

# Correlation between vitamin D deficiency and fibrocystic mastopathy

## Abstract

Fibrocystic dystrophy is one of the most frequent and common non-neoplastic pathologies whose symptomatology is represented by the appearance of painful nodules in the breast. Fibrocystic lesions have several etiological factors, the most important being considered the hormonal imbalance between estrogen and progesterone, manifested by excess estrogen that causes proliferations at the connective tissue level (fibrosis). The diagnosis of this pathology is based on symptoms and with the help of breast ultrasound, which can also be used in the puncture and drainage of large cysts. The treatment of fibrocystic breast disease is a medical one, by administering combined oral contraceptives, having a success rate of 70-90%. Breast ultrasound is an important technique for evaluating breast anatomy in benign and malignant pathologies. Fibrocystic mastopathy is most often associated with dense breasts with well-developed breast tissue. Epidemiological studies suggest that the level of vitamin D (25-hydroxycholecalciferol) below 20 ng/mL is associated with an increased risk of breast, colon and prostate cancer. In young people, vitamin D deficiency is associated with benign pathology (mammary cysts, fibroadenoma). This article presents a study in which 50 women, aged between 30 and 50 years old, were included, for a period of three years, all of them being diagnosed by ultrasound with fibrocystic mastopathy and all presenting vitamin D deficiency (below 20 ng/mL 25-hydroxyvitamin D) at the time of the examination.

**Keywords:** vitamin D, fibrocystic mastopathy, breast ultrasound

## Rezumat

Distrofia fibrochistică este una dintre cele mai frecvente și comune patologii non-neoplazice, a cărei simptomatologie este reprezentată de apariția unor noduli dureroși la nivelul sânelui. Leziunile fibrochistice au ca etiologie mai mulți factori, cel mai important fiind considerat dezechilibrul hormonal dintre estrogen și progesteron, manifestat prin exces estrogenic, care determină proliferări la nivelul țesutului conjunctiv (fibroză). Diagnosticul acestei patologii se face pe baza simptomatologiei și cu ajutorul ecografiei mamei, care poate fi utilizată și în puncția și drenarea chisturilor mari. Tratamentul bolii fibrochistice mamare este medicamentos, prin administrare de contraceptive orale combinate, cu o rată de succes de 70-90%. Ecografia mamară reprezintă o tehnică importantă pentru evaluarea anatomiei sânelui, a patologiei benigne și maligne. Mastopatia fibrochistică este asociată de cele mai multe ori cu sânul dens, cu țesut mamar bine dezvoltat. Studiile epidemiologice sugerează că nivelul de vitamină D (25-hidroxicolecalciferol) sub 20 ng/mL este asociat cu un risc crescut de cancer de sân, colon sau prostată, iar la persoanele tinere deficitul de vitamină D se asociază cu patologia benignă (chisturi mamare sau fibroadenom). Acest articol prezintă un studiu în care au fost incluse 50 de femei, pe durata a trei ani, cu vârste cuprinse între 30 și 50 de ani, toate fiind diagnosticate ecografic cu mastopatie fibrochistică și toate, la momentul examinării, prezentând deficiență de vitamină D (sub 20 ng/mL 25-hidroxivitamină D).

**Cuvinte-cheie:** vitamina D, mastopatie fibrochistică, ecografie mamară

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## Corelația dintre deficitul de vitamina D și mastopatia fibrochistică

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## Introduction

Fibrocystic dystrophy is one of the most frequent and common non-neoplastic pathologies whose symptomatology is represented by the appearance of painful nodules in the breast. Fibrocystic lesions have as their etiology several factors, the most important being considered the hormonal imbalance between estrogen and progesterone, manifested by excess estrogen that causes proliferations at the connective tissue level (fibrosis)<sup>(1)</sup>.

The most affected age category is between 20 and 40 years old, with the maximum prevalence before menopause<sup>(2)</sup>. Most of the patients present menometrorrhagia,

are nulliparous, with a history of spontaneous abortions in the past, early menarche and late menopause<sup>(3)</sup>. The main symptoms of fibrocystic mastopathy are mastodynia and increased breast sensitivity which can be associated with dysmenorrhea, menometrorrhagia and frequently ovarian cysts (40-60%). The diagnosis of this pathology is based on symptoms and with the help of breast ultrasound, which can also be used in the puncture and drainage of large cysts. The treatment of fibrocystic breast disease is medical, by administering combined oral contraceptives, with a success rate of 70-90%<sup>(4)</sup>.

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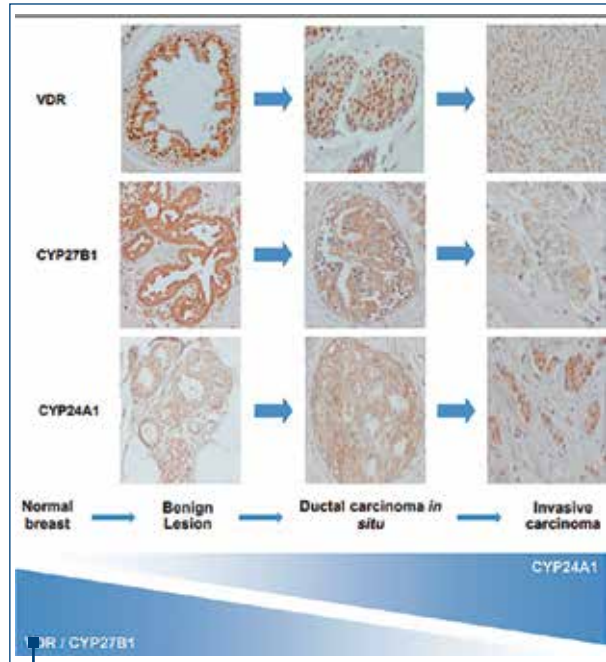
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Vitamin D was identified by Edward Mellanby, as a fat-soluble substance with antirachitic properties, classically associated with its physiological role of regulating calcium and phosphate in bone metabolism. People can get vitamin D from two main sources: from food and from exposure to the sun. Few foods contain vitamin D in significant amounts, among them being fish, eggs and mushrooms. However, the majority (90% to 95%) of the vitamin D requirement is produced by the skin when exposed to sunlight (ultraviolet B radiation)<sup>(5)</sup>. The biologically active form of vitamin D – 1 $\alpha$ ,25-dihydroxyvitamin D3 or 1 $\alpha$ ,25(OH)2D3 – is synthesized in the kidneys by the mitochondrial enzyme CYP27B1<sup>(6)</sup>.

Vitamin D is a steroid hormone that exerts most of its biological activities by binding to a specific and high-affinity receptor (vitamin D receptor; VDR). VDR belongs to the superfamily of nuclear receptors for steroid hormones and regulates gene expression by acting as a transcription factor<sup>(7)</sup>. Vitamin D can also induce VDR-independent effects; the anti-proliferative effects of vitamin D in MCF-7 cells are not solely dependent on the presence of VDR<sup>(8)</sup>.

It has been shown that vitamin D plays an important role in the development and function of the mammary gland, the VDR receptor being also present in normal breast tissue, through immunohistochemical tests<sup>(9)</sup>. The main enzymes involved in the metabolism of vitamin D in the normal breast are CYP27B1 and CYP24A1<sup>(10)</sup>, and an imbalance of those can cause the appearance of benign pathology or neoplasia.

Regarding the representation of differences in the expression of vitamin D receptor, CYP27B1 and CYP24A1 during breast carcinogenesis, vitamin D receptor and CYP27B1 expression decreases with breast carcinogenesis,

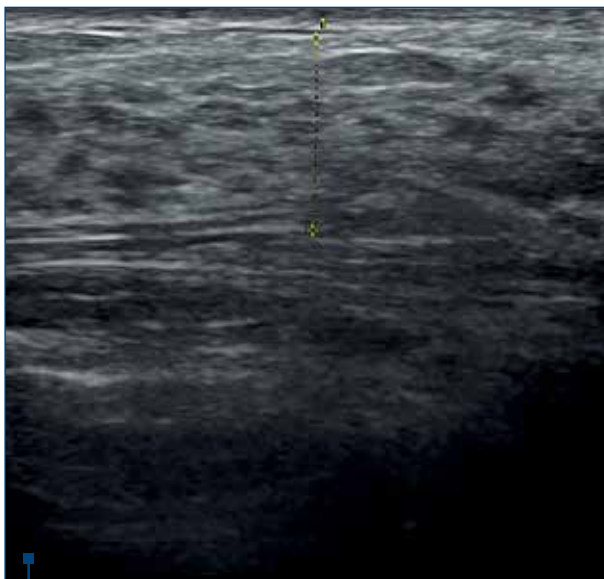


**Figure 1.** Representation of differences in the expression of vitamin D receptor, CYP27B1 and CYP24A1 during breast carcinogenesis

while CYP24A1 expression is increased (the level of brown coloring represents the intensity of gene expression)<sup>(11)</sup> – Figure 1.

In benign breast pathology, the aforementioned three proteins (VDR, CYP27B1 and CYP24A1) are in decreased amount compared to normal breast.

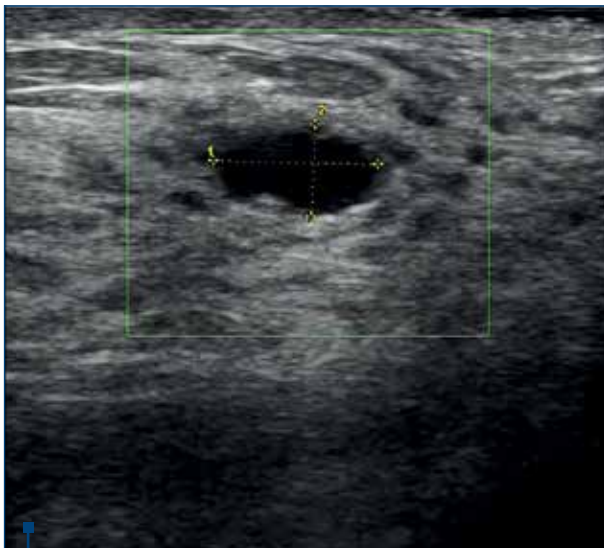
Epidemiological studies suggest that the level of vitamin D (25-hydroxycholecalciferol) below 20 ng/mL



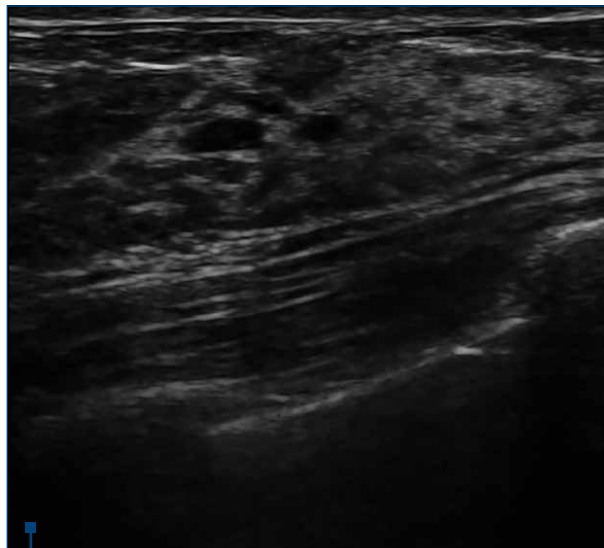
**Figure 2.** Dense breast (personal collection of Dr. Bogdan Botezatu)



**Figure 3.** Dense breast with a cyst (personal collection of Dr. Bogdan Botezatu)



**Figure 4.** Medium mammary cyst (personal collection of Dr. Bogdan Botezatu)



**Figure 5.** Small mammary cyst (personal collection of Dr. Bogdan Botezatu)

is associated with an increased risk of breast, colon and prostate cancer<sup>(12)</sup>. In young people, vitamin D deficiency is associated with benign pathology (mammary cysts, fibroadenoma)<sup>(13)</sup>.

Breast ultrasound is an important technique for evaluating breast anatomy, benign and malignant pathology. Fibrocystic mastopathy is most often associated with dense breasts with well-developed breast tissue (Figures 2 and 3).

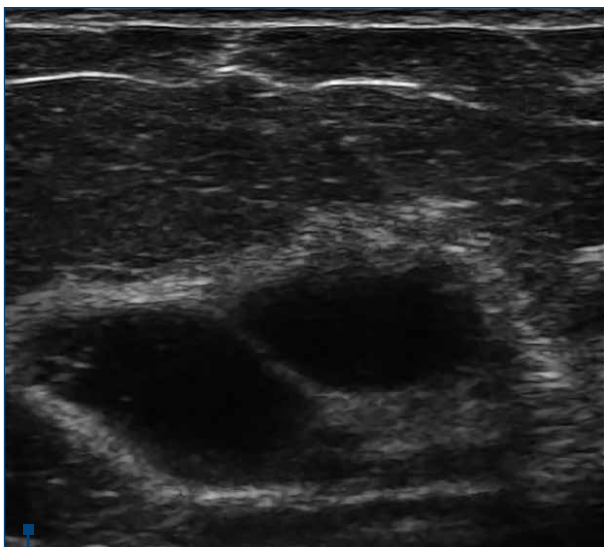
Fibrocystic mastopathy is highlighted sonographically by multiple anechoic images, well delimited with posterior acoustic accentuation, usually of medium or small size, present in both breasts; the anatomical

structure of the breast is preserved and there is no accentuation of the vascularization (Figures 4, 5 and 6).

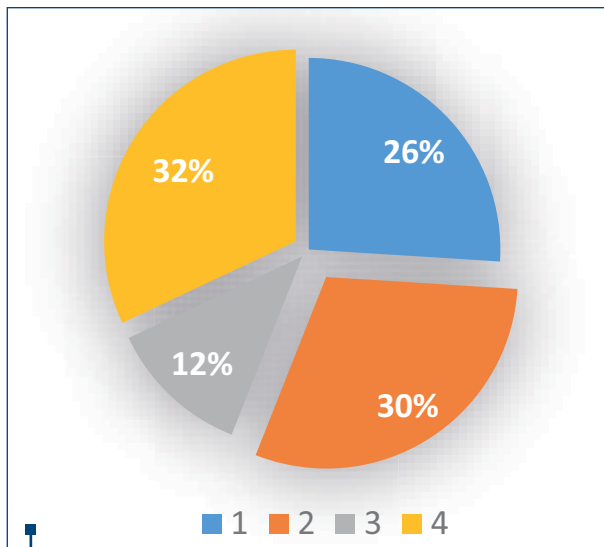
### Materials and method

The study included 50 women, for a period of three years, aged between 30 and 50 years old, all of them being diagnosed by ultrasound with fibrocystic mastopathy and all presenting vitamin D deficiency (below 20 ng/mL of 25-hydroxyvitamin D)<sup>(14)</sup> at the time of the examination.

After the administration of vitamin D3 (2000 UI) for at least six months and the correction of the vitamin deficiency (above 30 ng/ml of 25-hydroxyvitamin



**Figure 6.** Large mammary cyst (personal collection of Dr. Bogdan Botezatu)



**Figure 7.** Results after the administration of 2000 UI of vitamin D3

D), the bilateral breast ultrasound was performed again.

At the time of the ultrasound examination, all the cystic images in the four quadrants of the breast were described, measured and numbered.

## Results

Thirteen patients (26%) presented an important reduction in the number of breast cystic formations, by more than 50% than in the previous examination, 15 patients (30%) presented a moderate reduction (between 25% and 50% than the previous examination), and six patients (12%) presented a slight decrease, between 10% and 20% compared to the previous examination. Sixteen patients (32%) did not show

significant changes, or the number of cystic formations increased.

## Conclusions

1. Fifty-six percent of the patients showed a statistically significant reduction in the number of breast cystic formations, this revealing that a correction of vitamin D deficiency has beneficial effects on patients (Figure 7).

2. The sizes of the cysts decreased significantly in the patients who responded to the treatment and even in four patients in the non-responsive group.

3. The fact that 44% of patients were nonresponsive or had a poor response shows that other factors, besides vitamin D deficiency, are involved in fibrocystic breast dystrophy. ■

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