (by an increased AMP/ATP or ADP/ATP ratio, or both), phosphorylated AMPK (AMP-activated protein kinase) inhibits FAS and promotes FA oxidation by phosphorylating acetyl-CoA carboxylase (Galic et al., 2018; Ke et al., 2018).

Several studies have been conducted to uncover the complex interplay between AT metabolism, BCS status, nutritional level, and other physiological changes in insulin signaling during the periparturient period. McCann and Reimers (1985) provided the first evidence for this: using the intravenous insulin tolerance test, they demonstrated that blood glucose is less reduced in obese heifers than in lean heifers despite similar maximal responses to insulin. Holtenius et al. (2003) reported that the glucose clearance rate in overconditioned (BCS = 4.2) cows was about 20% lower than in optimal (BCS = 3.6) and underconditioned (BCS = 4.2) cows. However, data from this study included only 10 overweight cows, which may have limited the clinical relevance and biological significance of their results.
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2.6) cows after the glucose tolerance test performed 3 wk p.p. However, these results are not directly related to body condition, as Holtenius et al. (2003) obtained different BCS values by feeding different dietary energy contents, which could influence glucose kinetics (Schoenberg et al., 2012). Using the HEC test, De Koster et al. (2015) found that fat accumulation during pregnancy can negatively affect insulin action at the level of glucose metabolism, characterized by both decreased insulin sensitivity and decreased insulin responsiveness. Nevertheless, there is controversy about the effects of prepartum body condition on glucose and insulin tolerance in dairy cows as assessed by the HEC test (Weber et al., 2016) and intravenous insulin and glucose tolerance tests (Saed Samii et al., 2019). According to Weber et al. (2016), the HEC test showed little difference in insulin action depending on the metabolic type (i.e., cows with high or low total liver fat content or cows with high or low fat mobilization around calving); however, the reduction in glucose-dependent insulin release is the most important finding explaining impaired insulin function after calving. Saed-Samii et al. (2019) found that overconditioning during late gestation was not associated with changes in glucose or insulin tolerance, although overconditioned (BCS ≥ 4) cows displayed increased plasma FA and BHBA concentrations and elevated liver lipid content during the ante partum (a.p.) period. A common finding of IVGTT studies is little or no difference in glucose area under the curve but a substantial increase in insulin area under the curve in overconditioned cows compared with optimally conditioned cows (Bogaert et al., 2018; Jaakson et al., 2018), supporting the insulin resistance hypothesis. High insulin area under the curve is considered an indication of increased insulin secretion by the pancreas in response to peripheral insulin resistance (Bogaert et al., 2018).

Increased peripheral insulin resistance and refractory glucose metabolism have been attributed to pancreatic lipid infiltration and islet hyperplasia (Bogaert et al., 2018). Recent studies (Jaakson et al., 2018; Karis et al., 2020) have shown that AT insulin resistance, especially in overconditioned cows, develops prepartum. According to Karis et al. (2020), overconditioned cows (BCS ≥ 3.75) had the highest peak glucose and insulin secretion after glucose infusion and higher FA concentrations during the IVGTT compared with underconditioned cows (BCS ≤ 3.0), all suggesting that high adiposity in the a.p. period reduces the response of fat metabolism to insulin in insulin-sensitive tissues (Karis et al., 2020). They also found that overconditioned cows had a longer latency of FA during the IVGTT and the highest level of FA from d 21 to 7 a.p., possibly due to slower elimination and re-esterification of fats in the subcutaneous AT during the IVGTT, reducing lipogenesis compared with underconditioned cows.

At the tissue level, AT is one of the most important target tissues for the action of insulin, and the metabolic diseases associated with obesity are characterized by excessive AT insulin resistance (Zhang et al., 2021). Early studies examining changes in INSR numbers and binding affinity were conducted mainly in ewes and did not provide conclusive results (Vernon et al., 1981; Vernon and Taylor, 1988; Guesnet et al., 1991). In dairy cows, Sadri et al. (2010) showed that mRNA expression of INSR remained unchanged in the subcutaneous AT from 8 wk a.p. to 5 wk p.p. Recently, Zhang et al. (2019) found that INSR mRNA and protein abundance were lower in overconditioned cows (BCS > 4) than in optimally conditioned cows (BCS = 3.0 to 3.5) in the subcutaneous AT p.p., suggesting that the insulin response to glucose may be reduced in transition dairy cows. In addition, Liang et al. (2020) reported lower INSR mRNA abundance at d 7 p.p in overconditioned cows (BCS ≥ 3.5) compared with optimally conditioned cows (BCS ≤ 3.17). Zachut et al. (2013) reported that INSR phosphorylation and Akt activation in AT correlate with plasma insulin concentration. The authors concluded that cows with increased BCS loss and milk production suffered from AT-specific insulin resistance. According to Ji et al. (2012), close-up energy overfeeding did not affect mRNA expression of INSR or insulin-stimulated insulin receptor substrate 1 tyrosine phosphorylation (IRS1-PY), but expression of adipogenic and basal lipolysis regulators remained elevated in overfed cows until 7 d p.p. Liang et al. (2020) concluded that overconditioning (BCS ≥ 3.5) during the late a.p. period results in less AKT activation (ratio of phosphorylated AKT to total AKT) at d 7 p.p. and greater lipolysis after parturition; however, the AT of the overconditioned cows could activate compensatory mechanisms leading to the triggering of mTOR signaling. Several adipokines (such as adiponectin, chemerin, fibroblast growth factor 21, pigment epithelium-derived factor, retinol-binding protein 4, resistin, and visfatin) are produced and secreted by AT to control metabolic homeostasis, fat distribution, insulin sensitivity, and secretion (Rosen and Spiegelman, 2006; Coelho et al., 2013). For a detailed overview of the physiological and molecular processes and mediators of lipolysis and lipogenesis, as well as the differences in the production of cytokines and adipokines in the different AT depots, the reader is referred to the existing reviews on this topic (Häussler et al., 2022; Mann, 2022; Zachut and Contreras, 2022).

Ceramide is a potential antagonist of insulin-stimulated glucose utilization by AT and skeletal muscle tissue in dairy cows (McFadden and Rico, 2019). Rico et
Leung et al. (2020) evaluated plasma concentrations of ceramides in periparturient dairy cows as potential biomarkers of insulin resistance and found that certain ceramides (e.g., C24:0 ceramide) were positively correlated with FA concentrations and inversely correlated with insulin sensitivity. They also found that plasma concentrations of C18:0-, C18:1-, C20:0-, C22:0-, C22:1-, and C24:1-ceramide were significantly higher in overconditioned cows (BCS > 4.0 at d −30 a.p.) compared with underconditioned cows (BCS < 3.0 at d −30 a.p.) during the a.p. period (Rico et al., 2015). Ceramides and extracellular lipoproteins may also impair insulin sensitivity by inhibiting Akt-dependent mechanisms to reduce glucose uptake by AT and skeletal muscle in dairy cows (McFadden and Rico, 2019). Leung et al. (2020) characterized the sphingolipid profiles of 2 different fat depots (retroperitoneal and subcutaneous) in Holstein bulls and found that different sphingolipid profiles were present in the fat depots. According to Leung et al. (2020), some sphingolipid species such as dihydroceramide and ceramides were more concentrated in the retroperitoneal AT, whereas sphingolipid species such as dihydrosphingomyelin, sphingosine, sphingomyelin, and glycosphingolipids were more concentrated in the subcutaneous fat depot, suggesting that the activity of sphingolipid metabolic pathways, such as de novo synthesis of ceramide, was different in the retroperitoneal and the subcutaneous fat depot. According to these findings, the tissue-specific insulin sensitivity of fat depots could be explained by the distribution of sphingolipids in the retroperitoneal and subcutaneous fat depots (Leung et al., 2020). However, there is uncertainty about the mechanisms underlying ceramide-induced insulin resistance in dairy cows (McFadden and Rico, 2019).

**Metabolic Phenotyping**

*Metabolic phenotyping* refers to the process of examining biological fluids and tissue extracts at a comprehensive level (Nicholson et al., 2012). Technological advances in omics applications (i.e., transcriptomics, proteomics, metabolomics) have led to significant advances in metabolic phenotyping. To date, transcriptome analyses have been used in several studies to investigate the effects of BCS around calving in AT (Weber et al., 2013), liver (Akbar et al., 2015; Ghaffari et al., 2021), and circulating neutrophils (Vailati-Riboni et al., 2016; Crookenden et al., 2017). In addition to transcriptomics, proteomic profiling is a powerful tool for understanding the underlying pathophysiological processes in transition period-related diseases (Cho, 2007; Ceciliani et al., 2018). As part of extensive physiological experiments, proteomic analysis has been used in several studies in dairy cattle research over the past 5 years to obtain detailed information on the proteomic profile of various tissues (Zachut et al., 2017a,b, 2018; Takiya et al., 2019; Ghaffari et al., 2020b). The term proteomics refers to the large-scale characterization of all proteins in a cell line, tissue, or organism (Graves and Haystead, 2002) and is divided into expression, functional, or structural proteomics depending on the research application (Masood et al., 2018). At the metabolite level, a metabolomics approach is increasingly being used to identify the pathophysiology of adaptive responses to metabolic challenges during the transition period by examining metabolic profiles of blood, milk, and various tissues (Ceciliani et al., 2018). Metabolomics methods fall into 2 categories: untargeted metabolomics, which aims to measure all analytes in a sample, including unknown chemicals, and targeted metabolomics, which measures chemically characterized and biochemically annotated metabolites (Roberts et al., 2012), including several important metabolite classes (i.e., AA, biogenic amines, and acylcarnitines, phosphatidylcholine, and related lipids). To date, metabolomics analyses have examined the influence of differences in BCS or AT lipolysis on metabolic profiles in the blood (Humer et al., 2016; Ghaffari et al., 2019a,b,c; Wang et al., 2020), steroid profiles in blood, AT (Schuh et al., 2022), metabolic profiles in skeletal muscle (Sadri et al., 2020), and plasma ceramides (Rico et al., 2015) in dairy cows. In this systematic review, we aim to summarize and integrate recent omics research on metabolic phenotyping of cows, especially overconditioned cows.

In dairy cows, circulating FA levels increase immediately after calving, especially in overweight cows (Rico et al., 2015), and lipidomic analyses have identified changes in lipid metabolism after calving (Hailemariam et al., 2014; Imhasly et al., 2014; Rico et al., 2017). The ability to oxidize FA might be impaired in dairy cows during early lactation. Metabolic pathway enrichment analysis in a serum metabolomics study by Ghaffari et al. (2019a) showed that mitochondrial β-oxidation of long-chain FA along with FA metabolism were significantly enriched in overconditioned cows as compared with optimally conditioned cows during early lactation. In the liver, FA are predominantly oxidized to CO2 or incompletely converted to ketone bodies (i.e., BHB) and re-esterified to triacylglycerols (Andersen et al., 2002). When the lipid uptake by the liver exceeds its oxidative capacity and its ability to export lipids in the form of very-low-density lipoproteins, increased ketone bodies are formed in the liver (Boe et al., 2004). Accordingly, in a study using electrospray ionization liquid chromatography MS/MS-based metabolomics, higher levels of acetyl carnitine and long-chain acylcarnitines were found in high-mobilizing cows compared with...
low-mobilizing cows (Humer et al., 2016). In addition, Rico et al. (2018) found that overconditioned cows had higher plasma levels of C14:0-, C16:0-, C18:0-, and C20:0-carnitine than underconditioned cows. A decrease in carnitine palmitoyltransferase activity or depletion of intermediates of the tricarboxylic acid cycle can lead to an increase in long-chain acylcarnitines (Flanagan et al., 2010; Schooneman et al., 2013; Violante et al., 2013). Therefore, the profile of circulating acylcarnitines reflects the oxidation rate of FA and AA in different tissues, mainly in skeletal muscle and liver (Xu et al., 2011; Schooneman et al., 2013; Makrecka-Kuka et al., 2017). Further metabolomics studies have shown higher levels of acetylcarnitine and some long-chain acylcarnitines in the muscle and serum of overconditioned as compared with optimally conditioned cows during early lactation (Ghaffari et al., 2019a, 2020c; Sadri et al., 2020), indicating increased FA β-oxidation in mitochondria relative to tricarboxylic acid cycle flux (Ghaffari et al., 2020b, 2021). In a recent transcriptional study using microfluidic quantitative PCR, Ghaffari et al. (2021) investigated the effect of a.p. body condition on the hepatic mRNA expression of genes involved in FA metabolism and mitochondrial protein import system of dairy cows during the transition period. They found a greater mRNA abundance of genes related to hepatic mitochondrial FA oxidation and ketogenesis in the livers of overconditioned cows than in those of optimally conditioned cows on d 21 p.p., suggesting that impairment of the rate of β-oxidation and spillover of acylcarnitines into the circulation was induced by the overconditioning in early lactation (Ghaffari et al., 2021).

Phospholipids are key components of cell membranes and important substrates for enzymes such as phospholipase A (Arifin and Falasca, 2016). Multiple biological functions of lysophosphatidylcholines have been linked to cellular signaling processes, apoptosis induction, and inflammation (Wepy et al., 2019; Liu et al., 2020). In dairy cows, phospholipid-sphingomyelin metabolism-related signatures were associated with fat mobilization (Humer et al., 2016; Ghaffari et al., 2019a; Wang et al., 2020). According to the untargeted metabolomics study conducted by Wang et al. (2020), a total of 23 differential metabolites in plasma were affected by BCS shortly after calving, including 6 lysophosphatidylcholines and 1 phosphatidylethanolamine, which were lower in the overconditioned cows (BCS ≥ 4) than in the optimally conditioned cows (3.25 ≤ BCS ≤ 3.5). Using serum metabolomics, Humer et al. (2016) found that cows with excessive lipid mobilization (FA serum concentrations >0.7 mmol/L) had higher serum levels of various phosphatidylcholines with diacyl residues (ranging from 28 to 36 carbons) as well as long-chain sphingomyelins, but lower levels of phosphatidylcholines with longer chains (C40:3, C42:5, C42:6) compared with low-lipolysis (FA concentrations <0.4 mmol/L) cows. In another study, the serum concentrations of FA and BHB were negatively correlated with several long-chain phosphatidylcholine species in dairy cows (Ghaffari et al., 2019a). Glycerophospholipids (lyso-, diacyl-, and acyl-alkyl) are synthesized primarily in the liver via the cytidine diphosphate-choline pathway or by sequential methylation of phosphatidylethanolamine and released into the bloodstream as part of blood lipoproteins (Cole et al., 2011, 2012). As lipids, choline-containing phospholipids (mainly phosphatidylcholines) are essential for very-low-density lipoprotein synthesis in the liver and contribute to triglyceride export by the liver (Cole et al., 2012). It may be feasible to use abnormal decreases in specific phosphatidylcholines and sphingomyelin levels in dairy cows as a biomarker of hepatic lipidosis (Imhasly et al., 2014, 2015). Thus, the findings suggest that the mismatch between acetyl-CoA generation and entry into the tricarboxylic acid cycle or mitochondrial FA overload, as well as changes in blood phosphatidylcholines, results in higher circulating levels of acylcarnitines with short and long chain lengths and lower circulating levels of phosphatidylcholines in overconditioned cows.

By profiling the metabolome of skeletal muscle (M. semitendinosus) using targeted metabolomics, it was found that the levels of phenylethylamine and linoleylcarnitine in muscle were lower in overconditioned cows than in optimally conditioned cows, indicating altered phosphatidylcholine metabolism (Sadri et al., 2020). Skeletal muscle, which is the largest contributor to whole-body protein turnover due to its large protein mass (Frayn, 2010), contributes significantly to the maintenance of metabolic homeostasis and adaptation to the physiological demands of pregnancy and lactation (Phillips et al., 2003; Kuhla et al., 2011; Ji and Dann, 2013). The small changes in phospholipid levels in skeletal muscle might have wide-ranging effects on various functions related to mitochondria, cell growth, inflammation, and insulin sensitivity (Sadri et al., 2020). Further research is needed to determine how changes in muscle phospholipid composition may affect the action of membrane proteins involved in insulin signaling and energy metabolism in cows with different BCS.
In plasma, a quantitative proteomics approach based on a tandem mass tag was used to investigate differences in the proteome of optimally and overconditioned cows selected for diverging blood parameters (FA and BHB) during the transition from late gestation to early lactation (Ghaffari et al., 2020b). As a result of plasma proteomic analysis, a total of 24 differentially abundant proteins (16 in optimally conditioned and 8 in overconditioned) during the transition period were identified. Based on gene ontology analyses of these proteins, regulation of the complement system and coagulation cascades were associated with overconditioning around calving (Ghaffari et al., 2020b). In this study, the complement components C1q, C5, and coagulation factor IX proteins were more abundant, but complement components C3 and C3d were less abundant in overconditioned cows compared with optimally conditioned cows (Ghaffari et al., 2020b). In a quantitative shotgun proteomic study (nano liquid chromatography MS/MS) of the subcutaneous AT of cows with high (8.5 ± 1.7%) or low (2.9 ± 2.5%) BW loss during the first-month p.p., it was also found that the complement response was one of the major signaling pathways enriched in AT of cows with high BW loss compared with cows with low BW loss (Zachut et al., 2018). In obesity, increased levels of FA and insulin can activate the complement system, resulting in increased levels of complement fragments C3a and C5a (Phieler et al., 2013). By binding C3a and C5a to their respective receptors, the complement components could increase triglyceride formation by inhibiting lipolysis, increasing glucose and FA uptake, and indirectly decreasing their release (Phieler et al., 2013). Further research is needed to investigate the complement system’s role in AT inflammation, especially in overconditioned cows.

**Metabotypes of Overconditioned Cows**

The term “metabotype” was first coined by Gavaghan et al. (2000) in a rodent study. The underlying idea behind metabotyping is to identify metabolic phenotypes based on factors such as diet, anthropometric measures, clinical parameters, metabolomics data, and gut microbiota (Palmnäs et al., 2020). For dairy cows, the concept was first applied by Huber et al. (2016) and Zandkarimi et al. (2018) in the context of involuntary culling and mastitis, respectively. More recently, metabotyping was applied to determine whether a particular dairy cow has a balanced or unbalanced metabolic profile based on blood metabolites (Ghaffari et al., 2020a), liver metabolites (Schären et al., 2021a,b), or milk biomarkers (De Koster et al., 2019; Xu et al., 2019; Foldager et al., 2020). About overconditioning in dairy cows, observations made in human medicine that led to the notion of a metabolically healthy but obese phenotype are of particular interest: as reviewed by Blüher (2020), there is a subgroup of obese patients not showing the typical obesity-related morbidities.

We tested the idea that a variation in metabolic profiles derived during the transition period would enable the identification of divergent metabolotypes within groups predefined by body condition (Ghaffari et al., 2020a). Our classification model using serum metabolomics data revealed different metabolotypes in overconditioned cows (classified by BCS and BFT), and a subset of overconditioned cows was classified as overconditioned whose metabolic profiles did not differ from those of optimally conditioned cows, defined as “metabolically balanced over-conditioned” (MB-OC) cows (Ghaffari et al., 2020a; Figure 1). Although both overconditioned groups exhibited increased lipolysis as determined by increased circulating levels of FA, the degree of ketogenesis as determined by increased BHB levels in the metabolically unbalanced overconditioned (MUB-OC) cows was significantly higher than in the MB-OC cows (Ghaffari et al., 2020a; Figure 1). Compared with MUB-OC cows, the MB-OC cows had higher feed and energy intake but the same milk yield (Figure 1), resulting in less negative energy balance. In addition, the MB-OC cows had lower concentrations of glycerophospholipids (a.p.) and short- (C2, C3, and C4), medium- (C12), and long-chain (C16:0, C18:0, and C18:1) acylcarnitines (p.p.) in serum but similar blood concentrations of FA, insulin, insulin-like growth factor-1, leptin, adiponectin, haptoglobin, and glucose compared with MUB-OC cows (Ghaffari et al., 2020a; Figure 1). In a companion study by Sadri et al. (2021), the potential differences in the oxidative capacity of skeletal muscle (M. semitendinosus) were assessed by targeted metabolomics. The skeletal muscle concentrations of short-chain (C2, C4-OH, and C6-OH) and long-chain (C16, C18, and C18:1) acylcarnitines were more than 2-fold higher in MUB-OC cows than in MB-OC cows at wk 3 p.p. (Figure 1). The lower BHB levels in serum and greater acylcarnitine concentrations in skeletal muscle and serum of MUB-OC cows than in those of MB-OC cows may indicate a greater oxidative capacity for FA and utilization of BHB as fuel (reflected by lower C4-OH) in the muscle of MB-OC cows than of MUB-OC cows. In a companion study by Sadri et al. (2021), it was found that the mRNA abundance of key factors known to regulate lipolysis and insulin sensitivity in the subcutaneous AT did not differ between MUB-OC and MB-OC cows after calving, suggesting that the lipolytic response and probably insulin sensitivity in the subcutaneous AT of these cows are equivalent (Figure 1).
Figure 1. Metabolically balanced and unbalanced subgroups were identified in dairy cows classified as overconditioned based on body condition score (BCS ≥ 3.75) and backfat thickness (BFT > 1.4 cm) at calving. Metabolic clustering was performed by applying supervised machine learning-based classifiers to changes in serum metabolome concentrations during the transition period (Ghaffari et al., 2020a). Metabolically balanced overconditioned cows (MB-OC) were distinguished from metabolically unbalanced overconditioned cows (MUB-OC). Symbols indicate whether values were significantly increased, significantly decreased, or not significantly different between MUB-OC and MB-OC (P < 0.05). The differences in skeletal muscle metabolome and adipose tissue mRNA expression of genes related to lipid metabolism in overconditioned dairy cows differing in serum metabotype were described in the companion study by Sadri et al. (2021). NEFA = nonesterified fatty acids. The figure was created using BioRender (https://app.biorender.com; agreement number: VT246EF84J).
Although we know that not all overconditioned cows exhibit metabolic abnormalities, the field of MB-OC cows is relatively new, and we still have no idea of the stability of the phenotype in dairy cows over time. There is no standard definition of MB-OC or MUB-OC, so the prevalence of both phenotypes varies widely depending on how a balanced or unbalanced metabolic profile is defined. Considering that human metabolically healthy but obese status can be transient and evolve into an unhealthy state (Appleton et al., 2013; Sorriguer et al., 2013), it is perhaps appropriate to adopt a similar thought process when considering MB-OC in dairy cows. In general, the role of genetic and environmental factors in explaining the mechanisms leading to the different metabotypes in overconditioned cows remains to be elucidated. However, blood sampling and metabolic profiling to monitor the metabolic status of cows in a commercial setting are difficult and expensive.

**MANAGING TOWARD OPTIMAL BODY CONDITION**

Nutritional interventions such as feeding energy-rich diets administered during the period of greatest negative energy balance (i.e., 1 to 30 DIM) have only marginal effects on homeothermically directed lipolysis because dairy cows “genetically” partition nutrients consumed toward milk production during this period (McNamara and Hillers, 1986a,b; Roche et al., 2009). Several experiments have examined the effects of diet on the profile of BCS change between lactations. Supplemented a pasture-based diet with concentrates (3 or 6 kg DM/d) in early lactation had no effect on BCS loss after calving but shortened the time to nadir BCS and increased the nadir BCS and post-nadir BCS gain (Roche et al., 2006). A study by McCarthy et al. (2007) in Ireland reached the same conclusion. This lack of influence of diet on BCS loss in early lactation is reflected in other studies (Friggens et al., 2007; Pedernera et al., 2008; Delaby et al., 2009) and supports the general conclusion of McNamara and Hillers (1986a,b) that lipolysis is primarily genetically regulated, whereas lipogenesis is environmentally regulated. It should be noted that BCS loss after calving (wk 1 to 4 p.p.) can be minimally influenced by management and feeding until the somatotropic axis (including growth hormone, growth hormone receptor, and IGF-I) has recoupled and the natural period of insulin resistance has passed (Roche et al., 2009). The most effective time to influence BCS is in the middle to end of lactation when the cow has a positive energy balance (Bewley and Schultz, 2008).

In the middle and end of lactation, management and nutrition can be used to improve cow health and performance by influencing BCS. Overfeeding and underfeeding cows can amplify or even out differences in BCS at the herd level. Cows that are underconditioned can be fed a high-energy ration to achieve optimal BCS at calving, and cows that are already overconditioned or approaching it can be fed a lower-energy ration. Grouping dairy cows in late lactation can allow for more targeted feeding of groups of cows with nonoptimal body conditions to better meet their nutritional needs. The increased nutrient requirements of the fetus can lead to significant mobilization of maternal body tissues, which can have undesirable consequences on cow performance p.p. (Beever, 2006). Nutrient grouping management can be an effective approach to achieving optimal BCS because feed can be more accurately matched to the nutritional requirements of cows (Kalantari et al., 2016; Wu et al., 2019; Barrientos-Blanco et al., 2020). Nutritional accuracy of diets reduces the proportion of underfed and overfed cows (Kalantari et al., 2016; Bach et al., 2020) and increases milk production in high-yielding cows, and it reduces overconditioning in low-yielding cows (Allen, 2009). However, differences between herd management practices across dairy farms are a factor that must be considered when implementing a nutrient-grouping strategy.

Variations in the length of the previous lactation and dry period could be a factor in the variation of BCS at calving. A randomized control trial examined the effects of different dry period lengths (28, 56, and 90 d) and found that cows given a 90-d dry period had higher BFT and BCS at the time of dry-off than cows in the 28- and 56-d dry periods, suggesting that nutrient partitioning in these cows was more focused on fat accumulation and less on milk production (Weber et al., 2015). However, cows for the 28- and 56-d dry periods were randomly selected from a common pool, and cows for the 90-d dry period were dried off earlier when their milk yield dropped to less than or equal to 15 kg/d in the study (Weber et al., 2015). However, the duration of lactation might be important for maintaining a healthy BCS at the end of a long lactation (Burgers et al., 2022). If BCS is elevated in late lactation as a result of a prolonged voluntary waiting period for insemination, this could lead to an increased risk of disease after the next calving (Roche et al., 2009). A voluntary waiting period is a management decision not to inseminate cows during the initial phase of lactation, the period after calving, until the cervix and uterus are fully developed (Niozas et al., 2019; Burgers et al., 2022). Multiparous cows with a voluntary waiting period of 125 or 200 d had a higher BCS at the time of dry-off and in the first week of subsequent lactation than cows with a voluntary waiting period of 50 d (Burgers et al., 2021). It seems that reducing BCS variation in herds would be the most feasible solution to improve profitability, and dairy farmers should ad-
just their management practices accordingly. However, there is no widely accepted approach to minimize BCS variation that has been studied in depth to provide recommendations.

CONCLUSIONS AND FUTURE DIRECTIONS

Body condition assessment can be used for both research and farm management, with varying degrees of precision and consistency required in both cases. When developing nutritional and management approaches to support underconditioned cows in the periparturient period, it is important to understand the complex interplay between body condition, a plane of nutrition, and reproduction. In this review, we addressed the fact that several herd-level observational studies have found an association between suboptimal body conditions and increased risk of metabolic disease (e.g., ketosis) in early lactation. However, aggregation bias should be avoided—that is, associations between nonoptimal body conditions and metabolic disease at the herd level may differ substantially from those at the cow level and vice versa. In other words, cow-level data and herd-level data provide 2 different sources of (co)variability that together yield an overall phenotype. Dairy farmers, veterinarians, and nutritionists should consider a combination of proven strategies to improve cow BCS because practical decisions depend on practical scenarios. For BCS to be used in nutritional management decisions, all cows should be evaluated individually and treated accordingly. A single BCS value at calving does not provide information on tissue gain or loss, so repeated BCS assessments are needed. However, relatively few dairy farmers use BCS monitoring as part of their management strategy.

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