ISSN PRINT 2319 1775 Online 2320 7876

Research paper UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022

A Comprehensive Look at Vitamin D and Its Effects on the Intestine

Dr. Jyoti Batra[1], Dr. Juhi Aggarwal[2], Dr. Eram Hussian Pasha[3], Rana Sakshi Singh[4]

[1] Professor, Department of Biochemistry, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

[2] Professor & Head, Department of Biochemistry, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

[3] Assistant Professor, Department of Biochemistry, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

[4] MBBS Student, Batch 2021-22, Santosh Medical College and Hospital, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India.

Email- [1] dean.research@santosh.ac.in, [2] jaggarwal38@gmail.com, [3] pasha.eram7@gmail.com, [4] ranasakshi2604@gmail.com

ABSTRACT:

Increased calcium absorption from the gut is the primary function of vitamin D in the regulation of calcium levels in the body. This article provides a description of the early research that laid the groundwork for the first model of vitamin D-mediated calcium absorption. In addition, a review is made of other research that pertains to the function of vitamin D in the intestine, including studies that have cast doubt on the validity of the conventional model and shed light on the crucial part played by certain calcium transport proteins. The more recent work that has been done to identify novel targets of 1,25(OH)2D3 action in the intestine is summarised, together with the work that has been done to highlight the importance of 1,25(OH)2D3 action across the proximal/distal and crypt/villus axes in the intestine.

Keywords: actinomycin, enterocyte, paracellular, crypt.

INTRODUCTION:

Calcium is the sixth most abundant element in the human body and is required for the proper operation of a wide variety of physiological processes, such as the development of bones, the transmission of nerve impulses, the clotting of blood, and the secretion of hormones [1]. The consumption of food is the only source of calcium that can fulfil these absolutely necessary activities. Even before the underlying molecular mechanisms were understood, early studies indicated that vitamin D played a crucial role in the intestinal calcium absorption [2]. Later research demonstrated that vitamin D-mediated intestinal calcium absorption required the transfer of calcium against a concentration gradient. Additionally, the stimulatory effect of

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** **UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022**

vitamin D was shown to be inhibited by actinomycin D and required a lag time of between 8 and 16 hours in order to have its desired effect [3-7]. According to these findings, the production of RNA and proteins is necessary for the action of vitamin D in the intestine. The finding of a vitamin D increased calcium binding protein in chick intestinal mucosa at this time was a major discovery made by the Wasserman group [8]. This protein was the first identified target of vitamin D action. It was discovered that the concentration of this calcium binding protein, which was later given the name calbindin-D [9] (-D9k (9,000 Mr) in mammalian and -D28k (28,000 Mr) in chick gut), was directly proportional to the rate of vitamin D-mediated calcium absorption in the duodenum [8]. The 1,25-dihydroxyvitamin D (1,25(OH)2D3) was found to be the active form of vitamin D as a result of subsequent research. There was a correlation between the interaction of 1,25(OH)2D3 with intestinal mucosa chromatin and an increase in the amount of calcium that was transported by the intestinal mucosa [10-14]. The discovery that calbindin was the first known target of the action of vitamin D (its induction is still one of the most pronounced effects of 1,25(OH)2D3 in the intestine) laid the groundwork for the development of our fundamental understanding of the molecular mechanism underlying the action of 1,25(OH)2D3 [15, 16]. This article provides a summary of what has been accomplished since these early investigations related to our comprehension of the role that vitamin D plays in the intestine, as well as future research directions that should be investigated.

The Factors That Influence Vitamin D and Calcium Absorption in the Intestine

Active calcium transport: In the conventional facilitated diffusion model of active intestinal calcium absorption [17], calbindin played a pivotal role as a central component. According to this hypothesis, calcium "ferries" itself across the cell by first binding to calbindin and then being expelled from the enterocyte by an ATP-dependent calcium pump. Calcium enters the intestinal epithelial cell along a concentration gradient and enters through a calcium channel. Although calbindin was identified as the first known target of vitamin D in the intestine in 1967, it was not until 1991 that the intestinal plasma membrane ATPase (PMCA1b, which is encoded by the Atp2b1 gene) was found to be regulated by vitamin D and involved in the extrusion of calcium from the cell during active calcium transport [18]. This discovery was made despite the fact that calbindin was identified in 1967 as the first known target of vitamin D in the In subsequent research, it was discovered that Atp2b1 was induced in response to dietary calcium and phosphate shortages, that its induction by 1,25(OH)2D3 decreased with age, and that 1,25(OH)2D3 control of the expression of PMCA1b occurs at the level of transcription [19-21]. In more recent investigations, the chromatin immunoprecipitation and sequencing technique (ChIP-seq) was used to locate regions of vitamin D receptor (VDR) binding within the Atp2b1 locus [22]. It is necessary to conduct functional analysis in order to establish whether or not these locations are active sites of 1,25(OH)2D3 regulation. Studies conducted on mice lacking an intestine-specific copy of the Atp2b1 gene showed the in vivo physiological significance of PMCA1 in vitamin D-

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022

mediated calcium absorption [23]. The absence of Atp2b1 in the colon was linked to lower levels of intestinal calcium absorption in response to 1,25(OH)2D3, as well as lower levels of bone mineral density in the spine and femur [23]. There was no discernible shift in the serum calcium level. The regulation of PMCA requires additional research, as do studies involving these intestine-specific Atp2b1 knockout (KO) mice. In addition, further research is required concerning the regulation of PMCA.

In early research [24, 25], it was revealed that in reaction to vitamin D, the intestinal brush border membrane was able to absorb more calcium and that binding of calcium to components of the brush border region occurred more frequently. In spite of this, the molecular basis for vitamin D-dependent calcium entry into the enterocyte was not discovered until 1999, when the research led by Mathias Hediger reported the cloning of the apical calcium channel known as TRPV6. TRPV6 was found to be expressed in the duodenum, jejunum, and colon, but it was either not detected in the ileum or was present in very low levels. This is in contrast to the expression of calbindin-D9k and the VDR, both of which are found in all segments of the small and large intestine. It has been hypothesised that the low level of TRPV6 in the ileum may be to blame for the slower rate of calcium absorption in the ileum in comparison to the other segments of the intestinal tract. Calcium transport as well as intestine TRPV6 mRNA levels also rise in vitamin D deficient pregnant and lactating rats. This indicates that mechanisms other than 1,25(OH)2D3 may be able to modulate intestinal calcium transport. Estradiol and prolactin were each demonstrated to enhance intestinal calcium transport and TRPV6 mRNA levels when tested on mice with ovariectomies, VDR null mutations, or vitamin D deficiency [32-34]. Additionally, cooperative effects of prolactin with 1,25(OH)2D3 in the regulation of both intestinal TRPV6 and calbindin-D9k have been observed. These findings imply that both prolactin and estradiol can be key modulators of intestinal calcium absorption during pregnancy and breastfeeding.

Paracellular calcium transport: When the body's demand for calcium increases, as it does during growth, pregnancy, and lactation, or when serum 1,25(OH)2D3 levels increase as a result of diets deficient in calcium, the active, saturable transcellular process of intestinal calcium absorption occurs. Calbindin, PMCA, and TRPV6 are all involved in this process in some capacity. However, calcium can also be absorbed through the paracellular pathway, in addition to the transcellular pathway, therefore it is possible for calcium to pass past the intestinal barrier in more than one way. Because this movement occurs in direct proportion to the calcium content in the luminal medium, we can infer that it is a mechanism of passive diffusion. Because of this, the passive diffusion process accounts for the vast majority of the intestinal calcium absorption that takes place when dietary calcium intake is high. There is some controversy regarding whether or not vitamin D can regulate the transport of calcium across paracellular membranes. Early studies in rodents and Caco-2 cells reported that passive transport of calcium is not sensitive to vitamin D signalling. This was despite the fact that the regulation of intercellular adhesion molecules (such as claudin-2) in the intestine by

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022

vitamin D provides some support for the existence of 1,25(OH)2D3 regulation of paracellular calcium transport. However, this was found despite the fact that vitamin D regulates intercellular adhesion molecules in the intestine. To identify the physiological importance of the intercellular adhesion molecules regulated by 1,25(OH)2D3 in calcium absorption, further research is required, including research with mice that have been genetically altered to lack 1,25(OH)2D3 or mice that have been transgenic. Recent research has uncovered that modulation of tight junctions plays an important part in the process of clearing intestinal pathogens. It is probable that tight junction control by 1,25(OH)2D3 is also implicated in vitamin D-mediated protection from enteric infection. This is because the immune system is an additional target of vitamin D.

Research Employing Mice That Have Been Genetically Modified To Serve As Models

Rickets, hypocalcemia, hypophosphatemia, secondary hyperparathyroidism, and a substantial reduction in intestinal TRPV6 and calbindin-D9k expression have been seen in VDR null mice and animals defective in 25-hydroxyvitamin D3 1 hydroxylase (CYP27B1) [41-43]. Symptoms of rickets only appear in VDR null mice after they have been weaned, which is the time when active intestinal calcium absorption begins .

When VDR null mice or CYP27B1 defective mice are fed a diet that is high in calcium [45, 46], rickets is averted. This confirms that the primary physiological role of 1,25(OH)2D3/VDR in developing animals is to assist intestinal calcium absorption. In accordance with this theory, rescuing calcium homeostasis deficits in VDR null mice with intestine-specific transgenic expression of VDR, which results in an increase in intestinal TRPV6 and calbindin-D9k mRNA levels, is possible through transgenic expression of VDR.

In a strange turn of events, appropriate calcium levels had no impact on calcium and bone metabolism in TRPV6 or calbindin-D9k knockout (KO) mice as compared to wild type (WT) mice. In addition, 1,25(OH)2D3 treatment to vitamin D deficient TRPV6 or calbindin-D9k null mice significantly improved active duodenal calcium transport equivalent to WT vitamin D deficient mice. These findings suggest that other calcium channels or calcium binding proteins can compensate for the absence of these proteins and indicate that vitamin D-mediated calcium transport can occur even in the absence of these proteins. Additionally, the findings suggest that other calcium channels can compensate for their absence. For instance, calcium may also be sequestered by intracellular organelles, which may help to protection against calcium toxicity during elevated calcium inflow. This may also be the case. Other research, on the other hand, reveals that intestine-specific transgenic production of TRPV6 can restore calcium absorption and prevent rickets in VDR KO mice. This is in contrast to the investigations that were conducted on KO mice. Therefore, research conducted on KO mice suggests that in the absence of TRPV6 there is compensation by other proteins that have not yet been identified. However, research conducted on transgenic mice demonstrates that TRPV6 is a genuine contributor that plays an important role in calcium uptake during the

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022**

process of transcellular intestinal calcium transport. In addition, the results of this study demonstrated that the levels of calbindin-D9k increased in direct proportion to the increase in transcellular calcium absorption (i.e. the elevation in calbindin-D9k did not require regulation through the VDR). This finding suggests that increased calbindin-D9k levels following vitamin D treatment may be a secondary, protective response to increased cellular calcium fluxes rather than a primary driver of vitamin D regulated calcium absorption. 1) Research conducted using animals deficient in both VDR and CYP27B1 has revealed that calcium absorption is severely hindered in the absence of either 1,25(OH)2D3 or VDR. 2) Despite the fact that research conducted on transgenic mice that overexpress TRPV6 indicates the significance of calcium uptake via TRPV6 in intestinal calcium absorption, it has been shown that in the absence of TRPV6 this channel can be compensated for by another channel that has not yet been determined. 3) Calcium may be bound to calbindin in the cytosol in order to prevent dangerous quantities of calcium from accumulating in the intestinal cell during accelerated calcium transport. This is done to protect against an accumulation of calcium. In the absence of calbindin, calcium may be attached to other calcium binding proteins or it may be sequestered by the endoplasmic reticulum as a protective measure against overly high calcium levels. This was hypothesised based on research conducted in mice that lacked the calbindin-D9k gene.

Essential role for vitamin D in distal intestine segments and new intestinal vitamin D targets

The proximal gut has been the focus of the vast majority of research efforts on 1,25(OH)2D3-mediated calcium absorption. However, VDR, calbindin, and TRPV6 are present in all segments of the small and large intestine, and it has also been found that 1,25(OH)2D3 regulates calcium absorption in the distal intestine [24, 16]. The Christakos group developed animals with transgenic expression of VDR only in the distal intestine (ileum, cecum, and colon) of VDR KO mice. The goal of these experiments was to gain a better understanding of the role that vitamin D signalling plays in the distal intestine (VDRKO-Tg). They demonstrated that the expression of VDR specifically in the distal intestine of VDR KO mice to levels equivalent to WT mice prevented the abnormalities in calcium homeostasis and bone mineralization that are normally seen in VDR KO mice [14]. This was accomplished by expressing VDR at levels equivalent to those found in WT mice. These findings offered direct evidence for the relevance of 1,25(OH)2D3- mediated calcium absorption in the distal intestine. This is despite the fact that calcium is absorbed most rapidly in the duodenum when compared to other intestinal segments. After that, the Christakos team used transcriptome profiling to investigate the expression of VDR target genes in the intestines of the VDRKO-Tg mice. The typical 1,25(OH)2D3 target genes found in the proximal intestine of the transgenic mice [S100g (calbindin-D9k) and Trpv6] were also expressed in the distal intestine of the transgenic mice, and their expression was stimulated by 1,25(OH)2D3. These alterations in gene expression were shown to have a correlation with an increase in serum

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022

calcium in the VDRKO-Tg animals, which suggests that active transport plays a role in the rescue of VDR-dependent rickets by VDR expression in the distal intestine. In addition, treatment with 1,25(OH)2D3 inhibited expression of genes controlling drug metabolism (such as Cyp2c55 and Cyp3a25) and cell proliferation (such as Anax13) in the distal intestine of VDRKO-Tg mice ([22]; 22nd Workshop on Vitamin D), which suggests that vitamin D has an effect on the intestine that is more extensive than the control of intestinal calcium absorption. Slc30a10 was found to be one of the genes that was consistently induced by 1,25(OH)2D3 in the distal intestine of the Tg mice, as well as in both the proximal and distal intestines of 1,25(OH)2D3 treated vitamin D deficient mice. This finding is consistent with the hypothesis that was presented earlier. Protects against the harmful effects of manganese (Mn) exposure, the SLC30A10 manganese efflux transporter is found in the apical/luminal domain of the gut, as well as the liver and the brain [26]. Studies using Slc30a10 KO mice (from S. Mukhopadhyay, University of Texas at Austin), which have elevated Mn levels (56), indicate a marked decrease in intestinal vitamin D target genes Trpv6 and S100g (>90%) in the KO mice. These findings point to an association between elevated Mn levels and the KO mice ([55]; 22nd Workshop on Vitamin D). These data imply that TRPV6, calbindin-D9k, and SLC30A10 may interact together in the export of manganese. This is because it was revealed that SLC30A10 utilises a Ca2+ gradient for active counter-ion exchange [22]. There is a need for additional research to discover whether or not 1,25(OH)2D3 plays a role in the cellular homeostasis of other divalent cations in addition to the role it plays in the maintenance of calcium homeostasis.

The VDR and 1,25(OH)2D3- target the expression of genes along the axis of crypts and villus.

The developed absorptive epithelial cells that occupy the small intestine villus are responsible for a number of important functions, one of which is 1,25(OH)2D3-mediated responses. However, very little is known about the effect that 1,25(OH)2D3 has on crypts, and the question of whether or not the conventional intestinal responses to 1,25(OH)2D3 occur in crypts has been the subject of much discussion. In our preliminary research, we investigated the potential role of the gene CYP24a1, which codes for the enzyme 25-hydroxyvitamin D3 24-hydroxylase (CYP24A1), as a target of 1,25(OH) 2D3.

The enzyme CYP24A1 is found in every cell in the body that contains VDR and plays a role in the breakdown of 1,25(OH)2D3. It has been hypothesised that CYP24A1 not only controls the amount of 1,25(OH)2D3 that is circulating in the blood, but that it may also restrict the amount of 1,25(OH)2D3 that is present in cells, hence controlling the cellular response. The response of cells and tissues to 1,25(OH)2D3 has been evaluated with the help of CYP24A1. During the first stages of our research, we investigated Cyp24a1 in order to ascertain whether or not 1,25(OH)2D3 induced reactions and VDR are present not only in villi but also in crypt enterocytes. In the mouse, we found that enterocytes in both the villus and the crypts express VDR and respond to 1,25(OH)2D3 by promoting expression of Cyp24a1 (Fig. 1 AC). This

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved, UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022**

was discovered through our research (22nd Vitamin D Workshop). We are currently conducting transcript profiling on mouse crypt and villus preparations as well as on human enteroids with either a crypt-like phenotype (i.e. high proliferation, undifferentiated cells) or a villus-like phenotype in order to get a complete picture of the vitamin D response in the intestine. This will allow us to get a comprehensive understanding of the vitamin D response (i.e. low proliferation, differentiated cells). According to the results of our preliminary RNA-seq research of human enteroids, VDR can be found in crypt-like as well as villus-like enteroids. Additionally, we discovered that treatment with 1,25(OH)2D3 can increase some vitamin D target genes in both the villus and the crypts (such as TRPV6, CYP24Al, and SLC30A10), whereas the induction of other vitamin D target genes is limited to either the villus or the crypts (e.g. S100G is strongly induced only in villuslike cultures). Therefore, the effects of 1,25(OH)2D3 on the intestine are the same in humans as they are in other animals. Furthermore, these effects are more complex than one may assume based on evidence from whole tissue or mucosal scrapings.

CONCLUSION:

The classic paradigm of intestinal effects, which consists of three controlled steps (entry of calcium, transcellular transport of calcium, and energy-requiring extrusion of calcium), does not adequately describe the complicated actions of 1,25(OH)2D3 on the intestines. In both the proximal and the distal intestine, 1,25(OH)2D3 has an influence on a complex network that may involve overlapping and separate effects for calcium transport, as well as for the maintenance of intracellular calcium homeostasis and the regulation of intestinal adhesion molecules. Calcium-independent actions of 1,25(OH)2D3 include a potential role in the metabolic processes of xenobiotics, effects on cellular proliferation, and effects on the intestinal transit of other ions. Not only are responses mediated by 1,25(OH)2D3 found in the villi, but they are also found in the crypts. The effects of 1,25(OH)2D3 in the crypts include a potential part in the formation of stem cells as well as the modulation of the Wnt signalling pathway. In the future, research that find novel vitamin D targets in both the villus and the crypt, as well as in the proximal and the distal intestine, will provide new information on the processes by which 1,25(OH)2D3 controls numerous aspects of intestinal biology.

REFERENCES:

1. J.M. Gertner, Disorders of calcium and phosphorus homeostasis, Pediatr. Clin. North Am., 37 (1990) 1441-1465.
2. R. Nicolaysen, Studies upon the mode of action of vitamin D: The influence of vitamin D on the absorption of calcium and phosphorus in the rat, Biochem. J., 31 (1937) 122-129.
3. R.H. Wasserman, F.A. Kallfelz, C.L. Comar, Active transport of calcium by rat duodenum in vivo, Science, 133 (1961) 883-884.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** **UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022**

4. D. Schachter, D.V. Kimberg, H. Schenker, Active transport of calcium by intestine: Action and bio-assay of vitamin D, Am. J. Physiol., 200 (1961) 1263-1271.

5. R.H. Wasserman, Studies on vitamin D3 and the intestinal absorption of calcium and other ions in the rachitic chick, J. Nutr., 77 (1962) 69-80.

6. A.W. Norman, Actinomycin d and the response to vitamin D, Science, 149 (1965) 184-186.

7. J.E. Zull, E. Czarnowska-Misztal, H.F. Deluca, Actinomycin d inhibition of vitamin D action, Science, 149 (1965) 182-184.

8. R.H. Wasserman, A.N. Taylor, Vitamin D3-induced calcium-binding protein in chick intestinal mucosa, Science, 152 (1966) 791-793.

9. R.H. Wasserman, Nomenclature of the vitamin D induced calcium binding protein, in: S. Norman A.W, K., Griegoliet H.G, Herrath Dv (Ed.) Vitamin D: Chemical, biochemical, and clinical update : Proceedings of the sixth workshop on vitamin D, merano, italy, march 1985, De Gruyter, Berlin, 1985, pp. 321-322.

10. M.F. Holick, H.K. Schnoes, H.F. DeLuca, T. Suda, R.J. Cousins, Isolation and identification of 1,25- dihydroxycholecalciferol. A metabolite of vitamin D active in intestine, Biochemistry, 10 (1971) 2799-2804.

11. D. Fraser, E. Kodicek, Unique biosynthesis by kidney of a biologically active vitamin D metabolite, Nature, 228 (1970) 764-766.

12. M.R. Haussler, J.F. Myrtle, A.W. Norman, The association of a metabolite of vitamin D3 with intestinal mucosa chromatin in vivo, J. Biol. Chem., 243 (1968) 4055-4064.

13. Y. Tanaka, H.F. DeLuca, J. Omdahl, M.F. Holick, Mechanism of action of 1,25-dihydroxycholecalciferol on intestinal calcium transport, Proc. Natl. Acad. Sci. U. S. A., 68 (1971) 1286-1288.

14. A.W. Norman, J.F. Myrtle, R.J. Midgett, H.G. Nowicki, V. Williams, G. Popjak, 1,25-dihydroxycholecalciferol: Identification of the proposed active form of vitamin D3 in the intestine, Science, 173 (1971) 51-54.

15. G. Theofan, A.P. Nguyen, A.W. Norman, Regulation of calbindin-d28k gene expression by 1,25- dihydroxyvitamin D3 is correlated to receptor occupancy, J. Biol. Chem., 261 (1986) 16943-16947.

16. Y.C. Huang, S. Lee, R. Stolz, C. Gabrielides, A. Pansini-Porta, M.E. Bruns, D.E. Bruns, T.E. Miffin, J.W. Pike, S. Christakos, Effect of hormones and development on the expression of the rat 1,25- dihydroxyvitamin D3receptor gene. Comparison with calbindin gene expression, J. Biol. Chem., 264 (1989) 17454-17461.

ISSN PRINT 2319 1775 Online 2320 7876

Research paper **© 2012 IJFANS. All Rights Reserved,** **UGC CARE Listed (Group -I) Journal Volume 11, S Iss 4, 2022**

17. F. Bronner, D. Pansu, W.D. Stein, An analysis of intestinal calcium transport across the rat intestine, Am. J. Physiol., 250 (1986) G561-569.

18. J.M. Zelinski, D.E. Sykes, M.M. Weiser, The effect of vitamin D on rat intestinal plasma membrane capump mrna, Biochem. Biophys. Res. Commun., 179 (1991) 749-755.

19. Q. Cai, J.S. Chandler, R.H. Wasserman, R. Kumar, J.T. Penniston, Vitamin d and adaptation to dietary calcium and phosphate deficiencies increase intestinal plasma membrane calcium pump gene expression, Proc. Natl. Acad. Sci. U. S. A., 90 (1993) 1345-1349.

20. H.J. Armbrecht, M.A. Boltz, V.B. Kumar, Intestinal plasma membrane calcium pump protein and its induction by 1,25(oh)(2)d(3) decrease with age, Am. J. Physiol., 277 (1999) G41-47.

21. T.L. Pannabecker, J.S. Chandler, R.H. Wasserman, Vitamin-d-dependent transcriptional regulation of the intestinal plasma membrane calcium pump, Biochem. Biophys. Res. Commun., 213 (1995) 499-505.

22. S.M. Lee, E.M. Riley, M.B. Meyer, N.A. Benkusky, L.A. Plum, H.F. DeLuca, J.W. Pike, 1,25- dihydroxyvitamin D3controls a cohort of vitamin D receptor target genes in the proximal intestine that is enriched for calcium-regulating components, J. Biol. Chem., 290 (2015) 18199-18215.

23. Z.C. Ryan, T.A. Craig, A.G. Filoteo, J.J. Westendorf, E.J. Cartwright, L. Neyses, E.E. Strehler, R. Kumar, Deletion of the intestinal plasma membrane calcium pump, isoform 1, atp2b1, in mice is associated with decreased bone mineral density and impaired responsiveness to 1, 25-dihydroxyvitamin D3, Biochem. Biophys. Res. Commun., 467 (2015) 152-156.

24. D.D. Bikle, R.L. Morrissey, D.T. Zolock, The mechanism of action of vitamin D in the intestine, Am. J. Clin. Nutr., 32 (1979) 2322-2328.

25. S. Chandra, C.S. Fullmer, C.A. Smith, R.H. Wasserman, G.H. Morrison, Ion microscopic imaging of calcium transport in the intestinal tissue of vitamin D-deficient and vitamin D-replete chickens: A 44ca stable isotope study, Proc. Natl. Acad. Sci. U. S. A., 87 (1990) 5715-5719.

26. J.B. Peng, X.Z. Chen, U.V. Berger, P.M. Vassilev, H. Tsukaguchi, E.M. Brown, M.A. Hediger, Molecular cloning and characterization of a channel-like transporter mediating intestinal calcium absorption, J. Biol. Chem., 274 (1999) 22739-22746.