Report

The Role of Vitamin D_3 in Regulation of Calcium Homeostasis in Dairy Cattle Metabolism

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Introduction

Vitamin D_3 plays a major role in the regulation of calcium homeostasis, affecting skeletal development, Calcium (Ca) and Phosphorus (P) metabolism, cellular differentiation and proliferation, and activation of the immune system. Research in other species with high metabolic demand for calcium have led to a re-evaluation of the importance of vitamin D_3 for dairy cattle. In addition, the housing of dairy cattle in total confinement facilities, the feeding of prepartum negative DCAD diets, and the recognition of the impacts of subclinical hypocalcemia on dairy cattle health and performance have all placed more emphasis on the potential benefits of dietary vitamin D_3 supplementation during the transition period of the dairy cow. The aim of this report is to discuss the role of vitamin D_3 on dietary Ca absorption, bone resorption, and regulation of calcium metabolism.

Vitamin D Metabolism

Sources of vitamin D include vitamin D_2 from plants, vitamin D_3 synthesized endogenously in skin exposed to sunlight, and from supplemental sources of vitamin D_3 in the diet (Nelson et al., 2016). Once vitamin D_3 is synthesized or absorbed, it needs to be converted into the active form of $1,25(OH)_2$ D through a metabolic pathway to exert its effects on calcium metabolism.

Vitamin D_3 and Ultraviolet Radiation

Provitamin D (7-dehydrocholesterol) is synthesized from the cholesterol-forming system and can be converted to vitamin D_3 from photoconversion in epithelial cells exposed to sunlight. This can be a primary source of vitamin D_3 for dairy cattle housed outdoors and has the advantage of not being degraded by ruminal fermentation (Nelson and Merriman, 2014). The synthesized vitamin D_3 enters the blood and binds to vitamin D-binding protein. The half-life of vitamin D_3 in blood ranges from 36 to 78 hours, but is extended to approximately two months if stored in adipose tissue (Mostafa and Hegazy, 2015).

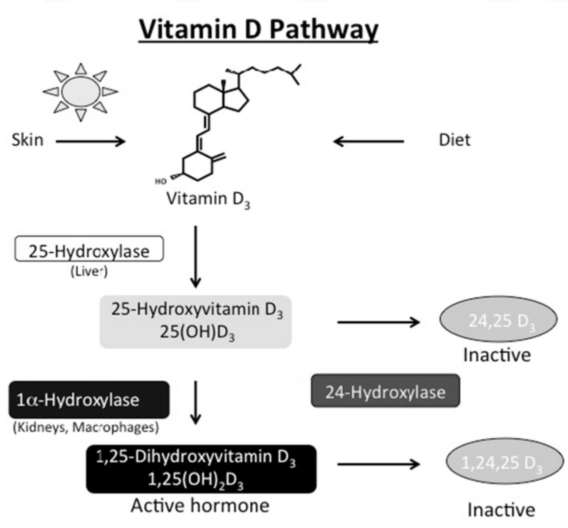
Dietary Vitamin D_3

In most dairy production systems, the vitamin D_3 synthesized in the epithelial cells, alone, is not able to meet animals' requirements for vitamin D_3, so dietary sources of vitamin D_3 become important to support a healthy and productive animal. Vitamin D_2 is obtained naturally by the ingestion of fungal ergosterol growing on the feed and vitamin D_3 is provided through nutritional supplements (Weir et al., 2016). As most of the ingredients used in dairy cattle feed are low in vitamin D_2, it is normal practice to add supplemental sources of vitamin D_3 to the diet (Nelson et al., 2016).

Vitamin D_3 Metabolic Pathway

Vitamin D_2 and vitamin D_3 are inactive forms of vitamin D which need to be activated via a metabolic pathway. In the first step of this pathway (Figure 1), vitamin D_2 and D_3 are hydroxylated to 25-hydroxyvitamin D_3 (25-OH D) in the liver. With that, 25-OH D is the most abundant vitamin D_3 form in the blood of dairy cattle. Normal serum concentrations of 25-OH D_3 for cattle are typically defined as 20 to 50 ng/ml (Horst et al., 1994). Conversion of vitamin D_3 to 25-OH D in the liver can be a limiting step, particularly when liver metabolism is impaired, such as during ketosis, and potentially throughout the transition period. Under such conditions, providing dietary 25-OH D may improve calcium homeostasis by reducing the total dependence on the liver to activate the Vitamin D_3.

Figure 1: General Vitamin D_3 Metabolic Pathway (Nelson, C. 2014)

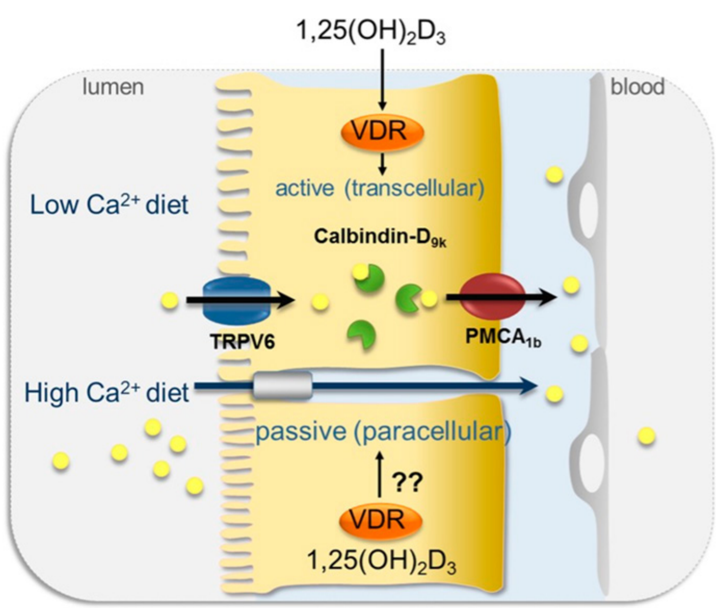


The final step of the pathway occurs in the kidney where 25-OH D is converted to the biologically active vitamin D_3 (1,25-dihydroxyvitamin D_3 ($1,25\text{-}(OH)_2$ D)). The concentration of active vitamin D_3 in the blood is tightly regulated and typically ranges from 5 to 20 pg/mL in serum of cattle, but can be elevated to more than 300 pg/mL during severe hypocalcemia (Horst et al., 1994). In the circulation, the active vitamin D_3 binds to vitamin D binding protein and it is transported to target organs to regulate calcium and phosphate homeostasis.

Effects on Calcium Metabolism

The active form of vitamin D_3 acts to upregulate the expression of genes related to calcium binding and transport, as well as bone remodeling (Nelson et al., 2016). Intestinal Absorption of Ca Calcium absorption in the intestine occurs via passive and active transport (Figure 2). Passive transport occurs when Ca concentration in the gut lumen is high. Active transport takes place when Ca concentration in the gut is low, and it is vitamin D_3-dependent. Active absorption is a three-step process that includes entry of Ca from the intestinal lumen through Ca channels, translocation of Ca from brush border to basolateral membrane, and the extrusion of Ca through the basolateral membrane into the blood. Each step in this process is under the regulation of the active form of vitamin D_3 and is initiated when 1,25 di-hydroxyvitamin D binds to the vitamin D receptor of intestinal cells and upregulates gene expression of proteins related to calcium binding and absorption.

Figure 2. Role of Vitamin D_3 on Calcium Intestinal Absorption (Christakos et al. 2014 - https://pubmed.ncbi.nlm.nih.gov/24605213/)



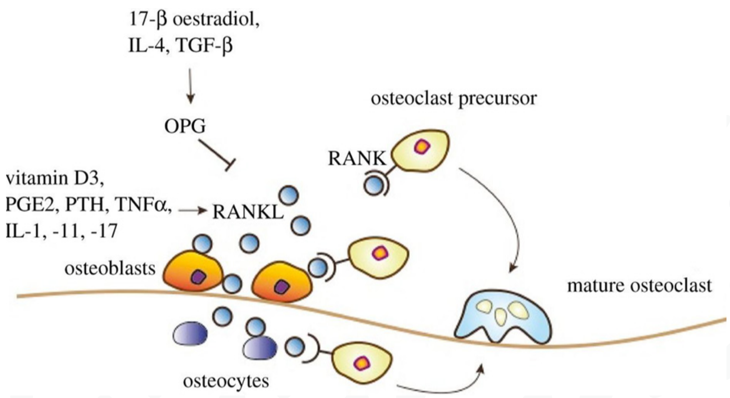
Bone Resorption

Vitamin D_3 also regulates Ca metabolism through bone resorption (Figure 3). Active vitamin D_3 regulates the expression of RANK, a cell surface receptor that controls and regulates bone mass and calcium metabolism. Via RANK, vitamin D_3 leads to bone resorption and initiates normal bone remodeling This is an important mechanism to maintain the pool of available Ca to the animal.

Summary

Vitamin D_3 increases Ca availability by promoting Ca intestinal absorption and bone resorption. This effect on Ca metabolism becomes extremely important during the periparturient period when Ca requirements increase approximately three-fold to support colostrum and milk production. Sun-exposed skin and diet are the two sources of Vitamin D_3 for dairy cattle. Due to its importance on Ca metabolism, it is a standard practice to add supplemental Vitamin D_3 in prepartum diets. Once Vitamin D_3 is absorbed, it needs to pass through a metabolic pathway in the liver and kidneys to be activated and perform its biological functions.

Figure 3: Role of Vitamin D_3 on Bone Resorption (Sigl et al., 2016 - https://royalsocietypublishing.org/doi/10.1098/rsob.160230)



References:

Christakos, S., Lieben, L., Masuyama, R., and Carmeliet, G. 2014. Review: Vitamin D endocrine system and the intestine. BoneKEy Reports 3, Article number: 496

Horst, R.L., Goff, J.P. and Reinhardt, T.A. 1994. Calcium and vitamin D metabolism in the dairy cow. Journal of Dairy Science 77: 1936–1951.

Mostafa, W.Z. and Hegazy, R.A. 2015. Vitamin D and the skin: Focus on a complex relationship: A review. Journal of Advanced Research. 6: 793-804

Nelson, C.D. and Merriman, K.E. 2014. Vitamin D Metabolism in Dairy Cattle and Implications for Dietary Requirements. Conference Paper. Florida Ruminant Nutrition Symposium.

Nelson, C.D., Lippolis, J.D., Reinhardt, T.A., Sacco, R.E., Powell, J.L., Drewnoski, M.E., O'Neil, M., Beitz. D.C., and Weiss, W.P. 2016. Vitamin D status of dairy cattle: Outcomes of current practices in the dairy industry. J. Dairy Sci. 99:10150–10160

Sigl, L.V. and Penninger, J.M. 2016. RANKL/RANK: from bone loss to the prevention of breast cancer. Open Biol. 6: 160230

Weir, R.R., Strain, J.J., Johnston, M., Lowis, C., Fearon, A.M., Stewart, S., and Pourshahidi, L.K. 2017. Environmental and genetic factors influence the vitamin D content of cows' milk. Proceedings of the Nutrition Society. 76:76–82

This information has been prepared for industry technical professionals.