Vitamin D Effects on Folliculogenesis via Ovarian Paracrine Factors

Vitamin D'nin Ovaryan Parakrin Faktörler ile Follikülogenez Üzerindeki Etkisi

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ABSTRACT

The folliculogenesis mechanism is a complex process involving various hormones, growth factors and signaling molecules. Future research on the mechanisms of follicular development will provide more comprehensive data on female reproductive life. Vitamin D affects folliculogenesis through steroidogenesis. Vitamin D receptor signaling in granulosa cells regulates hormone secretions through steroidogenic enzymes. Vitamin D and folliculogenesis associated mechanism is still not elucidated. Various ovarian-derived autocrine-paracrine factors involved in different stages of folliculogenesis have been shown in studies. Vitamin D effects on folliculogenesis via these factors are significant to understanding the underlying mechanism. Inhibitors of dormant primordial follicle activation are Forkhead box O3a, anti-müllerian hormone, Phosphatase and tensin homolog and p27. Among these factors, Forkhead box O3a is an important molecule for primordial follicle activity regulation and apoptosis mechanisms in the ovary. The factors involved in the development of preantral follicle from the primary follicle are Transforming Growth Factor-β, Growth and differentiation factor 9, Bone morphogenetic protein 4,7,15 and activin. Growth and differentiation factor 9 and Bone morphogenetic protein 15 induce granulosa cell proliferation and preantral follicle development. This review aims to describe the association between Vitamin D and folliculogenesis through steroidogenesis and ovarian paracrine factors.

Keywords: AMH, BMP15, FOXO, GDF9, steroidogenesis

ÖZET

Follikülogenez mekanizması çeşitli hormonları, büyüme faktörlerini ve sinyal moleküllerini içeren karmaşık bir süreçtir. Foliküler gelişim mekanizmaları üzerine gelecekteki araştırmalar, dişi reprodüktif yaşamı hakkında daha kapsamlı veriler sağlayacaktır. Vitamin D, steroidogenez yoluyla follikülogenezi etkiler. Granüloza hücrelerinde Vitamin D reseptör sinyali hormon salgılarını steroidojenik enzimler aracılığıyla düzenler. Vitamin D ve follikülogenez ile ilişkili mekanizma hala aydınlatılamamıştır. Follikülogenezin farklı evrelerinde yer alan çeşitli over kaynaklı otokrin-parakrin faktörler çalışmalarda gösterilmiştir. Bu faktörler yoluyla follikülogenez üzerindeki Vitamin D etkileri, altta yatan mekanizmayı anlamak için önemlidir. Sessiz primordial follikül aktivasyonunun inhibitörleri, Forkhead box O3a, anti-müllerian hormon, Fosfataz ve tensin homologu ve p27'dir. Bu faktörler arasından Forkhead box O3a, overde primordial folikül aktivite regülasyonu ve apoptoz mekanizmaları için önemli bir moleküldür. Primer follikülden preantral follikülün gelişiminde rol oynayan faktörler, dönüştürücü büyüme faktörü-β, büyüme ve farklılaşma faktörü 9, kemik morfogenetik protein 4,7,15 ve aktivindir. Bu derleme, steroidogenez ve ovaryan parakrin faktörler aracılığıyla VitD ve follikülogenez arasındaki ilişkiyi açıklamayı amaçlamaktadır

Anahtar kelimeler: AMH, BMP15, FOXO, GDF9, steroidogenez

Introduction

Vitamin D (VitD) plays a significant role in the reproductive system [1]. Maintaining the physiological level of VitD is critical to optimizing reproduction. VitD originates from the skin and this biologically inactive form is converted to 25-hydroxy VitD by hydroxylation in the liver. Finally, it is converted to biologically active 1,25dihydroxy VitD in the kidney. The VitD receptor binds to VitD response element regions in DNA and regulates the transcription of many genes [2]. VitD regulates cellular functions through VitD receptor. VitD receptor is abundant in reproductive organs [1]. Previous studies have shown that VitD plays an important role in the regulation of ovarian function, including follicular development [3]. The present article reviews the impact of VitD on folliculogenesis via ovarian steroidogenesis and paracrine factors. In the study, Pubmed and Google Scholar databases were searched from 2010 to identify relevant studies. Studies of 2021 and 2022 in the discussion sections were systematically searched and included in the review. The following keywords were used to find the association between VitD, ovarian steroidogenesis, and ovarian paracrine factors: "Vitamin D", "25-Hydroxyvitamin D", "Vitamin D supplementation", "Ovary", "Anti-mullerian hormone", "AMH", "Growth and differentiation factor 9", "GDF9", "Bone morphogenetic protein 15", "BMP15", "Forkhead box", "FOXO", "Folliculogenesis", "Steroidogenesis". The bibliographic lists of eligible studies were also scanned to detect any additional qualified ones. The inclusion criteria were as follows: (1). Original human, in vitro or animal studies (preferably mammalians); (2). Published in the English language; (3). Assessed at least one of the ovarian steroidogenic enzymes, ovarian paracrine factors, follicle developmental markers; (4). Assessed at least one of the ovarian steroidogenic enzymes, ovarian paracrine factors, follicle developmental markers in association with VitD. The

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exclusion criteria were as follows: (1). Pregnant, lactating, or postmenopausal women; (2). Male reproduction; (3) . Poster abstracts, case reports; (4). İncomplete data.

1. Vitamin D effects on follicle development and steroidogenesis

VitD receptor signaling in granulosa cells has an effect on hormone and consequently likely affect folliculogenesis. Granulosa cells promote follicle development by secreting estrogen in response to follicle-stimulating hormone (FSH) release from pituitary and androgen release from theca cells [4]. In tertiary follicles, LH-activated theca cells convert cholesterol to pregnenolone. Pregnenolone is a substrate for progesterone synthesis that is mediated via 3β-hydroxysteroid dehydrogenase [4, 5]. Progesterone is further converted to androstenedione. Androstenedione is converted in the granulosa cell to oestrone by FSH-activated aromatase [4]. This inactive form of estrogen is activated by 17β-hydroxy steroid dehydrogenase, yielding active estradiol [6]. VitD regulates these hormone secretions through steroidogenic enzymes. VitD administration to human healthy and PCOS granulosa cells increased aromatase and 3β-hydroxysteroid dehydrogenase activity [7]. In another study, VitD increased progesterone release by granulosa cells via an increment in 3β-hydroxysteroid dehydrogenase mRNA expression levels [8]. In an animal study, VitD increases estradiol and progesterone production while decreasing both receptors of AMH and FSH [9]. After VitD treatment administration, estrogen and progesterone synthesis increased with 3β-hydroxysteroid dehydrogenase and 17β-hydroxysteroid dehydrogenase expressions by cultured granulosa cells [2]. VitD affects follicle development as well as steroidogenesis. Preantral and antral follicles synthesize VitD receptors [3]. It has been observed that impaired folliculogenesis and decreased ovarian response to gonadotropins in VitD deficiency [10]. In a study, VitD deficiency resulted in impaired folliculogenesis and prolonged oestrus cycle [11]. VitD supplementation improved follicle viability and growth with increased serum levels of estrogen and progesterone in PCOS rats [12]. In another study, VitD supplementation increased preantral follicle survival, antral follicle growth and survival [3]. Although it is known that VitD is effective on follicle development and steroidogenesis, this mechanism related to folliculogenesis has not been clarified yet. For this reason, it is important to evaluate the effect of VitD on ovarian-derived paracrine factors involved in follicle developmental stages.

2. Ovarian paracrine factors

Investigation of the effects of VitD on ovarian paracrine factors will help to understand its mechanism. Folliculogenesis is a complex process with various growth factors and signaling molecules. During this process, inhibitors of dormant primordial follicle activation are FOXO3a, AMH, Phosphatase and tensin homolog (PTEN) and p27 [13]. The loss of inhibitory signal functionality causes premature primordial follicle activation. Kit ligand (KITL) and Leukemia inhibitory factor (LIF) stimulate the activation of primordial follicle [14]. A high rate of primordial follicle activation will lead to premature depletion of follicle reserve and premature ovarian failure [13]. The factors involved in the development of preantral follicle from the primary follicle are Transforming Growth Factor-β (TGF-β), GDF9, BMP4, BMP7, BMP15 and activin [14]. The source of BMP4 and BMP7 is theca cells, while BMP15 and GDF9 are produced by oocytes. AMH and activin are synthesized from granulosa cells [13]. In the following section GDF9, BMP15, FOXO and AMH among ovarian derived factors will be discussed.

2.1. GDF9, BMP15

GDF9 and BMP15 are members of the TGF-β superfamily. BMP15 binds to the anaplastic lymphoma kinase 6 (ALK6) and BMP receptor II (BMPRII) complex on the granulosa cell surface and activates maternal against decapentaplegic homolog (Smad) 1,5,8 pathway. GDF9, on the other hand, triggers the Smad 2,3 pathway by activating ALK5 and BMPRII receptors [15]. GDF9 and BMP15 are highly expressed in the secondary follicles [16]. These two factors not only improve the developmental competence of the oocyte but also act directly on the granulosa cells. GDF9 and BMP15 have critical effects on granulosa cell proliferation, differentiation, steroidogenesis, apoptosis and cumulus expansion [17]. BMP15 promotes follicle maturation since gonadotropin independent phases of folliculogenesis, regulates granulosa cell sensitivity to FSH and prevents granulosa cell apoptosis [18]. Recent studies have shown that BMP4,7,15 and TGF-β may modulate connexin 43 expression in granulosa cells. Connexin 43 is required for granulosa cell proliferation [19]. GDF9 is an antiapoptotic factor and leads to transition of follicles to later stages. Lack of GDF9 leads to blockage of follicular growth [20]. GDF9 also reducing luteinization via progesterone reduction [17]. GDF9 and BMP15 has an inhibitory effect on progesterone secretion in granulosa cells [21]. In a recent study, it was reported that BMP15 increased progesterone production by cumulus cells [22]. Both GDF9 and BMP15 can act as a potential biomarkers for the estimation of female infertility [23]. Decreased expression of GDF9 and BMP15 in polycystic ovary syndrome (PCOS) is due to decreased oocyte quality [24, 25]. VitD deficiency is likely related to the pathogenesis of PCOS. Hence, VitD supplementation seems to be a beneficial choice for PCOS patients [26, 27]. However, there are limited studies about association between VitD and GDF9/BMP15. In a study, after 2 weeks of VitD treatment, the levels of BMP15 and GDF9 mRNA in preantral follicles were observed comparable to the control

group [3]. In another study, it was reported that 600.000 IU VitD single-dose administration led to an increment of BMP15 and GDF9 levels in follicular fluid [28].

2.2. FOXO

FOXO superfamily includes transcription factors that regulate cellular differentiation, growth, survival, cell cycle, metabolism, stress and tumor suppression pathways in various tissues [29]. Therefore, FOXO3a is an important molecule for both follicle development and apoptosis mechanisms in the ovary [30]. FOXOs are downstream molecules of the phosphoinositide 3-kinase (PI3K)/Akt pathway and are negatively regulated by it. Phosphorylated FOXO by Akt translocates from the nucleus to the cytoplasm and loses its transcription effect on DNA [29]. Some downstream molecules of the FOXO family are apoptosis-associated ones such as Fas ligand (FasL), TNF-related apoptosis-inducing ligand (TRAIL), TNF receptor type 1 associated death domain (TRADD), Bcl-2 interacting mediator of cell death (Bim), Bcl-2 and Bcl-6 [31]. FOXO induces pro-apoptotic genes and attenuates cell progression [32, 33]. Among the FOXO family, PI3K/AKT/FOXO3a signaling is closely associated with ovarian function [34]. Disruption of PI3K/AKT/FOXO3a signaling pathways leads to inhibition of primordial follicle development [35]. Phosphorylation of the PI3K/Akt/FoxO3a pathway improves the ovarian response and restores ovarian reserve function in the treatment of cyclophosphamide-induced premature ovarian failure [36, 37]. Active FOXO3a causes infertility with insufficient oocyte and follicular development leading to anovulation. KITL activates the PI3K/Akt/FOXO3 pathway in the oocytes to exclude FOXO3a from the nucleus [38]. Activated FOXO3a reduces the expression of connexin 43 and BMP15, molecules important for gap junction structure in follicles [39]. A recent study showed that FOXO3a was increased in granulosa cells of PCOS patients [40]. There are several studies about VitD and FOXO tumor suppressor effects on cancer cells [41]. In one of these studies, it was reported that VitD increases FOXO3a binding to the promoter and blocks FOXO nuclear export on squamous cancer cells [42]. In another study, VitD inhibits the Akt pathway of melanoma via PTEN [43]. In cisplatin-induced ovarian toxicity mice model study, protective agent reduced apoptosis and maintained cell proliferation through PTEN and FOXO3a [44]. However, VitD association with FOXO3a in ovary is not completely elucidated. There is a study reported that GDF9 inhibits follicular apoptosis and induces proliferation of granulosa cells through the Akt-related FOXO3a inhibition pathway [45]. Further studies are needed for VitD effects on the Akt-FOXO3a pathway through GDF9. It has also been noted that BMP15 can act as a downstream molecule of the PI3K/Akt/FOXO3a signaling pathway [16].

2.3. AMH

AMH is a member of the TGFβ family. AMH is expressed in granulosa cells of small developing follicles and lost by the antral follicle stage [46]. Elevated AMH levels reduce granulosa cell sensitivity to FSH, resulting in decreased FSH- and LH-induced aromatase mRNA expression, dysregulated E2 production and follicle development [10]. The use of AMH also protects the primordial follicle pool during chemotherapy [47]. AMH produced by granulosa cells of developing ovarian follicles protects ovarian reserve via inducing autophagy in ovaries by inhibiting FOXO3a phosphorylation [48]. AMH is used predictively in the evaluation of ovarian reserve and in vitro fertilization outcomes [13]. High levels of AMH affect fertility by stopping primordial follicle activation. However, transgenic mice with moderate elevations in AMH levels retained primordial follicle activation. A large absence of early preantral follicles is observed in this study and this follicle stage was thought to be most susceptible to the effects of moderate AMH overexpression [49]. In a study, it was shown that GDF9 and BMP15 synergistically promote AMH expression via PI3K/AKT and Smad 2/3 pathways. FSH inhibited this AMH induction [50]. VitD is thought to be an inhibitor of the negative effect of AMH on granulosa cell proliferation through decrement in AMH receptors [9]. In vitro studies showed that the human AMH gene promoter contains VitD responsive element region and treating human cumulus granulosa cells with VitD led to a downregulation in AMH receptor. In addition, treating PCOS patients with VitD normalized their serum AMH levels [51]. However, the association between vitamin D and AMH according to the recent metaanalysis is still controversial [2, 52, 53]. These findings are likely due to the nonlinear relationship between VitD and AMH [52]. In follicle fluid, VitD levels are higher in metaphase I oocytes and lower in germinal vesicles. However, AMH levels of follicle fluid do not depend on these developmental stages. There was a positive correlation between VitD and AMH levels of follicle fluid in this study [54]. By contrast, another study reported a negative association between AMH and VitD for VitD concentrations up to 30 ng/mL [55]. VitD supplementation in infertile women with diminished ovarian reserve increase serum AMH levels and decrease FSH levels [56]. This possible ovarian reserve protective effect of VitD should be examined in detail through the FOXO3a mechanism. In healthy reproductive-aged women, it was reported that serum VitD levels were inversely correlated with AMH levels [57]. In another study, there was no significant VitD effect on AMH level in healthy or PCOS women with serum VitD <75 nmol/L at baseline [58]. Relationship of VitD and AMH levels is conflicting. VitD and AMH concentrations also show seasonal variations. The highest concentrations were reported between August and October [59].

Conclusion

Folliculogenesis is a complex process. Autocrine-paracrine signals originating from different compartments in the ovary play a role in follicular developmental stages. Therefore, besides the effects of VitD on steroidogenesis, the mechanism of action on these signals is also significant. In this review, the relationship between ovarian paracrine factors and VitD is described. GDF9 and BMP15 are ovarian derived paracrine factors affecting steroidogenesis in the ovary. Although the regulatory effects of VitD on steroidogenesis are known, studies on its association with BMP15 and GDF9 are limited. Studies should be conducted on the mechanism of VitD with these two factors as downstream molecules. GDF9 also plays an antiapoptotic role in the ovary through inhibition of other ovarian derived factor FOXO3a. The regulatory effect of VitD on FOXO3a in cancer studies is widely known. However, the signaling mechanism in the ovary has not been elucidated. The role of GDF9 in this mechanism also needs to be clarified. The relationship between AMH and VitD is still controversial. In future studies, it should be noted that this association may differ in the preovulatory follicle development stages and postovulation oocyte development stages. The relationship between VitD and AMH should also be investigated via the FOXO3a pathway. Detailed studies on this field will contribute to the literature, especially in terms of VitD mechanism of action on folliculogenesis. A comprehensive understanding of VitD pathways will provide critical insight into the impact of VitD on female reproductive health.

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CONFLICT OF INTEREST

The author has no competing interests to declare that are relevant to the content of this article.

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