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Phytochemical effects of soy isoflavones consumption on vitamin D and calcium levels in pre and postmenopausal women with hormone positive HER2 neu negative breast cancer

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SUMMARY

Breast cancer is the most common cancer in females, and it is ranked at level one in all cancer types list. Isoflavones are phenolic compounds with a chemical structure as same as estrogen which binds to hormone receptors. Calcitriol regulates proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis, and metastasis of BC. This study aimed to investigate the association of vitamin D and calcium levels with isoflavones in the premenopausal and postmenopausal women with hormone-positive Her2 neu negative BC treated with anti-estrogens and vitamin D. A randomized, interventional comparison study was carried out from October 2021 to May 2022. This study enrolled 120 BC, Iraqi women, with hormonal positive Her2 neu negative. The blood sample was collected in a gel tube and the serum is extracted as quickly as feasible. Then transferred into a new clean disposable plain tube to be utilized to assess the vitamin D3, and calcium for 3 months (at baseline, at a low dose, and a high dose of isoflavone). Their mean age was (47.66 ± 10.606) years with a median age of 46 years. The mean age of premenopausal women was (37.91 ± 3.476) years, while for postmenopausal females was (55.2 ± 8.12) years, with a highly significant difference (t=12.996; P<0.0001). There was a highly significant difference (t=3.175; P=0.003) between the BSA of post-menopause and pre-menopause women (1.78 ± 0.135 and 1.69 ± 0.143) Kg/m2, respectively. All postmenopausal women underwent surgical intervention (72, 100%), while thirty-nine premenopausal women were exposed to surgery, with a statistically significant difference (t=2.348; P=0.024). Four premenopausal women received Anastrazole (Arimidex) whereas 40(90.9%) received Tamoxifen, however, 62(86.1%) postmenopausal women received Arimidex, while the rest 10(13.9%) received Tamoxifen with highly statistically significant differences (t=-11.358-; P< 0.0001). According to one-way ANOVA analysis, the Ca^{2+} levels were raised significantly in both arms in particular during the administration of low and high doses of soya isoflavone (P<0.0001; 0.02). Moreover, the mean vitamin D concentrations at a low dose (35 mg) of soya isoflavone and a high dose (70 mg) of soya isoflavone in pre-menopause women were lower than in post-menopause women (23.48 ± 7.453 IU vs. 30.53 ± 10.981 IU; 26.7 ± 8.101 IU vs. 35.1 ± 9.395 IU), respectively. There was a high statistically significant difference (P <0.0001; P <0.0001), respectively. According to one-way ANOVA analysis, the vitamin D levels were raised significantly in both arms in particular during the administration of the low and high doses of soya isoflavone (P =0.046; <0.0001). Age, weight, co-morbid, and positive family history of married women are significantly different between pre-menopause and post-menopause. Calcium shows different ranges, mostly non-significant after isoflavone consumption whereas vitamin D shows significant changes.

Key words: breast cancer, vitamin D, calcium, isoflavone, soya

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INTRODUCTION

Breast cancer (BC) is the most common cancer in females, and it is estimated that one in eight women in the US will develop BC in their lifetime [1]. In Iraq, the number of BC cases reached 4,542 in 2014 according to a WHO report [2]. In 2021, about 7,515 new cases of BC were recorded in Iraq, and 3,019 deaths were estimated [3]. Globally, an update published by GLOBOCAN found that female BC account for 2,261,419 new cases and 684,996 new deaths, it is ranked at level one in all cancer types list [4]. Soy-rich foods or isoflavones can reduce the risk of several chronic diseases [5-8], including certain forms of cancer, especially BC, and prostate adenocarcinoma [9-14]. The soybean, soybean, or soya bean is a species of legume, which is a type of natural isoflavonoids [15]. Clinically, the soy benefits have been studied with some evidence associated with decreased incidences of coronary heart disease, atherosclerosis, type II DM, and some cancer types. Several trials investigated soybeans as a potential agent for atrophy, menopause, and postmenopausal symptoms [16]. There are three soybean isoflavones which are genistein, daidzein, and glycitein. These non-steroidal compounds are naturally found in soybean and non-fermented soy foods primarily in their beta forms [17]. In the soybean, approximately genistin/genistein, daidzin/daidzein, and glycitin/glycitein account for 55%, 45%, and 10% of total isoflavone content, respectively [18]. In terms of biochemistry, isoflavones are diphenolic compounds with a chemical structure as same as estrogen which binds to all ERα and ERβ [19, 20].

Vitamin D3 is the precursor to the potent steroid hormone calcitriol (1,25 dihydroxy vitamin D3 ($1,25(OH)_2D_3$)) that regulates the expression of many genes in most tissues of the body [21]. Dietary vitamin D3 is converted into 25 hydroxyvitamin D3 ($25(OH)D_3$) in the liver, which is subsequently hydroxylase to form calcitriol by the cytochrome P450 enzyme CYP27B1 in the kidneys. Calcitriol regulates multiple signaling pathways involved in proliferation, apoptosis, differentiation, inflammation, invasion, angiogenesis, and metastasis of BC, and it, therefore, has the potential to affect cancer development and growth. Recent findings indicate that calcitriol also regulates microRNA expression and may affect cancer stem cell biology [21, 22].

This study aimed to investigate the association of vitamin D and calcium levels with isoflavones in premenopausal and postmenopausal women with hormone-positive HER2 neu negative BC treated with anti-estrogens and vitamin D.

METHODS

Study design and setting

A randomized, interventional comparison study was carried out from October 2021 to May 2022. This study enrolled 120 BC, Iraqi women, with hormonal positive HER2 neu negative. A total of 72 women belonged to the postmenopausal group treated with anti-estrogen and the rest 48 women were in the premenopausal group.

Inclusion criteria

1. Patients should be diagnosed with BC hormonal positive ER+, PR+, and HER2 negative.
2. Patients start anti-estrogen treatment
3. The age is 25 years to 75 years.

Exclusion criteria

1. The age is under 25 years and older than 75 years.
2. Metastatic breast cancer.

Data Collection

A questionnaire will be filled out for each patient including the patient's characters and BC features, medical history, and frequency of soy food intake over the last year.

Blood sample

The blood sample was collected in a gel tube and the serum is extracted as quickly as feasible. For 10 minutes, the blood samples were centrifuged at 3000 rpm. Then transferred into a new clean disposable plain tube to be utilized to assess the Vitamin D3, and calcium for 3 months (at baseline, at a low dose, and a high dose of isoflavone).

Statistical analysis

Statistical analysis was performed using SPSS v24 (IBM Inc., Chicago, IL, USA). Descriptive statistics consist of numbers, and percentages were measured. Mean, median, and SD for categorical data were calculated. An association between premenopausal and postmenopausal was measured using an unpaired independent t-test. One-way ANOVA analysis was used to describe the association between groups. A two-sided P value of less than 0.05 was considered statistically significant.

RESULTS

This study enrolled 120 BC Iraqi females; their mean age was (47.66 ± 10.606) years with a median age of 46 years. Premenopausal women consisted of 48(40%), whereas postmenopausal females were 72(60%). The mean age of premenopausal women was (37.91 ± 3.476) years, while for postmenopausal females was (55.2 ± 8.12) years, with a highly significant difference (t=12.996; P<0.0001). The mean weight of premenopausal women (73.09 ± 12.421) kg was significantly lower than the weight of postmenopausal women (80.28 ± 17.063) kg, (t=2.058; P=0.046).

However, the overall mean and median weight was (76.27 ± 14.409; 75) kg. The mean height of premenopausal women (158.59 ± 7.167) cm was insignificantly lower than the height of postmenopausal women (159.61 ± 6.431) cm, (t=0.72; P=0.476). However, the overall mean and median height was (158.66 ± 6.767; 75) cm. As a result, the overall mean BSA was (1.74 ± 0.141) Kg/m^2 with a median of (1.7) Kg/m^2. There was a highly significant difference (t=3.175; P=0.003) between the BSA of post-menopause and pre-menopause women (1.78 ± 0.135 and 1.69 ± 0.143) Kg/m^2, respectively. Regarding marital status, there was a high significant difference between pre-menopause (married=35) and post menopause (married=71) women (t=2.702; P=0.01). In relation to job, there was insignificant difference between pre-menopause (yes=9) and post menopause (yes=10) women (t=-1.159-; P=0.253). There was a highly statistical difference between pre-menopause (yes=8) and post-menopause (yes=51) related to co-morbid conditions (t=6.312; P<0.0001), shown in (Table 1). According to past-surgical history, there was no relation between the two categories (t=0.476; P=0.636). Furthermore, there was no significant difference between pre-menopause (positive=18) and post-menopause (positive=22) women concerning family history, (t=-1.301-; P=0.2), (Table 1).

Table 2 showed the comparison between pre-menopause and post-menopause women in this study about BC features. Staging (T (t=1.425; P=0.161) and N (t=0.198; P=0.84)), IHC (ER (t=1; P=0.323), PR (t=1; P=0.323) and HER2 neu (t=NA)), management (chemotherapy (t=-1.431-; P=0.16), and radiotherapy (t=-0.703-; P=0.486) had no significant differences among both arms. Regarding surgery, all postmenopausal women underwent surgical intervention (72, 100%), while thirty-nine premenopausal women were exposed to surgery, with a statistically significant difference (t=2.348; P=0.024).

*Four cases were missed of follow-up Regarding hormonal therapy, four (9.1%) premenopausal women received Anastrazole (Arimidex) whereas 40(90.9%) received Tamoxifen, however, 62(86.1%) postmenopausal women received Arimidex, while the rest 10(13.9%) received Tamoxifen with highly statistically significant differences (t=-11.358-; P<0.0001).

All biochemical results of this study included baseline concentration, the concentration at a low dose (35 mg) of soya isoflavone, and the concentration at a high dose (70 mg) of soya isoflavone were analyzed. Calcium (Ca^{2+}) levels in post-menopause women and pre-menopause women were shown in Table 3.

Tab. 1. Patients of the study (n=120)

Variables		Premenopausal women (n=48)*	Postmenopausal women (n=72)	t -test	P value
Age (years)		37.91 ± 3.476	55.2 ± 8.12	12.996	<0.0001
Weight (Kg)		73.09 ± 12.421	80.28 ± 17.063	2.058	0.046
Height (cm)		158.59 ± 7.167	159.61 ± 6.431	0.72	0.476
BSA (m^2)		1.78 ± 0.135	1.69 ± 0.143	3.175	0.003
Married	Yes	35 (79.5)	71 (98.6)	2.705	0.01
	No	9 (20.5)	1 (1.4)		
Job	Yes	9 (20.5)	10 (13.9)	-1.159-	0.253
	No	35 (79.5)	62 (86.1)		
Co-morbid	Yes	8 (18.2)	51 (70.8)	6.312	<0.0001
	No	36 (81.8)	21 (29.2)		
Past-surgical history	Yes	47 (95.5)	71 (98.6)	0.476	0.636
	No	2 (4.5)	1 (1.4)		
Family history	Yes	18 (40.9)	22 (30.6)	-1.301-	0.2
	No	26 (59.1)	50 (69.4)		

Tab. 2. Breast cancer in this study (n=120)

Variables		Premenopausal women (n= 48)*	Postmenopausal women (n= 72)	t -test	P value
T	2	25 (56.8)	28 (38.9)	1.425	0.161
	3-4	19 (43.2)	44 (61.1)		
N	1-2	31 (70.4)	53 (73.6)	0.198	0.84
	3	13 (29.6)	19 (26.4)		
ER	Yes	43 (97.7)	72 (100)	1	0.323
	No	1 (2.3)	0		
PR	Yes	43 (97.7)	72 (100)	1	0.323
	No	1 (2.3)	0		
HER2 neu	Yes	0	0	NA	NA
	No	44 (100)	72 (100)		
Surgery	Yes	39 (88.6)	72 (100)	2.348	0.024
	No	5 (11.4)	0		
Chemotherapy	Yes	48 (100)	68 (94.4)	-1.431-	0.16
	No	0	4 (5.6)		
Radiotherapy	Yes	41 (93.2)	63 (87.5)	-0.703-	0.486
	No	3 (6.8)	9 (12.5)		
Types of hormonal therapy	Arimidex	4 (9.1)	62 (86.1)	-11.358-	<0.0001
	Tamoxifen	40 (90.9)	10 (13.9)		

Tab. 3. The comparison between mean levels of calcium of pre menopause and post menopause BC women

		Premenopausal women (n= 48)	Postmenopausal women (n=72)	t -test (P value)
Ca^{2+} (mg/dL)	**Baseline**	9.18 ± 1.685	9.2 ± 0.627	0.104 (0.918)
	1st	10.1 ± 3.497	9.39 ± 0.577	-1.45
	2nd	10.78 ± 3.835	9.71 ± 0.371	-1.859
ANOVA "F" (P value)		235.05 (<0.0001)	6.042 (0.02)	

1st (concentration at low dose (35 mg) of soya isoflavone); 2nd (concentration at high dose (70 mg) of soya isoflavone)

At baseline, the overall mean Ca^{2+} level in pre-menopause women (9.18 ± 1.685mg/dL) was lower than in post-menopause women (9.2 ± 0.627mg/dL), with no significant difference (P=0.918). Moreover, the mean Ca^{2+} concentrations at low dose (35 mg) of soya isoflavone and at high dose (70 mg) of soya isoflavone in post-menopause women were

Tab. 4. The comparison between mean levels of vitamin D of pre menopause and post menopause women

		Premenopausal women (n= 48)	Postmenopausal women (n=72)	t -test (P value)
Vitamin D	Baseline	17.08 ± 6.569	20.743±8.133	2.53 (0.015)
(IU)	1st	23.48±7.453	30.53 ± 10.981	3.785 (<0.0001)
	2nd	26.7 ± 8.101	35.1 ± 9.395	4.855 (<0.0001)
ANOVA "F" (P value)		3.648 (0.046)	12.504 (<0.0001)	

1st (concentration at low dose (35 mg) of soya isoflavone); 2nd (concentration at high dose (70 mg) of soya isoflavone)

lower than in pre-menopause women (9.39 ± 0.577mg/dL vs. 10.1 ± 3.497mg/dL; 9.71 ± 0.371mg/dL vs. 10.78 ± 3.835mg/dL), respectively, in addition, there were no significant difference (P=0.23; P=0.084), respectively. According to one-way ANOVA analysis, the Ca^{2+} levels were raised significantly in both arms in particular during the administration of low and high doses of soya isoflavone (P<0.0001; 0.02), as shown in Figure 1.

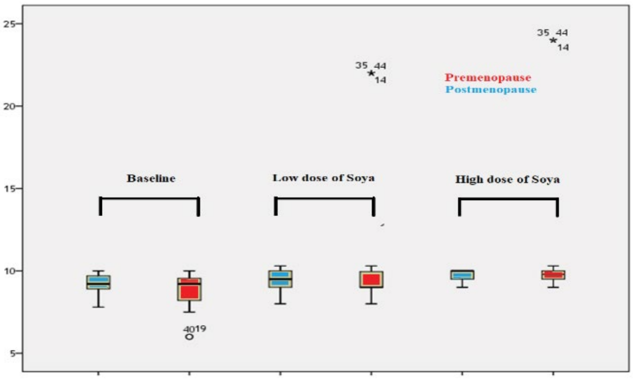

Fig. 1. Box plot compared between mean levels of calcium of pre menopause and post menopause women

Vitamin D levels in post-menopause women and pre menopause women were shown in Table 4.

At baseline, the overall mean vitamin D level in pre-menopause women (17.08 ± 6.569 IU) was lower than in post-menopause women (20.743 ± 8.133 IU), with a statistically significant difference (P=0.015). Moreover, the mean vitamin D concentrations at a low dose (35 mg) of soya isoflavone) and at high dose (70 mg) of soya isoflavone in pre-menopause women were lower than in post-menopause women (23.48 ± 7.453 IU vs. 30.53 ± 10.981 IU; 26.7 ± 8.101 IU vs. 35.1 ± 9.395 IU), respectively. There was a high statistically significant difference (P<0.0001; P<0.0001), respectively. According to one-way ANOVA analysis, the vitamin D levels were raised significantly in both arms in particular during the administration of low and high doses of soya isoflavone (P =0.046; <0.0001), as shown in Figure 2.

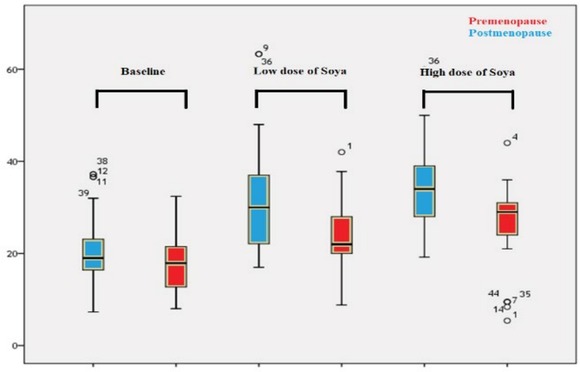

Fig. 2. Box plot compared between mean levels of vitamin D of pre menopause and post menopause women

DISCUSSION

This study included 120 breast cancer Iraqi females; their mean age was (47.66 ± 10.606) years with a median age of 46 years. Premenopausal women consisted of 48(40%), the mean age of premenopausal women was (37.91 ± 3.476) years, whereas postmenopausal females were 72(60%), their mean age was (55.2 ± 8.12) years, with a highly significant difference (P<0.0001). These findings agreed with Al-Naqqash et al. Al-Alwan et al. and Al-Rawaq [28]. Yasui et al [29], recruited women whose ages were 45 to 54 years as 217(39.9%) premenopausal women (aged=47(44-49) years) and 327(60.1%) postmenopausal women (aged=52(50-53) years) [23-29]. Age is an important factor in the incidence and treatment of breast cancer [30]. In most Arabian regions, breast cancer is more commonly detected in women under the age of 50, unlike the Western countries, where women aged 50 years and older are most commonly diagnosed [31]. It has been proposed that these differences are due to changes in exposure to hormones, diet, physical activities, and other risk factors such as ethnicity, religion, and localities [32]. Younger generations are continuously detected with breast cancer, which has been comprehensively shown in the Iraqi Cancer Registry [33-37] and other documented reports from neighboring countries [38-40].

There w as a highly s ignificant di fference (P=0.003) bet ween the BSA of post-menopause and pre-menopause women (1.78

± 0.135 and 1.69 ± 0.143) Kg/m2, respectively. These results are similar to data reported in previously Iraqi studies by Al-Naqqash et al., Al-Alwan et al., and Al-Rawaq [23, 26, 28]. However, different studies estimated BMI rather than BSA [41, 42]. In a pooled analysis of prospective studies in breast cancer women, the authors demonstrated the risk of breast cancer to be 30% higher in women with a BMI over 31 m2/Kg compared with women with a BMI of 20 [41].

Regarding marital status, there was a highly significant difference between pre-menopause (married=35) and post-menopause (married=71) women (P=0.01). In total, 106 (88.3%) women in this study were married, while disagreed with the study of Alhelfi and Alhashimi, when reported 69.4% of females were married [43]. Concerning jobs, there was an insignificant difference between pre-menopause (yes=9) and post-menopause (yes=10) women (P=0.253). In general, 15.8% of women in the present study were employed, whereas the rest were jobless. Alhelfi and Alhashimi , who agrees with these, reported that 83.5% of women were housewives, and only 16.5% were an employer[43]. There was a highly statistical difference between pre-menopause (yes=8) and post-menopause (yes=51) related to co-morbid conditions (P<0.0001). This could be explained by the association of co-morbid diseases with older age and hormonal changes. Furthermore, there was no significant difference between pre-menopause (positive=18) and post-menopause (positive=22) women concerning family history, (P=0.2). Approximately, 33.3% of women in this study had a positive family history of breast cancer; this is consistent with [43]. They mentioned that family history was documented in 32.9% of the sample study.

Many papers published by Al-Alwan et al., discussed breast cancer and its relation to family history, co-morbidities, medical and surgical history, and hormonal replacement therapy in Iraq, different percentages were obtained, respectively, with no significant differences [25-27]. These discrepancies between our study and other studies may be explained by there are no standard cancer registry programs, no accurate screening modalities, and may be related to socioeconomic and low educational levels.

The strongest predictors of distant metastasis, disease-free survival, and overall survival of breast cancer are predictively influenced by tumor size (T stage), which correlates strongly with time to progression and prognosis [41, 42].

The lymph node status is the most important prognostic and risk factor and is directly correlated to survival and the best predictor of systemic micro-metastases in the future [42, 44]. In this study, seem to be all women were hormonal positive and HER2 neu negative, which explained by the selection process of inclusion and exclusion criteria of the study.

Regarding hormonal therapy, four (9.1%) premenopausal women received anastrozole (Arimidex) whereas 40(90.9%) received Tamoxifen, however, 62 (86.1%) postmenopausal women received Arimidex, while the rest 10 (13.9%) received Tamoxifen with highly statistically significant differences (P<0.0001). Cuzick et al., confirmed the long-term superiority and safety of anastrozole (Arimidex) over tamoxifen as initial adjuvant therapy for postmenopausal women with hormone-positive early breast cancer [45] . ATAC was the first trial that showed that an aromatase inhibitor is more effective and has fewer serious side effects than tamoxifen in the management of breast cancer in an adjuvant setting in postmenopausal women.

Overall, there was no difference in the occurrence of non-breast cancers, although there were some differences for particular cancers. However, a causal relation for these differences is difficult to assess because of multiple comparisons [45].

Nowadays, EBCTCG mentioned that using an aromatase inhibitor rather than tamoxifen in premenopausal women receiving ovarian suppression will reduce the risk of breast cancer recurrence [46].

Lastly, the authors concluded for females with early-stage hormonal positive breast cancer, adjuvant treatment with five years of tamoxifen reduces their risk of death at 15 years by about one-third [47]. Aromatase inhibitors are an even more effective endocrine treatment than tamoxifen for postmenopausal women, with further proportional reductions in recurrence rates of about 30% [48].

At baseline, the overall mean Ca^{2+} level in pre-menopause women (9.18 ± 1.685) was lower than in post-menopause women (9.2 ± 0.627), with no significant difference (P=0.918). Moreover, the mean Ca^{2+} concentrations at a low dose and high doses of soya in post-menopause women were lower than in pre-menopause women (9.39 ± 0.577 vs. 10.1 ± 3.497; 9.71 ± 0.371 vs. 10.78 ± 3.835) mg/dL, respectively, with a non-significant difference. According to one-way ANOVA analysis, the Ca^{2+} levels were raised significantly in both arms in particular during the administration of low and high doses of soya isoflavone (P<0.0001; 0.02). Steinberg et al., disagrees with the findings of this study, reported that calcium level non-significant changed in placebo group (9.5 ± 0.3; 9.5 ± 0.37; 9.5 ± 0.4) mg/dL, 80mg/d isoflavone (9.6 ± 0.3; 9.6 ± 0.36; 9.5 ± 0.4) mg/dL, and 120mg/d isoflavone (9.4 ± 0.3; 9.4 ± 0.36; 9.4 ± 0.4) mg/dL for baseline (P=0.86), one year (P=0.201) and two years (P=0.903) period in menopause women [49] .

Zhang et al. studied premenopausal Chinese women and found that mean changes from their corresponding baseline values of bone minerals density, calcium/phosphorus, vitamin D, and glutathione peroxidase activity were significantly increased, however, those of phosphorus, osteocalcin, luteinizing hormone and follicle-stimulating hormone were significantly dropped in isoflavone combined with calcium group [50]. The findings showed that soy isoflavone, calcium, and isoflavone combined with calcium therapy were effective and safe in attenuating BMD loss in premenopausal women, and isoflavone combined with calcium therapy was better than soy isoflavone and calcium alone.

There is, however, a paucity of information in the previous literature reporting on the clinical outcomes concerning the health benefits and potential risks of calcium depletion of soy isoflavone supplementation in postmenopausal women [49].

At starting baseline of this study, the overall mean vitamin D level in pre-menopause women was significantly lower than in post-menopause women, (P=0.015). Moreover, the mean vitamin D concentrations at a low dose (35 mg) of soya isoflavone and high dose (70 mg) of soya isoflavone in pre-menopause women were lower than in post-menopause women with a highly statistically significant difference (P<0.0001; P<0.0001), respectively.

According to one-way ANOVA analysis, the vitamin D levels were raised significantly in both arms in particular during the administration of the low and high doses of soya isoflavone (P=0.046;<0.0001). These discrepancies are supported by Marini et al, who reported BMD increases were greater with genistein for both femoral neck and lumbar spine compared to placebo, and genistein also significantly increased bone-specific alkaline phosphatase, vitamin D, and osteoprotegerin levels. In addition, genistein exhibited a promising safety profile with positive effects on bone formation in a cohort of osteopenic, postmenopausal women [51].

Wietzke and Welsh [52], found both phytoestrogens (resveratrol red wine and genistein soy) up-regulated the transcription of the VDR promoter gene in the breast cancer cell, as measured by reporter gene activity, approximately two-fold compared to vehicle-treated norm cells. Co-treatment with the anti-estrogen tamoxifen (TAM) in T47D cells and transfection in an estrogen receptor-negative breast cancer cell line demonstrated that the effects of phytoestrogens on the VDR promoter act dependently on the estrogen receptor. Resveratrol and genistein also increased VDR protein expression as detected by Western blotting methods [53]. Using resveratrol for treatment did not affect cell number or cell cycle profile while using genistein increased cell number. Because resveratrol could up-regulate VDR without increasing breast cancer cell growth [54].

Wietzke and Welsh, hypothesized that soy genistein mediated increase in VDR expression would sensitize breast cancer cells to the effects of 1,25-dihydroxy vitamin D3 and Vitamin D3 analogs [52]. These data support the concept that dietary factors, such as phytoestrogens, may impact breast cancer cell sensitivity to Vitamin D3 analogs through regulationag of the VDR promoter [55-58].

Wietrzyk et al., concluded isoflavonoids exert a regulatory function on the expression of cytochrome P450 enzymes and also up-regulate the vitamin D3 receptor (VDR) on breast cancer cells, which increases their sensitivity to 1,25-dihydroxyvitamin D3, the hormonally active form of vitamin D3 [54].

Also, isoflavonoids can raise the active form of vitamin D3 in serum due to their inhibitory activity on CYP24, the enzyme involved in the degradation of 1,25-dihydroxy vitamin D3 and its precursor 25-OH-D (3) to inactive compounds [56, 57].

Lechner and their colleagues, mentioned extra renal synthesis of the active vitamin D metabolite 1,25-dihydroxy vitamin-D3 (1,25-D) has been seen in cells derived from human organs prone to breast cancer incidence [59]. Enhancement of the synthesizing hydroxylase CYP27B1 and reduction of the catabolic CYP24 could support the local accumulation of the antimitotic steroid, thus preventing the formation of breast tumors.

Soya derivatives such as 17 beta-estradiol and genistein induced CYP27B1 but reduced CYP24 activity. These data indicate a potential, new approach for cancer prevention by counteraction of the 1,25-D-driven negative feedback, i.e., down-regulation of CYP27B1 and up-regulation of CYP24, which prevent its local accumulation with high susceptibility of mammary cells [54, 55].

The prevention of BC depends on the optimal synthesis of the antimitotic pro-differentiating vitamin D hormonal metabolite 1,25-(OH) (2)-cholecalciferol (1,25-D3). Authors suggested that nutritional soya especially genistein can optimize vitamin D3 synthesis, which could result in growth control of breast cancer cells and, conceivably, in inhibition of the progression of tumors [60-63]. Several studies were published in Basrah city about BC, otherwise, no one dealt with soya's effect on estrogens and vitamin D [64-66].

CONCLUSION

To the best of our knowledge, this is the first time study to determine the association of vitamin D and calcium levels with isoflavone intake in hormone-positive HER2 neu negative BC (pre and postmenopausal women) treated with nti-estrogens and vitamin D, particularly in Iraq, and enerally in Eastern Mediterranean countries. Calcium shows different ranges, mostly non-significant after soflavone consumption whereas vitamin D shows significant changes.

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None

CONFLICT OF INTERESTING

None

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