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# Histological Study of Breast in Patients with Fibroadenoma in Correlation with Vitamin D Deficiency

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**ABSTRACT**

Fibroadenomas are common benign breast tumors comprising 95% of all biopsied breast masses. Vitamin D has a strongly indicated ability to modify the histology of the breast.

To correlate histological alterations in breast tissue with deficient vitamin D in women clinically diagnosed to have fibroadenoma.

Eighty women aged in a range between 25-45 year complaining from breast lump diagnosed as cases of fibroadenoma. Fifty women of them were agreed to undergo surgical excisional biopsy. Blood samples for testing 25(OH) D were collected from them before the operation .The specimens were collected from Mosul Daily Surgical Clinic in in Mosul city within a period starting from February 2023 to September 2023, the patients were alienated into 2 groups, group A (N=25) were women with sufficient serum 25(OH) vitamin D > 20 ng/ml regarded as the 'control' group for this study and group B (N=25) were the study group 'cases' having deficiency of 25(OH) D less than 20 ng/ml. Excisional biopsies of the breast lumps were collected and tissue specimens were processed and prepared for examination by light microscope. The demographic data and histological findings were statistically analyzed for comparison between group A and B.

The results revealed that number of women having fibroadenoma with deficient vitamin D were significantly more (70%) as compared to the control, the incidence of deficiency is increased with increased weight and parity and a significant relation of sunlight exposure and the occurrence of deficiency was determined. Histological examination of breast tissue from women of group B showed pericanalicular fibroadenoma in 70% of cases with more sever hyperplasia of the epithelial lining and showed intracanalicular fibroadenoma in 80% of cases with sever proliferation of stromal cells compressing the duct to be slit like spaces and lobulations expanded beyond the surrounding fibroblastic stroma in addition to sever adipose tissue deposition in 84% of cases and sever hyalinization of stroma.

The study concludes a significant association of the histological appearance of breast fibroadenoma with deficiency of vitamin D indicated by suppressing the epithelial and stromal proliferation of breast lesions thus vitamin D supplement might arrest the progression of fibroadenoma towards breast cancer.

**Keywords:** Histological, Breast, Fibroadenoma, Vitamin D, Deficiency

## Introduction

Vitamin D is fat soluble vitamin, it has many functions including bone resorption and regulation of calcium and phosphate thus optimal vitamin D level is crucial for many effective physiological and immune processes (1). It is produced inside the body following exposure to ultraviolet (UV) light and might be gained from foods like eggs, dairy products, and oily fish (2). Vitamin D induces its action on specific vitamin D receptor (VDR) that once activated, they induce a specific gene transcription mainly those involved in homeostasis (3). Still no established description of the most adequate level of 25(OH) D. Nevertheless, a serum level of > 20 ng/ml is supposed to be optimal for most individuals (4). A lot of literatures have been declared that vitamin D is potent to prevent various morbid illnesses like type 2 diabetes, rheumatoid arthritis, Crohn's disease, and stroke (5). Some researches emphasized that it is proficient protective factor against cancer and some recent studies elucidated the use of vitamin D in COVID-19 via downregulation of inflammation and hypoxia (6). Vitamin D deficiency means that the body is not attaining enough amount of vitamin D to remain healthy. However, serum 25-hydroxyvitamin D [25(OH) D] <50 nmol/l or 20 ng/ml) is widely reported as insufficiency and

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associated with critical skeletal consequences and less than 12 ng/ml is considered as a true deficiency (7).

Fibroadenomas are common type of breast masses, they account for 95% of biopsied breast lesions (8). Usually it is manifested as a well-defined, painless and unilateral breast lump with excessive mobility even named as 'breast mouse'. It is commonly seen in women in the age of 20 to 30 years largely less frequent in post-menopausal women (9). Some authors supposed an excessive interaction of breast tissue with estrogen hormone as etiologic theory of fibroadenoma, hence it commonly grows during pregnancy and degenerate after menopause (10). Intracanalicular and pericanalicular are the two distinct histological patterns of fibroadenomas. The glands are compressed into cleft-like spaces by their surrounding stroma in the intracanalicular pattern but they preserve their patent lumens in the pericanalicular form (11). Despite multiple histological patterns of fibroadenomas as juvenile, cellular, or giant types, they fortunately not deviate from their benign behavior, so in rare instances, carcinoma can occur in fibroadenoma (12). Many studies thoroughly investigated the relationship of low level of vitamin D with breast problems even so reviews and trials reported that keeping more serum concentration of vitamin D could protect against breast cancer (13).

The rational purpose of the ongoing study is to correlate the histological changes of the breast in women clinically diagnosed to have fibroadenoma with vitamin D deficiency.

## Material and Methods

This study was conducted in the College of Medicine, University of Mosul, Mosul, Iraq. The data were collected from Mosul Daily Surgical Clinic in Mosul city within a period starting from February 2023 to September 2023.

From the Breast Clinic Outpatient in Mosul city 80 cases complaining from breast lump were collected after they filled a questionnaire form. They were in a range of 25-45 years with a variable parity. They were previously diagnosed as cases of fibroadenoma by history and clinical examination of the breast lump confirmed by ultrasound imaging. Out of the total 80 examined women 50 of them were agreed to undergo surgical excisional biopsy of the breast lump. The operations were done in Mosul Daily Surgical Clinic in Mosul city, blood samples for testing 25(OH) D were collected from all the patients before excision of the lumps.

Those women who had not been pregnant or lactating in the previous 6 months were involved in the present study while the elimination criteria were those woman being repeatedly supplemented with vitamin D analogues 6 months prior to breast surgery and those reluctant to be tested for vitamin D levels. A signed consents from all contributors filling an inquiries about sharing in our study and about their standard of living and sun exposure have been obtained, and ethical approval of the study protocol was documented by the Medical Research Ethic Committee (MREC) in the College of Medicine, University of Mosul Ref. no.: UO M/COM/MREC/ 22-23 (49) in 14/6/2023.

In this case-control study, the operated 50 cases all had blood test for vitamin D level, they were distributed into two groups, group A (25 cases) were those with sufficient serum 25(OH) vitamin D > 20 ng/ml regarded as the 'control' group of this study and group B (25 cases) were the study group 'cases' having deficiency of 25(OH) D below 20 ng/ml. The limits of 25(OH) vitamin D were depended according to the laboratory values, and previous literature. Following lumpectomy under general anesthesia, the excisional biopsies of the breast lump were collected. The tissue specimens were put in 10% buffered formalin for 24 hours then dehydrated, implanted in paraffin wax, then the blocks were sectioned into slices of 5 microns thickness then stained with Harris Hematoxylin and Eosin (H&E) to be examined by light microscope.

**Statistical Analysis:** The collected data concerning some demographic parameters like age, parity, history of exposure to sunlight, and drug history of the cases enrolled in the study were statistically analyzed using SPSS "Statistical Package for the Social Sciences" version 26 and descriptive statistics were expressed as mean ± SD using Shapiro-Wilk test was used to determine whether the data were distributed normally or not. The significant differences between group A and group B was evaluated using Bonferroni multiple comparisons for post-hoc analysis with significant level set as $P < 0.05$ considering that P-values $< 0.05$ were statistically significant, while P-values more than 0.05 were non significance (14).

## Results

Table 1: illustrated Mean±SD of women of group A (control) showed serum 25(OH) D more than 20 ng/ml and those of group B (vitamin D deficiency group) having serum 25(OH)D lower than 20 ng/ml in correlation to some socio demographic parameters. The table revealed non-significant difference of women in the age group of 25-45 years having fibroadenoma with deficient vitamin D as compared to the control. The incidence of deficiency is increased with increased weight as compared to control, thus Mean ± SD of those women with >90 kg weight was significantly different from those weighing ≤ 90 (P-value=0.001). Furthermore, a significant difference was observed in multiparous women (>3) who suffered from deficiency of vitamin D more than those with low parity (1-3) when compared to control. Exposure to sunlight 1/2-1 hour per day induces a significant reduction in the incidence of vitamin D deficiency as compare to control while women exposed to sunlight for a period less than 1/2 hour per day were significantly more liable to deficient vitamin D level. Nonsignificant relation of positive family history of fibroadenoma with vitamin D deficiency (P-value =0112).

**Histological findings**: The women in the both control and study groups who are clinically diagnosed to have fibroadenoma of the breast by ultrasound imaging, upon histological examination of the sections of breast tissue taken from women of group A having a sufficient serum 25(OH) vitamin D > 20 ng/ml, the slide showed pericanalicular fibroadenoma in 30% of cases with hyperplasia of the epithelial ducts and hyperplasia of stroma in between ducts which appeared hypovascular (Fig.1) (Table 2). Intracanalicular fibroadenoma appeared in 20% of cases as proliferation of stromal cells compressing the duct into clefts like appearance (Fig.2) (Table 2). The slide taken from group B who presented with vitamin D deficiency showed pericanalicular fibroadenoma in 70% of cases with sever hyperplasia of the epithelial cells lining the ducts characteristically, the basement membrane is intact (Fig.3). In addition, group B showed intracanalicular fibroadenoma in 80% of cases with sever proliferation of stromal cells compressing the duct into cleft-like spaces surrounded by fibroblastic stroma (Fig.4). Sections from group A revealed fatty deposition with stromal hyalinization in 16% of cases (Fig.5) (Table 1). Such finding clearly observed in the sections obtained from group B as sever adipose tissue deposition in 84% of cases (Fig.6) (Table 2) and sever hyalinization of stroma (Fig.7).

## Discussion

The issues which inspect the association of vitamin D with benign lesions were still scarce thus intention of the current work is to define the correlation between vitamin D deficiency and fibroadenoma. In a trial to display this subject, some authors had declared that almost 85% of woman with benign breast disease have a considerably low serum levels of vitamin D (15). In the current study, the higher incidence of vitamin D deficiency in the age group between 25-45 years in those diagnosed to have fibroadenoma (group B) in comparison with women having normal vitamin D level (group A) could be explained due to extreme correlation of fibroadenoma with the hormonal status during the reproductive period, such finding assisted by previous work dealing with association between higher circulating hormones like prolactin and risk of breast problems proved by tumor expression of prolactin-related markers (16).

Similarly, it has been noticed that women who take oral contraceptives are more liable to have fibroadenoma particularly intracanalicular type (17). Fibroadenoma arises from both epithelial and stromal cells which contain receptors for both progesterone and estrogen thus fibroadenomas tend to proliferate during pregnancy due to extreme formation of reproductive hormones (18). A raised incidence of deficient vitamin D in obese women diagnosed to have fibroadenoma is noticed in the present study, a similar study done by A-Obaidy et.al, 2022 revealed that healthy lifestyle must be the first therapeutic choice for both obesity and vitamin D deficiency particularly in postmenopausal women (19).

The study revealed more incidence of vitamin D deficiency (80%) in women with low exposure to sunlight, such logic finding strongly agrees with the conclusion of previous studies which reported that Saudi women are at risk of vitamin D deficiency due to indoor lifestyle and fully covered traditional clothing (20). In this study, the women with family history of fibroadenoma have 90% frequency of deficient vitamin D, the same finding have been observed by previous workers (21). However, a therapeutic dose of vitamin D equaling 4000 IU/day was highly effective and to maintain a normal levels, vitamin D could be prescribed for 5 months (22). A suggestive

**Table 1:** Comparison of the Number of Women In Group A (control) and group B (Vitamin D Deficiency Group) in Correlation To Sociodemographic Parameters (Data expressed as Mean± SD)

| Parameters | Number | Group A No. of cases | (Mean ± SD) | Group B | (Mean ± SD) | P-value |
|---|---|---|---|---|---|---|
| Age (25-45 years) | 50 | 15 | 10±6.2 | 35 | 30±0.2 | 0.110(NS) |
| Weight | | | | | | |
| >90 kg | 50 | 12 | 8 ±0.6 | 38 | 35±0.5 | 0.001(S) |
| ≤ 90 kg | | 42 | 4±0.3 | 8 | 50±0.8 | 0.001(S) |
| Parity | | | | | | |
| 1-3 | 50 | 30 | 20±0.4 | 20 | 10±0.4 | 0.120(NS) |
| >3 | | 5 | 3±0.4 | 45 | 40±0.4 | 0.001(S) |
| Exposure to Sunlight | | | | | | |
| 1/2-1 hour per day | 50 | 44 | 40±0.3 | 6 | 4±0.3 | 0.001(S) |
| Less than ½ hour per day | | 10 | 6±0.2 | 40 | 30±0.5 | 0.001(S) |
| Family history of fibroadenoma | 50 | 5 | 2 ±0.4 | 45 | 40±0.5 | 0.112 (NS) |
| Positive | | 35 | 30±0.2 | 15 | 10±0.3 | 0.250(NS) |
| Negative | | | | | | |

SD= Standard deviation; S=Significant (P≤0.05); NS=Non-significant (P>0.05)

**Table 2:** Comparison of The Number of Women In Group A (control) and Group B (vitamin D Deficiency Group) in Correlation to Histological Findings (Data expressed as Percentage and Mean± SD)

| Histological findings | No. of cases | Group A | Percentage% | (Mean ± SD) | Group B | Percentage% | (Mean ± SD) | P-value |
|---|---|---|---|---|---|---|---|---|
| Pericanalicular fibroadenoma with hyperplasia of the epithelial ducts and hyperplasia of stroma | 50 | 15 | 30% | 10±0.5 | 35 | 70% | 30±0.2 | 0.001(S) |
| Intracanalicular fibroadenoma appeared as proliferation of stromal cells compressing the duct into clefts like appearance | 50 | 10 | 20% | 5±0.3 | 40 | 80% | 20±0.4 | 0.001(S) |
| Fatty deposition with stromal hyalinization | 50 | 8 | 16% | 5±0.2 | 42 | 84% | 38±0.1 | 0.001(S) |

SD= Standard deviation; S=Significant (P≤0.05); NS=Non-significant (P>0.05)

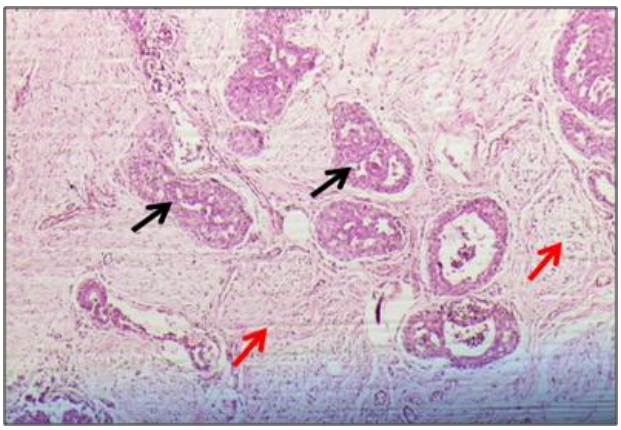

**Fig.1.** Micrograph of breast of group A showing pericanalicular fibroadenoma with hyperplasia of the epithelial ducts (black arrows) and hyperplasia of stroma in between ducts which appeared hypovascular (red arrows) (H&EX150)

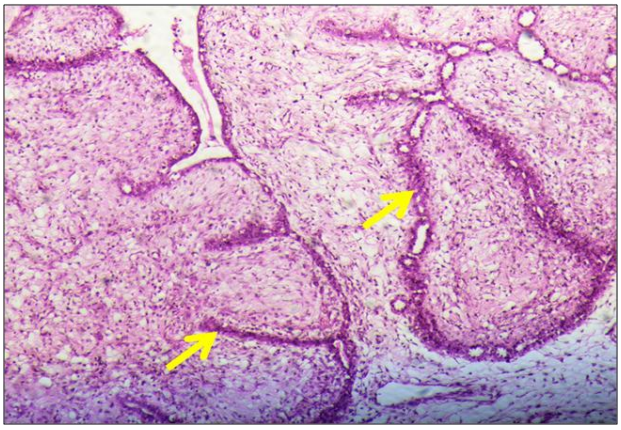

**Fig.2.** Micrograph of breast of group A showing intracanalicular fibroadenoma with proliferation of stromal cells compressing the duct into clefts like appearance (red arrows) (H&EX150)

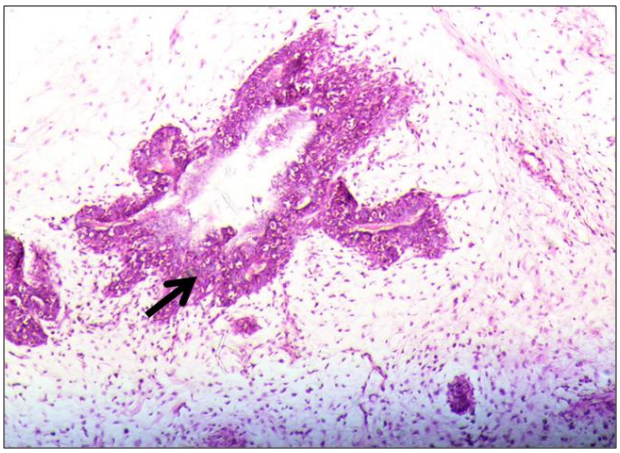

**Fig.3.** Micrograph of breast of group B showing pericanalicular fibroadenoma with sever hyperplasia of the epithelial cells lining the ducts (black arrow) (H&EX150)

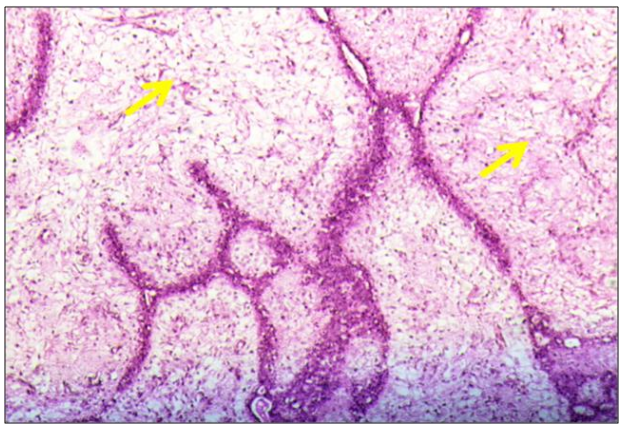

**Fig.4.** Micrograph of breast of group B showing intracanalicular fibroadenoma with sever proliferation of stromal cells compressing the duct into cleft-like spaces surrounded by fibroblastic stroma (yellow arrows) (H&EX150)

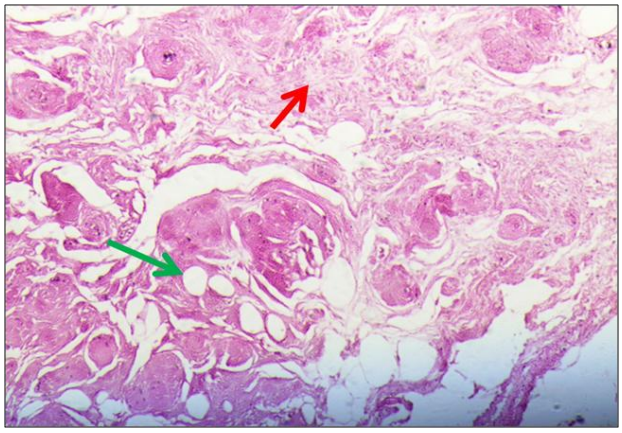

**Fig. 5.** Micrograph of breast of group A showing fatty deposition (green arrow) with stromal hyalinization (red arrow) (H&EX100)

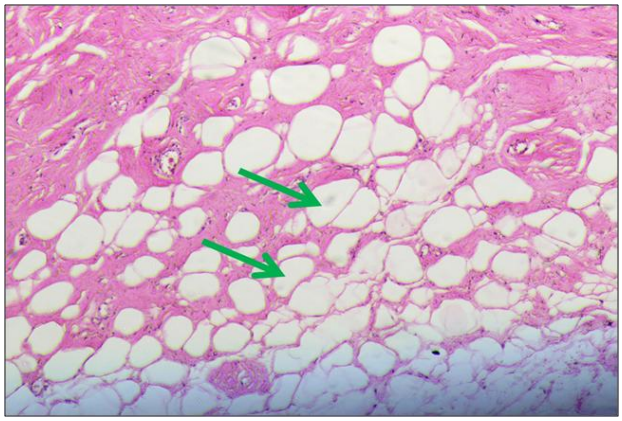

**Fig. 6.** Micrograph of breast of group B showing sever adipose tissue deposition (green arrows)

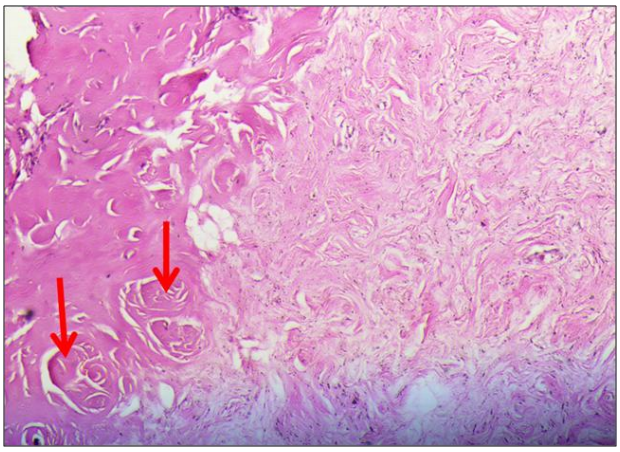

**Fig. 7.** Micrograph of breast of group B showing sever hyalinization of stroma (red arrows) (H&EX100)

opposite association has been detected between dietary vitamin D consumption and benign breast problems so those with maximum vitamin D intake had least chance of breast disease (23).

The link of vitamin D with breast diseases in the reproductive age has seldom been investigated particularly in the developing countries and still not deliberated extensively. However, a lot of articles revealed a contrary association between serum vitamin D and the prospect of breast cancer, best example could be mentioned is that on follow-up of postmenopausal ladies suffering from breast cancer, it has been evidenced that the risk was lower with adequate intake of vitamin D in premenopausal ladies (24). Furthermore, the review of literatures were in favor that vitamin D supplements is evidently can mediate cell growth and differentiation by binding with vitamin D receptor in healthy breast cells while recent studies attributed the anti-carcinogenic properties of vitamin D to the induction of apoptosis and histological differentiation and its inhibitory effects on breast cancer stem cells thereby reducing metastasis and poor survival (25). Meanwhile fortunately vitamin D is effectively functional in the prevention of proliferative benign breast disorders in susceptible populations (26). Fibroadenomas is mobile, painless, well defined type of benign breast masses showing a stromal and epithelial proliferation (27). Serum 25-hydroxyvitamin D has been involved as a hazard factor for histological abnormalities of the breast. Bolat and Erdogan, 2022 performed a study on 612 women presented with fibrocystic masses detected by ultrasound and mammogram and concluded that they had less vitamin D values (28). In the current study, 70% of enrolled cases have a deficient serum vitamin D level and their tissue specimen revealed pericanalicular fibroadenoma with sever hyperplasia of the epithelial cells lining the ducts with intact basement membrane as compared to those with normal vitamin D, such augmented histological alteration is linked to lower level of vitamin D indicating to its role in preserving breast tissue in patients with fibroadenoma. Similar result has been declared in previous in vitro studies that vitamin D actively slows down cellular growth and induces apoptosis thereby counteracts various genes responsible for mass formation (29). A systematic review points out a defending role of vitamin D against cancer of breast in premenopausal women and a significant inverse association was verified by Bauer et.al, 2013 (30) who compared vitamin D level in 100 cases of breast disease with 154 normal ladies and noticed an antithetical correlation between vitamin levels and risk of breast diseases in premenopausal.

The study exposed that 80% of group B with low vitamin D test showed intracanalicular fibroadenoma appeared with sever proliferation of stromal cells compressing the duct into spaces like slit and lobulations bulging above the surrounding fibroblastic stroma in agreement with Welsh, 2018 who stated that vitamin D receptors are extremely appeared in the mammary glandular and deficiency of vitamin D is more public in women with currently diagnosed fibrocystic breast (31). Recent met analysis of 474 scientific issues done by Voutsadakis A, in 2021 conveyed that deficiency of vitamin D is reasonably public among women suffering from breast cancer as compared to normal inhabitants and satisfying benefits obtained by adjusting the dose of vitamin D to modify the prognosis of the disease (32). Other workers reported that vitamin D correspondingly donates to patient wellbeing and suppressing metastasis of tumor by down-regulation of activated channel breast tumor (33). However, a randomized revision achieved by Jiang et al, in 2019 on 15000 breast cancer patients stated that vitamin D not affects the progress of breast tumor (34). Fatty deposition was sever with sever hyalinization of stroma in those women with low serum vitamin D level in the same finding was observed by Rafiq et.al, in 2019 who investigate the relations of body fat deposits with serum concentrations of vitamin D and concluded that in both women and men visceral adipose tissue deposition was inversely related with the concentrations of vitamin D (35).

Although malignant masses were not evaluated in the study, fibroadenoma were reported to be

significantly associated with low concentration of vitamin D in women with breast masses. Furthermore, an obvious contrary relationship of vitamin D levels and breast cancer was previously perceived by the above mentioned reviewed papers which could further augment the doubted relation between deficiency of vitamin D and transformation to malignancy.

The limitation of our work is the loss of followed patients who either refuse the operation or they were reluctant to do the blood test of vitamin D which is expensive for them. However we tried to conceive them about the value of frequent assessment of the masses. We hope this work being the first trial to evaluate the correlation of vitamin D with fibrocystic breast problems to be aware about future malignant transformation.

This study concludes a significant association of the histological appearance of breast fibroadenoma with deficiency of vitamin D indicated by exaggerated microscopic findings as equated to women with normal level providing a clue on the vital role of vitamin D in suppressing the epithelial and stromal proliferation of breast lesions which could be life threatening if not prevented. Multiparity, older age obesity and inadequate exposure to sunlight are crucial risk factors for deficiency of vitamin D thus obtaining adequate dietary vitamin D, frequent checking and advising vitamin D supplement to ladies with low or insufficient vitamin D, encouraging the exposure to sunlight all effectively arrests tissue proliferation and prevents the progression towards breast cancer.

Such outcomes need to be strengthened by professional centers and forthcoming studies on the part of the vitamin D in breast tumors which might expose novel opportunities in the avoidance of breast cancer.

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