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New outlook to vitamin D functions in dairy cows: non- classical roles

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ABSTRACT

In addition to the well-studied effects in regulating calcium and phosphorus balance, vitamin D has many non-calcemic effects that include acting as an immune modulator or an antioxidant. Cows acquire vitamin D either from photosynthesis in the skin or through swallowing fungi in the forage or vitamin D supplements. Although vitamin D deficiency is rare, today we are facing an increasing number of vitamin D deficiencies in cows due to the indoor housing away from sunlight exposure. According to the NRC recommendation, to maintain the vitamin D serum concentration in the range of 20 to 50 ng/ ml, it is necessary to administer 21,000 IU/ d of vitamin D in cattle. In addition, considering the involvement of vitamin D in various calcemic and non-calcemic effects, it seems that previously recommend levels of vitamin D supplementation have not been enough for preventing many diseases and disorders in cattle. Vitamin D toxicity may also occur due to over-supplementation of vitamin D or overgrazing in plants with high amounts of vitamin D metabolites. This review article will discuss various roles of vitamin D in dairy cattle health, normal physiology, and disease prevention.

Keywords

Calcitriol, Immune modulation, Oxidative Stress

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Abbreviations

TRPV6: transient receptor potential vanilloid 6
7- DHC : 7- dihydroxycholecalciferol
VDBP: vitamin D binding protein
PTH: parathyroid hormone
FGF23: fibroblast growth factor 23
DCAD: dietary cation anion difference
RANKL: receptor activator of nuclear factor kappa-B ligand
OPG: osteoprotegerin
RXR: retinoid- X receptor
iNOS: inducible nitric oxide synthase
TLR: toll like receptor

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Introduction

It can be said with confidence that vitamin D was one of the earliest hormones synthesized on the planet by phytoplanktons millions of years ago, possibly protecting these organisms from radiation. The ocean's environment was rich in calcium, and aquatic organisms could easily use it for their metabolic activities. As life spread from water to land, organisms faced a calcium deficiency crisis. Therefore, a strategy was created to absorb low calcium from the environment with maximum efficiency through the intestines. For unknown reasons, vitamin D gets a regulatory role in calcium absorption [8, 16].

Inscriptions on cave walls indicate that primitives praised the sun for its life-giving effects. With the industrial revolution and the development of urbanization in European countries, evidence of the vitality of sunlight appeared. People settled in building close to each other, and burning coal caused severe air pollution. Thus, the children of these cities were no longer exposed to sunlight and showed growth disorders [20].

More than a century ago, Sir Edward Mellanby discovered that the British people, especially the Scottish, were suffering from a high prevalence disease, which is probably related to their diet. Initially, the disease was known as English disease, which today is called rickets. Mellanby experimented on about 400 dogs for 5 years. He kept them away from sunlight exposure and fed them with an oatmeal diet, which was similar to the British diet at that time. After a while, the dogs showed similar symptoms to rickets. He managed to treat these dogs with cod fish liver oil. But he mistakenly called it vitamin A. Later, McCollum et al. named it Vitamin D. [1, 2, 3, and 4]. Not long after the discovery of vitamin D as an anti-rickets agent, its importance in the natural growth of cattle was revealed [32].

Vitamin D photobiology

Vitamin D has two types: Vitamin D2 or ergocalciferol, which is present in several plants that can convert ergosterol to vitamin D, and Vitamin D3 or cholecalciferol, which is derived from 7- dihydroxycholecalciferol [7- DHC] of animal products [6,40, 55]. They differ in chemical structure in a side chain [15]. Metabolites of both types of vitamin D are present in the blood of cattle, but using vitamin D3 is preferable [6, 40]. Cattle gain vitamin D from three main sources, vitamin D3 supplements through the diet, sunlight exposure, and vitamin D2 from ingesting fungus in forages [40, 51].

Exposure to sunlight is essential for the synthesis of endogenous vitamin D. Penetration of UVB photons (270- 315 nm) into the stratum basale and stratum spinosum layers converts 7- DHC in human's skin to pre-vitamin D3. This compound is unstable and immediately undergoes thermal isomerization and is converted to vitamin D [7, 8, 10]. Vitamin D formation in the skin alters with UVB exposure which may be modifiable through different factors [10, 12].

One factor relates to fur or hair coat pigmentation; the higher the melanin concentration of the skin and the darker the skin, the longer it takes to form vitamin D [7, 11].

The second factor is UVB intensity which varies through latitude, altitude, clouds, and air pollution [10]. In general, the radiation intensity is lower at higher latitudes, especially in winter, when the day length is shorter. At higher altitudes, because animals are exposed to more intense radiation for a longer period, vitamin D3 is converted to biologically neutral sterols and is excreted from the shedding of skin keratinocytes [7, 11].

The third factor is 7-DHC amounts in the skin [12]. In fur-covered animals such as rabbits and rats, the 7-DHC appears to be at the site of the sebaceous glands in the skin, where it can be exposed to radiation and swallowed by animals grooming [13]. But in cows, there were three hypotheses about the production of vitamin D in the skin. a) According to previous studies on rats, cows received the required vitamin D3 by self-grooming or grooming each other. b) Scattered-hair areas of the body, including the udder and snout, are the main sites for vitamin D synthesis. c) Vitamin D is synthesized all over the skin with hair coat. Hymøller et al. 2010 conducted an experiment on cattle. They were able to prove that in cows, vitamin D is produced throughout their body despite hair coat, and the grooming hypothesis in cows was rejected [14].

Metabolic pathway of vitamin D

Vitamin D3, produced in the skin, is transported by the vitamin D binding protein (VDBP) to be stored in adipose tissue or must be taken to the liver to become active. VDBP or transcalciferin is a type of albumin that has a high affinity to bind to various metabolites of vitamin D, including calcitriol or calcidiol, so that about 0.01% and 1% of these metabolites are free in plasma, respectively. Other functions of VDBP include connection to actin, activating macrophages, and carrying fatty acids [6]. The initial stage of hydroxylation at carbon-25 is mediated by cytochrome P450 hydroxylase enzymes such as CYP27A, CYP3A4, CYP2R1, and CYP2J3 in the liver. Due to the binding of 25-(OH) D3 to VDBP, its half-life is about 2 to 3 weeks. 25-(OH) D3 (calcidiol) is the most abundant form of vitamin D in cattle's blood and is

used to assess the status of vitamin D in the body [6, 15]. The conversion of vitamin D3 to 25-[OH) D3 is not under strict control and almost all the vitamin D3 of the body is immediately converted to 25-(OH) D3 [6,7]. The association of CYP2J2 genes in cattle with 25-(OH) D3 synthesis indicates their role in mediating hydroxylation reaction in cattle likewise [6]. In the second stage of activation, vitamin D is transported through VDBP and undergoes hydroxylation in the site of carbon-1 in proximal tubules of the kidney with 1- α- hydroxylase (CYP27B1) and converted to 1, 25-$(OH)_2$D3, which is known as calcitriol [6,7,15]. After this stage, vitamin D is taken to the target organs by VDBP to perform its functions (Figure 1).

The function of the 1-α-hydroxylase enzyme is controlled strictly by the parathyroid hormone (PTH), negative feedback of calcitriol concentration, and calcitonin. When the concentration of ionized calcium in the blood drops, PTH stimulates the production of the 1-α-hydroxylase, and the amount of calcitriol production rises. At a sufficient amount of ionized calcium, calcitonin suppresses the activity of 1-α-hydroxylase and instead increases the conversion of active vitamin D to inactive forms by increasing activity of 23,24- hydroxylase [6, 12]. Phosphorus can also affect the activity of 1-α-hydroxylase, independent of PTH function and calcium levels. A high concentration of phosphorus enhances 1-α-hydroxylase activity, while lower levels of phosphate distract calcitriol production through fibroblast growth factor 23 (FGF23) and phosphatonin [6,7]. The proportion of the ratio of 1-α-hydroxylase to 24- hydroxylase in dairy cattle during the transition period is very consequential. The higher this ratio, the easier it will be to increase the amounts of 1, 25- $(OH)_2$D3. Any factor that increases the secretion of the PTH hormone and enhances the signaling of receptors can increase this ratio. Increased sensitivity of PTH is achieved with lower dietary cation-anion difference (DCAD). Acidic conditions with low DCAD make the receptors of this hormone more sensitive in the kidney. Also, keeping the FGF23 amounts low may elevate this ratio [17].

Catabolic pathway of vitamin D

It has been shown that CYP24A1 is responsible for hydroxylation reactions in the side chain at C-

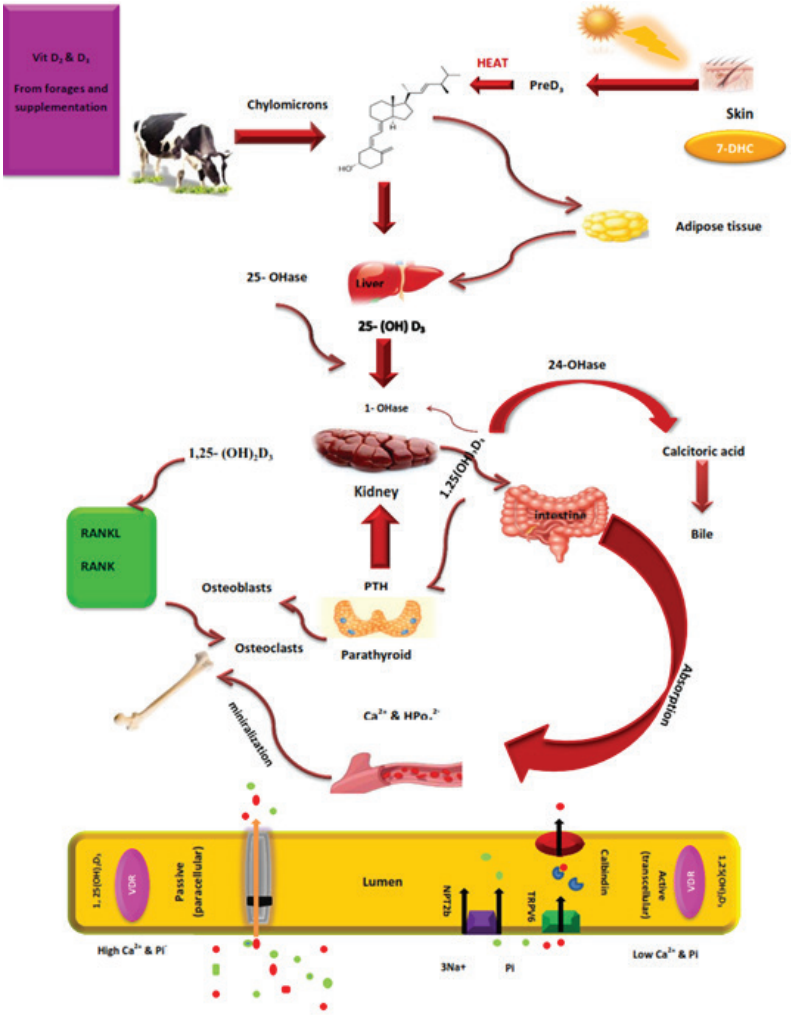

Figure 1.
The metabolism of vitamin D and its classical effects on calcium and phosphorus homeostasis.

24 and C- 23 carbon sites of either 25- (OH)D3 and 1,25- $(OH)_2$ D3. In the C- 24 oxidation pathway, 1, 25- $(OH)_2$ D3 is converted to calcitoric acid, a biliary catabolite, whereas in the second reaction1, 25- $(OH)_2$ D3, is converted to 1,25(OH) -26,23 lactone by 23-hydroxylation [5,7]. CYP24A1 is also involved in the hydroxylation of 25-(OH) D2 and 1, 25$(OH)_2$ D2 side chains and produces a series of hydroxylation products [5]. There are two VDREs in the promoter region of the CYP24A1 gene, which allow 1, 25- $(OH)_2$ D3 to regulate the expression of CYP24 via VDR and cause its catabolism. PTH and serum phosphorus levels also play a role in regulating of vitamin D catabolism pathway. Under conditions of normal calcium concentration and suppression of PTH production, CYP24A1 production is stimulated and 25-(OH] D3 is converted to 24, 25-$(OH)_2$ D3 and 1, 25- $(OH)_2$ D3 is catabolized subsequently. However, a decrease in phosphate concentration reduces the expression of CYP24A1, which leads to a decrease in 1, 25- $(OH)_2$ D3 catabolism [7].

Vitamin D functions

A substantial role of vitamin D is to preserve the concentration of calcium and phosphorus in a narrow range. These two ions are responsible for very vital functions in the body. The four main target organs for this function of vitamin D are the guts, kidneys, skeletal system, and parathyroid glands [7].

Intestine: Calcium can be transported from the guts through both transcellular and paracellular pathways. The absorption of calcium through the intestines is mediated via transient receptor potential vanilloid 6 (TRPV6) channels that are induced in the apical site of villi by 1, 25-$(OH)_2$ D3. It is revealed that these channels can interact with proteins like calmodulin, S100A10-annexin 2 complexes, and Rab11a [18]. TRPV6 channels carry calcium ions inside the cells where they join Calbindin- D9K proteins to pass across the cells. Plasma membrane ATPase (PMCA1b) and sodium-calcium exchanger (NCX1) then pump the calcium ions into the bloodstream [7]. The number of TRPV6 channels and calbindin- D9K is regulated by vitamin D to increase blood calcium levels and suppress the expression of TRPV6 leading to a decline in intestinal calcium absorption. Unlike transcellular calcium transport, paracellular calcium transport is not limited in its capacity. Paracellular calcium transport occurs through tight junctions, which are independent of 1, 25-$(OH)_2$ D3 [19]. The majority of calcium absorption of the diet is in the distal part of the guts, especially in the ileum, but the highest amount of active transport of calcium occurs in the duodenum [18]. In normal ranges of vitamin D, 30% of calcium is absorbed through the intestines, but in conditions of vitamin D deficiency, only 10 to 15% of calcium is uptaken from the diet, however, conditions such as growth, lactation, and pregnancy can increase absorption up to 60-80% [20]. Most of the phosphorus uptake occurs passively through the mechanism of diffusion throughout the intestine, but 70% of the absorption is in the small intestine. Even in severe hyperphosphatemia, dietary phosphate uptake continues and is only slightly less than normal. Albeit, phosphorus active transport is mediated by 1, 25-$(OH)_2$ D3 by increasing the number of Na+-Pi cotransporter [7,19].

Skeletal system: Longitudinal bone growth in juveniles occurs with mineralization of the bone matrix and vascular invasion. In vitamin D deficiency status, minerals no longer deposit in the matrix, leading to rickets in juveniles and osteomalacia in adults. Another function of vitamin D is to maintain serum calcium levels constant in cooperation with the parathyroid glands. Bones act as a reservoir of calcium in deficiency conditions [12]. 1, 25-$(OH)_2$ D3 has been shown to regulate the development of osteoblasts. 1, 25-$(OH)_2$ D3 elevates the expression of RANKL (Receptor activator of nuclear factor kappa-B ligand) on the surface of osteoblasts, which in turn stimulates osteoclastogenesis. Osteoclast differentiation from its precursor and maturation and bone resorption occurs with the attachment of the RANKL to the RANK (receptor activator of nuclear factor kappa-B) and Ca^{2+} ions efflux to blood flow. Production and maturation of osteoclasts are stopped by the attachment of RANKL to its antagonist osteoprotegerin (OPG) [7, 21,22].

Kidney: Approximately 65% of excreted Ca^{2+} is reabsorbed along with water and sodium in renal proximal tubules, 20% is reabsorbed through the cortical thick ascending limb of the Henle loop (CTAL). About 15% of the luminal Ca^{2+} is transported into the cells through the TRPV5 channels located at the apical region of the renal epithelial cells, where then the calbindin-D28K transports it across the cells. The Ca^{2+} ions are finally released into the bloodstream through active transport via NCX1 [23].

Vitamin D receptors

The biological functions of 1, 25-$(OH)_2$ D3 are carried out by vitamin D receptors (VDRs) [24]. The VDR is a superfamily of steroid hormones that create a heterodimer by interacting with the retinoid- X receptor (RXR). VDR/RXR heterodimers attach to the vitamin D responsive elements (VDRE) of the genome inside the nucleus [24, 25]. The expression of VDRs in various organs, including the skin keratinocytes, pancreas, guts, breast epithelial cells, prostate, activated lymphocytes, mononuclear cells, etc., indicates their extensive effects beyond calcium homeo-

stasis [12, 20].

Non- calcemic functions of vitamin D

Vitamin D modulates both innate and acquired immune systems (Figure 2). The VDR is abundantly expressed on immune cells such as B and T lymphocytes, NK cells, and antigen-presenting cells (APCs) [24]. Vitamin D can be converted to 1, 25-$(OH)_2$ D3 inside the cells of the immune system, acting locally [26, 27]. Recent studies on humans revealed that vitamin D plays an important role in immune cell mitosis, proliferation, and differentiation [26]. 1,25-$(OH)_2$ D3 enhances the production of type 2 anti-inflammatory cytokines including interleukin 4 (IL-4), interleukin 5 (IL-5), and interleukin 10 (IL-10], and decreases type 1 pro-inflammatory cytokines, for instance, tumor necrosis factor α (TNF-α), interferon γ (INF-γ), interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin (IL-9], interleukin 12 (IL-12), and interleukin 17 (IL-17) [27]. 1, 25-$(OH)_2$ D3 also elevates the production of H_2O_2 which has antimicrobial and tumoricidal activity [26]. In humans, vitamin D can also have inhibitory effects on inflammatory and autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), diabetes mellitus type 1, psoriasis, lupus erythematosus, inflammatory bowel disease (IBD), asthma, respiratory tract infections (RTI), etc. [27]. However, the effects of vitamin D on the human immune system cannot be generalized to other species, because the target organ of innate immunity in cattle is different from humans, while the acquired immunity of humans, mice and cow has many similarities [37]. For example, cathelicidin antimicrobial peptide [CAMP), which is stimulated by vitamin D, is unique to primates [28].

Studies in cattle have demonstrated that 1, 25-$(OH)_2$ D3 is in association with the innate immune system [28]. According to studies of Merriman et al. (2015) and Nelson et al. (2012), in bovine macrophages, which are the main source of calcitriol, toll-like receptor (TLR) activates 1-α-hydroxylase by pathogen's peptidoglycan, lipopeptide, and lipopolysaccharide recognition, which eventually leads to vitamin D-related immune responses. The responses

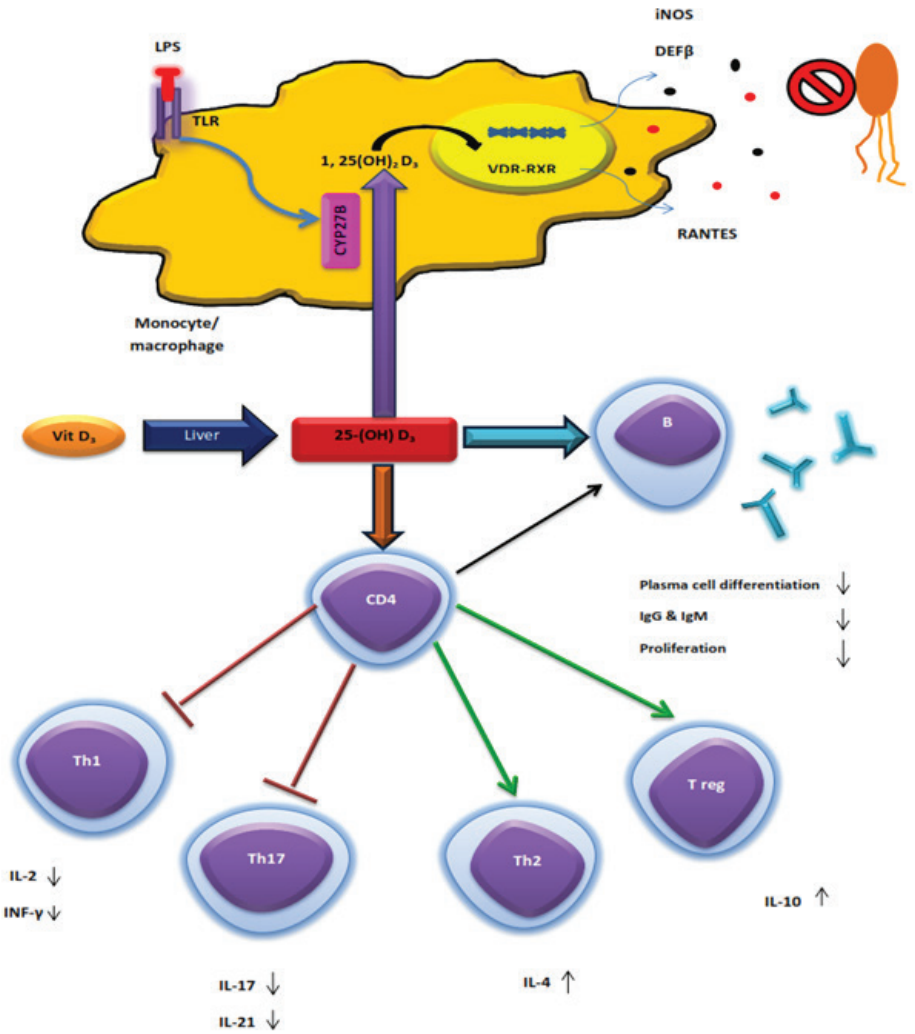

Figure 2.
The effects of vitamin D on innate and adaptive immune responses.

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include inducible nitric oxide (iNOS), RANTES, and five ß-defensins (DEFB3, DEFB4, DEFB6, DEFB7, and DEFB10) which are related to 1, 25- $(OH)_2$ D3 levels *in vitro* [6, 29]. It has previously been proved that vitamin D has an inhibitory effect on the production of IL-4, IL-17, and INF-γ [63, 74]. Hassanabadi et al. showed that prepartum vitamin D injection has an increasing effect on IL-6 levels in dairy cows [50]. In contrast, Xu et al. (2021) showed that vitamin D supplementation has an inhibitory effect on IL-6 production [48].

1,25-$(OH)_2$ D3 may suppress the proliferation of mammary gland epithelial cells through cell cycle regulators, such as p21 and p27P21 [6]. However, a later *in vivo* study conducted by Merriman et al. (2016) demonstrated that vitamin D leads to an increase in iNOS and DEFB7 in mammary glands, while other ß-defensins were not affected [29]. Elevated induction of iNOS in bovine udder induces strong bactericidal effects in macrophages. Likewise, ß-defensins located in the udder, have potent antimicrobial effects against common mastitis-related bacteria [30]. Lippolis et al. proved this claim and by injecting intermammary 25-(OH) D3, they showed that mammary glands' immunity was significantly increased against *Streptococcus uberis,* and somatic cell count (SCC) was reduced in milk (31).

The results of the study of Martinez et al. (2018) were in agreement with previous findings. They showed that high levels of calcidiol and calcitriol in cattle's blood amplify the innate immune system and reduce the risk of periparturient diseases. 25-(OH) D3 elevates the number and activity of neutrophils with bactericidal properties and may prevent retained placenta and the establishment of bacteria in the uterus [33]. In the retained placenta, the immune system is unable to identify semi-allogeneic fetal tissues [34]. Thus, boosting innate immunity with vitamin 25-(OH) D3 may have inhibitory effects on the retained placenta and metritis [35]. Because, in cattle, bacteria settle in the uterus after parturition [36]. Calcidiol prevents metritis by its effects on immune cells and secretion of antimicrobial peptides [37].

Studies show that 25-(OH) D3 levels are decreased during the transition period in cattle, thus susceptibility to oxidative stress and diseases are enhanced. In general, calving causes an inflammatory condition, and the highest amount of Haptoglobin and C-reactive protein was recorded in Holstein Friesian cattle during the first month of calving compared with prepartum and late lactation [38]. Systemic inflammatory conditions like parturition and oxidative stress, deplete vitamin D metabolites due to elevated intracellular hydroxylation of 25- (OH)D3 to 1,25-$(OH)_2$ D3 [39]. Also, increased milk production in the mammary glands and cholesterogenesis reduce the amount of 25- (OH) D3 [40].

Calcitriol has been proved to stimulate the production and secretion of prolactin from the pituitary gland, decidua, and immune cells in rats and endometrium in humans [41, 42]. In dairy cattle, prolactin is not necessary for milk yield and has permissible impacts on steroids, but a prolactin surge occurs before calving [43], indicating that it is necessary for milk production [44]. Calcitriol also stimulates the expression of RANKL, which is an important paracrine factor in alveologenesis induced by progesterone [45]. The prepartum calcitriol administration in cows elevates the absorption of IgG through the mammary cells and raises its amount in the colostrum [33]. It is probably due to the increased production of IL-10, which leads to increased secretion of immunoglobulins from plasmablasts [47]. The results of a study conducted by Hassanabadi et al showed that injection of a single dose of vitamin D in dairy cows leads to an increase in glutathione peroxidase (GSH-PX) in hemolysate [50]. The findings of Xu et al. were consistent with this result. Xu et al. (2021) reported that vitamin D administration in cows can elevate the amounts of total antioxidant capacity (T-AOC), total superoxide dismutase (T-SOD), and GSH-PX [48]. The results of a survey indicated that vitamin D is a potent antioxidant factor in cell membranes. Therefore, administration of vitamin D declines the levels of malondialdehyde (MDA) and thiobarbituric acid reactive substance (TBARS), which are indicators of oxidative damage to cells [49].

John's disease or paratuberculosis is an inflammatory disease of the guts caused by *Mycobacterium avium* subsp. paratuberculosis. According to research by Sorge et al., there is a direct relationship between the severity of the disease and vitamin D levels. They found a significant difference between the vitamin D levels of healthy and sick cows. They mentioned three explanations for it. The first reason, cows with lower vitamin D levels are more susceptible to paratuberculosis infection. The second reason is that in the development of paratuberculosis, the absorption of vitamin D from the intestine is decreased. The last reason is that most of the vitamin D in the body is used to modulate the hyperactive immune response in paratuberculosis. The prevalence pattern of this disease is similar to Crohn's disease in humans and the incidence is high in coordinates with less radiation [26].

Requirements

Dairy cattle gain the required vitamin D, either by eating forages that contain vitamin D2 and consuming vitamin D3 supplements or from direct sun exposure, which produces vitamin D3 endogenously [51,

52]. Cattle can get significant amounts of vitamin D2 from forages such as alfalfa, which contains 2,500 IU of vitamin D2 /Kg of DM, and silage, which contains 500 IU of vitamin D2 /Kg of DM [53, 54]. However, vitamin D3 is the main form in blood circulation [55]. Due to the inefficient metabolism of vitamin D2 [56, 57] and raising cows indoors away from sunlight, the likelihood of vitamin D deficiency is high [26]. Thus, NRC recommends administering 21,000 IU/d vitamin D3 in dairy cattle to maintain 25(OH) D3 levels between 20 and 50 ng/mL and regulate calcium and phosphorus homeostasis [58]. Although the amount of vitamin D intake in most dairy cows is about 1.5 to 2.5 times the amount recommended by the NRC, the average vitamin D is about 60 to 70 ng/mL [32]. Dairy cows also experience a decrease in vitamin D levels in the postpartum period. At early lactation, cows are more susceptible to oxidative stress and metabolic disorders, which is probably due to vitamin D insufficiency or deficiency. A threshold of 30 ng/ml has been suggested in human studies to improve immune functions but is not yet conclusive [59]. In cattle, the optimal amount of vitamin D has not been determined for the proper functioning of the immune system. Nelson et al. (2012) reported that vitamin D improves performance in macrophages of the immune system *in vitro* up to 100 ng/ml. For instance, there was no difference between calves with 175 ng of 25-(OH) D3 and those with 30 ng of 25-(OH) D3 against the respiratory syncytial virus (RSV) [6].

Deficiency

Vitamin D deficiency in cattle along with calcium and phosphorus imbalance causes rickets in calves due to lack of calcium deposition in the growing bone matrix and osteomalacia in adult cows due to calcium loss from developed bone [60]. Clinical symptoms of vitamin D deficiency include loss of appetite, gastrointestinal upset, stiffness in gait, severe weakness, difficulty in breathing, irritability, and sometimes tetany and seizures. Swelling and erosions on joints lead to difficulty in motion, arching of the back, and bending of the legs [60, 61]. Calves born to mothers with vitamin D deficiency may be malformed, weak, or even dead [62]. The metacarpal and metatarsal bones begin to thicken, and as the disease progresses, the anterior limbs bend forward or to the sides. In advanced cases of vitamin D deficiency, long bone deformity occurs as a result of normal muscle tension. Beading appearance occurs at the junction of the ribs in the sternum due to the enlargement of bone and accumulation of cartilage [61]. Eating is difficult due to the softness and thickening of the mandible. In older cattle, the bones are very fragile, which can lead to posterior paralysis with vertebral fractures. Decreased milk production and lack of estrus are observed in vitamin D deficient dairy cattle [58]. The probability of vitamin D deficiency in beef cattle is very low unless a diet poor in vitamin D is consumed and housed away from sunlight. In this case, the symptoms of deficiency appear in less than 6 to 10 months [64]. In general, calving rates are very low in deficient herds, and newborns are often very weak and die immediately after birth [60].

Milk fever is a metabolic disorder that occurs due to excessive demand for calcium periparturient period [52, 65]. Milk fever begins about 3 days after parturition and continues with depression, general paralysis, circulatory collapse, coma, and death. The most important feature of the disease is a decrease in calcium levels to values between 3 to 7 mg/dl [12]. Milk fever is more likely to occur in older cows than in heifers [66]. Older cows show reduced production and reduced response to calcitriol. There are also fewer osteoclasts to respond to calcitriol and increased plasma calcium levels through bone dissolution [65]. They also have lower levels of 1-α hydroxylase [52, 65]. We also face with decreased number of VDRs and the activity of osteoblasts in the periparturient period [67, 68]. But a low-calcium, adequate- phosphorus prepartum diet followed with a high calcium diet postpartum can prevent milk fever [52]. A low-calcium diet induces calcitriol production through PTH [69, 70].

Toxicity

Vitamin D toxicity may occur due to overfeeding with calcinogenic herbs or taking high doses of vitamin D supplements, leading to calcification in soft tissues. 400 ng/ mL of vitamin D in plasma could be safe [71, 72]. According to the NRC recommendation, cows can tolerate 2200 IU D3/kg for 60 days and 2,500 IU D3/kg for shorter periods. Hibbs et al. determined that for the inhibition of milk fever without any toxicity feeding with high doses of vitamin D could be more effective than parental administration. Administration of 20 to 30 million IUD2 for 3 to 8 days prepartum was able to reduce 80% of milk fever cases while prolonging the duration of treatment to 20 days prepartum led to toxicity [73]. Calcinogenic plants include Solanum malacoxylon, Cestrum diurnum, Trisetum flavescens, and Nierembergia veitchii. These plants contain 1, 25-$(OH)_2$ D3 or its glycosides. These glycosides are activated through microbial digestion in the rumen. Clinical signs of calcinosis include weight loss, increased respiratory rate, tachycardia, impaired mobility, fertility problems, and decreased survival. However, some calcinogenic plants can be useful in preventing hypocalcemia [26].

Conclusion

In summary, it should be noted that beyond its classical roles in calcium and phosphorus homeostasis, vitamin D is an immunomodulatory agent and has protective effects against oxidative stress. These functions are important in preventing numerous diseases, especially peripartum diseases in cattle. Therefore in future studies, it is essential to determine the optimal concentration of vitamin D for the best function of the immune system and reduction of oxidative stress that minimizes the economic burden of disease in the dairy cattle industry.

Authors' Contributions

SAS: Investigation; Writing-original draft; MM: Conceptualization; Supervision; Writing-review & editing.

Competing Interests

The authors have no conflicts of interest to declare that are relevant to the content of this article.

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