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IN PATIENTS WITH BREAST CANCER, THE LEVELS OF S100 CALCIUM-BINDING PROTEIN B (S100B) AND SOME BIOCHEMICAL MARKERS ARE RELATED TO ORAL HEALTH

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ABSTRACT
The most common cancer in women is breast cancers. Therefore, even though additional indicators are needed to improve accuracy, early detection of breast cancer is beneficial for treatment. The objectives of the research were to ascertain how these markers affect breast cancer patients, how S100B levels contribute to early breast cancer diagnosis, and how these markers connect to oral health. There were a significant increase in levels of ALP and S100B in breast cancer women in comparison with pathological and healthy controls . While there were no significantly differ in levels of S100B,when compared pathological controls to healthy controls.
These S100B and ALP values can be utilized to distinguish between benign and malignant breast cancers.While a significant decrease in 1,25(OH)2 Vitamin D, phosphorus patients with breast cancer in comparison with healthy controls. These values make these parameters highly significant for early diagnosis and progression of breast cancer. Serum calcium and fibroblast growth factor 23 (FGF23) levels were shown to be significantly elevated in breast cancer and were suggested as useful disease indicators. For the development and upkeep of dental health, FGF23 and vitamin D are essential. Together with calcium, phosphorus contributes to the development of strong enamel, which is essential for preventing cavities and rotting in teeth.

KEYWORDS: Cancer Antigen 15 -3 (CA 15-3), S100 calcium-binding protein B (S100B), Alkaline Phosphatase (ALP). Fibroblast growth factor 23 (FGF23).

INTRODUCTION

The leading cause of cancer-related mortality for women is still breast cancer. While additional indicators are needed to improve accuracy, early identification of breast cancer is beneficial for treatment. Treatment decisions will be aided by the prognostic significance of serial measurements of these biochemical markers. Patients with bone and liver metastases had higher serum levels of ALP. Patients with certain tumor types, such as colorectal and breast cancer, have been linked to poor diagnosis when their ALP expression is reduced [(1)]. Metastasis is indicated by a progressive increase in serum ALP activity with breast cancer. ALP activity is typically higher in breast cancer patients than in healthy, normal women [(2)]. Breast cancer patients benefit from early detection and treatment of distant breast cancer metastases because the bone is likely where these metastases are located [(3)].The calcium-binding protein family's S100 has become a crucial regulator in the mammary gland and has been linked to the onset and spread of breast cancer. However, dysregulation of S100 proteins may have a role in the onset and advancement of breast cancer [(4)]. S100 proteins play a significant part in the growth and spread of several cancer types, including lung, breast and melanoma. Consequently, it has also been shown that members of the S100 family are interesting diagnostic markers and possible novel therapeutic targets [(5)]. The connection between S100 proteins and other malignancies is receiving more attention because of their role in biological processes that are directly related to the development and spread of cancer as well as the functional consequences of their expression in breast cancer. The S100 members showed promising as indicators for breast cancer prognosis [(6)]. Serum S100B concentrations increase significantly in breast cancer patients during chemotherapy. This increase is correlated with worsening in some neurocognitive outcomes from pre-to post-chemotherapy [(7)].
Serum calcium levels are usually higher in advanced breast cancer. Significantly greater serum calcium levels were linked to larger breast cancers in postmenopausal individuals [(8)]. Following Ca2+ binding, the target protein will interact with the hydrophobic amino acid residues found in the S100 protein. Therefore, for the S100 protein to be involved in tumor spreading, it must interact with Ca 2+ [(9)]. Minimum molecular weight The S100 subfamily of calcium-binding proteins has both structural and functional diversity. Among the many different functions that S100 members carry out in a healthy

cell are the storage and transfer of calcium (calcium homeostasis), which is crucial for both inflammation and cellular homeostasis [10].

Over time, women who self-reported having breast cancer experienced more alterations in bone mineral density than those who did not [11]. Tumor-suppressor p53 is an important regulator of the cell's response to DNA damage. DNA damage initially dephosphorylates p53, which is then rephosphorylated to help p53 separate from promoters and stop p53-mediated transcription. This mechanism affects the activation and termination of p53-mediated transcriptional programs at various phases of the cellular DNA damage response [12]. When S100B attaches itself to the p53 tumor suppressor protein, it stops p53 from phosphorylating, tetramerizing, and functioning as a tumor suppressor and preventing apoptosis [13] . Calcium and 25-OH vitamin D levels affect several biological processes, such as cell signaling, apoptosis, and proliferation. The role of phosphate in the metabolism of cancer is particularly significant for breast cancer [14]. In order to perform its biological duties, vitamin 1,25(OH)2D3 interacts with the vitamin D receptor (VDR), a transcription factor that controls the expression of particular genes in tissues that are targets of vitamin D [15] .

Vitamin D to improve the intestinal absorption of calcium. Maintaining appropriate calcium levels in the body is essential, especially for the growth of teeth and bones. However, this process is hampered by low vitamin D levels, which increases the risk of decay in the mouth and weakens tooth enamel [16]. Increased FGF23 secretion in breast cancer causes hypophosphatemia through decreased phosphate reabsorption through activation of the proximal renal tubular epithelial cells to internalize sodium phosphate cotransporters and decreased activation of vitamin D3 through inhibition of the renal enzyme 1-α hydroxylase. Reduced intestinal phosphate absorption and poor osteoid matrix mineralization [17].

Aspects of Ethics: In compliance with Iraq's ethical regulations, the institutional ethics committee's approval and the written informed consent of each participant were obtained prior to the execution of study-related procedures.

MATERIALS & METHODS

Fifty five women with newly diagnosed breast cancer were split into 34 (stage 1), 21 (stage II) patients with ages ranging from (25 to 59) years and another 55 women with benign breast masses (pathological control) with ages ranging from (19 to 60). From the 55 patients with breast cancer who had undergone treatment, 15 were selected. From January 2024 to January 2025, these patients received treatment at the Al-Amal National Cancer Hospital in Baghdad, Iraq. The other 55 women were regarded as a healthy control group. Additional staging tests, such as a chest radiograph, bone scan, and computed tomography (CT) scan of the abdomen, are frequently performed on women with malignancies that have positive axillary lymph nodes. These additional tests are not necessary for patients with smaller tumors and negative lymph nodes unless they have symptoms like skeletal pain that could indicate metastatic involvement. According to the Union for International Cancer Control Classification (UICC 1997), the final diagnosis was verified by cytology, histological investigation (biopsy), and mammography. According to the American Cancer Society medical 2017, cases were categorized using the TNM classification, and tumors were identified as invasive lobular and invasive ductal, as shown **in figure (1).** The field examination form has been manually completed by all patients and study participants on the location of swelling (right or left), if the address is urban or rural, and whether the patient is married or single. All patients had their blood collected, coagulated at lab temperature, and then centrifuged for ten minutes at 3000 rpm. Separation of the resulting sera and assay has been manually done, Serum S100B and FGF23 were determined by ELISA kit , the methods were used to determined calcium , phosphorus , levels of 25-OH Vitamin D and measure the activity of ALP using their kits.

Features	Patients. No	Features	Patients. No
Total No. of subjects	55	T1N1M0 , T2N0M0 , T2N1M0 ,T3NOMO	stage II,(21)
Left breast	35	No malignant disease in family	22
Right breast	20	Malignant disease in family	33
Ductal cancer	34	Address Urban	37
Papillary cancer	21	Rural	18
T1N0M0	Stage 1,(34)	Marital status Married Marital status Single	45 10

Figure (1) General features of patients with breast cancer

*T0 : No evidence of primary tumor. *Tis : Carcinoma in suit .
*T1,T2,T3,T4 : Size and / or extent of the primary tumor.
N0 : No regional lymph node involvement .
*N1,N2,N3: Involvement of regional lymph nodes
*M0 : No distant metastasis . *M1 : Distant metastasis .

RESULTS & DISCUSSION

Breast cancer is the most common cancer among women. Breast cancer may be detected and monitored by changes in blood levels of particular biochemical markers.

Results in table (1): When compared to healthy controls, women with breast cancer had significantly higher ALP levels (P<0.05*). When compared to pathological controls, ALP levels from breast cancer were significantly higher (P<0.05**). Serum ALP levels did not significantly differ between pathological controls and healthy controls. The findings showed that ALP expression and activity are aberrant in patients with breast cancer. Serum ALP levels are increased for individuals with liver and bone metastases [(1)].

Table (1): The comparison of ALP and S100B levels of healthy controls, pathological controls and breast cancer women.

Serum biochemical markers	Breast cancer/55 (stage I,II)	Pathological controls/55	Healthy controls/55
(Mean±SD) ALP (U/L)	93.41±22.75	66.89±18.63	62.49±17.71
Probability	< 0.05*	< 0.05**	NS
Serum (S100B) (µg/L)	3.31±0.91	0.19±0.08	0.16±0.08
Probability	< 0.05*	< 0.05**	NS

* Significant at the 0.05 level of significance using the student t-test between two independent means.

Table (2): Showed that the serum ALP had high validity values (79.4% sensitivity , 81.6% specificity , 66.3% positive predictive value , 45.1% negative predictive value and 81.9% accuracy test). These values make these parameters with highly significance in the study of women with breast cancer.

Table (2) predictive values of biochemical parameters levels in breast cancer women as compared to pathological control using (mean+1SD) of healthy control as (a cut off).

Serum Chemical tests	*Sensitivity	*Specificity	*Positive predictive	*Negative predictive	*Accuracy test
ALP	79.4%	81.6%	66.3%	45.1%	81.9%
S100B	83.2%	84.5%	72.6%	46.0%	82.4%
FGF23	81.4%	81.6%	71.2%	45.0%	81.3%

*Sensitivity : It is a percentage of True Positive result.
*Specificity : It is a percentage True Negative result
* Positive predictive : It is the percentage of all Positive tests that are true positive.
*Negative predictive :It is a percentage of all Negative values.
* Accuracy : Percentage of patients correctly classified by the test results as having or not having the disease.

Levels of ALP provides useful information in a diagnosis of breast cancer especially in early stage disease. The findings were consistent with Singh A.K. et al.'s 2013 study. Serum ALP activity gradually increases with breast cancer, indicating metastasis. The most significant indicators for predicting bone metastases in breast cancer were elevated ALP and CA15-3 [(2)]. Elevated alkaline phosphatase travels to the bone in breast cancer patients and is beneficial for early detection.

Results in table (1): Showed that the levels of S100B in breast cancer women was a significant increase in comparison with healthy controls (P< 0.05*) .The S100B levels from breast cancer was significantly increased when compared to pathological controls (P< 0.05**). While there was no significant differences in serum S100B levels when compared pathological controls to healthy controls. It is possible to differentiate between benign and malignant breast cancers using these values.In patients with metastatic breast cancer, serum levels of the protein S100B may be useful as a biomarker and predictive.

Table (2): Showed that the serum S100B had high validity values (83.2% sensitivity , 84.5% specificity , 72.6% positive predictive value , 46.0% negative predictive value and 82.4% accuracy test).These values make the parameter with highly significance in the study. The findings supported the conclusions reached by Darlix A. et al. (2016). Serum CA15-3 and S100B are likely associated with metastatic tumors and can be helpful independent prognostic indicators in patients with breast cancer[18].According to a 2013 study by Donato, R. et al., S100B binds to the p53 tumor suppressor protein and inhibits apoptosis and differentiation while encouraging cell migration and proliferation to prevent p53 phosphorylation, tetramerization, and the subsequent tumor suppressive action [13] .

Table (3): Showed a significant decrease levels of ALP after treatment compared to its level before treatment in patients with breast cancer (P<0.05*). Also the level of S100B significantly decreased after treatment compared to its level before treatment in patients with breast cancer (P<0.05*). Patients with breast cancer often have higher levels of the markers ALP and S100B in their bodies. It is essential to identifying diseases, evaluating the effectiveness of treatment, and making early diagnoses.

Table (3): Comparison of ALP , S100B level of breast cancer before and after treatment.

	Breast cancer before treatment/15	Breast cancer after treatment/15	Comparing before and after treatment		
Chemical tests	Mean±SD	Mean±SD	t - test	Standard Error of Mean	Probability
Serum ALP (U/L)	94.31±42.02	61.12±17.05	-2.835	11.709	<0.05*
Serum (S100B) (µg/L)	3.11±0.81	1.91±0.51	-4.855	0.247	<0.05*

* Significant using student t-test between two independent means at 0.05 level of significance.

Blood levels of S100B may be associated with survival rates after chemotherapy. It is acknowledged as a helpful marker as well. S100B expression can be used to predict metastases from breast cancer. The results were consistent with those published by Weide B. et al. (2013). Reduced levels of S100B are associated with a favorable response to treatment, whereas increased levels are associated with metastases and a worse prognosis. Furthermore, it has been discovered that S100B is a significant indicator for evaluating a patient's reaction to treatment [19]. Thus, new biomarkers are helpful for managing breast cancer in a clinical environment. According to Chantal Allgöwer et al. (2020), S100 proteins are expressed calcium-binding proteins that are involved in several cellular processes, including proliferation, death, and Ca2+ homeostasis. S100 proteins play a crucial part in the emergence and metastasis of numerous cancer forms, including breast cancer. As a result, it has also been demonstrated that the S100 family represents intriguing diagnostic markers and potential novel therapeutic targets [20]. Abnormal S100B has been linked to a number of neurological disorders and cancers. S100B recognizes effector proteins and requires calcium to bind them. There is evidence that S100B and p53 interact [21] .

Therefore, elevated S100B levels in biological fluids (CSF, blood, and saliva) are considered a biomarker of pathological diseases such as oral inflammation, especially when evaluating pulpitis, periodontal disease, and oral nerve injury [22] . Increased S100B, a calcium-binding protein that functions as a Damage-Associated Molecular Pattern (DAMP), is a biomarker for neuroinflammation and the advancement of periodontal, Parkinson's, and Alzheimer's diseases [23] .

Findings in table (4): Demonstrated that women with breast cancer had significantly lower serum phosphorus levels than healthy controls (P<0.05*). In patients with breast cancer, there was no discernible rise in serum phosphorus levels following treatment compared to those prior to treatment. These outcomes supported Shreedhar Adhikari et al. 2021's findings. Hypophosphatemia is a common consequence of phosphorus homeostasis disruption in cancer patients. Phosphorus homeostasis is frequently disturbed in cancer patients, which can lead to hypophosphatemia . Numerous factors, including the kind of cancer, treatment plan, nutritional state, and illness, affect the development of hypophosphatemia [24] . Phosphorus is crucial for the formation and maintenance of dental health.Together with calcium, this mineral contributes to the development of strong enamel, which is essential for protecting teeth from decay and cavities. Cells and tissues are rich in inorganic phosphate (Pi). The mineralized matrix of bones and teeth contains most

of the body's Pi. Pi and inorganic pyrophosphate (Ppi) equilibrium in turn influences mineralization in bones and teeth [25].

Findings in table (4): Indicated that women with breast cancer had significantly higher calcium levels than healthy controls (P<0.05*). Patients with breast cancer had significantly lower calcium levels following treatment than they did prior to treatment (P<0.05*).

Table (4) Biostatistical calculations and student t-test for phosphorus ,Calcium & 1,25(OH)2D Vitamin D, in sera of breast cancer before and after treatment , normal healthy controls, and breast cancer women.

Serum phosphorus (mg/dL)	**Before treatment**	**After treatment**	**Breast cancer/55 (stage I,II)**	**Normal healthy controls /55**
Sample size	15	15	55	55
Mean±SD	3.16 ± 0.71	3.34 ± 0.76	3.17±0.81	4.15± 0.88
P-value	NS		0.05 *	
Serum Calcium (mg/dL)	Before treatment	After treatment	Breast cancer/55 (stage I,II)	Normal healthy controls /55
Sample size	15	15	55	55
Mean±SD	14.45 ±2.18	11.42 ± 1.73	13.81±2.31	11.41 ±2.21
P-value	0.05 *		0.05 *	
Serum 1,25$(OH)_2$D Vitamin D (ng/mL)	Before treatment	After treatment	Breast cancer/55 (stage I,II)	Normal healthy Controls/55
Sample size	15	15	55	55
Mean±SD	18.77±1.93	19.61 ±1.98	19.23 ±1.88	24.71 ± 2.17
P-value	NS		0.05 *	
Serum (FGF23) (p g/mL)	Before treatment	After treatment	Breast cancer/55 (stage I,II)	Normal healthy controls /55
Sample size	15	15	55	55
Mean±SD	296.81 ± 22.7	63.32 ±15.7	293.71 ±26.6	62.41 ±12.8
P-value	0.05 *		0.05 *	

* Significant at the 0.05 level of significance using the student t-test between two independent means.

These outcomes concurred with the study's conclusions. Serum calcium levels are usually higher in advanced breast cancer. In postmenopausal patients, larger breast tumors were linked to significantly higher serum calcium levels [8] . The S100 protein mediates a number of functions, such as controlling cell division, apoptosis, and calcium homeostasis. The S100 calcium-binding protein family includes inflammatory proteins that contribute to the tumor's growth. The hydrophobic amino acid residues in the S100 protein interact with the target protein after Ca^{2+} binding, according to FLi, X Men, and W Zhang's 2014 study.Therefore, the S100 protein's role in tumor metastasis depends on its interaction with Ca^{2+} [9]. Hypercalcemia can occur in patients with breast cancer, whether or not they have bone metastases. Chemotherapy lowers calcium levels. The findings aligned with this investigation. Chemotherapy lowers calcium levels in people with breast cancer who were previously hypercalcemic [26]. Reducing a high calcium level makes it easier to continue taking cancer chemotherapy medications and relieves symptoms, in people with metastatic breast cancer. Oral health, vitamin D insufficiency, and bone mineral density are all correlated.

Results in table (4): Revealed that women with breast cancer had significantly lower serum 1,25(OH)2D vitamin D levels (ng/mL) than healthy controls (P<0.05*). In individuals with breast cancer, there was no apparent rise in serum 1,25(OH)2 Vitamin D levels following treatment compared to those prior to treatment. There are several prodifferentiating, anti-inflammatory, and antiproliferative properties associated with 1,25(OH)2D vitamin D levels. These findings supported the study's conclusions. J. Van Hevel et al. (2022). Vitamin D, or 1,25(OH)2D, has well-known anti-proliferative, proapoptotic, and anti-inflammatory actions on cancerous cells, particularly breast cancer [(27)]. Aboubacar D. T. et al. (2023) reported that the findings indicated a potential link between 1,25(OH)2D vitamin D and a decreased risk of breast cancer [(28)]. Also reported by J. Vanhevel et al. (2022). One of the main functions of vitamin 1,25-dihydroxyvitamin D, the active form, is to maintain the balance between calcium and phosphate. A higher risk of breast cancer has been linked to low levels of 1,25-dihydroxyvitamin D [(27)] . These results provide support to the idea that women who are deficient in vitamin D have a higher risk of breast cancer. The results of James David Mackey et al. (2023) were consistent with these findings. Breast cancer risk has been associated with low vitamin D levels [(29)]. The results of this research pointed to a possible connection between vitamin D and a decreased risk of breast cancer. Breast cancer, particularly invasive breast cancer, is more likely to arise and progress when periodontal disease is present [(30)]. Reducing the risk of breast cancer would require effective periodontal therapy [(31)] . A higher risk of periodontitis is linked to low vitamin D and high calcium levels [(32)]. Breast cancer patients' dental health was negatively impacted by vitamin D deficiency . Therefore, screening for vitamin D deficiency and taking supplements [(33)].

The pathophysiology of breast cancer involves vitamin D3 and vitamin D receptors (VDR). Therefore, VDR, which is expressed at a systemic level, may function as a negative tumor suppressor regulator in physiological settings and may be compromised in cancer patients, thereby increasing cancer transformation and other cancer-related consequences, such as decreased bone health [(34)].

Results in table (4): Showed that the women with breast cancer had significantly higher serum levels of FGF23 (p g/mL) than healthy controls (P<0.05*). In patients with breast cancer, serum (FGF23) levels (p g/mL) significantly decreased following treatment as compared to pretreatment levels (P< 0.05*).

Table (2): Showed that the serum FGF23 had high validity values (81.4% sensitivity , 81.6% specificity , 71.2% positive predictive value ,45.0% negative predictive value and 81.3% accuracy test). Because of these values, this measure is extremely important for studying women who have breast cancer. FGF23 levels in the serum may be a very helpful diagnostic and prognostic indicator for patients with metastatic breast cancer. When diagnosing breast cancer, levels of FGF23 are particularly helpful in the early stages of the disease. Breast cancer-induced elevation of fibroblast growth factor 23 (FGF23) lowered vitamin D3 activation by inhibiting renal enzyme 1-α hydroxylase and hampered phosphate reabsorption by stimulating proximal renal tubular epithelial cells [(17)]. Phosphorylation is a significant alteration that influences the control of p53 activity. The tumor-suppressor p53 is first dephosphorylated and then rephosphorylated to assist p53 in removing from promoters and preventing p53-mediated transcription. Phosphorus is a key regulator of the cell's response to DNA damage [(12)]. The FGF signaling network plays a key role in tumorigenesis and is recognized as a potential therapeutic target [(35)] .

Elevated fibroblast growth factor 23 (FGF23) in X-linked hypophosphatemia (XLH) results in rickets and phosphate wasting, manifesting by severe bone and dental abnormalities [(36).]

CONCLUSION

This study revealed that, as compared to healthy controls, women with breast cancer had significantly higher levels of ALP, S100B, and (FGF23). The validity values (sensitivity, specificity, and accuracy test) of serum ALP, S100B, and FGF23 are very high. Because of these values, these factors are extremely important for the early detection and progression of breast cancer. The best markers were FGF23, S100B, calcium, phosphorus, vitamin D, and ALP. The S100 protein's participation in tumor metastasis depends on its interaction with Ca 2+.For tumor-suppressor p53, phosphorylation is an important modification involved in the control of p53 activity. S100B binds the p53, inhibiting p53 phosphorylation. Therefore, early identification and diagnosis of these parameters in breast cancer patients is beneficial for the progression of treatment. Additionally, there is a connection between oral health, vitamin D deficiency, and bone mineral density in women with breast cancer. Elevated (FGF23), S100B, hypophosphatemia, and oral disease are connected.

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