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Review Article

Vitamin D Deficiency in Farm Animals: A Review

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ABSTRACT

One of the most effective Vitamins in the musculoskeletal structure and immune system of farm animals is Vitamin D. The widespread risk of Vitamin D deficiency states is known widely resulting in autoimmune diseases, diabetes, rickets, metabolic bone diseases, and cancers. The aim of this review is to address the subject of Vitamin D deficiency in farm animals and the role of Vitamin D in health and deficiency states. Although Vitamin D deficiency is generally defined as < 20 ng/mL in serum, but this level remains to be discussed. Vitamin D synthesis in the skin is the major source of Vitamin D in the body and is influenced by genetic and several environmental factors, such as length of sun exposure, season, and latitude. Sun exposure might be limited during winter in some areas, such as northern latitudes. Thus, food sources can play essential roles in supplying the demand for Vitamin D. Some animal species have more sensitivity to Vitamin D deficiency due to their different metabolism, homeostasis, and adaptation to specific diets and environments. Farm animal species, such as cattle, pigs, llamas, Alpacas, small ruminants, and broiler chickens are more sensitive to Vitamin D deficiency. However, some farm animal species including horses and donkeys usually have a low risk of Vitamin D deficiency. Therefore, the management of Vitamin D deficiency and its consequences are critical in some species. The inclusion of Vitamin D in the body of farm animals depended on farming practices, sun exposure in different seasons, and the content of diets. Due to the diversity of species, regulation of many ongoing processes in animals' bodies, the complexity of Vitamin D metabolism, and different metabolites, more studies are necessary to find the vital roles of Vitamin D in the prevention and control of diseases in farm animals.

1. Introduction

The prevalence of Vitamin D deficiency is very common in humans and farm animals[1,2]. Since one of the primary roles of Vitamin D in farm animals is its participation in the metabolism of calcium and phosphorus, Vitamin D deficiency results in bone diseases, such as rickets in farm animals, and severely affects immunity and cell differentiation[2,3].

Vitamin D3 is synthesized in the skin as a result of sun exposure which is the major source of Vitamin D in the body. Vitamin D3 synthesis depends on sunlight factors such as season and day-length and latitude can be limiting[4,5]. Vitamin D insufficiency could increase in animals due to decreased sunlight exposure, and resulting in musculoskeletal disorders[6]. Sun exposure might be limited during winter in some areas, such as northern latitudes, therefore intake from food sources of Vitamin D such as season and day-length and latitude can be limiting[4,5]. Vitamin D insufficiency could increase in animals due to decreased sunlight exposure, and resulting in musculoskeletal disorders[6]. Sun exposure might be limited during winter in some areas, such as northern latitudes, therefore intake from food sources of Vitamin D

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becomes essential in these areas[7]. Vitamin D deficiency is associated with an increased risk of hypertension, autoimmune diseases, diabetes, and cancers in humans[4]. One of the natural contents of Vitamin D is fatty fish. In comparison to fatty fish, meat and dairy product have a lower content of Vitamin D, but their contribution to the total Vitamin D intake is significant in places with a high intake of meat and dairy products. For instance, dairy product intake contributes to about 12% of the total Vitamin D intake in Denmark[8].

There is a controversy regarding the optimal level of Vitamin D for maintaining the health of farm animals[6]. According to the Institute of Medicine (IOM) report, Vitamin D deficiency is the content of 25(OH)D3 less than 20 ng/mL in serum[1].

A study reported that cutaneous synthesis of Vitamin D3 in cows is independent of hair coverage but does depend on the length of sun exposure[9]. In winter, the lack of Vitamin D in dairy cows can be compensated by dietary supplementation of Vitamin D status[10]. In the winter, due to low sun exposure, the whole milk of cows kept in a stable is 6 times lower than their whole milk in the summer, when the cows are regularly on pasture[11]. Notably, a study revealed that there is an association between sunlight exposure and Vitamin D3 content in human breast milk[12].

Given that the prevalence of Vitamin D deficiency is common in farm animals and it is associated with some diseases that impact farm animals' health, the current study aimed to review the studies addressing the effect of Vitamin D on farm animals' bodies and understand different aspects of Vitamin D deficiency on farm animals health to manage and prevent Vitamin D deficiency consequences.

2. Biology of Vitamin D

2.1. Activation of Vitamin D

Ultra-violate light (UVB) within the range of 270-315 nm is required to convert 7-dehydrocholesterol (7-DHC) to pre-Vitamin D3 in the skin. A reversible thermoisomeriation reaction occurs and converts pre-Vitamin D3 into Vitamin D3. The pigmentation of the skin and the range of UVB are very important in the synthesis of Vitamin D in the skin[13]. In heavily pigmented skin (dark), a longer duration of sunlight is needed to synthesize Vitamin D[13]. Latitude and altitude are two other factors that have an influence on UVB exposure to the skin. Less UVB reaches the skin at high latitudes and low altitudes, particularly in seasons like winter when daylight is shorter [4]. When the sunlight is extreme in high-altitude areas, animals might be subjected to extreme UVB. In this condition, pre-Vitamin D3 is converted to biologically inert metabolites, such as tachysterol and lumisterol, and sloughed off by skin turnover with keratinocytes[14,15].

Vitamins D2 and D3 are two sources of Vitamin D. Vitamin D3 can be synthesized from the isomerization of 7-DHC following exposure to sunlight, in the skin, and D2 is obtained from the diet[4]. Some foods are sources of Vitamin D2 like cod liver oil and fish like sardines. Moreover, Plants are the source of Vitamin D2. Vitamin D2 is created in the plant from ergosterol following exposure to sunlight[13].

Vitamin D that is synthesized in the skin binds to a Vitamin-binding protein and transfers to the liver or is stored in body fat. Vitamins D2 and D3 take part in two hydroxylation reactions to become activated[16]. The 1,25-dihydroxy Vitamin D3 (1,25(OH)2D3) is the activated form of Vitamin D. The 25-hydroxylation occurs mainly in the liver and the second 1α-hydroxylation takes place in the kidney then Vitamin D is converted to the activated form[13]. Measurements of the blood's 25(OH)D levels indicate dietary consumption or skin synthesis of Vitamin D[14,16]. Calcium levels in the blood could influence Vitamin D activation. If the ionized calcium concentration is low, renal 1α-hydroxylation of 25(OH)D synthesizes 1,25(OH)2D3. 25(OH)D converts to an inactive metabolite by 24-hydroxylation when being in the normal range[14]. Parathyroid hormone (PTH), calcitonin, and feedback inhibition of 1,25(OH)2D3 also affect renal 1α -hydroxylase activity[17].

Phosphate levels in the blood could influence 1,25(OH)2D3 synthesis. When the plasma phosphate level is low, it could induce 1α-hydroxylation activity independent of PTH and calcium levels but when the phosphate level is high it inhibits 1,25(OH)2D3 formation[18-20].

2.2. Functions of Vitamin D

The main target organs for Vitamin D include the intestines, bones, kidneys, and parathyroid glands. Vitamin D has a main role in the control of calcium and phosphorus in the normal range[13]. In this regard, 1,25(OH)2D3 increases the absorption and transport of calcium in the intestines. Moreover, it could increase the absorption of phosphate by enhancing the expression of the Na-P_i transporter that changes intestinal cell membrane lipid composition[21,22]. In bones, 1,25(OH)2D3 is responsible to increase the mobilization of calcium from bone stores to keep plasma calcium levels in the normal range[23,24].

A decrease in serum level of Vitamin D reduces calcium levels and results in parathyroid hyperplasia and also secondary hyperparathyroidism[13,24]. In addition, 1,25(OH)2D3 could suppress parathyroid cell growth by reducing growth factors and increasing the inhibitors of cell growth[25]. One of the main roles of 1,25(OH)2D3 in the kidneys is to regulate its synthesis by the inhibition of renal 1α-hydroxylase and stimulation of CYP24 (24-hydroxylase), which affects PTH and consequently increases the absorption of calcium and phosphate by intestines[13]. The method of transferring calcium across epithelial cells is similar to the intestinal epithelium. Accordingly, 1,25(OH)2D3 could increase the transportation of calcium across distal convoluted tubules by increasing PTH. Furthermore, 1,25(OH)2D3 could increase reabsorbing of phosphate from renal tubules, in the presence of PTH[26].

2.3. Other roles of Vitamin D

A few reports have indicated that Vitamin D can reduce cell growth in tumor cells and there is a negative correlation between Vitamin D levels in the body and the incidence of some cancers[27,28]. Additionally, Vitamin D influences immune system function and could prevent some diseases, such as cardiovascular disease, hypertension, and diabetes mellitus, and have treatment effects on rheumatoid arthritis, inflammatory bowel disease, psoriasis, and multiple sclerosis[29,30].

2.4. Toxicity

An increase in Vitamin D levels can be toxic and result in tissue mineralization, in association with hypercalcemia and hyperphosphatemia. Clinical signs of intoxication of Vitamin D in farm animals are hypertension, nervous signs, arrhythmia of the heart, severe gastrointestinal signs, and death[15]. According to[31] cows can tolerate feed with 2200IU D3/kg of diet for a long duration, and recommended dosage of Vitamin D in the diet is 30IU/kg of body weight. The parenteral dose of 15 million IU of Vitamin D3, 32 days before parturition, and the second injection of 5 million IU D3, 7 days later, were toxic in dairy cattle[32]. In some countries where cholecalciferol is used as a pesticide, it could result in toxicity. The toxicity is not completely understood but serum 25(OH)D concentrations are 10 to 20 times greater than the normal range in intoxicated animals. In addition, some calcinogenic plants, such as *Solanum malacoxylon*, *Cestrum diurnum*, *Trisetum flavescens*, and *Nierembergia veitchii* could result in toxicities in cattle, sheep, goats, pigs, horses, and buffalo[33,34].

3. Metabolism of Vitamin D in farm animals

Vitamin D deficiency is associated with metabolic bone diseases in animal species due to the role of Vitamin D in the metabolism and homeostasis of calcium and phosphorus[6]. Some factors, such as genetics and environment, have affected Vitamin D metabolism in animal species[35]. The function of Vitamin D in different animal species is different due to their adaptation to particular diets and environments[36]. Metabolism of Vitamin D is completely different in various animal species but it could result in similar symptoms. So, treatment and prevention protocols for Vitamin D deficiency and consequences should not be similar[35].

The ability to synthesize Vitamin D in the skin is different in animal species. Similar UVB exposure in rats could 40-fold increase in Vitamin D3 synthesis in the skin compare to dogs and cats. It might be due to the activity of the 7-DHC-D7-reductase enzyme that degrades 7-DHC in dogs and cats skin[15]. In dogs, seasonal variations in Vitamin D levels are not obvious. So, pet animals, particularly dogs and cats must obtain their Vitamin D requirements from diets[6].

Herbivores can synthesize Vitamin D from their skin following UVB exposure[15]. Llamas and alpacas developed thick hair coats with heavy cutaneous pigmentation that protects them from extreme UVB in their natural environment although they are very susceptible to Vitamin D deficiency[37]. If they are moved to places with limited solar irritation, particularly in winter, their Vitamin D concentration will decrease significantly[37]. The Vitamin D requirement in calves for the prevention of rickets is 6.7 IU Vitamin D/kg of BW[3]. Cattle could acquire parts of their needs for Vitamin D2 from forages. For example, alfalfa hay and corn silage can contain as much as 2,500 IU of Vitamin D2/kg of dry matter (DM) and approximately 500 IU of Vitamin D2/kg of DM, respectively. Vitamin D2 content in forage is highly variable (160 to 2,500 IU/kg of DM for alfalfa hay) so forage is not a reliable source of Vitamin D3.

Vitamin D2 is not converted as efficiently as Vitamin D3[38]. Vitamin D3 is the major circulating form in cattle blood. Supplemental Vitamin D that is often provided to cattle is Vitamin D3. The best indicator of Vitamin D status in animals is the concentration of 25(OH)D in serum similar to humans. Circulating 25(OH)D concentrations of 20-50 ng/mL of serum have traditionally been described as normal for cattle, and concentrations below 10 ng/mL are indicative of Vitamin D deficiency[38].

3.1. Vitamin D deficiency in non-ruminant

3.1.1. Horses

Vitamin D has a very important role in the regulation of Ca and P, the proliferation of the cell, the physiology of bones, and the integrity of epithelial tissue in horses[15]. Vitamin D could increase intestine absorption of Ca and P as well as increase reabsorption of Ca and P in kidneys. Vitamin D has an important role in the control of osteoblast activity and deficiency of Vitamin D could result in skeletal irregularity[39]. Another important function of Vitamin D is anti-carcinogenic, anti-inflammatory effects, and immunomodulation in horses[40]. Vitamin D level in horses' blood is very low (6.6 IU per kilogram of body weight) and this level would be considered as Vitamin D deficiency in other species[41]. Horses' intestines have a high ability to absorb calcium. In other words, horses have high levels of calcium in their blood, with low Vitamin D metabolite levels[42]. Moreover, they have low sensitivity of their parathyroid gland to calcium[39].

Rickets is not common in horses since they developed a mechanism for calcium hemostasis[15]. A study revealed that there were no differences in 25(OH)D3 concentration between horses with blankets and horses without blankets[43]. The result was surprising because skin coverage directly influences 25(OH)D3 synthesis in other species. There is a seasonal pattern in horses for 25(OH)D2 levels that decreases in winter and increases in summer. These results indicated that horses might rely on diet for their Vitamin D requirements [43]. A study showed that signs of rickets may appear in Shetland ponies due to limited exposure to sunlight and a deficient Vitamin D diet. Compared to other species, Shetland ponies showed an obvious increase in serum calcium and 1,25(OH)2D concentrations during Vitamin D intoxication[9]. In healthy foals, Vitamin D concentration is lower than that of adult horses. Low Vitamin D levels in foals are associated with an increase in the occurrence of disease and death[44].

3.1.2. Pigs

Pigs are very susceptible to Vitamin D deficiency and diseases associated with Vitamin D deficiency include rickets and osteomalacia[45]. Early weaning, living in the indoor environment, rapid growth, and limited exposure to UVB in modern pig farms are factors associated with an increase in Vitamin D deficiency in pigs, and it shows that Vitamin D supplementation in pigs' diets is essential[46]. A study showed that exposure to sunlight is more effective in increasing Vitamin D levels in pigs than supplementation of Vitamin D in the diet[45]. Another study indicated that supplementation of a pig diet with 25(OH)D3 was more efficient in increasing Vitamin D levels and resulted in faster growth in piglets[47].

3.1.3. Llamas and alpacas

Llamas and alpacas are living in high-altitude places and they are adapted to extreme UVB also they extremely depend on the skin synthesis of Vitamin D[35]. A study showed that when Llamas and alpacas move to another climate, particularly temperate regions they become more susceptible to Vitamin D deficiency[48]. Seasonal variation is also very obvious in these species, for instance, crias born in October to February have lower Vitamin D levels and are more susceptible to rickets than crias born in summer[49]. Compared to sheep, alpacas are more susceptible to rickets and a study revealed that in New Zealand alpacas become hypophosphatemia and showed signs of rickets in winter, whereas, lambs that pasture in the same area did not develop signs of rickets[50].

3.1.4. Donkeys

Vitamin D has a remarkable impact on calcium and phosphorus metabolism in donkeys. However, Vitamin D deficiency is not common in donkeys due to the mechanism of calcium absorption in the intestines, and the reabsorption of Ca and P from kidneys, which is similar to that of horses[53].

Donkey milk products have recently been used for some reasons in the human diet[51]. The value of donkey milk has been known since ancient times. In recent years, scientific community interest has been attracted to donkey milk as a therapeutic product for children with bovine milk protein allergy[52]. In addition, the Vitamin D content of donkey milk is high and could be a good substitution for cow milk[51]. Although the bacterial count in donkey milk is low for preventing foodborne disease, thermal treatment is recommended[53]. Pasteurization of milk is known to eliminate pathogenic microorganisms and guarantees its preservation. However, the effect of pasteurization on nutritional characteristic are not investigated well. The nutritional characteristic of donkey milk is targeted for consumption by children due to its similarity with human milk. Moreover, donkey milk is rich in calcium content, low in fat, and easily digestible[51].

3.2. Vitamin D deficiency in ruminants

3.2.1. Small ruminants

Compared to adults, lambs and kids are less susceptible to Vitamin D deficiency and they can compensate for Vitamin D deficiency through skin synthesis of Vitamin D[54]. Some studies revealed higher Vitamin D levels in New Zealand herds than Scottish Blackface and Soay flocks[54-56]. It might be due to differences in skin pigmentation. Romney sheep in New Zealand have less skin pigmentation than Soay sheep and the Scottish Blackface sheep, which have dark skin with heavy pigmentation[54].

A study showed that sheep with heavy skin pigmentation have lower Vitamin D levels, compared to shorn sheep with white faces and legs. Moreover, it was revealed that Vitamin D levels depend on the season, and during pregnancy demand for Vitamin D will increase[54].

Small ruminants could not modify renal calcium in response to dietary calcium deficiency[57].

Compared to sheep, goats are less susceptible to challenges of calcium hemostasis. Moreover, sheep are more influenced by dietary Vitamin D intake than goats. The skin levels of 7DHC in goats' skin are 10 times more than in sheep, resulting in a low incidence of rickets in goats[58]. Lambing is related to the seasonal reduction and Vitamin D status in ewes. Vitamin D supplementation in ewes' diet improves the Vitamin D status of lambs[57,59]. Vitamin A, D3, and E administration is associated with a reduction in vaginal prolapse in pregnant ewes and an increase in spermatogenesis and sperm maturation in sheep[59].

3.2.2. Cattle

Vitamin D has a very significant role in the prevention of rickets, osteomalacia, and hypocalcemia (milk fever) in dairy cows. Vitamin D levels in cows after calving is lower than in cows at late pregnancy also newborn calves have lower Vitamin D levels, compared to adult[60].

The recommended dosage for the prevention of hypocalcemia in cattle is 20-30000IU Vitamin D/day in the diet[5]. In addition, supplementation of Vitamin D in the diet of dairy and beef cows is very important due to the farming practices that cause limited sunlight exposure also the requirement for Vitamin D increase before calving in cows[60]. Therefore, Vitamin D supplementation is essential to adjust calcium hemostasis[61].

Consumers gain more benefits from these products by increasing Vitamin D levels in milk and meat. Supplementation of 25(OH)D3 in dairy cows' diets can increase Vitamin D levels in blood more efficiently. A study indicated that some factors such as UVB exposure, diet, farming practices, breed, hair color, age, and stage of lactation could influence Vitamin D hemostats in dairy cows[62]. These results suggest that farmers could manipulate these factors to increase the Vitamin D content of milk[62,63].

Some studies reported that Vitamin D could influence the immune systems of dairy cows. There is a negative relationship between Vitamin D levels and infectious diseases, such as metritis and retained placenta in dairy cows[63,64].

3.3. Vitamin D deficiency in poultry

Protection and improving the immune system in fast-growing chickens such as broilers is critical. The recommended dosage of Vitamin D in broiler chicken is 200 IU [65]. Vitamin D can affect the cell-mediated immune response of female broiler chickens[66]. It seems Vitamin D deficiency is not a big concern in male chickens; its requirement in males is less than in females[67].

Herbal and synthetic sources of Vitamin D are supplemented in the poultry diet to provide their requirement of Vitamin D. In addition, one of the advantages of using herbal sources of Vitamin D3 is increasing of feed intake ratio of broiler chickens[68]. Increasing dietary supplementation of Vitamin D can cause enhancing concentration of this Vitamin in the meat and egg yolk of domestic birds. Consumers could gain more benefits from these products [69,70]. However, a study indicated that increasing the dietary level of Vitamin D to 1800 IU could not affect the level of antibody titers and heterophil/lymphocyte ratio, although it reduced bone strength[71]. In another study, increasing the dietary level of Vitamin D to 4000 IU in the pre-oviposition stage causes positive effects on the growth performance of quails[72].

4. Conclusion

Vitamin D involves in many body organ functions, such as the musculoskeletal system. Notably, Vitamin D deficiency could result in musculoskeletal disorders like rickets. Some factors influence Vitamin D concentration in the body, such as duration of sun exposure, season, the content of Vitamin D in the diet, and latitude, also some genetic factors. According to some studies, Vitamin D deficiencies are common in some species, particularly farm animals and humans, importantly due to the lack of sun exposure in some areas. Species that are more susceptible to Vitamin D deficiency are cattle, small ruminants, llamas and Alpacas, broiler chickens, and pigs, and is rarely common in species, such as horses and donkeys.

Therefore, methods to prevent Vitamin D deficiency and its consequences are vital. Factors that could influence the Vitamin D concentration in farm animals' bodies are farming practices, duration of sun exposure, Vitamin D content in the diet, and season. Therefore, managing these factors could be effective in the prevention of Vitamin D deficiency in farm animals. Due to the complexity of Vitamin D metabolism and the diversity of its metabolites, more study needs to evaluate the Vitamin D role in diseases and the regulation of many ongoing processes in animals, also protocols for the prevention of Vitamin D deficiency in farm animals.

Declarations

Competing interests

There is no conflict of interest.

Authors' contribution

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Ethical considerations

Ethical issues (including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy) have been checked by all the authors.

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