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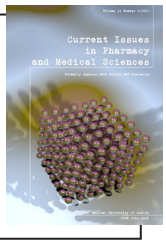

# Insights into the perspective correlation between vitamin D and regulation of hormones: sex hormones and prolactin

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**ABSTRACT**

**Aim.** Vitamin D is currently an exciting research target, besides its obvious role in calcium homeostasis and bone health, enormous work is being directed at examining the effects of this vitamin on various biological functions and pathological conditions.

**Material and methods.** The review of the literature and the analysis took about six months and was carried out through PubMed. This is a search engine opening mainly the MEDLINE database of trusted references. We called up all studies written in English that were published between the years 2004 to 2021 and that came through using the applied search terms, and analysed all those that met the criteria.

**Results.** The endocrine system with its many glands and hormones and their essential roles in the maintenance of normal body functioning cannot be far from interactions with vitamin D. Male and female sex hormones are no exceptions and many studies have investigated the correlations between these hormones and vitamin D. As such, direct and indirect relationships have been found between vitamin D, its receptors or one of its metabolising enzymes with sex hormones and the development of reproductive organs in males and females.

**Conclusion.** This review summarises the research investigating the associations of vitamin D with sex hormones and reproductive organs in males and females, and thus may pave the road for future studies that will investigate the clinical significance of vitamin D in the management of reproductive system disorders. Despite some conflicting results about the relationship between VD and the effectiveness of the reproductive system, many studies confirm the presence of receptors for this vitamin in the reproductive system, and this supports the direct or indirect relationship between VD and prolactin or VD and testosterone through $PO_4$ and $Ca^{2+}$ homeostasis, or production of osteocalcin. Therefore, VD is positively associated with semen quality and androgen status. Furthermore, a direct relationship between VD and the production of progesterone, estrogen and estrone in human ovarian cells has been supported by many studies.

## INTRODUCTION

The main vitamin D (VD) function in the human body is phosphate ($PO_4$) and calcium ($Ca^{2+}$) homeostasis, hence it is a key regulator of bone calcification. However, several studies indicate that VD has other non-classical binding sites and targets, including the male and female reproductive systems. VD can be considered more than just a vitamin due to its binding to the steroid hormone receptors [1].

The tight link between VD and sex hormones or prolactin is indispensable when determining the effects of VD in non-classical targets. All *in vivo* studies with systemic variations in VD may also have variations in sex hormones and/or changes in prolactin [2,3]. These variations may either decrease or boost the supposed VD effects and should therefore be addressed in all research reviewing VD.

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The probable function of VD in the regulation of sex hormones has effects outside the sex organs where some of these hormones such as inhibin, insulin-like factor 3 (INSL3), testosterone, and estradiol have been shown to mediate actions (e.g. kidney and skeleton). As such, this review attempts to shed light on the relationship and mutual influence between VD and sex hormones, which may pave the way for linking the clinical use of this vitamin in treating imbalances, directly or indirectly in some sex hormones, as these imbalances play a major role in some diseases of the reproductive system, fertility and reproduction. Additionally, this review is one part of an ongoing review series regarding the correlations between VD and different hormones.

This review relied mainly on gathering references and extracting information from reliable and up-to-date sources, which were published between 2004 and 2021, through the use of PubMed which is a search engine opening mainly the MEDLINE database of trusted references. We used the following search terms: vitamin D, gonadotropin-realising hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin in addition to 25-hydroxyvitamin D (25(OH)D), 1,25-dihydroxyvitamin D, and calcitriol.

## VITAMIN D METABOLISM

Exposing the skin to sunlight is the first step in the production of VD. The ultraviolet rays in sunlight convert the 7-dehydrocholesterol into cholecalciferol [4]. The latter is a biologically inactive form of VD that needs to convert through enzymatic reactions in the liver into an intermediate compound called 25-hydroxy cholecalciferol. It then becomes fully activated after being converted into 1,25-dihydroxy cholecalciferol in the kidneys [5]. CYP2R1 is the main enzyme (but not the only one) involved in converting the cholecalciferol into 25-hydroxy cholecalciferol. CYP2R1 is predominantly secreted by the liver and testicles. Despite the ability of 25-hydroxy cholecalciferol to bind to VD receptors, it has a weak affinity for these receptors compared to 1,25-dihydroxy cholecalciferol, so the former is also considered as being an inactive form of VD, and a second enzyme called CYP27B1 is involved. This enzyme is secreted by the kidney and is responsible for the formation of active VD, which has a high affinity to bind to VD receptors [2,3]. The renal cytochrome is specifically regulated by endocrine hormones and especially by fibroblast growth factor 23, parathyroid hormone, calcitonin and sex steroids [6,7]. On the other hand, the inactivation enzyme (CYP24A1) is a key regulatory enzyme in controlling and regulating all forms of circulating VD by metabolizing them to 24,25-(OH)2D3 and therefore it is involved in normal VD homeostasis [3].

## MALE REPRODUCTIVE SYSTEM

### Hormonal regulation and physiology of male reproductive system

The male reproductive system consists of testicles, penis and other adjunct sex organs. The main function of this system is to produce and inject the mature and viable semen into the female reproductive system [8]. The testicles are the main components of the reproductive system and are responsible for the production of male sex hormones and for spermatogenesis [9]. Spermatogenesis is a complicated series of processes ending in the production of male gametes (sperms) in the seminiferous tubules [1]. A sperm subsequently transports to the epididymis to mature and develop its motility and becomes capable to move to the ovum and fertilize it [10].

Both the nervous system and endocrine system are responsible for the regulation of the reproductive system functions [8]. The hypothalamic-pituitary axis is the hormonal pathway responsible for the control of testis functions (Figure 1) [11]. This is mediated by secretion of gonadotropin-realising hormone (GnRH) from the hypothalamus [11]. GnRH then stimulates the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) from the pituitary gland [11]. LH stimulates testicular interstitial cells of Leydig to secrete testosterone which is a primary androgenic hormone that plays a role in the induction and maintenance of all aspects of the male phenotype [12].

The sensitivity of LH receptor on the surface of Leydig cells (L. cells) is additionally increased by the prolactin secreted from the pituitary [11]. FSH triggers Sertoli cells (S. cells) in the testis to regulate a number of cellular functions such as the negative feedback to the pituitary and hypothalamus mediated by inducing the secretion of inhibin to control the release of FSH and GnRH [13]. Although testosterone is important for the production of sperm within the testicles, it also transports to the peripheral circulation and the somniferous fluid, where it is subjected to metabolism by 5 α-reductase to form dihydrotestosterone and by aromatase to form estradiol [14]. Dihydrotestosterone has an important regulatory role in epididymal and accessory sex organ functions, while estradiol is an important regulating factor, mainly in the epididymis and efferent ducts [11].

Overall, the male reproductive system is controlled by a series of regulatory hormones. In spite of that, the testicle is also sensitive to a verity of behaviours and lifestyle factors such as smoking, obesity, pharmacological agents, nutrition and vitamin intake [15].

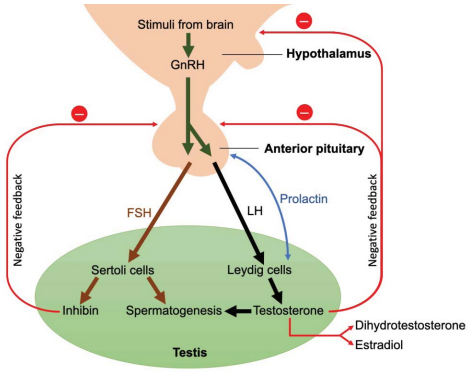


***Figure 1.*** Hormonal pathway of testis with feedback loops

### Vitamin D and male reproductive hormones

This part summarizes the current information about the effect of VD on the male reproductive system hormones (Table 1). VD mediates its action by stimulating VD receptors (VDR) which are located in different tissues such as

parathyroid glands, skeleton and reproductive tissues [16]. Before binding to its receptor, VD needs to be activated in the presence of VD metabolizing enzymes; CYP2R1, CYP27B1, and CYP24A1. Previously, the expression of these enzymes was thought to be limited to the kidney and liver [5]. A recent study showed that the enzymes are also available in different tissues, including the male reproductive organs [17]. VDR and VD metabolizing enzymes are specifically expressed in the human prostate, epididymis, testis, seminal vesicle, and spermatozoa [18,19].

***Table 1.*** Vitamin D and male reproductive hormones

| Hormones | Increase | Decrease | No effect |
|---|---|---|---|
| Testosterone | ↑ [9,27-37,40] | ND | — [9, 21-26] |
| Luteinizing hormone (LH) | ↑ [36] | ND | — [9, 21, 24] |
| Sex-hormone-binding-globulin (SHBG) | ↑ [35] | ↓ [27] | ND |
| Inhibin | ↑ [35] | ND | — [9] |
| Follicle-stimulating hormone (FSH) | ↑ [36] | ND | — [9] |
| Anti-Müllerian hormone (AMH) | ↑ [44] | ND | ND |
| Insulin-like factor 3 (INSL3) | ND | ND | — [21] |

This table summarizes studies conducted to evaluate the relationship between VD and male sex hormones. ↑ - increase; — - no effect; ↓ - decrease; ND - not determined
The superscript numbers indicate the reference numbers

L. cells are responsible for the production of testosterone, which is essential for male sex characteristics, including primary characteristics (from birth) and secondary characteristics (emerge at puberty) [9]. The biosynthetic production of testosterone is regulated by placental human chorionic gonadotropin (HCG) in the foetus, then by LH when the pituitary begins to secret it [20].

In a comparative study between wildtype and VDR-null mice, results referred to that the serum level of LH and testosterone were not significantly different, although low ratio of testosterone: LH and hyperplasia of L. cell were noticed in VDR-null mice [21]. Moreover, 3 children suffering from inherited 1α,25 dihydroxyVD3-resistant rickets (unfunctional VDR) showed a normal testosterone response [22,23]. In addition to that, infusion of VD for 3 days resulted in insignificant changes in the level of serum testosterone or LH in healthy men [9]. These outcomes are in accordance with the equivalent serum concentration of LH and testosterone found in healthy young men and adolescents with or without VD deficiency [24]. Also, in middle-aged healthy males with normal baseline testosterone, VD treatment did not have any significant effect on testosterone levels, but it did significantly reduce the quantitative insulin sensitivity check index [25]. Similarly, in middle-aged healthy males with low testosterone concentrations, VD therapy had no effect on blood testosterone concentrations [26].

All these data indicate that there is no direct relationship between the level of VD or the activation of its receptors and serum level of testosterone or LH sensitivity. However, contradictory results were obtained from other clinical trials. For example, the levels of VD, testosterone and sex-hormone-binding-globulin (SHBG) were assessed in a cross-sectional study that revealed that males with sufficient VD levels had significantly higher concentrations of testosterone with significantly lower amounts of SHBG, in comparison to those participants with insufficient and deficient VD levels. The study concluded that there is significant correlation between VD, testosterone and SHBG levels [27].

In a similar scenario, a randomized controlled trial has reported an increase in testosterone level following supplementation with 3332 IU of VD to overweight men who are undergoing a weight-loss program [28]. Three different studies conducted on two age groups, middle-aged and elderly, showed supporting findings to the positive relationship between VD and testosterone [29-31]. One of these studies demonstrated that VD may increase the risk of prostate cancer, as its concentration could influence the level of circulating testosterone [29].

The potential link between VD and sexual performance has recently received much interest. In one study, by using retrospective and longitudinal approaches, including clinical, molecular and sexual characteristics, higher levels of VD were found to be substantially linked with higher levels of total testosterone and all the parameters of the International Index of Erectile Function (IIEF) questionnaire in the entire study group. Higher concentration of serum total testosterone, on the other hand, was related to increased levels of erectile function and the IIEF total score in a favourable and significant way. Total and free testosterone levels improved after VD replacement therapy, and erectile function recovered, while other sexual indicators remained unchanged. As a result, the study concluded that VD is necessary for healthy male sexual function, and VD supplementation promotes such healthy sexual function [32].

Confirming the aforementioned studies, a lower level of VD was linked with a higher incidence of hypogonadism in men [33,34]. Similarly, infertile men with low VD levels had reduced sperm motility, overall number of motile sperms, testosterone/estradiol ratio, SHBG and inhibin B, but greater levels of free sex steroids than those infertile men with normal VD status, according to an observational study [35]. Furthermore, a randomized clinical trial assessed the effect of VD supplementation (25000 IU per week for 2 months) on reproductive hormones (testosterone, LH and FSH) and seminal fluid parameters in infertile men with VD deficiency and the study found a significant effect of VD supplementation on sperm motility, volume and concentration, in addition to prolactin level after 2 months of therapy, indicating a significant link between VD, sex hormones and prolactin [36].

In the elderly men (>57 years old) [1], a few studies have shown a positive relationship between serum level of VD (25hydroxyVD) and testosterone level, in addition to seasonal fluctuation in levels of testosterone that are commensurate with the periodic (seasonal) variation in the values of 25-hydroxyVD [27,37,38]. Disappearing of the association between serum concentration of 25-hydroxyVD and testosterone after controlling health status and associated diseases in elderly males also indicates the indirect effect of VD levels [37]. Herein, LH stimulates steroidogenesis by rising cAMP production and the intracellular level of $Ca^{2+}$ in L. cells, where 1α,25-dihydroxy$VD_3$ could exert an indirect effect by modifying this calcium dependent LH response [39].

Both VD and parathyroid hormone regulate the absorption of calcium in the intestine and its excretion through

the kidneys. Therefore, the concentration of calcium in the blood serum can change as a result of the change in the concentration of VD. For that reason, VD deficiency is usually associated with hypocalcaemia, which might, therefore, lead to indirect effect in the target tissue instead of a direct VDR-mediated effect [9]. These findings are consistent with a study carried out on rats, which showed that the level of testosterone in rats suffering from VD deficiency will increase two to five times following injections of 1α,25-dihydroxyVD$_3$ [9,40].

Another indirect effect of VD on testosterone could be mediated by osteocalcin protein. The gene that encodes this protein is controlled by VD [41]. An animal study showed that testosterone production could be stimulated by osteocalcin through GPRC6A receptor activation in L. cells [42].

In summary, testosterone production could be indirectly affected by VD through $PO_4$ and $Ca^{2+}$ homeostasis, or production of osteocalcin. However human conclusions need more confirmations. Also, 1α,25-dihydroxyVD$_3$ could repress the conversion of testosterone to estradiol as 1α,25-dihydroxyVD$_3$ binds to VD receptors in the promoter of CYP19A1 aromatase which converts testosterone to estradiol. Zanatta *et al*., for example, concluded that aromatase expression in immature rat S. cells was induced by 1α,25-dihydroxyVD$_3$ [43]. Moreover, VD receptor null mouse models showed a noticeable effect of 1α,25-dihydroxy VD$_3$ on oestrogen signalling in testicle and epididymis [21].

On the other hand, a study conducted in 2012 stated a significant direct relationship between serum concentrations of 25-hydroxyVD and anti-Müllerian hormone (AMH). The latter is mainly produced in undeveloped S. cells and participates in the male reproductive system maturity. This study reported that AMH creation was modified by administration of VD only in adult males, but not in children [44].

Stimulation of AMH by VD is reasonable due to the presence of VD receptors on the AMH promoter in immature human S. cells [9]. While AMH is solely expressed in undeveloped (immature) S. cells, inhibin B and sex hormone binding globulin (SHBG) are secreted from mature S. cells [9]. Inhibin B produces adverse feedback on excretion of FSH, whereas SHBG governs the level of free hormone in the reproductive system of men. In cohort studies conducted in healthy males, no relations were discovered between serum levels of VD and inhibin B or FSH [9] , consequently, VDR seems to be unnecessary for inhibin B or SHBG secretion from testis [43] , while there is a weak relation with AMH in humans and this relation requires more validation.

Moreover, with regard to INSL3, a peptide hormone which plays a role in testicular descent during maturation [9] , and which is produced by L. cells, a study has revealed that it is not differently produced between VD receptor-null mice and their wild type. Hence, INSL3 is not reliant on VD receptor expression [21]. In addition, although, progesterone (P) production is stimulated by 1α,25-dihydroxyVD$_3$ in the ovaries and placenta [45] , the supposed effect of VD on P synthesis in the L. cells needs to be tested in both animals and humans.

## FEMALE REPRODUCTIVE SYSTEM

### Hormonal regulation and physiology of female reproductive system

The female reproductive system is a complex system including the hypothalamus, pituitary gland, ovaries, uterus (endometrium and cervix) and vagina [46]. The hypothalamic-pituitary-gonadal axis is responsible for coordinating the reproductive system in females [47]. The primary signal of regulatory pathway starts by the release of GnRH from the hypothalamus, which controls the activity of the anterior pituitary resulting in regulated secretion of FSH and LH (Figure 2) [47].

LH and FSH stimulate ovulation and promote secretion of the female sex hormones, including estradiol (estrogen) and P from the ovaries [46]. These hormones produce modifications in the uterine endometrium former to enable implantation of the fertilized ovum. In addition, they stimulate the target organs of the female reproductive system (eg, breasts, uterus, vagina) [46].

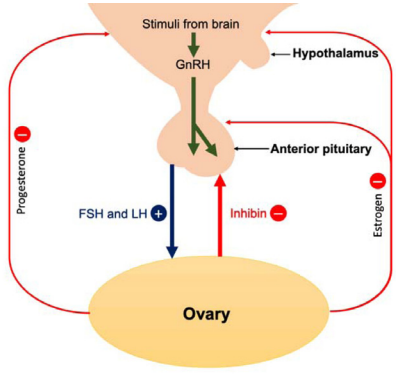


***Figure 2.*** Hormonal pathway of ovary with feedback loops

### Vitamin D and female reproductive hormones

As mentioned before, the biological activities of VD start by binding with VDRs which spread in different tissues such as the parathyroid glands, bones and sex organs (Figure 3) [48].

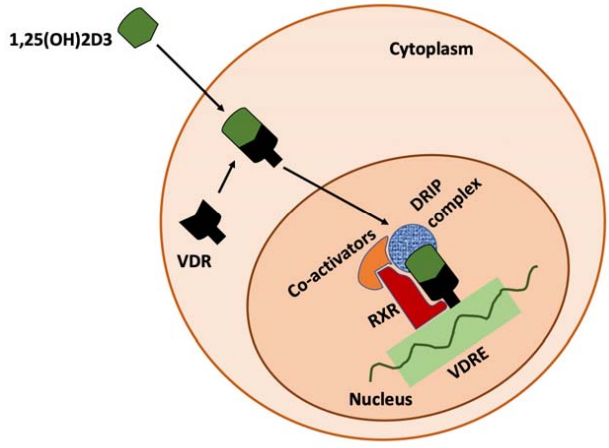


***Figure 3.*** 1,25(OH)2D3 binds to the cytoplasmic vitamin D receptor (VDR)

The combined vitamin D then transfers to the nucleus. In the nucleus, it complexes with co-activators such as retinoid X receptor (RXR) and the DRIP complex. This transcriptional unit binds to the vitamin D response element (VDRE) in the promoter region of genes in order to regulate transcription [48]. Many female reproductive hormones may affect by VD and its level (Table 2).

***Table 2.*** Vitamin D and female reproductive hormones

| Hormones | Increase | Decrease | No effect |
|---|---|---|---|
| Estrone | ↑ [45] | ND | ND |
| Estradiol | ↑ [45, 51] | ND | – [52-55] |
| Progesterone | ↑ [45] | ND | ND |
| Testosterone | ↑ [57] | ↓ [56] | ND |
| Anti-Müllerian hormone (AMH) | ND | ↓ [58] | – [57,59,60,61,62] |

This table summarizes studies conducted to evaluate the relationship between VD and female sex hormones. ↑ - increase; – - no effect; ↓ - decrease; ND - not determined
The superscript numbers indicate the reference number

Several studies have shown a high expression of VDR in female sex tissues, especially in human follicular cells [45]. These findings propose that VD could have a role in the production of estrogen and androgen and could influence their follicular and serum levels in women [49]. Hodgins and Murad found that incubation of human fibroblasts with the active form of VD improved the CYP19A1 activity [50]. Furthermore, culture of humane ovarian cells treated with the active form of VD will elevate estrone production by 21% and estradiol production by 6% when compared with untreated cells [45]. In addition, an animal study using VDR-null mice showed uterine hypoplasia, decrease in aromatase activity and low level of serum estradiol, as well as a rise in FSH and LH.

All these findings suggest a peripheral problem rather than a central malfunction [51]. These disturbances in the aromatase activity and low level of estradiol were improved with estradiol and calcium supplementation [51]. Another *in vitro* study has found a direct relationship between VD and the production of progesterone, estrogen and estrone in human ovarian cells [45]. These results are in contrast to results from other human studies which stated that there is no correlation between serum VD and estradiol level [52-55]. These contradictory results warrant further studies to clarify the relationship between reproductive hormones in women and VD.

Few studies have dealt with the relationship between VD and androgens in females, as androgens are produced in small amount in women. One of these studies tested the level of VD in 100 obese and nonobese women suffering from polycystic ovary syndrome, and stated a negative correlation between VD and testosterone [56]. In contrast, a positive correlation has been found between testosterone and VD in 73 healthy women as reported by Chang *et al*. [57].

Both AMH and insulin-like growth factor-1 (IGFBP-1) are peptide hormones. AMH is produced in female ovaries and is responsible for adjusting the follicular response to FSH [58]. In 2012, an *in vitro* study stated that VD reduced AMH expression in granulosa cells from animals [58]. Other studies conducted on granulosa cells from human demonstrated that the active form of VD has no effect on the AMH level, while the expression of AMH II receptor was decreased [59].

A cross-sectional study including 388 premenopausal women and another study including 33 premenopausal women have observed a positive correlation between VD and AMH [59,60]. Furthermore, a seasonal variation in VD level was associated with a drop in AMH level during wintertime. This positive correlation between AMH and 25OHD was supported by low variation in the level of AMH when VD was given [58]. On the other hand, some other studies showed different results and reported that there is no obvious correlation between AMH and 25OHD and no alteration in the serum level of AMH after VD supplementation [57,61,62]. The inconsistency may be attributed to variances in geographic location, ethnicity, kind of AMH assay or VD status between the studied participants [58].

Human clinical trials concerning *in vitro* fertilization (IVF), a popular approach for gathering information on this subject, are relatively limited and controversial. Generally, in mammals, VD insufficiency and deficiency have been shown to influence fertility, but the evidence in humans is less clear. The association between plasma levels of VD, implantation, and actual pregnancy rates in females who experienced an euploid blastocyst embryo transfer has been studied in a retrospective cohort study. The findings demonstrated that VD had no influence on pregnancy outcomes in women having euploid embryo transfer. Also, the possibility of euploid blastocysts implanting is not predicted by serum VD levels [63]. Conversely, A prospective cross-sectional research was performed to explore the success of IVF in women who had low VD levels in their blood. According to the findings, VD could be a new factor promoting female fertility and IVF success.

More studies are urgently needed to demonstrate a causal association and look into the potential therapeutic effects of VD supplementation [64]. In line with this suggestion, A multicentre randomized, double-blind, placebo-controlled intervention is now underway to determine the effect of VD administration prior to IVF on the healthy birth rates in women with polycystic ovarian syndrome. The study began in July 2020, with a recruitment period of 18 months (the last participant is planned to be recruited in December 2020). The results of this study will be essential in revealing the exact effect of VD on fertility and IVF success [65].

In the same way, the literature in reproduction medicine, continues to be conflicted on the impact of VD on intracytoplasmic sperm injection outcomes (ICSI). In this regard, a randomized double-blinded controlled study had been performed with the primary goal of determining the relationship between the levels of VD and pregnancy rates in a large group of IVF cases. This study included 80 infertile couples who had undergone ICSI procedures. The study's findings stated that females with adequate VD levels are generally more likely than those with deficient levels to achieve pregnancy after ICSI, and that supplementation with VD could help increasing the rates of embryo implantation and the rates of continuing pregnancy by lowering the rate of first trimester miscarriage [66].

**Prolactin and vitamin D**

Lactotrophs are specialized cells of the anterior pituitary gland, which take their fundamental role in the secretion of the polypeptide hormone, prolactin [67]. In addition to the role of prolactin in lactation, it has around 300 other different biological activities, including homeostatic functions in the body organs [67,68]. Different regulatory pathways are responsible for the release of prolactin from lactotrophs which could be summarised by four categories: autocrine, juxtacrine, endocrine and paracrine [69]. Herein, the autocrine pathway emanates from lactotrophs via their own production of autocrine agents, while the juxtacrine pathway originates from the interaction between lactotrophs and the extracellular matrix of adjacent cells. In addition, the endocrine pathway starts from the hypothalamus, gonads and neuronal lobe of pituitary, reaching the lactotrophs through a hormonal pathway, while paracrine agents are released from cells of intermediate and interior lobes and received by lactotrophs via diffusion [69,70].

Prolactin production is controlled by a large additional variety of internal and external stimuli [67,71]. The most important stimuli that increase pituitary secretion of prolactin are lactation, stress and increased production of steroids and estrogen from ovaries [67,72]. These stimuli trigger the transduction pathway through the hypothalamus, which leads to elaborate prolactin releasing factors (PRF) and prolactin inhibitory factors (PIF).

The well-accepted and widespread concept is that lactotrophs cells have a spontaneous prolactin secretion capacity. Consequently, the regulation of prolactin secretion from the pituitary gland, and specifically from the lactotrophs, is under inhibitory control exerted by hypothalamus [73]. Emphasis is placed on the role of dopamine in the regulating of prolactin secretion [73]. Dopamine acts via receptors (dopamine type-2 receptors) expressed on the surface of lactotrophs, as the primary inhibitor of prolactin. On the other hand, different kinds of peptides and growth factors can stimulate prolactin secretion either by affecting the dopamine input to lactotrophs or by directly affecting the lactotrophs [69].

Many studies have tested the relationship between the prolactin and VD. One of these studies found that prolactin has a positive effect on the activity of renal 25-hydroxycholecalciferol-1-hydroxylase as this enzyme has a role in the activation of VD by converting the 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol, to produce the active form of the vitamin via further hydroxylation taking place in the kidney [74]. Through another mechanism, prolactin can increase the 1,25(OH)2D3 level by lowering serum of fibroblast growth factor 23 which participates in phosphate and VD metabolism and regulation [74].

In one animal study, cells treated with VD displayed an obvious reduction in the production of prolactin [75]. Moreover, reversed data obtained from other studies indicate that treating anterior pituitary cells with 1,25dihydroxy-cholecalciferol results in an obvious rise in prolactin secretion compared to control [76,77]. However, 25-hydroxycholecalciferol alone or with 1,25-dihydroxycholecalciferol had no significant effect on the prolactin secretion.

This data suggests that 1,25-dihydroxycholecalciferol probably interferes with the prolactin secretion and 25-hydroxycholecalciferol possibly blunts the stimulating effects of 1,25-dihydroxycholecalciferol [76]. Most studies support the theory of a positive relationship between VD and prolactin secretion. However, a high level of prolactin could negatively affect the function of the testicles by adversely affecting sperm production (spermatogenesis), and interfering with testosterone production (the main male sex hormone) [78,79]. This positive effect, between VD and prolactin secretion, supports calcium concentration dependence, as VD is able to increase the intracellular concentration of calcium [80]. Based on the data stating stimulation of cytoplasmic prolactin messenger RNA by calcium, the calcium may regulate prolactin gene expression [74,80].

## CONCLUSION

All in all, VD, VDR, and VD homeostasis regulatory factors including metabolizing enzymes entirely appear to participate in controlling several functions of the male and female reproductive systems in addition to prolactin secretion, and the opposite could be possible. Studies investigating the relationship between circulating level of VD, VDR, VD metabolizing enzymes and serum testosterone and the effect of this relationship on the function of male reproductive system have concluded that there is no direct relationship between the level of VD or the activation of its receptors and serum level of testosterone or LH sensitivity. However, testosterone production could be indirectly affected by VD through $PO_4$ and $Ca^{2+}$ homeostasis, or production of osteocalcin. Also, VD could indirectly affect the development of the male reproductive system through the positive relationship between VD and AMH. P production may also affect VD levels, but this effect needs further research and investigation. In addition to confirming the presence of VD receptors in the female reproductive system, most research has established a positive relationship between VD and the secretion of estrogen and androgen, although there are few studies opposing these results, while the results remained conflicting about the relationship between VD and the anti-Müllerian hormone in female reproductive organs. In addition, there is the positive cross-effect between prolactin and VD. Until today there is no evidence-based VD treatment for male and female reproductive system diseases. Supplementation of VD might manage some reproductive system problems, at least some of the idiopathic cases of diseases, in a harmless and non-invasive approach. In spite of that, new clinical studies are required to expand our knowledge and establish whether supplementation will improve the diseases related to the reproductive system. In the meanwhile, translational and interdisciplinary approaches including *in vivo* and *in vitro* study models are basic to discover new physiological sides regarding VD and reproduction diseases.

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## ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable

## AUTHORS' CONTRIBUTIONS

All authors significantly contributed to the production of this work. MEQ, MNA, and FAA have a major contribution to writing the manuscript, conceptualizing, designing the topic, and searching of literature. MHMJ and MA contributed to plagiarism testing and English language editing. All authors have read and approved the manuscript.

## CONSENT FOR PUBLICATION

Not applicable

## COMPETING INTERESTs

The authors declare that they have no competing interests

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## FIGURES AND TABLES

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