BreastCare

Original Article

Breast Care 2016;11:333–337
DOI: 10.1159/000451074

Published online: October 13, 2016

Evaluation of Serum Vitamin D Levels in Adolescents with Pubertal Gynecomastia

Melis Pehlivantürk Kızılkan[a] Sinem Akgül[a] Filiz Akbıyık[b] Orhan Derman[a] Nuray Kanbur[a]

[a]Department of Pediatrics, Division of Adolescent Medicine, Hacettepe University Ihsan Dogramaci Children's Hospital, Ankara, Turkey; [b]Department of Medical Biochemistry, Hacettepe University Hospital, Ankara, Turkey

Keywords

Pubertal gynecomastia · 25-Hydroxyvitamin D · Vitamin D deficiency

Summary

Background: Since vitamin D has an inhibitory function on ductal morphogenesis of the pubertal mammary gland, it may have a role in the development of gynecomastia. The aim of this study was to determine the effect of vitamin D deficiency on the development of pubertal gynecomastia. **Methods:** Serum 25-hydroxyvitamin D (25D) levels in 50 adolescents with pubertal gynecomastia and 54 healthy controls between the ages of 11 and 17 years were compared. **Results:** Mean 25D level was 14.03 ± 6.38 (5.0–32.5) ng/ml in the pubertal gynecomastia group and 15.19 ± 6.49 (5.0–33.2) ng/ml in the control group (p = 0.361). According to the vitamin D status classification of the American Academy of Pediatrics, 66% of the pubertal gynecomastia group was found to be deficient and 14% were insufficient. In the control group these values were 53.7% and 29.6%, respectively (p = 0.158). **Conclusion:** From our results we hypothesize that, rather than low serum levels of 25D, a dysregulation of the vitamin D signal pathway, vitamin D metabolism or vitamin D storage within the mammary tissue might be the contributing factors to the development of gynecomastia.

Introduction

Pubertal gynecomastia is the benign proliferation of male mammary tissue in puberty [1]. The development of the mammary gland during puberty depends on healthy elongation and branching of the ducts, and vitamin D plays an important role in the regulation of ductal morphogenesis [2, 3]. When exposed to physiological doses of 25-hydroxyvitamin D (25D), normal mammary tissue synthesizes 1,25-dihydroxyvitamin D (1,25D) through the action of 1-α hydroxylase (CYP27B1) [4]. 1,25D has been shown to inhibit estrogen-related ductal proliferation and ductal branching and to modulate differentiation and apoptosis of mammary epithelial cells via the vitamin D receptor (VDR) [3, 5]. VDR expression also occurs in the mammary gland [6, 7]. Loss of VDR in mammary epithelial or adipocyte cells has been shown to cause accelerated ductal proliferation and branching in puberty [8]. These changes observed in the pubertal mammary gland in the absence of VDR signaling are quite similar to the histological findings of gynecomastia [9].

The most important proliferative hormone of the pubertal mammary gland is estrogen, and estrogen excess is believed to be the cause of gynecomastia [10]. Both vitamin D and estrogen regulate each other's signal pathways within the mammary tissue. Estrogen modulates CYP27B1 activity and vitamin D inhibits the growth-stimulating impact of estrogen via receptor down regulation [11–13]. It was shown that in the absence of VDR mammary tissue exhibits increased response to estrogen [2].

Considering these regulatory functions of vitamin D on ductal morphogenesis of the pubertal mammary gland, we hypothesized that vitamin D deficiency could play a role in the pathogenesis of pubertal gynecomastia. To our knowledge this is the first study investigating this relationship.

KARGER

Fax +49 761 4 52 07 14
Information@Karger.com
www.karger.com

Accessible online at:
www.karger.com/brc

Dr. Nuray Kanbur
Department of Pediatrics, Division of Adolescent Medicine
Hacettepe University Ihsan Dogramaci Children's Hospital
Hacettepe Mh., 06230 Ankara, Turkey
nuraykanbur@hotmail.com

Methods

Study Population

This prospective study took place between October 2013 and March 2014. 50 adolescents with pubertal gynecomastia and 54 healthy controls between the ages of 11 and 17 years were included in the study. Weight, height and body mass index (BMI) of the study and control groups were matched. All patients were examined by the same pediatrician. Adolescents with a Marshall-Tanner pubertal stage between II and V and whose gynecomastia disc diameters were ≥ 0.5 cm were included in the study. Diameters of 0.5–0.9 cm were classified as stage 1 (mild hypertrophy), 1–2.9 cm as stage 2 (medium hypertrophy) and ≥ 3 cm as stage 3 (advanced hypertrophy). Adolescents were separated into 2 groups according to the time required for the changes in the histological findings of gynecomastia to occur: 'florid phase' if ≤ 6 months had passed from the onset of the symptoms to the measurement of vitamin D levels and 'fibrous phase' if the interval was more than 6 months [9].

Adolescents were excluded from the study if they were at pre-pubertal stages, had a chronic disease, had used prescribed or illicit drugs or if they had been exposed to exogenous estrogen. If the gynecomastia disc diameter was ≥ 2 cm or the medical history and the physical examination of the adolescent were not sufficiently valid to exclude an underlying pathology, the following were measured: serum estradiol (E2), total testosterone, sex hormone binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEA-S), human chorionic gonadotropin (β-HCG), follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid stimulating hormone (TSH) and free thyroxin (fT4) levels. To eliminate adolescents with risk factors that could affect the results, such as substance use or disordered eating, a detailed psychosocial interview was conducted by the same physician with every adolescent included in this study. Written informed consent was obtained from the parents and adolescents. The Research Ethics Board of Hacettepe University approved this study.

Vitamin D and Other Hormonal Measurements and Evaluations

All venous blood samples were obtained during the months in which sun has a similar angle of incidence for the region in which this study was performed and samples were stored at -20°C until testing. Plasma was separated after centrifugation for 4 min at 4,000 ×*g*, and stored at -80°C for a maximum of 24 h. For the determination of serum 25D levels, high-performance liquid chromatography application was used (Shimadzu Prominence system). For this analysis method the intra-assay coefficient of variation is 2.6% and inter-assay coefficient of variation is 4% [14, 15]. Serum vitamin D levels were classified according to the guidelines of the American Academy of Pediatrics (< 5 ng/ml represents severe deficiency, 5–15 ng/ml mild-to-moderate deficiency, 15–20 ng/ml insufficient and > 20 ng/mL sufficient) [16]. Measurements of serum FSH, LH, E2, prolactin, TSH, and fT4 levels were obtained by the 2-step chemiluminescence microparticle immunoassay. DHEA-S and total testosterone levels were tested by solid-phase chemiluminescence immunoassay. SHBG were measured by immunoradiometric assay.

Statistical Analysis

The SPSS 'Statistical Package for Social Sciences' (SPSS Inc. Chicago, IL) v20 was used for the statistical analysis of the data. Demographic characteristics of the cases and controls were evaluated using descriptive statistics; data are given in means ± standard deviations (SDs) and frequencies. Student's t test was used for the comparison of 25D serum levels between the 2 groups. Chi-square test was used for the comparison of non-parametric values. Comparison between multiple variants was made by one -way variant analysis. Spearman correlation analysis was used for the assessment of the association of ranked variables. Pearson correlation analysis was used to evaluate the correlation between parametric values. p values of < 0.05 were accepted to be statistically significant.

Table 1. Clinical characteristics of the adolescents with pubertal gynecomastia and control group

	Pubertal gynecomastia group	Healthy controls
n	50	54
Age, years (range)	13.8 ± 1.6 (11.0–17.3)	13.8 ± 1.8 (11.0–17.5)
Weight, kg (range)	57.0 ± 14.3 (32–89)	56.8 ± 18.1 (29–111)
Height, cm (range)	162 ± 10.7 (142–193)	162 ± 13.8 (131–186)
BMI, kg/m^2 (range)	21.4 ± 3.5 (14.8–28.3)	21.2 ± 4.5 (14.8–35.8)
Testicular volume, n (%)		
4–5 ml	4 (8.0)	4 (7.4)
8–10 ml	9 (18.0)	12 (22.2)
12–15 ml	17 (34.0)	18 (33.4)
20–25 ml	20 (40.0)	20 (37.0)
PH stage, n (%)		
Stage 2	15 (30)	15 (28)
Stage 3	15 (30)	13 (24)
Stage 4	14 (28)	16 (30)
Stage 5	6 (12)	10 (18)

[a]Data are presented as mean ± SD unless otherwise indicated. For all comparisons p > 0.05.
PH = Pubic hair.

Results

Characteristics of the Study and Control Groups

Parameters of age, weight, height, BMI, testicular volume distribution and pubic hair stages were similar between the 2 groups (p > 0.05) (table 1). Gynecomastia was bilateral in 34 (68%) of the study group. Of the unilateral gynecomastia, 69% were located on the left side. According to the disc diameter measurements, 30% were classified as stage 1, 38% as stage 2 and 32% as stage 3. β-HCG, FSH, LH, estradiol, testosterone, DHEA-S, SHBG, prolactin, TSH, and fT4 levels were measured in 26 adolescents with a disc diameter of > 2 cm and in 2 adolescents whose disc diameter was < 2 cm but were suspected to have prepubertal gynecomastia because the time of initiation of the symptoms were not clear. All hormonal evaluations were normal (table 2). No significant correlation between hormonal measurements and vitamin D status was found.

Evaluation of the Relationship between Pubertal Gynecomastia and Vitamin D Levels

Mean vitamin D levels for the study and control groups are given in table 3. The difference between mean vitamin D values was not statistically significant (p = 0.361). Since all vitamin D levels were above 5 ng/ml, results were classified into 3 subgroups: mild-to-moderate deficiency, insufficient and sufficient. The distribution between study and control groups according to this classification was not statistically significant (p = 0.158) (table 3).

Table 2. Mean serum FSH, LH, E2, testosterone, DHEA-S, prolactin, SHBG, TSH and fT4 levels of adolescents with pubertal gynecomastia

Hormonal parameters, n = 28[a]	Mean ± SD (minimum–maximum)	Range
FSH, mIU/ml	2.88 ± 1.74 (0.54–6.90)	1.2–19.3
LH, mIU/ml	1.50 ± 1.14 (0.2–3.74)	1.2–8.6
Estradiol, pg/ml	28.33 ± 10.25 (20–46)	20–60
Testosterone, ng/dl	172.80 ± 154.30 (10.0–585.4)	10–572
DHEA-S, µg/dl	144.30 ± 72.80 (44.4–369.9)	20–555
Prolactin, ng/ml	8.50 ± 3.50 (3.3–14.5)	2.6–13.3
SHBG, nmol/l	30.60 ± 14.90 (11.0–67.0)	13.9–86.6
TSH, µIU/ml	2.26 ± 1.25 (0.46–4.84)	0.34–5.6
fT4, pmol/l	12.90 ± 2.60 (9.0–18.5)	7.8–14.4

[a]Estradiol values of < 60 pg/ml were accepted as normal for males and all estradiol measurements (n = 28) were at normal ranges for this study. However, because values of < 20 pg/ml could not be analyzed quantitatively by our laboratory (n = 22), mean estradiol value of the remaining 6 patients is given in the table.
FSH = Follicle-stimulating hormone, LH = luteinizing hormone, DHEA-S = dehydroepiandrosterone sulfate, SHBG = sex hormone binding globulin, TSH = thyroid-stimulating hormone, fT4 = free thyroxin.

Table 3. Comparison of vitamin D serum levels of adolescents with and without pubertal gynecomastia according to mean, median 25D levels and vitamin D status classification[a]

	Study group	Control group
n	50	54
Vitamin D serum levels, ng/ml		
Mean values ± SD	14.03 ± 6.38	15.19 ± 6.49
Median values (min–max)	12.2 (5.0–32.5)	14.7 (5.0–33.2)
Vitamin D status classification		
Mild-moderate deficiency, n (%)	33 (66)	29 (53.7)
Insufficient, n (%)	7 (14)	16 (29.6)
Sufficient, n (%)	10 (20)	9 (16.7)

[a]Mild-moderate deficiency 5–14.9 ng/ml, insufficient 15–24.99 ng/ml, sufficient > 259 ng/ml.
25D = 25-hydroxyvitamin D, SD = standard deviation.

The relationship between the duration of the gynecomastia and the vitamin D status was also evaluated. The period from the onset of the gynecomastia symptoms to presentation at the hospital was determined from the history given by the adolescent and his parents. 5 adolescents whose gynecomastia was detected during a routine physical examination and 7 adolescents who did not recall when their symptoms had begun were excluded from this evaluation. The mean interval between the onset of the symptoms and presentation was 7.3 months for the other 38 cases. No significant association was found between the duration of the gynecomastia and the vitamin D status (p = 0.971). The mean vitamin D levels of the 26 adolescents assessed at the florid phase and the 12 adolescents assessed at the fibrous phase were 13.18 ± 5.60 (5.0–27.1) ng/ml and 15.13 ± 6.68 (7.5–29.5) ng/ml, respectively. The difference between the acute and chronic phase was not significant (p = 0.354). Association between vitamin D levels and gynecomastia disc diameters were also evaluated. The mean 25D level of the 15 adolescents with stage I gynecomastia was 13.14 ± 3.65 ng/ml, for the 19 with stage II gynecomastia 13.38 ± 6.12 ng/ml, and for the 16 adolescents with stage III gynecomastia 14.75 ± 7.17 ng/ml. Although vitamin D levels were lower in stage I, this difference was not statistically significant (p = 0.517).

Discussion

Pubertal gynecomastia is a physiological yet discomforting condition seen in male adolescents and as yet no underlying cause could be found for the majority of cases [17]. Based on the effect of vitamin D on the normal development of pubertal mammary gland, and the similarity between the histological findings of gynecomastia and those observed in mammary tissue in the absence of vitamin D, we hypothesized that vitamin D deficiency could be an underlying mechanism of pubertal gynecomastia.

The development of mammary glands during puberty depends on a healthy ductal morphogenesis, including the elongation, proliferation and branching of the ducts. It is known that vitamin D has an inhibiting effect on ductal morphogenesis, by regulating the proliferation, differentiation and apoptosis of the mammary tissue [2, 6, 13, 18, 19]. During early puberty, at the proliferative state of the mammary gland, strong VDR expression is observed. When the pubertal phase of glandular development is largely complete, VDR expression is downregulated [13]. In the absence of VDR, pubertal mammary tissue exhibits accelerated ductal branching and elongation [2].

Histologically, gynecomastia is characterized by ductal hyperplasia, ductal elongation and increased periductal stromal connective tissue as a result of the infiltration of inflammatory cells [20–22]. In a study by Zinser et al. [2], mammary glands of VDR-knockout mice exhibited enhanced ductal proliferation, secondary branch points and increased numbers of terminal end buds, compared to the wild-type mice. In a study by Welsh et al. [23], histological sections of the mammary tissue of the VDR-knockout mice stained with hematoxylin and eosin showed dense clusters of inflammatory cells along the ducts, supporting chronic inflammation.

An imbalance between the proliferating effects of estrogen and the inhibitory effects of free androgens on the mammary tissue are thought to cause gynecomastia [24]. During pubertal development of the mammary gland, although estrogen is known to be the main proliferative hormone, vitamin D may be a modulator of the estrogen signal pathways. 1,25D and other VDR agonists

participate in negative growth regulation by inhibiting estrogen-induced ductal proliferation and branching. Zinser et al. also demonstrated that VDR-knockout mice exhibited enhanced growth in response to exogenous estrogen, both in vivo and in organ culture, compared with wild-type mice. Vitamin D also downregulated estrogen receptors in human breast cancer cell lines [2, 6, 7]. Estrogen also regulates VDR signaling in breast tissue. Although studies observing the relationship between estrogen and vitamin D signaling pathways are mainly on breast cancer, findings from these studies are beneficial for the understanding of the normal mammary gland physiology. Analysis of human breast cancer cell lines suggests that VDR expression is lower in estrogen-independent lines when compared to estrogen-dependent lines [25]. It was also demonstrated that estrogen receptor-positive breast cancer cell lines are more sensitive to 1,25D-mediated growth regulation than estrogen-negative cell lines [5]. In the light of these findings, we hypothesized that, apart from estrogen/androgen imbalance, an imbalance between the growth inhibitory effects of vitamin D and stimulatory effects of estrogen could also result in gynecomastia.

Prostaglandin E2 (PGE2) produced by the cyclooxygenase-2 (COX-2) enzyme expressed in breast tissue is a proliferative agent [26]. Recently, it was shown that COX-2 is downregulated by VDR activation in mice mammary gland tissue and, in VDR-knockout mice, overexpression of COX-2 resulted in mammary gland hyperplasia and precocious mammary gland development [27, 28]. Several studies also showed that COX-2-derived PGE2 has a stimulatory effect on aromatase activity [29]. Irahara et al. [30] demonstrated that the expressions of aromatase and COX-2 in the duct epithelial cells of florid-type gynecomastia were higher than that in the fibrous type, and it was suggested that COX-2 upregulates aromatase expression. These results show that vitamin D deficiency could also have a role in the development of gynecomastia through the activation of COX-2.

In our study no significant difference was detected between the serum 25D levels of adolescents with and without pubertal gynecomastia. The fact that there are many pathophysiological mechanisms suggestive of an association between vitamin D deficiency and pubertal gynecomastia, raises the question of whether serum levels of 25D also reflect that of the tissue? Adipose tissue of the mammary gland is an important paracrine source for vitamin D signal pathways as it stores lipophilic 25D [8]. CYP27B1 and CYP24A1 are the main 2 enzymes responsible from the metabolism of vitamin D, and both the epithelial and stromal environment of the normal mammary tissue synthesizes them. Therefore, 25D could be stored, bioactivated or degraded within the mammary tissue in a manner that is independent of serum 25D levels [31]. Although serum 25D levels of adolescents in the study and control groups were not significantly different, adolescents with gynecomastia could have a potential problem in the bioactivation or storage of 25D within their mammary tissues.

Normal mammary tissue expresses VDR, which is crucial in the development of pubertal breast tissue. For 1,25D to exhibit its growth inhibitory effects it has to form a complex with VDR. Therefore, gynecomastia could be caused through a dysregulation in the function or in the expression of the receptor, independent from the serum levels of the ligand. In vitro studies demonstrated that in the absence of VDR, 1,25D could not exhibit its growth inhibitory effects [2, 13]. Immunohistochemical staining for VDR or VDR gene polymorphism studies could provide evidence for this theory.

Our study did not include either the response of gynecomastia to vitamin D treatment, or the spontaneous regression rate of gynecomastia discs of adolescents with higher vitamin D status. Longitudinal clinical trials are needed to investigate these hypotheses [32]. The dose at which vitamin D shows its inhibitory effects on ductal elongation and branching morphogenesis during pubertal development of mammary gland is not clear. Although some studies showed that vitamin D inhibits the proliferation and differentiation of human breast cancer cell lines at physiological doses, others suggest the dose needed is much more higher [5, 33]. A recent study demonstrated that genomic changes observed in cell lines derived from normal mammary tissue in response to vitamin D status are highly specific to the cell type, and such changes are likely to be distinct from individual to individual [34].

Review of the literature did not reveal much information on the effects of vitamin D on male breast tissue. Male breast tissue is primarily composed of ductal structures with rare secondary branching and rare-to-no lobular elements. Gynecomastia occurs with the proliferation of this secondary branching and the surrounding stroma. Considering the histological resemblance between the male and the female breast tissue; it could be assumed that findings from the studies evaluating the effect of vitamin D signal pathways on the development of normal pubertal female mammary tissue could be interpreted for the male breast tissue as well [35].

In conclusion, this is the first study evaluating the effects of vitamin D deficiency on the development of pubertal gynecomastia. No significant difference was detected between the 25D serum levels of adolescents with gynecomastia and healthy controls. Given the fact that in the pubertal mammary tissue 1,25D and other VDR agonists participates in negative growth regulation by inhibiting estrogen-induced ductal proliferation and branching and that the histological changes observed in the absence of VDR are highly similar to the histological findings of gynecomastia; it could be hypothesized that vitamin D signal pathways could have a role in the development of pubertal gynecomastia and further studies are needed for this association to be demonstrated.

Disclosure Statement

This study was funded by Hacettepe University Scientific Research Unit (project number: 014 T01 101 001). The authors have no conflicts of interest to disclose.

References

1 Sansone A, Romanelli F, Sansone M, et al.: Gynecomastia and hormones. Endocrine 2016;[Epub ahead of print].
2 Zinser G, Packman K, Welsh J: Vitamin D(3) receptor ablation alters mammary gland morphogenesis. Development 2002;129:3067–3076.
3 Narvaez CJ, Zinser G, Welsh J: Functions of 1alpha,25-dihydroxyvitamin D(3) in mammary gland: From normal development to breast cancer. Steroids 2001;66:301–308.
4 Kemmis CM, Welsh J: Mammary epithelial cell transformation is associated with deregulation of the vitamin D pathway. J Cell Biochem 2008;105:980–988.
5 Kanazawa T, Enami J, Kohmoto K: Effects of 1alpha,25-dihydroxycholecalciferol and cortisol on the growth and differentiation of primary cultures of mouse mammary epithelial cells in collagen gel. Cell Biol Int 1999;23:481–487.
6 Zinser GM, Welsh J: Accelerated mammary gland development during pregnancy and delayed postlactational involution in vitamin D3 receptor null mice. Mol Endocrinol 2004;18:2208–2223.
7 Welsh J: Cellular and molecular effects of vitamin D on carcinogenesis. Arch Biochem Biophys 2012;523:107–114.
8 Johnson AL, Zinser GM, Waltz SE: Loss of vitamin D receptor signaling from the mammary epithelium or adipose tissue alters pubertal glandular development. Am J Physiol Endocrinol Metab 2014;307:E674–685.
9 Cuhaci N, Polat SB, Evranos B, et al.: Gynecomastia: Clinical evaluation and management. Indian J Endocrinol Metab 2014;18:150–158.
10 Nordt CA, DiVasta AD: Gynecomastia in adolescents. Curr Opin Pediatr 2008;20:375–382.
11 Stoica A, Saceda M, Fakhro A, et al.: Regulation of estrogen receptor-alpha gene expression by 1, 25-dihydroxyvitamin D in MCF-7 cells. J Cell Biochem 1999;75:640–651.
12 Swami S, Krishnan AV, Feldman D: 1alpha,25-Dihydroxyvitamin D3 down-regulates estrogen receptor abundance and suppresses estrogen actions in MCF-7 human breast cancer cells. Clin Cancer Res 2000;6:3371–3379.
13 Welsh J, Wietzke JA, Zinser GM, et al.: Impact of the vitamin D3 receptor on growth-regulatory pathways in mammary gland and breast cancer. J Steroid Biochem Mol Biol 2002;83:85–92.
14 HPLC for the determination of 25-OH Vitamin D3 in plasma and serum. Immuchrom GmbH, Heppenheim, 2006, pp. 1–9.
15 Reichel H, Koeffler HP, Norman AW: The role of the vitamin D endocrine system in health and disease. N Engl J Med 1989;320:980–991.
16 Misra M, Pacaud D, Petryk A, et al.: Vitamin D deficiency in children and its management: Review of current knowledge and recommendations. Pediatrics 2008;122:398–417.
17 Braunstein GD: Gynecomastia. N Engl J Med 1993;328:490–495.
18 Zinser GM, Welsh J: Effect of vitamin D3 receptor ablation on murine mammary gland development and tumorigenesis. J Steroid Biochem Mol Biol 2004;89–90:433–436.
19 Matthews D, LaPorta E, Zinser GM, et al.: Genomic vitamin D signaling in breast cancer: Insights from animal models and human cells. J Steroid Biochem Mol Biol 2010;121:362–367.
20 Lapid O, Jolink F, Meijer SL: Pathological findings in gynecomastia: Analysis of 5113 breasts. Ann Plast Surg 2015;74:163–166.
21 Braunstein GD: Clinical practice. Gynecomastia. N Engl J Med 2007;357:1229–1237.
22 Ma NS, Geffner ME: Gynecomastia in prepubertal and pubertal men. Curr Opin Pediatr 2008;20:465–470.
23 Welsh J, Zinser LN, Mianecki-Morton L, et al.: Age-related changes in the epithelial and stromal compartments of the mammary gland in normocalcemic mice lacking the vitamin D3 receptor. PLoS One 2011;6:e16479.
24 Rochefort H, Garcia M: The estrogenic and antiestrogenic activities of androgens in female target tissues. Pharmacol Ther 1983;23:193–216.
25 Buras RR, Schumaker LM, Davoodi F, et al.: Vitamin D receptors in breast cancer cells. Breast Cancer Res Treat 1994;31:191–202.
26 Chang SH, Ai Y, Breyer RM, et al.: The prostaglandin E2 receptor EP2 is required for cyclooxygenase 2-mediated mammary hyperplasia. Cancer Res 2005;65:4496–4499.
27 Thill M, Reichert K, Woeste A, et al.: Combined treatment of breast cancer cell lines with vitamin D and COX-2 inhibitors. Anticancer Res 2015;35:1189–1195.
28 Qin W, Smith C, Jensen M, et al.: Vitamin D favorably alters the cancer promoting prostaglandin cascade. Anticancer Res 2013;33:3861–3866.
29 Subbaramaiah K, Morris PG, Zhou XK, et al.: Increased levels of COX-2 and prostaglandin E2 contribute to elevated aromatase expression in inflamed breast tissue of obese women. Cancer Discov 2012;2:356–365.
30 Irahara N, Miyoshi Y, Taguchi T, et al.: Possible involvement of aromatase overexpression induced by cyclo-oxygenase-2 in the pathogenesis of idiopathic gynecomastia. Endocr Res 2005;31:219–227.
31 Matthews DG, D'Angelo J, Drelich J, Welsh J: Adipose-specific VDR deletion alters body fat and enhances mammary epithelial density. J Steroid Biochem Mol Biol 2015;pii: S0960-0760(15)30091-1.
32 Kim Y, Je Y: Vitamin D intake, blood 25(OH)D levels, and breast cancer risk or mortality: A meta-analysis. Br J Cancer 2014;110):2772–2784.
33 Milani C, Katayama ML, de Lyra EC, et al.: Transcriptional effects of 1,25 dihydroxyvitamin D(3) physiological and supra-physiological concentrations in breast cancer organotypic culture. BMC Cancer 2013;13:119.
34 Beaudin SG, Robilotto S, Welsh J: Comparative regulation of gene expression by 1,25-dihydroxyvitamin D3 in cells derived from normal mammary tissue and breast cancer. J Steroid Biochem Mol Biol 2015;148:96–102.
35 Macias H, Hinck L: Mammary gland development. Wiley Interdiscip Rev Dev Biol 2012;1:533–557.