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Serum Ferritin, Vitamin D and Pathological Factors in Breast Cancer Patients

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Abstract

Background: Breast cancer is one of the most common cancers. Researchers are trying to diagnose the disease through easier and safer methods. Serum markers such as ferritin and vitamin D level would be very helpful. This research could pave the way for more comprehensive studies on how to use this serum factor in breast cancer screening, as well as early detection of the disease in its early stages.

Methods: This study consisted of two groups, the first group comprising patients diagnosed with breast cancer before undergoing any treatment and the second group as control were healthy people. Serum ferritin and vitamin D levels were measured. Pathological information of the patient's tumor, including ER, HER2, KI67, lymphovascular invasion, and disease stage, were collected as well. Data were analyzed by IBM SPSS advanced statistics version 23.0 (SPSS Inc., Chicago, IL). P-value of ≤0.05 was considered significant.

Results: Eighty-eight subjects were enrolled in this study, 29 (33%) breast cancer patients and 59 (67%) healthy women. In breast cancer patients, serum ferritin levels were 106.55±111.25, which were higher than healthy women's serum ferritin 52.71±36.95 (p=0.083). Furthermore, 18 (66.7%) of breast cancer patients and 55 (93.2%) of healthy women had low serum ferritin levels (p=0.001). 3 (11.1%) patients in the cancer group had serum vitamin D deficiency, while all subjects in the control group had serum vitamin D higher than 10 ng/dl (p =0.009).

Conclusion: The results of this study showed a correlation between breast cancer and vitamin D deficiency, and elevated ferritin. Perhaps with further studies, there could be a role in predicting the prognosis and screening of breast cancer for these associations.

Keywords: Ferritin, Vitamin D, Breast Cancer

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Introduction

Breast cancer is the most common cancer among women and an important public health problem in developed countries (1). Researchers are trying to diagnose the disease through easier and safer methods. Mammography is the standard method for screening of breast cancer, and Serum biomarkers such as CEA and CA15-3 are useful in metastatic disease surveillance, but not for the diagnosis of localized breast cancer (2). Serum markers such as ferritin and vitamin D level would be very helpful and their link to breast cancer has been studied over several years

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↑What is "already known" in this topic:
There have been many studies on the role of vitamin D deficiency and increased ferritin in breast cancer, most of which have not examined the association with the pathological features of the tumor.

→What this article adds:
In this article, unlike previous articles, the relationship between vitamin D and ferritin and pathological features of the tumor such as ER, HER2, KI67, lymph vascular invasion, and disease stage has been investigated.

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(3, 4).

Ferritin is a large protein macromolecule mainly synthesized in the liver, spleen, and myocardium, storing iron in the serum, but it also has other biological roles (5). Recently, the role of this molecule in the pathogenesis of a number of diseases, including breast cancer, has been shown with inflammation and oxidative pathways being the most important factors. Cytokines play an important role in cancer pathogenesis and ferritin is produced in response to cytokines (6).

Several studies have been done linking vitamin D deficiency to various types of disease, including cancers such as breast, colon, and prostate cancer (3, 7). Vitamin D is the precursor of 1,25 dihydroxy vitamin D in the body, a steroid hormone that is involved in various processes in the body, including cancer-stimulating pathways. Dihydroxy vitamin D can act as a protector against cancer through various mechanisms including apoptosis induction, stimulation of cell differentiation, anti-inflammatory and anti-proliferative effects, and inhibition of angiogenesis, invasion, and metastasis (8).

Many studies have been conducted to prove the relationship between serum ferritin as well as vitamin D levels and breast cancer in different populations, but not so many in Iranians. This research could pave the way for more comprehensive studies on how to use this serum factor in breast cancer screening, as well as early detection of the disease in its early stages. In this study, the relationship between ferritin and vitamin D with other pathological markers such as ER, HER2, KI67, as well as the lymphovascular invasion was also investigated.

Methods

This study consisted of two groups, the first group comprising patients diagnosed with breast cancer through biopsy before undergoing any treatment, including surgery, chemotherapy and radiotherapy. Blood tests for measurement of serum ferritin and vitamin D level would be done for them. The second group as control were healthy people from the hospital staff who came for an annual blood test. Serum ferritin and vitamin D levels were also measured. The two groups were compared according to the mentioned parameters.

Initially, the study design was discussed with a surgeon with a specialty in the field of breast cancer, and after explaining the plan and its goals, it was decided to include patients who underwent a biopsy due to breast mass and were diagnosed with cancer. Other inclusion criteria were as follows: not receiving any oncology treatment including hormone therapy, chemotherapy, radiotherapy and surgery; no history of chronic or rheumatic diseases and other malignancies; no history of acute inflammation such as common cold; not being smoker or alcoholics; normal renal and hepatic function; hemoglobin above 10 mg/dl; BMI: 18.5-25 and not taking medications such as iron, levothyroxine and vitamin D supplement a few months before the lab test in both group. The living area of both groups was the same.

Once the patients entered the study, serum ferritin and vitamin D levels were measured in one of the three reference laboratories. Pathological information of the patient's tumor, including ER, HER2, KI67, lymphovascular invasion, and disease stage, were collected as well. The measured parameters in both groups were compared, followed by statistical analysis.

Based on normal laboratory range, ferritin above 115 ng/ml is considered high and vitamin D below 10ngl/ml is regarded as vitamin D deficiency. Meanwhile, for Ki-67, nuclear expression was quantitatively recorded. As Atif Ali Hashmi et al. (9) estimated, at least 1000 cells were estimated to calculate the mean. Based on the percentage of staining, ki67 index was further divided into four groups: <14, 15-24, 25-44, and > 45.

Ethical considerations: As all patients with breast cancer should be checked for blood indices before surgery, blood tests are mandatory in all, and therefore the desired parameters can be checked at the same time. The cost of the tests was covered by the plan. Accordingly, there was no ethical consideration respectively.

Statistical Analysis

Data were analyzed by IBM SPSS advanced statistics version 23.0 (SPSS Inc., Chicago, IL). The descriptive measures were presented in frequency (percentage) and Mean ± SD. Comparison between two groups of quantitative data was made using independent t-test and Mann-Whitney test (non-parametric t-test based on the result of the Shapiro-Wilk test of normality). The comparison of qualitative variables was performed using the Chi-square test or Fisher exact test. P-value of ≤0.05 was considered significant.

Results

Eighty-eight subjects were enrolled in this study, 29 (33%) breast cancer patients and 59 (67%) healthy women. The mean age of healthy women was 48.05±12.35 and in breast cancer patients was 51.51±12.81 years (p=0.25). In breast cancer patients, 21(72.4%) had early N stages (N0-1), 24 had (82.8%) early T stage (T1-2), and 18 (62.1%) were low grade. Also, 19 (65.5%) were ER-positive, 12 (18.2%) positive for LVI, and 10 (15.2%) HER2-positive breast cancer patients.

In breast cancer patients, serum ferritin levels were 106.55±111.25, which were higher than healthy women's serum ferritin 52.71±36.95 (p=0.083). Furthermore, 18 (66.7%) of breast cancer patients and 55 (93.2%) of healthy women had low serum ferritin levels (p=0.001). The clinical characteristics of breast cancer patients according to serum ferritin levels are presented in Table 1.

Three (11.1%) patients in the cancer group had serum vitamin D deficiency, while all subjects in the control group had serum vitamin D higher than 10 ng/dl. (p=0.009) (Table 2).

Discussion

In this study, not only the relationship between vitamin D as well as ferritin levels and breast cancer were investigated, but also the relationship between other pathological indices of the tumor such as ER, HER2, KI67, LVI with the serum level of ferritin and vitamin D was examined.

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Table 1. Ferritin association with the pathological features of the tumor

	No. (%) of participants		
	Ferritin level		
Variable	<115	>115	p-value
Grade			
Low	11 (61.7)	5 (55.6)	0.782
High	7 (38.9)	4 (44.4)	
T			
Low	14 (77.8)	8 (88.9)	0.484
High	4 (22.2)	1 (11.1)	
Node			
N0-1	13 (72.2)	6 (66.7)	0.766
N2-3	5 (27.8)	3 (33.3)	
Stage			
1	12 (70.6)	6 (66.7)	0.837
2	5 (29.4)	3 (33.3)	
ER			
-	8 (44.4)	2 (22.2)	0.260
+	10 (55.6)	7 (77.8)	
HER2			
-	11 (61.1)	6 (66.7)	0.778
+	7 (38.9)	3 (33.3)	
LVI			
-	10 (55.6)	5 (55.6)	0.999
+	8 (44.4)	4 (44.4)	
KI67			
1	3 (16.7)	2 (22.2)	
2	14 (77.8)	6 (66.7)	0.799
3	1 (5.6)	1 (11.1)	

Table 2. Vitamin D association with the pathological features of the tumor

	No. (%) of participants		
	Serum vitamin D level		
Variable	<10	>10	p-value
Grade			
Low	1 (6.3)	15 (93.8)	0.332
High	2 (18.2)	9 (81.8)	
T			
Low	2 (9.1)	20 (90.9)	0.484
High	1 (20.0)	4 (80.0)	
Node			
Low	2 (10.5)	17(89.5)	0.882
High	1 (12.5)	7 (87.5)	
Stage			
1	2 (11.1)	16 (88.9)	0.919
2	1 (12.5)	7 (87.5)	
ER			
-	2 (20.0)	8 (80.0)	0.260
+	1 (5.9)	16 (94.1)	
HER2			
-	1 (5.9)	16 (94.1)	0.260
+	2 (20.0)	8 (80.0)	
LVI			
-	2 (66.7)	13 (86.7)	0.332
+	1 (8.3)	11 (91.7)	
KI67			
1	0 (0.0)	5 (100.0)	
2	3 (15.0)	17 (58.0)	0.554
3	0 (0.0)	2 (100.0)	

This could clarify the relationship between the pathology of the disease and these parameters.

The results of this study showed a correlation between breast cancer and vitamin D deficiency and elevated ferritin, but there was no association between vitamin D and ferritin levels and pathological tumor indices such as tumor stage, LVI, ER, HER2, and KI67.

Contrary to our results, Linnea Huss et al. (10) found that positive expression of the vitamin D receptor in the nucleus and cytoplasm of breast cancer cells was associated with tumor characteristics such as smaller size, lower grade, estrogen receptor positivity, progesterone receptor positivity, and lower Ki67 expression indicating a better prognosis. In addition, patients were associated with lower mortality.

In a systematic review and meta-analysis in 2019, Sharmin Hossain et al. (7) reviewed 22 studies evaluating the association of serum 25 (OH) D (both in serum and

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diet) with the incidence of breast cancer. 25 (OH) D deficiency was directly associated with breast cancer incidence, while total vitamin D and vitamin D supplementation were inversely related.

Angel Arnaout et al. (11) conducted an RCT study in 2019 to investigate the effect of vitamin D intake in breast cancer patients on their pathologic indices. For that purpose, 83 newly diagnosed breast cancer patients 2 to 6 weeks before breast surgery were randomized to receive 40,000 IU of vitamin D3 per day or a placebo. The initial findings showed a relative change in proliferation (Ki67) and apoptosis (cleaved caspase 3 apoptotic assay [CC3]) in primary breast cancer cells before and after treatment, but in the final result, there was no significant association between vitamin D intake and KI67 or CC3 (1.6% vs. 16.7%, p=0.25) or CC3 (-55.9% vs. -45.9%, p=0.28). Despite significantly higher serum 25-OHD levels in the vitamin D-treated group, this was not associated with any significant effect on tumor proliferation or apoptosis.

The study of Orlandi R. et al. (12) showed serum hepcidin and ferritin light chain could be a good predictor of breast cancer, but they were weaker markers for benign breast disease. The study of Marcus DM et al. (13) compared the level of serum ferritin between breast cancer patients and the normal population. The result showed 41% of breast carcinoma patients and 67% locally advanced or metastatic breast cancers had ferritin levels upper than 146 ng/ml. As such, these results showed that ferritin level might be a factor for evaluating or monitoring treatment response monitoring in these patients. Coombes RC et al. (14) also found that 88% of 51 patients with overt metastatic breast cancer had abnormal serum ferritin.

Tappin JA. et al. (15) showed that breast cancer patients have higher than normal serum ferritin before treatment. After a mastectomy or partial mastectomy, the level of serum ferritin decreased due to reduction of mass or removal of inflammatory tissue. In another study, survival had a significant inverse relationship with serum ferritin in metastatic breast cancer patients (16).

According to the above studies, there is a close relationship between vitamin D deficiency as well as high ferritin levels and the incidence and even severity of the disease. Perhaps with further studies, there could be a role in predicting the prognosis of breast cancer for these associations.

But some other studies point to other reasons for elevated serum ferritin, including inflammatory conditions and iron overload syndromes (17). Therefore, these conditions decrease the specificity of this marker.

Our study had several limitations. One is that due to the lack of a sufficient number of cases for analysis in each age group, we could not divide people into different age groups. Finally, some possible confounding factors such as physical activity, eating habits, and socioeconomic status were not considered. To our knowledge, this is the first study in Iran to link vitamin D and ferritin to the pathological indices of breast cancer.

Conclusion

In conclusion, this study showed that there is a significant relationship between breast cancer and increased ferritin, but no significant relationship was found with vitamin D plus ferritin levels in pathological tumor parameters such as tumor stage, LVI, ER, HER2, and KI67, also vitamin D deficiency was more in the breast cancer group. Future studies with more cases are highly recommended.

Conflict of Interests

The authors declare that they have no competing interests.

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