

Review Article

Nutrigenomic Interventions to Address Metabolic Stress and Related Disorders in Transition Cows

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For dairy cattle, the period involving a shift from late pregnancy to early lactation termed transition or periparturient is an excruciating phase. Health-related disorders are likely to happen in this time frame. Timely postpartum and metabolic adjustments to this new physical state demands correct management strategies to fulfill the cow's needs for a successful transition to this phase. Among the management strategies, one of the most researched methods for managing transition-related stress is nutritional supplementation. Dietary components directly or indirectly affect the expression of various genes that are believed to be involved in various stress-related responses during this phase. Nutrigenomics, an interdisciplinary approach that combines nutritional science with omics technologies, opens new avenues for studying the genome's complicated interactions with food. This revolutionary technique emphasizes the importance of food-gene interactions on various physiological and metabolic mechanisms. In animal sciences, nutrigenomics aims to promote the welfare of livestock animals and enhance their commercially important qualities through nutritional interventions. To this end, an increasing volume of research shows that nutritional supplementation can be effectively used to manage the metabolic stress dairy cows undergo during the transition period. These nutritional supplements, including polyunsaturated fatty acids, vitamins, dietary amino acids, and phytochemicals, have been shown to modulate energy homeostasis through different pathways, leading to addressing metabolic issues in transition cows.

1. Introduction

In dairy cattle, transition period is known to be a critical physiological stage because majority of the diseases related to infections and metabolism are likely to happen during this phase [1, 2]. The transition period involves several biological changes that involve various complex biochemical interactions. These alterations take place in a series of reactions that starts three weeks prior to calving, lasting an estimated duration of three to four weeks following parturition [3].

The transition period in cows can be one of the most detrimental phases in terms of their overall well-being and productivity [4]. During the transition phase, cows face

severe metabolic challenges requiring high energy and nutrient intake. This is because the production of colostrum and milk in cows during lactation requires higher than normal amount of nutrients and energy. Conversely, it is also generally observed that cows' feed intake during transition periods is reduced. There can be different reasons for lower feed intake in dairy cattle during the transition period including environmental factors, physiological changes, level of production, feed digestibility, feed processing, and consistency of ration ingredients, but the main factors observed for decreased feed intake are effects on rumen capacity [5], heat stress [6], and hepatic oxidation [7]. Transition dairy cows are reported to have a large volume of fetus during the last

3 weeks of gestation, affecting the rumen capacity and adaptation, leading to decreased feed intake. The high energy requirements coupled with less intake of feed create negative energy balance (NEB) and nutrient deprivation [8]. Moreover, the lower feed intake is usually associated with reduced appetite in cows during the transition phase, which is believed to be caused by various molecular mechanisms, including acute inflammation. In response to inflammation in the transition phase, the body produces more inflammatory mediators, including complement proteins, cytokines, and eicosanoids. These molecules form a complex network and regulate different systemic responses, including reduced appetite and enhanced heart rate [9]. The NEB also invigorates metabolic changes that can be detrimental to cow's health, like increased accumulation of body fat such as non-esterified fatty acids (NEFA). The higher storage of body fat causes the accumulation of beta-hydroxybutyric acid (BHBA) in the blood. Such nutritional responses can be considered a normal process. However, cows generally fail to adapt to such metabolic changes during the transition period, causing an increase in the rate of metabolic and infectious diseases that influence cows' reproductive and productive capability [8].

The inefficient transition from the pregnancy stage to lactation frequently brings about the loss of 4.5 to 9 kilograms of milk compared to peak production times [10], that is, equivalent to 907 to 1814 kilograms of untapped milk production from each cow [8]. Regardless of huge advances in comprehension of transition cow biology, there is still a high occurrence of diseases related to infection and metabolism that has been accounted as occurring after the early lactation phase [11, 12]. The frequency of metabolic diseases in transition cows such as fatty liver, ketosis, and milk fever accounted from 7.8 to 16.8%, infections of mammary gland such as udder edema and mastitis accounted from 2.8 to 12.6%, and reproductive diseases such as retained placenta and dystocia accounted from 6.7 to 19.2% in high milk-producing cows [13, 14]. Hence, a delicate transition is crucial for managing health-related disorders and improving productivity of cows during transition period. Therefore, managing stress that occurs during the transition period is important for the animals' wellbeing and for maintaining their maximum productivity.

2. Risk of Metabolic Disorders during the Transition Period

Specific desirable outcomes are required for a cattle farm's successful and profitable operation, including the successful adaptation of cows to metabolic challenges during the transition phase with minimum or no disease rate, no culls, and good reproductive performance. However, the truth frequently contrasts incredibly. Poor side effects of the production process are self-evident. The expression "production disease" was generally viewed as incorporating the important metabolic issues such as ketosis, hypocalcemia, and hypomagnesemia of dairy cows. More diseases like metritis, laminitis, and abomasum have been incorporated into this term [15]. With the development and expansion of the dairy

industry worldwide, the sensitivity of diagnostic methods used for identifying cattle diseases has also improved. Despite improvements in diagnostic methods and better farm management practices, dairy farms still continuously face high rates of metabolic disorders that negatively impact dairy cows' health, reproduction, and productivity [16, 17]. Extensive research has addressed the correlations between cows' metabolism with various periparturient diseases, physiological adaptations, and nutritional requirements in the transition phase. According to a study by LeBlanc (2013), 30 to 50% of dairy cows during calving are influenced by some metabolic and infectious disorders that significantly affect dairy production. Frequency rates of compiled periparturient disease are listed in Table 1. However, contrary to the scientific evidence, research by Van and Sniffen (2014) reported that most dairy farmers still believe that the metabolic disorders affecting dairy cattle have no substantial effect on the milk production performance and cows can maintain their milk production capacities even in the presence of metabolic disorders.

As opposed to the extensive informational collections on the performance attributes of dairy cows, the testing of metabolic diseases is usually confined to information from single scientific examinations. In contrast to clinical infections, subclinical metabolic illnesses are much harder to distinguish as they require extra screening tests, and getting a whole image is not generally conceivable. This refers not exclusively to the seriousness of subclinical diseases but also to the impacts these metabolic disease may have on the risk of getting infectious and fertility disorders. Previously, equivalently not many examinations have been done to explore connections over an expanded range of medical conditions with reference to the production of milk. For instance, in the case of subclinical ketosis, hyperketonemia has been reported in the initial two months of lactation, which went broadly from 8.9% to 34% in different investigations [19, 20]. It would not be helpful to compare the current incidence rate of diseases to those from past years as records are unreliable. Moreover, higher quantity milk-yielding cows than their mates in herds are not consequently at higher risk of getting disorders [21]. As indicated by Mulligan and Doherty [15], the concept that high-yielding cows consequently have elevated levels of production disorders is probably erroneous as the speculation that lower-yielding dairy animals experience the lower levels of diseases related to production.

Drackley [1] reported in his study that unnecessary the NEB in times of early lactation leads to uncontrolled lipid metabolism that paves the way for numerous health complications in dairy cows. These metabolic changes increase the chances of hypocalcemia, ketosis, hepatic lipidosis, and other metritis and mastitis like infectious diseases [22–24]. However, considerable variation in the concentration of plasma of substrate during diurnal and in subsequent days in early lactation has been observed. For instance, the concentration of plasma BHBA is considered the indicator for developing ketosis in cows, contrasting broadly as does the higher concentration of plasma estimated in dairy animals that do not develop clinical ketosis in the initial six weeks lactation [25]. Variation in metabolites and hormone concentration in the

TABLE 1: Compiled periparturient prevalence of metabolic disorders from various published studies according to [18].

| Diseases name | Median incidence risk (%) | Range of incidence risk (%) |
|--------------------------|---------------------------|-----------------------------|
| Hypocalcemia | 6.5 | 0.3-22 |
| Metritis | 10.1 | 2-37 |
| Subclinical metritis | 53 | 37-74 |
| Lameness | 7 | 1.8-30 |
| Retained fetal membranes | 8.6 | 1.3-39.2 |
| Subclinical hypocalcemia | 2.2 | 8-54 |
| Clinical mastitis | 14.2 | 1.7-54.6 |
| Subclinical mastitis | 30 | 15-60 |
| Ketosis | 4.8 | 1.3-18.3 |
| Retained fetal membranes | 8.6 | 1.3-39.2 |

period of postpartum vary remarkably among animals held under comparable and exceptionally normalized conditions provided in the research farm, demonstrating that the ability to adapt to metabolic pressure fluctuates impressively between individual cows [26].

Sordillo and Raphael [27] reported the potential associations between dysfunctional inflammation responses and the mobilization of fat that may be associated with increased mortality and morbidity in the phase of transition. On the other hand, an effective inflammatory response eliminates the invading microbe, returns tissues back to normal morphology and function, and reestablishes the homeostasis of the immune system. This causes various aspects of cows' immune systems to be undermined around the hour of calving, particularly affecting inflammatory responses [28]. Sordillo and Raphael [27] presumed in their study that an adequate response of inflammation is required for the ideal clearance of pathogen because; during the state of transition in cows, swift return to immune homeostasis is generally lost. Suppression of the immune system is observed to be a common phenomenon in the periparturient dairy cows which has been connected to the poor status of metabolism and NEB [29, 30]. Immunoresistant genes are observed to be upregulated in the cows that suffer NEB [31], while the genes involved in acquired immune responses are downregulated [32]. Huzzey et al. [33] reported that cows suffering from severe metritis ate less than healthy cows during the half-month preceding the clinical indications of metritis [33]. Less food intake is related to expanded NEFA concentration that may directly [34] or indirectly [35] play a role in hampering the function of neutrophils. Both higher pathogen challenges and metabolic need force the cattle to regularly experience the significant oxidative pressure in early lactation [36] and also confer a proinflammatory response that destabilizes the defense mechanism [37]. Metabolic pressure is a significant fundamental factor in the progress of diseases in transition cows, which occurs when cows fail to adjust physiologically to higher requirements of nutrients during parturition and early lactation [37]. The cumulative impact of oxidative stress, impaired nutrient metabolism,

and impaired inflammatory response can shape destructive input loops that worsen the metabolic stress and induce health complications [19].

The role of such pathways that are associated with inflammation in the processes of adaptation is not yet wholly comprehended. Farney et al. [38] recommend that in some cases, insulin resistance induced by inflammation is an adaptive phenomenon instead of a pathological one, and that successful adaptation requires some level of inflammation. The increased number of analytes related to inflammation and stress during the periparturient phase is related to a lower yield of milk and while impaired reproductive ability is related to the later phase of lactation [39]. The overexpression of reactive oxygen species is an essential factor of an impaired inflammatory response leading to oxidative stress [40]. Conversely, free radicals play a fundamental role in physiological phenomena, but their excessive or imbalanced production plays a vital role in disease pathogenesis. Oxidative stress has been distinguished as a connection between inflammation and nutrient metabolism during the phase of transition [37].

Numerous investigations have revealed the close relationship between fertility disorders and NEB [41–44]. A large number of locomotive problems increase the duration of NEB in transition cows [45]. Essential drivers and the confounding components which add to the advancement of metabolic diseases are complex and differ impressively from farm to farm. These variables are identified as feeding regimes and convoluted by different administration problems. Regardless of the normal production of milk, a few farms do well, while others fail notably in decreasing clinical and subclinical issues. Vastly unique nourishment and executive programs produce great or poor success in corresponding to metabolic problems [1].

3. Strategies to Alleviate Biological Stress during the Transition Period

The transition period in cows is characterized by dietary, hormonal, metabolic, and immunological variations, causing various infections and metabolic illnesses. The continuous NEB state in dairy cows during the transition period necessitates higher energy intake than from ingested food [46]. It reduces glucose levels in blood and the mobilization of biological reserves to supply extra energy, resulting in metabolic imbalances and immune suppression [47–50]. Therefore, improving the energy balance in the transition period of dairy cows can significantly lower the prevalence of diseases associated with this period. Several methods have been proposed to achieve this purpose, including routine monitoring of the health status of cows during pregnancy and lactation, improving husbandry practices, nutritional supplementation, and optimal feeding. However, nutritional supplementation has received the most attention during last few years [51, 52]. In the upcoming sections, we will describe the metabolic changes cows face during the transition period and how nutritional supplementation can help minimize the destructive effects of metabolic changes during this period.

3.1. Metabolic and Physiological Adaptations from Gestation to Lactation. Previous studies have extensively demonstrated the traditional homeorhetic, physiological, and metabolic adaptations that cows go through from late gestation to early lactating [24, 53–55]. All these adaptations have been summed up in the current review related to the consequent fertilization period. Amidst the late gestation and primal lactation, certain changes in the endocrine and neuroendocrine system cause alteration in the nutrient segregation from fetal maturation up until the milk synthesis [54]. During the non-lactation period, the higher quantity of insulin and leptin is associated with the balance of energy, in comparison to the late lactating period [56]. These hormones are involved in and are responsive towards energy storage inside the adipose tissues. Fetal calf and placenta require more nutrients throughout the last month of gestation [57]. It is necessary for cows to provide their fetus with the required nutrients through diet, though dry matter intake (DMI) should be reduced up to 10-30% from the early nonlactating period [58]. However, stressors and severely limited DMI can cause NEB ahead of delivery; yet, the chances are much reduced as compared to what happens following parturition. Near parturition, the release of growth hormone (GH) depends on required nutrients [59]. In response to prepartum reduction in insulin concentration, milk production, and GH mobilized nutrients, fats storage primarily in adipose tissues is affected [60]. Noticeable reduction in important hepatic GH receptor (GHR-1A) causes acute reduction in the secretion of insulin-like growth factor 1 (IGF-1). Consequently, feedback suppression of the secretion of GH via IGF-1 is prevented due to the uncoupling of somatotrophic mechanism, that maintains the elevated quantities of GH [60].

3.1.1. Lipid Metabolism. The prolific reduction in insulin and increased GH directs the adipose tissues to mobilize the triacylglycerols (TAG) reservoir. In adipocytes, repeated esterification of NEFA is reduced because of the complete inhibition of lipogenesis. The significant antilipolysis effect on the fatty tissues get also that are removed due to the reduced concentration of insulin. GH increases the sensibility and the response towards catecholamines present in the fatty tissues, causing enhanced lipolysis of triacylglycerols [24, 53, 61]. Additionally, several components including interleukin-1 (IL-1), interleukin-6 (IL-6), and cytokines, i.e., tumor necrosis factor- α (TNF α) are secreted as a responsive action to stress, infection, and trauma which increases NEFA and TAG concentrations in the blood and heart [62]. Thus, stress inducers and poor management of the nutrients reduce DMI, enhancing the mobility of TAG and NEFA instantly after calving. During NEB, upon restricted glucose supply, ketogenesis is increased which causes ketosis [53]. Excessive uptake of fatty acids, with their oxidation into the ketone entities or CO₂, gets reconverted to triacyl glycerides. Ruminant animals cannot efficiently export hepatic triacyl glycerides—low density lipoproteins which consequently leads to the accumulation of fatty liver.

3.1.2. Glucose and Protein Metabolism. Dairy cows meet their glucose demand by relying on propionate hepatic glu-

coneogenesis. After calving, limited DMI limits the availability of propionate; therefore, increased conversion of amino acids mainly, alanine and glutamine, and glycerol from the diet or skeletal muscle and glycerol from mobilized adipose TAG assists glucose synthesis. Increased gluconeogenesis in liver tissue around and after calving aids in the sustainable supply of glucose to the mammary gland to prevent hypoglycemia [24]. In dairy cows, the estimation of plasma concentrations of 3-methyl-histidine during the first week after calving related with prepartum values revealed increased mobilization of limited proteins, reserved primarily in the form of skeletal muscle protein [63]. Even before calving or before the initiation of fat mobilization, loss of muscle mass might begin [63]. Different disorders like ketosis and other periportal diseases which reduce fertility rate are linked to the deficient stock of metabolizable proteins; therefore, it is essential to maintain maternal protein reserves for long-term health, productivity, and reproduction [25, 57, 61, 64],

3.1.3. Immune System Function. During the transition phase, the ability of the immune system to encounter infectious challenges get suppressed, which likely increases the incidence rate for environmental mastitis as well as the high incidence of metritis, more specifically around calving [54, 65]. Retained placenta has also been associated with failure of the immune system to identify the placenta as a foreign tissue [66]. Reasons for the declined immune functioning are not clear yet. Both vitamins A and E, as well as trace minerals (selenium, copper, zinc), boost immune functions. Cows show a significant decline in body condition score (BCS) and high chances of sickness when stressed either by nutrition or environmental factors. Negative energy balances or an inadequate supply of metabolizable protein could also be a serious contributing factor to impairment of the immune functions [54, 65, 67, 68] found impaired and insufficient neutrophils content (reserve glucose as fuel for neutrophil functions) with reduced glycogen in early postpartum cows.

3.1.4. Calcium Metabolism. The calcium concentrations abruptly drop in blood due to high demand required and with sudden onset of milk synthesis at calving, leading to milk fever. Subclinical hypocalcemia is more prevalent, with over 40% of cows entering the second or higher lactation getting affected [69]. This leads to disorders like displaced abomasum and ketosis by decreasing smooth muscle function essential to normal function of the digestive tract [70], reducing DMI, and also making animal immunocompromised [71]. Before the digestive tract improves the required calcium absorption, calcium must be attained from bone resorption. A negative dietary cation-anion difference (DCAD) triggers metabolic acidosis to facilitate calcium mobilization from bones, whereas a high potassium and positive DCAD inhibit this mobilization [70, 72]. Meanwhile, magnesium is found to be regulating bone resorption [70]. Nutritional intervention to start at least 14 days before calving effectively prevents hypocalcemia [53].

DeGaris et al. [73] reported that the optimal consumption of calcium in cows in diet before calving improved

pregnancy rates in two of three commercial herds and cow's impregnation rates at 6 weeks and 21 weeks after the start of the insemination period.

3.2. Nutrient-Gene-Metabolism Nexus Associated with Metabolic Adaptation in Transition Cows. Under the same circumstances and production level, variation in the accomplishment of adaptation early in lactation among cows revealed that these modifications may possess a genetic baseline [74, 75]. Different genes, metabolites, and main pathways in the plasma came to be earlier established that they have critical role in controlling the endocrine and metabolic adaptations in dairy cows [76, 77]. Nevertheless, these genes and metabolic processes may express at a specific time in the candidate [74]. For instance, a few genes which change the glucose level may be expressed at the start of lactation and a few others that change the affluence of NEFA, for instance, are expressed 4 weeks before or after 13 weeks of calving. Analyzing, pinpointing the genes, and regulating processes are significant biological roles during particular physiological conditions of dairy cattle that can assist in recognizing the DNA variants that influence milk production and, consequently, fertility [78].

The starting phase of lactation in dairy cows goes hand in hand with increased milk production. These adaptations are involved in metabolic regulation in peripheral tissues (comprising adipose tissues, mammary gland, kidney, and the skeleton muscles) and liver and are further involved in movement of body reservoirs and hyper lipid metabolism [79]. Mapping based on genes and identification of pathways revealed that three processes (steroid hormone biosynthesis, ether lipid metabolism, and glycerophospholipid metabolism) cooperatively influence the amount of β -hydroxybutyric acid, nonesterified fatty acids, and glucose in cows during transition interval. The main genes presumed to control the energy metabolism in different tissues include ACACA, PPARA, FASN, PCK1, FBP2, ACSL1, FABP3, PPARGC1A, AGPAT6, ACOX1, LPIN1, ACSL, CPT I, and CPT II [76, 80–84]. These genes influence the absorption of fatty acids mostly in the liver and mammary glands, oxidation of mitochondrial and peroxisomal fatty acids in the liver, ketone body metabolism, and cholesterol metabolism (in the liver) during the early stages of lactation in dairy cattle [85] (Figure 1). Therefore, alteration in the expression of these genes results in metabolic disruption in transition intervals in dairy cows.

For instance, ketosis is one of the primary metabolic diseases during transition intervals in dairy cows. Zhou et al. studied the changes in gene expression and genes linked with ketosis in Holstein cows. The RNA-seq process was utilized for analyzing the gene expression, from which a total of 27,233 genes were quantified with four billion premium reads. Consequently, the researchers realized that 75, along with four differentially expressed genes (DEGs) among sick and control dairy cows at postpartum and prepartum, subsequently, show that sick and control cows possess the same gene expression sequence at prepartum. However, there were 95 DEGs among postpartum and prepartum sick cows, which revealed depressed variations of the gene expression

in the transition interval compared to healthy cows (428 DEGs). Functional examination shows that DEGs linked with ketosis were the fundamental reason for biological stress response, ion homeostasis, amino acids metabolism, energy signaling, and disease-related processes [86].

In another examination, Laguna et al. [87] examined the expression of genes that encode for the enzymes and different processes linked with the metabolism of lipids and carbohydrates of 2 genetic classes of dairy cows in the transition phase. Examination of the expression of cytosolic phosphoenolpyruvate carboxykinase (*PEPCK-C*), glucose-6-phosphatase (*G6PC*), β -hydroxybutyrate dehydrogenase-2 (*BDH2*), methylmalonyl-CoA mutase (*MUT*), carnitine palmitoyltransferase-2 (*CPT2*), acetyl-CoA carboxylase (*ACC*), glucose transporter-2 (*SLC2A2*), 3-hydroxy-3-methylglutaryl-CoA reductase (*HMGCR*), and the transcription factor peroxisome proliferator-activated receptor α (*PPARA*) was directed, and a comparison was established between Holstein and F1 Holstein-Gir cows. The results revealed that the expression of *PEPCK-C*, *G6PC*, *ACC*, *BDH2*, *CPT2*, *SLC2A2*, *HMGCR*, and *PPARA* genes was not different among the genetic group excluding the *PEPCK-C*. Furthermore, no association between genetic groups and the experimental period was examined. In both dairy cows, *PEPCK-C* and *G6PC* gene expression was not prominent and decreased compared to the gene expression with 21 and 36 DIM and increased in d 51 postpartum. The expression of *MUT* was not the same among 2 studied groups and showed a noticeable increase after d 36 postpartum, whereas mRNA level of *HMGCR* likely to increase when compared d 21 and 36 to d 51 postpartum. The expression of *MUT* gene was not the same among 2 studied groups and showed a notable increase after d 36 postpartum, whereas mRNA level of *HMGCR* was likely to increase when compared d 21 and 36 to d 51 postpartum. Moreover, glucose levels were also not the same between the two groups and were sufficiently higher in the plasma of F1 Holstein-Gir cows compared to Holstein cows. However, no significant difference in glucose level was observed within each group during the analysis period. β -Hydroxybutyrate and NEFA concentrations were not different in both genetic groups but showed a high level from prepartum to d 6 and 21 postpartum [87]. The altered expressions of these different genes in liver are linked with metabolic stress in transition dairy cows.

3.3. Nutritional Interventions to Modify Gene Expression during the Transition Period

3.3.1. Nutritional Supplementation. Nutritional interventions for dairy cows during the transition period are primarily intended to ameliorate the effects of metabolic changes indicated above. Many nutrients have been reported to induce metabolic adaptations and regulate NEB by controlling the expression of many genes in different signaling pathways (Table 2) (Figure 2). The most significant effects have been observed by polyunsaturated fatty acids (PUFAs). Mammals can produce all types of fatty acids necessary to carry out normal physiologic functions, excluding PUFAs, especially from omega-3 and omega-6 families known as essential

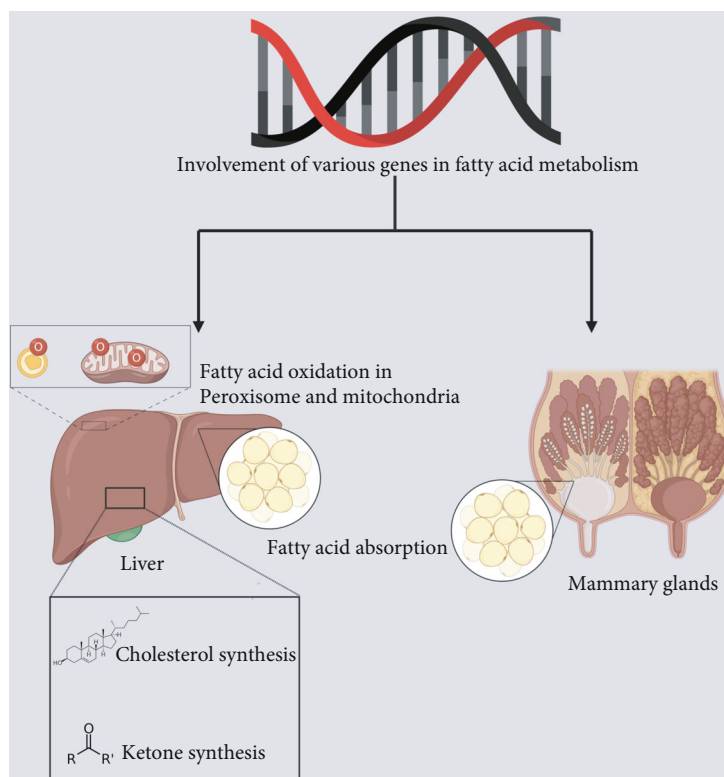


FIGURE 1: Phenotypic effects of various genes involved in fatty acid metabolism.

TABLE 2: Regulation altered gene expression through nutrients in transition cows.

| Nutrients | Effect on gene expression regulation and on various traits | References |
|-------------------------------------|--|---------------|
| Rumen protected methionine (RPM) | Enhance the expression of ABCG2 and GHR genes during lactation Improved milk production and butterfat content | [93, 94] |
| Rumen protected choline (RPC) | (1) Regulate the expression of genes for acetylcholine and acetylcholine receptor (2) Enhanced the expression of FA transport protein 5 and carnitine transporter SLC22A5 in the liver (3) Reduce lipolysis of adipose tissues, thereby treats fatty liver | [95, 96] |
| Calcium supplementation | Treatment of hypocalcaemia, improving leukocyte function, improvement in impregnation and pregnancy rates, and management of transition period related stress | [73, 97, 98] |
| Yeast supplements | Regulate the expression of inflammation-related genes in dairy cows during transition period. Increase DMI content through increasing availability of fiber content | [99–101] |
| Polyunsaturated fatty acids (PUFAs) | Control the altered expression of many key genes (TLR2, PPAR) and transcription factors (NF- κ B) implicated in metabolic stress Also exerts immune modulation effects to control inflammatory processes | [96, 102] |
| n-3 PUFA | Inhibit the expression of adhesion molecules involved in inflammation Essential for the central nervous system (CNS) and reproductive system development and thereby improves embryo survival | [95, 103–105] |
| n-6 PUFA | Enhance mRNA levels of estrogen receptor 1 and oxytocin receptor and decrease insulin growth factor levels | [106] |
| Conjugated linolenic acid | Upregulate the transcription of many genes, including insulin signaling, TLR4, inflammatory cytokines, and protein kinases for metabolic adaptation | [107] |
| Long chain fatty acids (LCFAs) | Improvement in adjusting to the transition period stress and milk and milk fat yield | [108] |

fatty acids. During the transition phase in cows, the concentration of PUFA lessens sufficiently in every part of the body compared to the mid-lactation cows [36, 88], whereas

the proportion of different saturated fatty acids (SFAs) is elevated. The fundamental source of omega-3 fatty acids in ruminants is forage, specifically for grazing cattle, as a

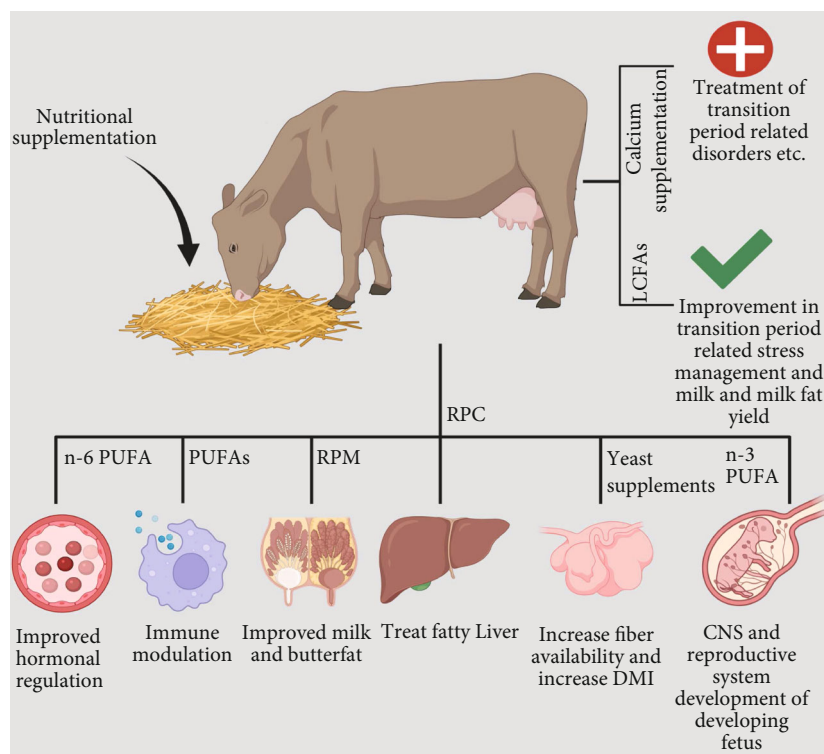


FIGURE 2: Effects of different nutritional elements on dairy cows’ health, productivity, and reproductive ability. In the figure, the effects of individual nutritional compounds are shown. In reality, each compound can affect several organs and physiological functions. Moreover, each trait can be shared by various compounds.

huge amount of alpha α -linolenic acid (ALA) is found in forage galactolipids. A supplemental source of the n-3 PUFA in dairy cows’ diets includes docosahexaenoic acids (DHA) and eicosapentaenoic (EPA) from fish oil and ALA from flaxseed [89].

On the other hand, n-6 PUFA is present in various other feeds, including sunflower, soybean, cottonseeds, and corn, and their ingestion increases sufficiently during and after calving. Supplementing requisite PUFAs (as rumen-protected mainly) directly influences the immune cells by modulating the expression of various transcription factors exerting pro- or anti-inflammatory activities. All n-3 PUFAs downregulate the expression of adhesion molecules intricate in inflammatory interactions between leukocytes and endothelial cells [90]. Linoleic acid and specifically its isomers cis-9, trans-11 and trans-10, and cis-12 were linked with peroxisome proliferation activated receptors (PPAR)- γ , while long-chain n-3 (EPA and DHA) was linked with toll-like receptors- (TLRs-) 2 and 4, PPARs, and sterol reaction element-binding protein family [91, 92]. All these genes play a major role in controlling NF- κ B that orchestrates the synthesis of proinflammatory cytokines in both immune and nonimmune cells. The absence of n-3 and n-6 PUFAs in the postpartum interval can cause uncontrolled inflammation. Besides fatty acids, other vital nutrients profoundly impact cow’s health, productivity, and reproduction. An extended list of nutrients and their effects is shown in Table 1 and Figure 2.

3.3.2. Nutrients as Metabolic Modifiers

(1) *Water*. The nutrient that has the primary daily requirement for most life forms is water, and it is 56-81% of BW. Milk contains 85-88% water. For milk production, water is predicted to be 4 : 1 (water: milk) by McCandless and Gaessler (1919). Water required for 1 kg of milk is 2.0-2.7 kg [109]. Loss of water in the body occurs through urine, faeces, sweating, and expiration. The quality of water is defined by many aspects such as organoleptic qualities, physicochemical properties, mineral content, and presence of toxic chemicals and bacteria [109].

As environmental temperature increases, intake of water also increases [110]. Water helps to conserve body temperature via evaporation. Dairy farms situated in the hot areas have fitted cooling systems that use the mechanism of evaporative cooling to maintain the cow’s core body temperature. Water deprivation is more deadly than starvation. Rumen water kinetics was integrated to demonstrate rumen VFA kinetics [111]. Rumen osmolality increases after feeding. Water from the body moves into the rumen to decrease the osmotic pressure of the rumen. The passage rate of water and feed particles increases with the rumen’s osmolality. Buffering effect of bicarbonate salts is less due to less time spent in the rumen.

Due to the strong positive relationship between water and solid feed intake, greater water intake can lead to greater

feed consumption, rumen stability, and regulation of rumen pH. A recent study showed the positive effect of drinking warm water on rumen functionality in beef cattle [112]. Drinking warm water reduced the time during which the ruminal pH was below pH 5.8 or 5.5, and the time during which the temperature was lower than 37 or 39°C. It has been reported that the rumen temperature and pH are correlated with the gene expression in rumen epithelium (RE). Rumen acidosis caused by low pH in rumen might alter the expression of genes and cytokine expression in RE [113]. Water helps to maintain the rumen pH so that it can act to modify the expression of genes and cytokine concentration in RE. Thus, water is an essential metabolic modifier in transition dairy cows.

(2) *Protein and Amino Acids.* In a dairy ration, the costliest ingredient is protein supplements. For an ideal economy, the effective use of protein supplements must also consider the utilization of this important nutrient by bacterial communities present in an animal. Virtanen was presented Nobel Prize on his development of a fodder preservation method. Later, he verified that cows could produce in a single lactation 4,200 kg of milk on a protein free ration [114].

Proteins are made up of 20 amino acids (AAs) for maintenance and production. Out of 20 AAs, ten are non-essential (NEAA), and ten are essential amino acids (EAA). NEAA are those which body can synthesize on its own, while (EAA) are those that the body cannot synthesize and must be provided in the feed to meet the body's requirement.

Protein in meals from the whole oilseeds is soluble in the rumen. Rumen bacteria degrade the protein to ammonia, which gets assimilated into microbial protein. Microbial protein is highly digestible, but a net loss of nitrogen occurs from them. Rumen degradation decreases, and rumen bypass increases of oilseed meals and whole oilseeds by heat and chemical methods [115–117]. The extent of rumen bypass and total tract digestibility depends on the temperature and total time when supplements are exposed. Due to overheating of meals and seeds, a reaction occurs between reducing sugars and AAs, resulting in decreased protein degradation in the rumen and digestibility in the small intestine. This whole reaction is called the Maillard reaction. Cows fed recombinant bST and rumen-bypass protein that have increased milk yield [118]. Rumen cellulolytic bacteria cellulolytic require ammonia which they degrade to produce essential proteins for their growth. The more fermentable energy, the more the growth rate of rumen bacteria. Satter and Slyter [119] studied that when ammonia concentration exceeds 5 mg/100 mL, ammonia overflow occurs from continuous cultures. Satter and Roffler [120] studied that when NPN sources are added to the ration beyond 12 to 13% of CP, milk production does not increase. These experiments started a discussion among nutritionists, and new ideas were evolved on how to create rumen bypass protein supplements [120, 121]. Chalupa [122] studied that protein from the ration must escape rumen degradation and reach the small intestine for increased milk production. Applying

heat to protein meals and whole seeds increases rumen undegradable protein [123].

Rumen bacteria destroy the trypsin inhibitor and other compounds that are present in the whole soybeans. Soybeans should be processed to destroy these compounds when given to young calves to avoid these. Reddy et al. [124] fed calves from birth to 10 weeks of age. The whole soybeans were heated at a temperature 99 to 163°C. And they found that the most significant gain occurred when soybeans were roasted at 143 to 146°C for 30 min. Protein meals treated with formaldehyde had increased rumen bypass protein [125] but milk production was notably lacking in most experiments. Formaldehyde is cancer-causing in nature. The FDA prohibited feeding formaldehyde-treated feeds to livestock.

The most limiting essential amino acids in dairy cows are lysine and methionine. Two conditions must be considered: grams of absorbable AA per 100 g and Lys: Met ratio. Lysine comprises of 16.3 of lean tissue and 16.0 of milk proteins, while Met 5.1 of lean tissue and 5.5 of milk proteins [109]. The lysine requirement for maximum use by tissue is 7.2 g/100 g and for Met is 3.2 g/100 g of absorbed AA [109]. Methionine has a half-life of almost 2.4 h [126]. Supplementation of methionine increased milk protein and weight of milk protein [127]. Vyas and Erdman [128] determined that when both Lys and Met approached requirements, the marginal efficiency of use Lys and Met decreased.

From nutrigenomic perspective, EAA are reported to increase milk yield and milk protein synthesis via regulation of different genes. Methionine supplementation is shown to be associated with high milk yield via increased expression of β -casein in [129]. Valine, leucine, and histidine are also reported to increase the milk yield in dairy cows via increase in casein and β -casein mRNA abundance [129, 130]. Enhanced methionine supplementation during the periparturient period is reported to increase dry matter intake and milk yield in dairy cows. Liang et al. studied the nutrigenomic potential of methionine supplementation in Holstein cows during their periparturient period [131]. They reported that enhanced methionine supply led to greater overall mRNA abundance of Gln (SLC38A1), small zwitterionic α -AA (SLC36A1), Glu (SLC1A1), and neutral AA (SLC1A5) transporters. Moreover, abundance of AKT1, RPS6KB1, and EIF4EBP1 was also upregulated in response to methionine. Furthermore, the increased supply of methionine upregulated the expression of peroxisome proliferator-activated receptor-gamma, mTOR, and fatty acid synthase.

During the transition period, dairy cows experience inflammation and oxidative stress. Methionine supply can profoundly alter these biological processes in transition dairy cows via fine-tuning of oxidative stress-related genes, inflammatory cytokines, improved liver function, and glutathione metabolism. Methionine is also studied to upregulate PPAR α through DNA methylation during the transition period in cows and is considered a suitable mechanism to explain consistent improvement in the performance of a dairy cow [132]. Arginine and glutamine are also known to mediate metabolic stress via modulation of PPARs [84]. In addition, plasma levels of cysteine are reported to decrease

around parturition in dairy cows, and studies suggested that cysteine supply helps lower the oxidative stress and expression of proinflammatory cytokines, which are hallmarks of stressful conditions in cows [133]. Hence, amino acids and proteins have much nutrigenomic potential and can be utilized as metabolic modifiers in transition dairy cows.

(3) *Lipids*. Lipids contain fatty acids that are absorbed in the small intestine and then enter the lymphatic system where they are transported to the liver. An enzyme lipase acts on the lipids and releases glycerol and fatty acids which are then used by tissues as an energy source even by the brain, in severe NEB. In the tissues, fatty acids are hydrolyzed to 2- and 4-carbon and enter the Krebs cycle to produce ATP. It may result in ketosis if excessive oxidation occurs. Fatty liver may result from incomplete utilization of fatty acids. In a positive energy balance, adipose tissue absorbs the acetate and butyrate and converts into storage form as triglyceride. Among fatty acids, the main source of energy for the cows are long-chain fatty acids. These fatty acids are given to the cows via oil seeds, animal-vegetable blends, or ruminal inert fat. In the rumen, the unsaturated fatty acids are converted into C18:0 and C18:1. Rate of fermentation and extent of fermentation decrease by unsaturated fatty acids. When given dietary fat, it was found that the milk response was curvilinear with 16% of ME from fat equals to 600 to 700 g or 3% added fat. Forages and grain contain an average of 3 to 4% fat. One should remember that the diet's total fat should not exceed 7% of total DM [134]. Fatty acids that are long chained and unsaturated are toxic to rumen bacteria. To overcome this effect, biohydrogenation of UFA is done. To avoid the increase of fat solubility in the rumen, rumen-protected fats are used, e.g., calcium soaps and amides.

Sutton [135] gave an intriguing tale from Eckles at the University of Missouri, who kept in touch with Powell in 1927: "as far as anyone is concerned, this or some other investigation in the nation has not as of late directed experiments to decide whether feed would influence the composition of milk. It is looked on as a very unsettled inquiry." Powell [136] later gave proof that actual qualities of roughage, did truth be told, influence rumen fermentation with a significant impact on milk fat percent. That trait of forage was depicted as "physically effective fiber." Chewing, saliva secretion, and rumen pH are affected by this forage quality [137].

In another study, the impact of diet on intermediary metabolism and fat content of milk was surveyed. The following three hypotheses were examined: (1) decreased acetate production in the rumen, (2) insufficiency of BHB in the mammary gland, and (3) endocrine variables. Amount of forage, forage: concentrate ratio, carbohydrate fractions of the concentrate, lipids, and meal frequency were found to be the variables influencing milk fat composition [135]. Beitz and Davis [138] compared 3 diets for milk fat: (1) control diet, (2) high grain ration, and (3) diet containing cod liver oil. The researchers found that the grain intake and milk fat quantity differed between the three groups. Milk fat percent averaged 3.21, 2.16, and 1.77 for the 3 rations, respec-

tively. High-grain diet had increased rumen propionate. Fish oil and high-grain diets had lower milk fatty acids, and all double bonds stated were in the cis position. Earlier, Davis and Brown [139] and later Bauman et al. [140] also observed that an increase in trans 18:1 in milk fat was associated with decreased milk fat percent.

Increased C18:1, C18:2, and C18:3 in milk are due to oil from plant sources. Unsaturated fats of the plant have double bonds in the cis position at each 3-carbon unit starting at carbon-9 from the C end. Fish and plant oils cause a significant decrease in milk fat % and change the fatty acid composition of milk fat [141]. The substance of C20:5n-3 and C22:6n-3 is improved by fish oil [142, 143].

Unsaturated fats are harmful to rumen bacteria. Rumen bacteria utilize metabolic hydrogen to detoxify UFA. This effect by bacteria to UFA results in an increment of milk fat [144]. Cows fed with an animal-vegetable blend of fat, coconut oil, safflower oil, flaxseed, and monensin in a diet had increased trans C18:1 [145, 146]. Medium-chain fatty acids were decreased in all diets. Total protozoal numbers and ruminal NDF digestion were decreased in a coconut oil feed [146]. Fatty acids less than C16 were reduced, and trans C18:1 and trans-10 and cis-12 CLA in milk fat were increased when monensin was fed [147]. Cows fed with low fiber and unsaturated fat had lower milk fat % and milk yield, around 30% and 35% as compared to high forage ration and saturated fat [148]. Cows showed increased trans-10 C18 UFA in milk and decreased milk and fat yields when fed with low fiber and unsaturated fat compared to high forage rations. Baumgard et al. [149] recognized trans-10, and cis-12 isomer is produced in rumen and a potent inhibitor of de novo milk fat synthesis. Two isomers that also inhibit milk fat synthesis are cis-10, trans-12 and trans-9, and cis-11, and these are CLA isomers.

Supplementing fat to increase the energy or caloric density in the diet of lactating dairy cows has a long history. Dietary long-chain fatty acids (LCFA) have prominent nutrigenomic effects on several components of different organs in dairy cows during their transition period. In an in vivo study, the supplementation of saturated lipids to dairy cows showed higher expression of lipogenic genes in mammary tissue resulting in higher milk yield [150]. In another study, greater expression of lipogenic genes was observed in mid-lactation dairy cows when they were supplemented with a mixture of oil [151]. However, the nutrigenomic effects of saturated LCFA were not prominent. In contrast, in a recent experiment, Schmitt et al. observed the increased expression of nuclear receptor coactivators, lipogenic genes, and related transcription factors when cows were supplemented with high saturated LCFA diet for 30 days [152]. Furthermore, in the same experiment, Akbar et al. investigated the hepatic expression, and the results uncovered the strong nutrigenomic effect of saturated LCFA supplementation prepartum and larger nutrigenomic effect of fish oil supplementation postpartum [153]. Interestingly, overall supplementation of lipid diet resulted in low expression of CPT1A, FGF21, and ACOX1 but the expression of PPAR α is reported to be upregulated by lipid diet. This data seems to indicate that supplementation of lipids might be

advantageous in liver prepartum which can further manage the metabolic stress in transition dairy cows.

Among the short-chain fatty acids (SCFA), butyrate exerts nutrigenomic effects in dairy cows. Butyrate is reported to induce an immune response and cell cycle arrest in dairy cows and goats [154]. The nutrigenomic effects of butyrate are evident in ruminal papillae of dairy cows by modulating the expression of genes related to lipogenesis and glycolysis [155]. The effects of propionate are also observed on free fatty acid receptor 3 (FFAR3) in transition dairy cows. Lemor et al. have studied the effects of propionate, and they reported the increased expression of FFAR3 and adiponectin genes from pregnancy to lactation in bovine adipose tissue which can regulate the lipid metabolism, energy expenditure, and insulin sensitivity [156].

Recent studies in cows and rodents have shown the importance of lipids in regulating gene expression in mammary tissues and the liver. For example, dietary lipids regulate lipogenesis through interaction with several transcription factors, including PPARs and sterol-regulatory element binding protein (SREBP) [157, 158]. Polyunsaturated fatty acids (PUFA) are the main FA that act at the level of nucleus in connection with these transcription factors to regulate the expression of different lipogenic genes. PUFA reduces SREBP-1a and 1c by accelerating the decay of *SREBP-1c* mRNA, therefore lowering their hepatic content to regulate lipid metabolism and FA oxidation [159]. PUFA and eicosanoids are also shown to bind directly with PPAR α , controlling gene expression and metabolic networks to enhance milk yield. Thus, insight into the nutrigenomic potential of lipids highlighted their importance as metabolic modifiers in transition dairy cows.

(4) *Minerals*. Minerals and micronutrients are considered to fulfill various functions such as regulating body water balance, building bones, immunomodulation, and influencing muscle functions for optimal functioning of dairy animals and acquisition of their products [160]. In particular, the ability of minerals to regulate the expression of gene products through modulation of transcription and translation is now being recognized. The deficiency of certain nutrients is evident in dairy cows during their transition period. Bone contains 98% of total body calcium, and the other 2% is extracellular fluid. The concentration of calcium in the blood is around 9 to 10 mg/100 mL, and it is regulated by a hormone called parathyroid hormone (PTH). Release of PTH depends upon the blood calcium level. When calcium in the blood is low, PTH release increases the mobilization of Ca from bone to maintain the concentration to calcium to normal. 1,25-Dihydroxycholecalciferols regulate calcium absorption, and it is derived from vitamin D. Bones become less responsive to calcium release with age. As blood calcium declines, cows become subclinical, partial, or full paralysis with recumbency occurs at a calcium level of ≤ 5 to 6 mg/100 mL. With the increase in calving and low calcium levels, the risk of parturient paresis (milk fever) increases. Minerals have been identified to reduce the severity of parturient paresis when supplemented to transition cows in their diet [161]. These include the amount and ratio of Ca and P,

administration of vitamin D per os or by injection, and manipulating alkalinity in diets.

Magnesium oxide (MgO) is a source of elemental magnesium (Mg), and it is absorbed by ruminal epithelium. Particle size MgO affects the rate of solubility in rumen [162]. Rumen fluid solubility ranges from 25 to 75% in a pH of 5.5 to 6.5 [163]. When pH increases beyond 6.5, the solubility of ruminal fluid decreases. Mg absorption (% of intake) is about 26% but it ranges from 9.9 to 73.9%. Forages are rich in potassium (K), and K decreases the Mg absorption; so, with forages, the high Mg concentration must be also be given to an animal. Grass tetany occurs in the spring in cows by grazing on rapidly growing grass with a high K concentration [164]. Lactating cows fed with a positive dietary cation-anion difference (DCAD) rations have increased DMI and milk fat in a curvilinear response [165]. Magnesium has numerous roles in the immune system functioning that can exert nutrigenomic effect in dairy cows. In experimental animals, Mg deficiency is correlated with altered proinflammatory status in which systemic IL-6 increases and increase in correlates of oxidative stress. In a trial, dietary Mg supplementation improves the metabolic profile by regulating the metabolic and inflammatory biomarkers, including decreased C-peptide concentrations, TNF- α concentration, and increased calcium and leptin levels. Moreover, certain genes linked to metabolic and inflammatory pathways, including C1q and tumor necrosis factor-related protein 9 (C1QTNF9), were downregulated [166]. Mg has been also shown to interact with miRNA machinery. Mg interacts with RNA-induced silencing complex (RISC) being an Mg²⁺-dependent protein and involved in binding of specific miRNAs to argonaute protein for cleavage of miRNA targets to control the gene expression. Therefore, Mg supplementation can improve the miRNA profile in dairy cows during their dry-off period for metabolic adaptation.

Many feedstuffs are deficient in selenium because the soils are low in selenium. One of the diseases due to deficiency of selenium in sheep is white muscle disease. Selenium is a cofactor of the enzyme glutathione peroxidase [167]. According to FDA, diets should be supplemented with selenium with a concentration up to 0.3 mg/kg [109]. Selenium deficiency in diet is associated with oxidative stress and autoimmunity [168]. Oxidative stress and autoimmunity are the hallmarks of disease conditions in transition dairy cows. In cows, the roles of selenium include participation in the cattle farms' antioxidant defense. Selenium supplementation may reduce the incidence of metritis and ovarian cysts during the postpartum period. Selenium has been reported to regulate the levels of proinflammatory cytokines and burden of free radicals in the body by downregulating the expression of IL-6, TNF- α and NF κ B at the RNA level [169]. Furthermore, dietary supplementation of selenium can also potentially affect thyroid hormone metabolism and redox-active proteins to improve the immune response of dairy cows [170]. In rodents, selenium-enriched probiotics have also been reported to improve lipid metabolism, histopathological lesions, and antioxidative status via upregulation of PPAR α

[171]. In this context, dietary supplementation of minerals or trace elements can be good for metabolic modification in transition dairy cows.

3.4. Nutrigenomic Perspectives: Challenges and Opportunities.

The notion that dietary elements interact with the cellular environments at the molecular level to alter biological activities has transformed nutritional science [172]. Nutrients, in such respect, are more than simply cellular fuel and building blocks; they are also molecular messages sensed by the sensors of cells that cause a shift in the biology of cells; hence, nutritional components are active biomolecular compounds [173]. Dietary components can also have nutrigenomic impacts without bioactive, such as dietary calorie restriction [174]. It is possible to fine-tune an organism's diet since dietary substances can interact with the genome, especially transcription regulators. Such methods have paved a path for developing a relatively recent area of science called nutrigenomics, which is defined as studying the effect of nutrients on gene expression in an organism [175]. In the ever-changing world of nutrition science of animals, nutrigenomics research aids in understanding how nutrient-gene interaction occurs that ultimately affects productivity and reproduction. The use of nutrigenomics in the animal nutrition provides many benefits, including improved animal productivity, fertility, feed efficiency, and immune functions. Transcriptomics and metabolomics are two potential nutrigenomic tools for understanding the molecular processes occurring in a genome obtaining nutritional cues and reacting to them via unique metabolic reactions in an organism. The nutritional requirements for an organism's upkeep and growth vary depending on its genetic variability, allowing nutrigenomic-based selection to be used to produce animals with superior traits for improved feed efficiency. It is especially important during the transition period and in the first few months of lactation as animals in this time period are more vulnerable to nutritional deficiencies [176]. We have highlighted a number of nutritional intervention strategies that can improve the performance and productivity of dairy cattle during the transition period. One example of such a nutrient is LCFA, the presence of which in the diet induces the expression of genes in the mammary gland that induces higher production of milk and milk fats in lactating cows and improves the management of stress during the transition period [108].

Though the research in nutrigenomics in animal nutrition has interesting potential implications in promoting animal well-being and productivity, this research area requires an extensive amount of research. Each animal species contains around thirty thousand to forty thousand genes, and their interaction with innumerable metabolites or nutritional elements cannot be ascertained within a short period of time and with limited resources. Though the sequencing techniques related to omics have improved over the years, it is still not feasible to find interaction of every known metabolite with each gene in a particular species [176, 177]. Future research in the development of more cost-effective and robust omics approaches is required to integrate nutrigenomics research to promote animal health and their productivity. Moreover, most of the nutrigenomic research

been done on the beneficial effects of nutrients on animals' health. The nutrients' toxic and potentially detrimental effects should also be investigated in detail. A detailed investigation of the nutrigenomic effects of the nutrients will help farmers formulate better feed formulations and curtail the use of antibiotics, the resistance against which is becoming an alarming situation around the world [178, 179].

4. Conclusions

The transitional period can be challenging for farmers and cattle alike. To sustain health of animals and attain projected production results, a smooth transition from late pregnancy to early lactation is required. In the transition period, implementing optimum management methods for dairy cows can significantly enhance their metabolic and immunological health, leading to increased cow wellbeing, health, and productivity. The scientific data support the usage of nutritional supplements in the periparturient period to improve metabolic and immunological responses while also reducing the production of biochemical signals that cause inflammation, immune dysfunction, and metabolic adaptation impairments. The nutritional research from dairy cattle generally demonstrates that the existing approaches for developing diets for dairy cattle are blind regarding the nutrigenomic impacts of dietary components, which, by modifying the animal's metabolism, are expected to modify its various metabolic pathways. The knowledge acquired from nutrigenomics research can better understand the genes and biochemical pathways influenced by dietary components and the impact such nutritional supplementation can have on the modulation of these molecular species. It is expected that the inclusion of nutrigenomics research in the diet formulation of dairy cows during metabolically challenging times like the transition period can help in planning more rational dietary plans that produce optimal results. Thus far, the potential of nutrigenomic research appears promising; nevertheless, the operational applicability of nutrigenomics in animal nutrition has not been implemented as of now. This is partially due to the intricacy of the biological systems under study and the further need to improve the technologies used for studying them. For this reason, we do not believe that practical nutrigenomic-based dietary formulations will be accessible very soon. More fundamental research is required before valuable applications may be developed.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Authors' Contributions

Faiz-ul Hassan and Asif Nadeem contributed equally to this work.

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