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Vitamin D Level in Newly Diagnosed Breast Cancer Patients

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Abstract

Background: Vitamin D insufficiency is considered most prevalent nutritional deficiency that is untreated and undiagnosed globally. This vitamin deficiency has proliferated to pandemic levels, even though it is created in the human body when exposed to sunlight. One steroid hormone that is necessary for preserving reproductive health is vitamin D.

Materials and method: This study was conducted at Azadi Hospital - Specialized Oncology Center. The study included most of the patients with breast cancer who visited the center between February 2025 and May 2025 and the control samples taken from healthy subjects. Samples from women who were taking vitamin D supplements and osteoporosis treatment were excluded. Samples were analyzed using a Cobas instrument which depended on the spectrophotometer principle.

Results: The findings showed that the vitamin D levels in three grade I, II, and III individuals who were pre-menopausal and menopausal increased in a non-significant ($P > 0.05$) manner.

Conclusion: Statistical analysis of the data showed that, in comparison to healthy subjects, the vitamin D levels in general in-patient breast cancer patients of all grades declined.

Keywords: **Breast cancer, vitamin D deficiency, grade, newly diagnosed.**

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Introduction

Breast cancer: -

Breast cancer represents the second-leading cancer-related mortality cause amongst women, after lung cancer, which is the most prevalent malignancy among women[1]. There are roughly 571,000 deaths every year. Radiation, surgery, and systemic therapy are the main treatments for breast cancer when detected early[2] . Risk factors for Breast cancer include a physical activity lack, consumption of alcohol, a paternal and maternal family history of breast cancer, late menopause, postmenopausal obesity, nulliparity, early menarche, and a first childbirth after 30 years. The invasive breast cancer risk in women is increased by ductal carcinoma in situ, atypical ductal carcinoma hyperplasia, and lobular carcinoma in situ. Another risk factor is early ionizing radiation exposure[1] .

Vitamin D

A woman's risk of hip fractures could be reduced by getting enough vitamin D, which is highly important for the health of bones. Furthermore, there is mounting proof that vitamin D influences other body systems and that sufficient intake of vitamin D is essential for better health [3]. First found a negative relationship between the mean annual solar energy reaching ground and age-adjusted mortality of breast cancer in US in 1990. The most likely mechanism that links sun exposure to lower risks of breast cancer is an increase in vitamin D photosynthetic activity. In women who have breast cancer at an early stage, the serum 25-hydroxyvitamin D (25(OH)D) level had since been related to inverse correlations with breast cancer progression, death, and recurrence risk. This study includes the most recent information on correlation between breast cancer and vitamin D, the optimum dosage of vitamin D for preventing breast cancer, and the mechanism and metabolism of action of vitamin D [4] .

Vitamin D metabolism and mechanism

Vitamin D can also be acquired through nutrition, along with exposure to the sun. Dietary sources include fortified dairy products, eggs, as well as oily seafood, such as salmon. Ergocalciferol, often known as vitamin D2, comes from plants, whereas cholecalciferol (vi), one of the two naturally occurring vitamin D forms, vitamin D3, comes from animals. When 7-dehydro-cholesterol in skin is subjected to ultra-violet B (UVB) radiation, vitamin D-3 is naturally produced, which accounts for the majority of vitamin D in circulation [(4)]. Through the activity of 25-hydroxylases in the liver, vitamin D is converted into 25 (OH)D, the main circulating metabolite [4]. 1-alpha-hydroxylase then catalyzes a second 25(OH)D hydroxylation in kidney, which results in 1,25 di-hydroxyvitamin D (1,25(OH)2D). The biologically active vitamin D form is 1,25(OH)2D, which is also referred to as calcitriol, which works by the interaction with intracellular vitamin D receptor (VDR) [5]. As ligand-activated factor of transcription, VDR, which had first been discovered in breast cancer cell line in 1979, is a nuclear receptor superfamily member for steroid hormones and regulates expression of genes [5]. About 200 genes involved in cellular differentiation, growth and apoptosis are impacted by VDR activation besides its basic

function of controlling extra-cellular calcium levels . Since 25(OH)D has much longer half-life in comparison with vitamin D or 1,25(OH)2D [6], It is the most accurate indicator of total body vitamin D stores. Since there are typically few food sources of vitamin D, exposure to sunlight has the biggest impact on serum 25(OH)D concentration. Without enough exposure to the sun, vitamin D insufficiency could occur rapidly. Inadequate nutrition, obesity, less sun exposure, darker skin, and advanced age are all factors that might lead to vitamin D insufficiency [7].

Effect of vitamin D on proliferation cellular[8]

Vitamin D3's effect on cellular proliferation, it has long been known that 1,25(OH)2D3 prevents BC cells from moving from the G0/G1 phase of cell cycle to S phase. Through VDR binding, 1,25(OH)2D3 has anti-proliferative effects, as shown by the absence of growth inhibition with exposure to 1,25(OH)2D3 in VDR knockout cells. Cyclin-dependent kinase inhibitors (CDKIs), like CDKN1A (p21), CDKN2D (p-19), and CDKN1B (p-27), are upregulated in response to growth reduction caused by 1,25(OH)2D3, while cyclins (cyclin A1, cyclin D1/3, and cyclin E1) and cyclin-dependent kinases (CDK 2/4) are downregulated. Moreover, 1,25(OH)2D3-induced elevation of CDKI expression levels results in decreased CDK activity, particularly CDK4/6, which in turn leads to decreased retinoblastoma (Rb) phosphorylation, which is a tumor suppressor protein that is crucial for controlling the progression of cell cycle. As a result, Rb remains linked to E2F transcription factors, which results in a decrease in the transcription regarding cell cycle genes regulated by E2F, such as CDK2. Moreover, 1,25(OH)2 D3's antiproliferative effects in ER+ MCF7 cells were facilitated by the upregulation of the expression of C/EBPα and the ensuing rise in VDR transcript levels. Moreover, 1,25(OH)2 D3 affects expression of small RNAs called miRNAs.

Inhibition of invasion and metastasis

To keep bones healthy, vitamin D is necessary. Increased parathyroid hormone (PTH) secretion from vitamin D insufficiency activates the osteoblastic PTH receptor, which in turn increases expression of receptor activator of nuclear factor-κB ligand. Both bone resorption and osteoclast recruitment are significantly aided by this ligand. It was shown that the deficiency of vitamin D increases human breast cancer cells' growth in nude mice bones, suggesting that vitamin D might lead to promoting the development of cancer via the alteration of the micro-environment of the bone. 1,25(OH)2 D increases expression of E-cadherin in some breast cancer cell lines, which prevents metastasis and invasion. Additionally, 1,25(OH)2D has strong antiangiogenic characteristics, which probably contribute to its ability to prevent tumor invasion. It was shown that 1,25(OH)2D increases plasminogen activator inhibitor and MMP inhibitor 1 expression, whereas decreasing matrix metallo-proteinases (MMPs) activity, urokinase- and tissue-type plasminogen activator [10] .

Estrogen pathway inhibition

1,25(OH)2D could inhibit estrogens' synthesis and biological activities, according to a number of studies [11]. Through the reduction of expression of gene encoding aromatase, enzyme converting the androgens into estrogens, 1,25(OH)2 D suppresses estrogen path-way. The nuclear receptor mediating estrogen activities, the estrogen receptor (ER)-α, is downregulated by 1,25(OH)2 D, which is capable of lowering estrogen levels and the receptor mediating their signaling[11].

Blood sample

Five ml of venous blood has been withdrawn by the puncture of the vein with the use of plastic syringe with gauge 21 stainless needles. Blood has been separated in a simple poly-ethylene tube, left to clot at the temperature of the room, and after that centrifuged for 10 minutes at 704 xg. Samples that have been hemolyzed were discarded. The presented work employed fifty blood samples, twenty-five of which were from patients who have breast cancer and twenty-three healthy subjects. From February 17 to the end of June 2025, those women visited the medical city's Kirkuk oncology hospitals, where specialized experts diagnosed them with the condition. Any cases that might have affected this study were eliminated, such as samples from women receiving treatment for osteoporosis as well as vitamin D supplements.

Materials and methods

Levels of total 25OH vitamin D in human blood and plasma may be quantitatively determined using Elecsys Vitamin D total III test, which is utilized on Cobas analyzers. The test is crucial for determining a person's level of vitamin D deficiency.

Methodology

There are numerous crucial phases in the measuring process:

1. Sample Preparation: • Pretreatment Step: Serum samples undergo initial treatment to liber ate bound 25OH vitamin D from vitamin D binding protein.
   *This is accomplished through the incubation of the sample with pretreatment reagents that disrupt protein binding.
2. Incubation with Ruthenium
   labeled Vitamin D Binding Protein: • Following vitamin D release, pretreated s ample undergoes incubation with ruthenium-labeled vitamin D binding protein.
   This intricate formation enables the assay to be primed for detection.
   3. Formation of Complex: • An incubation follows with streptavidin-
   coated micro-particles and biotinylated 25(OH) vitamin D. The interactions among these components form a complex essential for detection.
   4. Electrochemiluminescence Detection: The reaction mix is introduced into measuring cell of the analyzer, where microparticles are magnetically retained on electrode surface.
   A voltage is applied, resulting in chemi-luminescent emission that is subsequently detected and quantified.
   The emitted light intensity is inversely related to concentration of 25OH vitamin D in the sample.
   5. Calibration and Results Interpretation: The luminescence signal is processed using a calibration curve tailored to the instrument, facilitating precise quantification of vitamin D levels in ng/mL or nmol/L.

Statistical analysis

Graph Pad Prism version 19 was used for data analysis. Percentages and frequencies have been used for preventing the descriptive measurements and demographic factors in the controls and cases. The t test was used for the determination of correlation

between vitamin D deficiency and grades among different tumor histopathological characteristics. A t-test has been used for comparing vitamin D levels between premenopausal and postmenopausal status.

Results

The average age regarding the healthy has been 51.3±8.06 years, while the average age of the cases has been 51.0±10.17 years. Among women with breast cancer, 46.7% were premenopausal and 53.3% were postmenopausal. Table (1) shows the vitamin D level and another parameter as comparison between breast cancer patients and healthy subject. Table (2) shows tumor grade frequency, while Table (3) shows the tumor frequency in relation to menopausal stats.

Table (1): Level of vitamin D in newly diagnosing patients of breast cancer and healthy subjects

Variable	Cases (n=23)	Controls (n=23)	p-value
Vitamin D (ng/mL)	15.12 ± 10.40	19.72 ± 7.29	0.0899
Age (years)	51.0 ± 10.17	51.3 ± 8.06	0.90

Table (2) Frequency of tumor grade in the cases

Tumor Grade	Percent
Grade I	**36.80**
Grade II	**47.40**
Grade III	**15.80**

Table (3) menopausal state percentage in the cases

Timing in relation to menopause	Percent
Premenopausal	**34.80**
postmenopausal	**65.20**

Discussion

Although vitamin D levels had been lowered in patients who have breast cancer compared to controls, the difference wasn't statistically significant (p = 0.0899).

Vitamin D is known for its role in bone health, but it also contributes to immune modulation, regulation of cell growth, and induction of apoptosis. Deficiency in vitamin D has been linked with increased susceptibility to breast cancer and, in

some studies, with more aggressive (higher grade) tumors. The proposed explanation is that vitamin D may act as a protective factor against uncontrolled cellular proliferation, so its absence could promote tumor progression.

Still, the trend aligns with observational literature showing lower serum vitamin D among breast cancer patients and inverse correlation between vitamin D and cancer risk [12]. Meta-analyses show consistent association: ~6% reduced risk per 5 nmol/L 25(OH)D increase, in both pre- as well as post-menopausal women [13]. Menopause introduces major hormonal changes, particularly a decline in estrogen and progesterone. While reduced estrogen might decrease the incidence of hormone receptor–positive tumors, it also contributes to lower bone density and higher prevalence of vitamin D deficiency. Postmenopausal women, therefore, may face a dual challenge: increased risk of vitamin D deficiency and its potential impact on breast cancer grade and progression [14]. When considered together, breast cancer grade, vitamin D status, and menopausal state intersect in a clinically meaningful way. Postmenopausal women are more prone to vitamin D deficiency, which may in turn influence tumor biology, possibly leading to higher-grade breast cancers. This highlights the importance of assessing vitamin D levels as part of the holistic evaluation of breast cancer risk and prognosis, especially in postmenopausal women

Age matching ($p = 0.90$) strengthens internal validity by eliminating age as a confounder. Majority of our patients (65.2%) were post-menopausal—a demographic with higher breast cancer incidence and often lower vitamin D levels [15]

Conclusion

The present study findings suggest a non-significant but consistent trend toward lower serum vitamin D levels in patients who have breast cancer versus healthy controls. The age-matched design and menopausal distribution mirror broader epidemiologic patterns. Larger studies controlling for lifestyle and supplement factors are recommended to clarify whether vitamin D status plays a causal role or serves as a biomarker.

ETHICAL APPROVAL

The research protocol was approved by the Ethical Research Committee of Kirkuk Health Authority, Kirkuk, Iraq.

INFORMED CONSENT

Participants were aware of the purpose of the study and provided informed consent prior to the participations.

FUNDING: No funding

HUMAN AND ANIMAL RIGHTS

All procedures performed in studies involving human participants were in accordance with the ethical standards of institutional and/or research committees and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT FOR PUBLICATION

Participants were aware of the purpose of the study and provided informed consent prior to accessing the questionnaire and participation.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

All data generated or analyzed during this study are included in this published article.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

AUTHORS CONTRIBUTION

Al the authors contributed in the Study conception and design, Data collection, Analysis and interpretation of results, Draft manuscript and all authors reviewed the results and approved the final version of the manuscript.

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