The fine crosstalk between vitamin D and pituitary gland

Simona Bolamperti, Isabella Villa, Andrea Giustina

Endocrine and Osteometabolic Lab, Institute of Endocrine and Metabolic Sciences, IRCCS San Raffaele Hospital, Milan, Italy

ABSTRACT

Vitamin D, unlike other vitamins, is a fat-soluble steroid hormone rather than a cofactor for enzymatic reactions. The main role of vitamin D is to regulate bone metabolism and calcium-phosphate homeostasis. Lack of vitamin D causes osteomalacia and osteoporosis in adults, and rickets in children. Vitamin D receptor (VDR) expression levels throughout the body are quite variable. Interestingly, VDRs are found in pituitary tissue. Unsurprisingly, vitamin D levels might impact hypophyseal production or activity of hormones such as growth hormone, gonadotropins (follicle-stimulating hormone, luteinizing hormone), prolactin, corticotropin, and thyroid-stimulating hormone (TSH). On the other hand, pituitary hormones also influence vitamin D metabolism and several pituitary diseases are known to impact bone health. The aim of the present review is to collect available data on the crosstalk between vitamin D and the pituitary gland.

KEYWORDS

Vitamin D, pituitary, hormones.

Introduction

Vitamin D is known mainly for its role in regulating bone metabolism and calcium-phosphate homeostasis. A hundred years ago, it was first demonstrated that severe vitamin D deficiency causes rickets in children [1]. In adults, lack of vitamin D causes osteomalacia and osteoporosis. The peculiarity of vitamin D is that, unlike other vitamins, it functions as a fat-soluble steroid hormone rather than a cofactor for enzymatic reactions.

Considering that the vitamin D receptor (VDR) is almost ubiquitously expressed, researchers in recent decades have endeavored to demonstrate that vitamin D, functioning like a real hormone that affects several organs and tissues, is involved in a number of extra-skeletal activities [1]. In particular, recent clinical and laboratory studies suggest that vitamin D may be essential for physiological pituitary function, but the mechanisms by which it regulates the pituitary and hormone release are not yet fully understood. Hypovitaminosis D has also been suggested to be a mechanism through which pituitary diseases may negatively impact bone health in humans.

The aim of the present review is therefore to collect the data thus far available on the crosstalk between vitamin D and the pituitary gland in order to provide a concise overview of this important subject.

Vitamin D

Vitamin D is a fat-soluble secosteroid whose central role is to maintain calcium homeostasis in vertebrate organisms through direct actions on intestine, kidney, and bone, as well as indirectly through feedback inhibition of parathyroid hormone (PTH) production in the parathyroid glands [1]. Vitamin D exists in two forms, vitamin D2 and vitamin D3, which differ from each another only in their side chains, where vitamin D2 has a double bond and an extra methyl group. Vitamin D3 is produced in the skin from 7 dehydrocholesterol via a process involving ultraviolet B (290–315 nm) radiation [2], whereas vitamin D2, contained in several vegetables and in some yeasts, is taken up through the diet [3].

Vitamin D per se has limited biological actions; it probably plays a role in protecting the skin against the carcinogenic effect of UVB radiation [2]. To become active, both vitamin D2 and vitamin D3 must be hydroxylated to 25-hydroxyvitamin D (25OHD) by the 25-hydroxylase enzyme CYP2R1. This reaction occurs primarily in the mitochondrial and microsomal fractions of the liver [4]. In mammals the importance of CYP2R1 might vary depending on the species in question. *Cyp2r1*–/– mice show only reduced 25OHD production with little effect on serum calcium and phosphate [5], therefore it seems likely that other 25-hydroxylases might compensate for the lack of CYP2R1. Conversely in humans, mutations in CYP2R1 induce a greater reduction in 25OHD levels, resulting in rickets [6].

25OHD, the major circulating form of vitamin D, is further hydroxylated in the kidney by the enzyme CYP27B1 to 1,25(OH)2D, which is the real bioactive form. CYP27B1, which is the only 25OHD-1α hydroxylase described to date,

Article history

Received 6 Mar 2023 – Accepted 15 May 2023

Contact

Andrea Giustina; giustina.andrea@hsr.it

President, European Hormone and Metabolism Foundation,
Prorector and Head, Institute of Endocrine and Metabolic Sciences,
San Raffaele Vita-Salute University and IRCCS Hospital
Via Olgettina 60 - 20132- Milan, Italy. Phone (Secretary) +39 02 26435136.

was first identified in mitochondria of renal cells. PTH stimulates CYP27B1 activity, whereas fibroblast growth factor 23 (FGF23) and 1,25(OH)2D inhibit it. Other tissues were then shown to express CYP27B1, such as bone, placenta, epidermis and other epithelial tissues, and immune cells [7]. In non-renal tissues, CYP27B1 is regulated by various cytokines including interferon-γ and tumor necrosis factor-α (TNFα). Although renal and extrarenal CYP27B1 have the same sequence, different regions of the promoter can be activated by different regulators in different cell types [8]. Both 25OHD and 1,25(OH)2D are finally catabolized by the enzyme CYP24A1, which is present in most tissues. Some of the catabolites of vitamin D seem to have important biological effects. Indeed, bone and skin tissues have a specific receptor for the catabolite 24,25(OH)2D, which has been shown to play a role in fracture repair [9].

25OHD and 1,25(OH)2D circulate in the serum, with around 85% of the total available amount being bound to vitamin D binding proteins (DBPs), and around 15% to albumin, which presents lower affinity [10]. The DBP gene is the most polymorphic gene known with 1,242 polymorphisms currently listed in the NCBI database. Human DBP is around 58 kDa depending on its glycosylation state, and it is mainly produced by the liver [11]. DBP expression is increased by estrogen [12], dexamethasone, and certain cytokines such as IL-6, but inhibited by TGFβ [13]. Neither vitamin D nor any of its metabolites regulate DBP production [11].

As seen with the other lipophilic hormones, it is the free form of 25OHD that enters the cells. Once inside, HSP70 functions as an intracellular carrier to deliver 25OHD to the mitochondria where CYP27B1 converts 25OHD to 1,25(OH)2D, which in turn migrates to the nucleus to exert its genomic actions [14]. Nevertheless, in some tissues, namely the kidney and parathyroid gland, the 25OHD-DBP complex enters the cells via the megalin and/or cubilin transport system [15]. Once in the nucleus 1,25(OH)2D exerts its action by binding a specific nuclear receptor, the so-called VDR. The human VDR contains 427 amino acid residues and has high affinity for 1,25(OH)2D [16]. The classic genomic mechanism through which the 1,25(OH)2D3-VDR complex regulates gene expression consists of a heterodimerization with retinoid X receptor (RXR) α. The heterodimer then translocates to the nucleus, and binds the specific DNA sequence, the vitamin D response element (VDRE) [17]. VDR/RXR localization on the VDRE induces the recruitment of several co-regulatory complexes that modify nucleosome occupancy, and alter the chemical state of histones in order to facilitate the entry of the transcriptional machinery (RNA polymerase) [18]. Besides VDR, RXRa is able to dimerize with a variety of hormone receptors, including thyroid receptor, peroxisome proliferator-activated receptor, and other retinoic acid receptors, thereby regulating many endocrine processes [19]. VDR expression levels in the body are quite variable and highly dependent on the differentiation state of the cell analyzed [20]. The highest concentration of VDR can be found in intestine, kidney and bone, but its presence has also been discovered in many other tissues not directly involved in calcium homeostasis (e.g., pancreas, skin, immune cells), suggesting that vitamin D affects many cellular processes beyond calcium homeostasis [20,21].

Interestingly, VDRs are also found in pituitary tissue, as demonstrated by different research approaches over the years: autoradiography [22], ligand bind assay [23], and mRNA expression with relative immunohistochemistry [24].

Vitamin D and the pituitary gland

Among the transcription factors fundamental for the production of hormones by the pituitary cells, the most studied and first discovered is pituitary factor 1 (Pit-1), also known as POU1F1. Pit-1 is regulated by another transcriptional factor called prophet of Pit-1, which is necessary for the differentiation and specialization of somatotrophs, lactotrophs, thyrotrophs, and gonadotrophs [25]. Interestingly, Pit-1 has been demonstrated to be a vitamin D target and to regulate VDR expression. 1,25(OH)2D3 supplementation of MCF-7 cells causes a significant decrease in Pit-1 mRNA and protein expression. Chromatin immunoprecipitation (CHIP) analyses showed that VDR binds the Pit-1 promoter on specific VDREs even in the absence of RXR, causing a decrease in Pit-1 transcription [26]. Pit-1 in turn regulates the transcription of VDR in MCF-7 cells. External administration of Pit-1 to the cells triggers a significant increase in VDR expression, both mRNA and protein, which is prevented by silencing Pit-1 via siRNA techniques. CHIP and reporter gene assays demonstrated that Pit-1 directly binds VDR promoter, and that Pit-1 recruits VDR on its own promoter to increase its own transcription. Therefore, it seems that VDR control by Pit-1 might be dependent on the amount of VDR already present in the cells [27].

The crosstalk between Pit-1 and VDR suggests that the regulation of pituitary function by vitamin D is very specific. Pituitary adenomas indeed correlate with lower levels of vitamin D in the serum. In a cohort of patients with pituitary adenomas, 70.4% had vitamin D deficiency, 21.6% had vitamin D insufficiency, and only 8% had adequate levels [28]. Therefore, it is not surprising that vitamin D levels might impact hypophyseal production or the activity of hormones such as growth hormone (GH), gonadotropins (follicle-stimulating hormone, FSH, luteinizing hormone, LH), prolactin, corticotropin, thyroid-stimulating hormone (TSH).

Vitamin D and growth hormone

Vitamin D and the GH/IGF-I axis are essential to skeletal growth and bone maintenance. Vitamin D can interact with the GH axis at multiple levels. In the liver, 1,25(OH)2D3 regulates IGF-I synthesis and secretion, whereas at the pituitary level, in GH-secreting cells, 1,25(OH)2D3 binds to its specific receptor to stimulate GH secretion [29]. The finding that 1,25(OH)2D3 binds the pituitary VDR to stimulate GH secretion is further supported by a study demonstrating that specific polymorphisms in VDR regions of GH promoter correlate with growth hormone deficiency (GHD) [30]. GH itself modulates vitamin D metabolism.

In rats it has been demonstrated that GH can stimulate the renal production of 1,25(OH)2D3 and affect intestinal calcium absorption [31]. In male volunteers, pharmacological dosage of GH induced a significant increase in total vitamin D after 7 days

of treatment [32], and GH infusions increased 1,25(OH)2D3 levels within 36h [33]. In adult patients with GHD an increased risk of prevalent and incident morphometric vertebral fractures has been observed [34-36]. In these patients, vitamin D levels, measured as 25(OH)D or 1,25(OH)2D3, seem to be lower than in healthy controls [29], thus possibly contributing to bone health impairment in this clinical setting. On the other hand, the direct effect of vitamin D production on GH production causes a secondary effect on the synthesis of IGF-I by the liver, thus contributing to the multifactorial etiology of GHD. Furthermore, IGF-I itself directly stimulates the production of 1,25(OH)2D3 by kidney cells *in vitro*, independently of GH [37].

Patients suffering from acromegaly with GH excess due to a pituitary adenoma are known to also present a specific form of osteopathy with modest or no reduction in BMD and an increased risk of vertebral fractures [38-40]. Altered DBP levels [41] as well as resistance to vitamin D have been reported in acromegaly leading to the hypothesis that, in this disease too, dysregulated vitamin D action may play a role in frequently observed bone damage.

Vitamin D and gonadotropins

The production of gonadotropins by the pituitary gland is controlled by the hypothalamic secretion of gonadotropin-releasing hormone (GnRH). Vitamin D deficiency has a negative impact on the reproductive system [42] and *Vdr*-null female mice display hypergonadotropic hypogonadism. In human ovarian cells vitamin D increases progesterone, estrogen and estrone production [43]. Similarly, in human granulosa cells, treatment with 1,25(OH)2D3 increases progesterone production [44]. In a human testis model, vitamin D had a significant direct effect on testosterone production, and men with impaired gonadal function and low vitamin D had lower testosterone/estradiol ratios [45].

On the other hand, the involvement of vitamin D in gonadotrope function has not been fully elucidated. A very recent study in rats demonstrated that freshly collected hypothalamic and hypophyseal tissues exposed to a vitamin D receptor antagonist displayed increased expression of GnRH and reduced expression of LH and FSH, suggesting that there is fine regulation of gonadotropins by vitamin D [46]. Not only, it appears that VDR expression in the pituitary fluctuates during the estrous cycle and correlates with the expression of pituitary factors such as annexin A1 (Anxa1), Anxa5, and inhibin/activin subunits, which in turn regulate FSH production [47]. Female mice exposed to maternal vitamin D deficiency have been found to develop irregular estrous cycles with less LH on the evening of proestrus, suggesting that maternal vitamin D deficiency determines reproductive dysfunction in adult female offspring through adverse effects on hypothalamic function [48].

Vitamin D and prolactin

Vitamin D also modulates prolactin levels. It has been reported that lack of VDR (in *Vdr*-null mice compared with wild-type littermates) causes a change in serum prolactin, likely due to higher pulsatile secretion from the pituitary. Altered regulation of prolactin secretion has been thought to be responsible for the behavioral changes observed in *Vdr*-null mice, i.e., increased anxiety, motor deficits, impaired nest building [49]. The interaction between prolactin and vitamin D is mutual. In osteosarcoma cells prolactin can block VDR genome activity [50], and patients suffering from prolactinoma have lower levels of vitamin D, whose deficiency is associated with larger prolactinoma size and higher prolactin levels [51]. Therefore, although a recent study performed in rats showed an enhancing effect of prolactin on serum levels of vitamin D [52], it can be hypothesized that, in this context too, the increased fracture risk [53,54] may be linked at least in part to altered vitamin D metabolism [55].

Vitamin D and corticotropin (ACTH)

Adrenocorticotropin (ACTH) has been shown to have crosstalk with vitamin D. Chronic ACTH supplementation in mice was found to regulate, among other factors, Cyp27b1 and Cyp24a1 (factors involved in vitamin D metabolism), by inducing a significant increase in their gene expression [56]. In a clinical case study, a female suffering from ACTH deficiency displayed low levels of circulating 1,25(OH)2D3 [57]. On the other hand, vitamin D has been proven to inhibit corticotropin-releasing hormone (CRH) by modulating the expression of several microRNAs [58]. Simultaneous administration of ACTH and vitamin D to human osteoblast cultures resulted in an increase in genes related to osteogenesis such as *RUNX2*, osterix, and collagen, and stimulation of intracellular pathways such as ERK1/2 or cAMP, compared with controls or the hormones alone [59]. This synergistic effect of ACTH and vitamin D may in part explain why patients with Cushing's disease have an increased risk of fractures as compared with control subjects (due to ACTH-dependent hypercortisolism) [60], but a lower risk than patients with adrenal Cushing's syndrome [61].

Vitamin D and TSH

Thyrotropes have been shown to be affected by 1,25-(OH)2 vitamin D3, which regulates their TSH secretion [62]. Patients with hypothyroidism, who are characterized by high levels of circulating TSH, have been found to display significantly reduced TSH serum levels after 12 weeks of vitamin D [63]. The decrease in TSH levels in response to high vitamin D are also secondary to the increase in thyroid hormone levels [64] since vitamin D exerts a modulatory action on thyrocytes as well [65]. Interestingly, *Vdr*-null mice display only modestly decreased TSH levels [66]. TSH and vitamin D levels correlate negatively in euthyroid individuals, but positively in pregnant women [67], suggesting that vitamin D has both direct and indirect effects on TSH release and that their interaction is also dependent on the hormonal status of the subject [68].

Conclusions

The primary goal of this review was to group the most relevant data from basic research studies on how vitamin D modulates pituitary function, and also how this gland plays a role in vitamin D metabolism. The available data point to a correlation between vitamin D deficiency and impaired production and/or action of hypophyseal hormones. The vitamin D status of the subject as well as receptor and enzyme polymorphisms all

play a role in the crosstalk and in the maintenance of pituitary physiology and should be taken into account when diagnosing patients. The possible role of altered vitamin D metabolism and function in the bone damage observed in pituitary diseases is an interesting working hypothesis and deserved to be investigated in ad hoc human studies.

References

1. Holick MF, Garabedian M. Vitamin D: photobiology, metabolism, mechanism of action and clinical applications. In: Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. 6th edition, American Society for Bone and Mineral Research Washington, DC, USA, 2006:106-14.
2. Bikle DD. Vitamin D and the skin: physiology and pathophysiology. Rev Endocr Metab Disord. 2012;13(1):3-19.
3. Jäpelt RB, Jakobsen J. Vitamin D in plants: a review of occurrence, analysis, and biosynthesis. Front Plant Sci. 2013;4:136.
4. Bhattacharyya MH, DeLuca HF. Subcellular location of rat liver calciferol-25-hydroxylase. Arch Biochem Biophys. 1974;160(1):58-62.
5. Zhu JG, Ochalek JT, Kaufmann M, Jones G, Deluca HF. CYP2R1 is a major, but not exclusive, contributor to 25-hydroxyvitamin D production in vivo. Proc Natl Acad Sci U S A. 2013;110(39):15650-5.
6. Thacher TD, Fischer PR, Singh RJ, Roizen J, Levine MA. CYP2R1 mutations impair generation of 25-hydroxyvitamin D and cause an atypical form of vitamin D deficiency. J J Clin Endocrinol Metab. 2015;100(7):E1005-13.
7. Bikle DD, Patzek S, Wang Y. Physiologic and pathophysiologic roles of extra renal CYP27b1: case report and review. Bone Rep. 2018;8:255-67.
8. Meyer MB, Benkusky NA, Kaufmann M, et al. A kidney-specific genetic control module in mice governs endocrine regulation of the cytochrome P450 gene Cyp27b1 essential for vitamin D3 activation. J Biol Chem. 2017;292(42):17541-17558.
9. Martineau C, Naja RP, Husseini A et al. Optimal bone fracture repair requires 24R,25-dihydroxyvitamin D3 and its effector molecule FAM57B2. J Clin Invest. 2018;128(8):3546-57.
10. Bikle DD, Gee E, Halloran B, Kowalski MA, Ryzen E, Haddad JG. Assessment of the free fraction of 25-hydroxyvitamin D in serum and its regulation by albumin and the vitamin D-binding protein. J Clin Endocrinol Metab. 1986;63(4):954-9.
11. Chun RF. New perspectives on the vitamin D binding protein. Cell Biochem Funct. 2012;30(6):445-56.
12. Hagenfeldt Y, Carlström K, Berlin T, Stege R. Effects of orchidectomy and different modes of high dose estrogen treatment on circulating "free" and total 1,25-dihydroxyvitamin D in patients with prostatic cancer. J Steroid Biochem Mol Biol. 1991;39(2):155-9.
13. Guha C, Osawa M, Werner PA, Galbraith RM, Paddock GV. Regulation of human Gc (vitamin D--binding) protein levels: hormonal and cytokine control of gene expression in vitro. Hepatology. 1995;21(6):1675-81.
14. Wu S, Ren S, Chen H, Chun RF, Gacad MA, Adams JS. Intracellular vitamin D binding proteins: novel facilitators of vitamin D-directed transactivation. Mol Endocrinol. 2000;14(9):1387-97.
15. Nykjaer A, Dragun D, Walther D, et al. An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. Cell. 1999;96(4):507-15.
16. Carlberg C, Molnár F, Mouriño A. Vitamin D receptor ligands: the impact of crystal structures. Expert Opin Ther Pat. 2012;22(4):417-35.
17. Griffin AC 3rd, Kern MJ, Kirkwood KL. MKP-1 is essential for canonical vitamin D-induced signaling through nuclear import and regulates RANKL expression and function. Mol Endocrinol. 2012;26(10):1682-93.
18. Pike JW, Zella LA, Meyer MB, Fretz JA, Kim S. Molecular actions of 1,25-dihydroxyvitamin D3 on genes involved in calcium homeostasis. J Bone Miner Res. 2007;22 Suppl 2:V16-9.
19. Mangelsdorf DJ, Evans RM. The RXR heterodimers and orphan receptors. Cell. 1995;83(6):841-50.
20. Wang Y, Zhu J, DeLuca H F. Where is the vitamin D receptor? Arch Biochem Biophys. 2012;523(1):123-33.
21. Christakos S, Dhawan P, Verstuyf, A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev. 2016:96(1):365-408.
22. Stumpf WE, Sar M, Reid FA, Tanaka Y, DeLuca HF. Target cells for 1,25-dihydroxyvitamin D3 in intestinal tract, stomach, kidney, skin, pituitary, and parathyroid. Science. 1979;206(4423):1188-90.
23. Haussler MR, Manolagas SC, Deftos LJ. Receptor for 1,25-dihydroxyvitamin D3 in GH3 pituitary cells. J Steroid Biochem. 1982;16(1):15-9.
24. Pérez-Fernandez R, Alonso M, Segura C, Muñoz I, García-Caballero T, Diguez C. Vitamin D receptor gene expression in human pituitary gland. Life Sci. 1997;60(1):35-42.
25. Pang ALY, Chan WY. Chapter 22 - Molecular basis of diseases of the endocrine system. In: Coleman WB, Tsongalis GJ (eds.), Molecular Pathology, 2nd edition, Academic Press, 2018, 407-505.
26. Seoane S, Perez-Fernandez R. The vitamin D receptor represses transcription of the pituitary transcription factor Pit-1 gene without involvement of the retinoid X receptor. Mol Endocrinol. 2006;20(4):735-48.
27. Seoane S, Ben I, Centeno V, Perez-Fernandez R. Cellular expression levels of the vitamin D receptor are critical to its transcriptional regulation by the pituitary transcription factor Pit-1. Mol Endocrinol. 2007;21(7):1513-25.
28. Ozcelik S, Celik M. 25-OH vitamin D levels in patients with pituitary adenoma. Biomed J Sci & Tech Res. 2019;18(1):13223-5.
29. Caputo M, Pigni S, Agosti E, et al. Regulation of GH and GH signaling by nutrients. Cells. 2021;10(6):1376.
30. Giordano M, Godi M, Mellone S, et al. A functional common polymorphism in the vitamin D-responsive element of the GH1 promoter contributes to isolated growth hormone deficiency. J Clin Endocrinol Metab. 2008;93(3):1005-12.
31. Spencer EM, Tobiassen O. The mechanism of the action of growth hormone on vitamin D metabolism in the rat. Endocrinology. 1981;108(3):1064-70.
32. Brixen K, Nielsen HK, Bouillon R, Flyvbjerg A, Mosekilde L. Effects of short-term growth hormone treatment on PTH, calcitriol, thyroid hormones, insulin and glucagon. Acta Endocrinol (Copenh). 1992;127(4):331-6.
33. Bianda T, Hussain MA, Glatz Y, Bouillon R, Froesch ER, Schmid C. Effects of short-term insulin-like growth factor-I or growth hormone treatment on bone turnover, renal phosphate reabsorption and 1,25 dihydroxyvitamin D3 production in healthy man. J Intern Med. 1997;241(2):143-50.
34. Mormando M, Chiloiro S, Bianchi A, et al. Growth hormone receptor isoforms and fracture risk in adult-onset growth hormone-deficient patients. Clin Endocrinol (Oxf). 2016;85(5):717-24.
35. Mazziotti G, Doga M, Frara S, et al. Incidence of morphometric vertebral fractures in adult patients with growth hormone deficiency. Endocrine. 2016;52(1):103-10.
36. Mazziotti G, Bianchi A, Bonadonna S et al. Increased prevalence of radiological spinal deformities in adult patients with GH deficiency: influence of GH replacement therapy. J Bone Miner Res. 2006;21(4):520-8.
37. Condamine L, Menaa C, Vrtovsnik F, Friedlander G, Garabédian M. Local action of phosphate depletion and insulin-like growth factor 1 on in vitro production of 1,25-dihydroxyvitamin D by cultured mammalian kidney cells. J Clin Invest. 1994;94(4):1673-9.
38. Giustina A. Acromegaly and vertebral fractures: facts and questions. Trends Endocrinol Metab. 2020;31(4):274-5.
39. Chiloiro S, Giampietro A, Gagliardi I, et al. Impact of the diagnostic delay of acromegaly on bone health: data from a real life and long term

follow-up experience. Pituitary. 2022;25(6):831-41.
40. Frara S, Melin Uygur M, di Filippo L et al. High prevalence of vertebral fractures associated with preoperative GH levels in patients with recent diagnosis of acromegaly. J Clin Endocrinol Metab. 2022;107(7):e2843-50.
41. Mazziotti G, Maffezzoni F, Giustina A. Vitamin D-binding protein: one more piece in the puzzle of acromegalic osteopathy? Endocrine. 2016;52(2):183-6.
42. Dicken CL, Israel DD, Davis JB, et al. Peripubertal vitamin D(3) deficiency delays puberty and disrupts the estrous cycle in adult female mice. Biol Reprod. 2012;87(2):51.
43. Parikh G, Varadinova M, Suwandhi P et al. Vitamin D regulates steroidogenesis and insulin-like growth factor binding protein-1 (IGFBP-1) production in human ovarian cells. Horm Metab Res. 2010;42(10):754-7.
44. Merhi Z, Doswell A, Krebs K, Cipolla M. Vitamin D alters genes involved in follicular development and steroidogenesis in human cumulus granulosa cells. J Clin Endocrinol Metab. 2014;99(6):E1137-45.
45. Holt R, Juel Mortensen L, Harpelunde Poulsen K, et al. Vitamin D and sex steroid production in men with normal or impaired Leydig cell function. J Steroid Biochem Mol Biol. 2020;199:105589.
46. Khan H, Khan MB. Assessment of vitamin D3 deficiency and insufficiency in age and gender groups. Rawal Medical Journal. 2022;47(2):290-2.
47. Murata T, Chiba S, Kawaminami M. Changes in the expressions of annexin A1, annexin A5, inhibin/activin subunits, and vitamin D receptor mRNAs in pituitary glands of female rats during the estrous cycle: correlation analyses among these factors. J Vet Med Sci. 2022;84(8):1065-73.
48. Nicholas C, Davis J, Fisher T, et al. Maternal vitamin D deficiency programs reproductive dysfunction in female mice offspring through adverse effects on the neuroendocrine axis. Endocrinology. 2016;157(4):1535-45.
49. Keisala T, Minasyan A, Järvelin U, et al. Aberrant nest building and prolactin secretion in vitamin D receptor mutant mice. J Steroid Biochem Mol Biol. 2007;104(3-5):269-73.
50. Deng C, Ueda E, Chen KHE, et al. Prolactin blocks nuclear translocation of VDR by regulating its interaction with BRCA1 in osteosarcoma cells. Mol Endocrinol. 2009;23(2):226-36.
51. Aboelnaga MM, Abdullah N, Shaer ME. 25-hydroxyvitamin D correlation with prolactin levels and adenoma size in female patients with newly diagnosed prolactin secreting adenoma. Endocr Metab Immune Disord Drug Targets. 2017;17(3):219-25.
52. Saki F, Sadeghian F, Kasaee SR, Koohpeyma F, Ranjbar Omrani GH. Effect of prolactin and estrogen on the serum level of 1,25-dihydroxy vitamin D and FGF23 in female rats. Arch Gynecol Obstet. 2020;302(1):265-71.
53. Mazziotti G, Porcelli T, Mormando M, et al. Vertebral fractures in males with prolactinoma. Endocrine. 2011;39(3):288-93.
54. Mazziotti G, Mancini T, Mormando M, et al. High prevalence of radiological vertebral fractures in women with prolactin-secreting pituitary adenomas. Pituitary. 2011;14(4):299-306.
55. di Filippo L, Doga M, Resmini E, Giustina A. Hyperprolactinemia and bone. Pituitary. 2020;23(3):314-21.
56. Dunbar DR, Khaled H, Evans LC, et al. Transcriptional and physiological responses to chronic ACTH treatment by the mouse kidney. Physiol Genomics. 2010;40(3):158-66.
57. Kato A, Shinozaki S, Goga T, Hishida A. Isolated adrenocorticotropic hormone deficiency presenting with hypercalcemia in a patient on long-term hemodialysis. Am J Kidney Dis. 2003;42(2):E32-6.
58. Wang B, Cruz Ithier M, Parobchak N, Yadava SM, Schulkin J, Rosen T. Vitamin D stimulates multiple microRNAs to inhibit CRH and other pro-labor genes in human placenta. Endocr Connect. 2018;7(12):1380-8.
59. Tourkova IL, Liu L, Sutjarit N et al. Adrenocorticotropic hormone and 1,25-dihydroxyvitamin D3 enhance human osteogenesis in vitro by synergistically accelerating the expression of bone-specific genes. Lab Invest. 2017;97(9):1072-83.
60. Frara S, di Filippo L, Doga M, Loli P, Casanueva FF, Giustina A. Novel approaches to bone comorbidity in Cushing's disease: an update. Pituitary. 2022;25(5):754-9.
61. Frara S, Allora A, di Filippo L, et al. Osteopathy in mild adrenal Cushing's syndrome and Cushing disease. Best Pract Res Clin Endocrinol Metab. 2021;35(2):101515.
62. Sar M, Stumpf WE, DeLuca HF. Thyrotropes in the pituitary are target cells for 1,25 dihydroxy vitamin D3. Cell Tissue Res. 1980;209(1):161-6.
63. Talaei A, Ghorbani F, Asemi Z. The effects of vitamin D supplementation on thyroid function in hypothyroid patients: a randomized, double-blind, placebo-controlled trial. Indian J Endocrinol Metab. 2018;22(5):584-8.
64. Chailurkit LO, Aekplakorn W, Ongphiphadhanakul B. High vitamin D status in younger individuals is associated with low circulating thyrotropin. Thyroid. 2013;23(1):25-30.
65. Clinckspoor I, Gérard AC, Van Sande J, et al. The vitamin D receptor in thyroid development and function. Eur Thyroid J. 2012;1(3):168-75.
66. Clinckspoor I, Verlinden L, Mathieu C, Bouillon R, Verstuyf A, Decallonne B. Vitamin D in thyroid tumorigenesis and development. Prog Histochem Cytochem. 2013;48(2):65-98.
67. Babić Leko M, Gunjača I, Pleić N, Zemunik T. Environmental factors affecting thyroid-stimulating hormone and thyroid hormone levels. Int J Mol Sci. 2021;17;22(12):6521.
68. Babić Leko M, Jureško I, Rozić I, Pleić N, Gunjača I, Zemunik T. Vitamin D and the thyroid: a critical review of the current evidence. Int J Mol Sci. 2023;24(4):3586.