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RESEARCH ARTICLE

Association of 25-hydroxyvitamin D, Cyclooxygenase-2 and Prostaglandin E2 Serum Levels in Breast Cancer Patients

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Abstract

BACKGROUND: Serum levels of 25-hydroxyvitamin D (25(OH)D), prostaglandin E2 (PGE2), and cyclooxygenase 2 (COX2) expression differ between breast cancer stages. Since, previous studies showed mixed results, in this study, we aimed to analyze vitamin D levels related to breast cancer stages and serum levels of COX2 and PGE2 in Indonesia.

METHODS: This was a cross sectional study involving 75 breast cancer patients. Subjects were divided into 3 groups, namely operable early stage (K1), locally advanced stage (K2), and advanced stage (K3). Venous blood samples were taken from each subject, then were analyzed for the 25(OH) D, COX2, and PGE2 serum levels by enzyme-linked immunosorbent assay (ELISA) method.

RESULTS: There were significant differences in 25(OH) D among groups ($p=0.012$); between K1 and K2 ($p=0.009$)

and between K1 and K3 ($p=0.023$). However, there was no significant difference in serum COX2 level ($p=0.328$). There were significant differences of PGE2 among groups ($p=0.002$); between K1 and K2 ($p=0.036$) and between K1 and K3 ($p=0.001$). Correlation test showed that there were correlation between 25(OH)D serum level and PGE2 serum level ($r=0.306$, $p=0.008$) and also inverse correlation between 25(OH)D serum level and breast cancer stage ($r=-0.229$; $p=0.048$)

CONCLUSION: There were differences in serum Vitamin D and PGE2 levels at various stages of breast cancer. Serum 25(OH)D levels had weak correlation with breast cancer stage and PGE2 serum level. Serum vitamin D level in advanced breast cancer were lower than early stage breast cancer and indicate a poor prognosis.

KEYWORDS: breast cancer, 25-hydroxyvitamin D, cyclooxygenase 2, prostaglandin E2

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Introduction

Breast cancer, malignancy of breast tissue, is originated from ductal or lobulated epithelium.(1) Breast cancer is the most frequently diagnosed cancer and the number one cause of death by cancer in women in the world and in Indonesia. Five year survival rate increases to 99% when diagnosed at early stage and most patients are tumor-free for the rest of their lives.(2,3)

Calcifediol/25-hydroxyvitamin D (25(OH)D) is the main form of vitamin D in circulation.(4) Calcitriol (1,25(OH)2D) is produced by hydroxylation of 25(OH)D in the circulation by cytochrome P450 enzyme CYP27B1 in the kidney and synthesized locally by CYP27B1 present in extrarenal tissues including cancer tissue (paracrine).(5,6) Levels of 25-hydroxyvitamin D (25(OH)D) are associated with breast cancer risk and severity. Several meta-analyses state that the risk of breast cancer in postmenopausal women decreases with increasing levels of 25(OH)D and there

is a direct association between vitamin D deficiency and breast cancer.(7,8) Low levels of vitamin D (<20 ng/mL) give poor prognosis, about 94% patients have metastases and 73% die at an advanced stage.(9,10) However, other studies on vitamin D and breast cancer show mixed results. Some studies show low levels of vitamin D in breast cancer patients.(11-14) But there's also a study that found low level of Vitamin D in more advances cases of lymph node involvement or larger tumor.(14)

Cyclooxygenase 2 (COX2), an enzyme, catalyzes the formation of phospholipase A2-released arachidonic acid (AA) into prostanoids such as prostaglandins and thromboxane.(15) Several studies show higher COX2 expression in breast cancer cells than benign breast cells.(16,17) Examination of COX2 serum levels is less invasive than COX2 expression in tissues. There have been no studies on serum COX2 levels in breast cancer patients. Prostaglandin E2 (PGE2) is derived from the metabolism of arachidonic acid by cyclooxygenase. Its levels increase in inflammation and cancer. Increased COX1 and COX2 activities cause increased PGE2 levels.(18)

Calcitriol (1,25 dihydroxyvitamin D, active form of vitamin D) interferes with the COX-2/PGE2 pathway and other pathways, inhibiting cancer cell proliferation.(5,19) Calcitriol also increases 15-hydroxyprostaglandin dehydrogenase (15-PGDH) expression, an enzyme which cleave PGE2 and have opposite effect on COX2.(5,20,21) Lower 25(OH)D levels are inversely related to tissue COX2 and 15-PGDH levels in breast cancer cells.(22)

Vitamin D levels are determined by skin synthesis from exposure to sunlight, however, a study showed that eventhough breast cancer patients in Indonesia get sunlight throughout the year, but breast cancer number remains high.(4) This shows the low association of vitamin D in most breast cancer patients in tropical countries that get sunlight all year round. Other studies assessed 25-hydroxyvitamin D levels differences based on breast cancer stage but was conducted in subtropical countries and countries with tropical and subtropical climate variations.(10,13,16,23-25) Therefore, in this study, we analyzed the differences in serum cyclooxygenase-2 of breast cancer patients, which had never been done before. The use of serum samples for COX2 in this study is less invasive than other studies that used more invasive technique to acquire tissue samples.(17,26) This study of serum prostaglandin E2 levels was different from previous studies because PGE2 levels are differentiated based on the stage of breast cancer.(16) By recognizing the importance of vitamin D in tumor development via inflammation pathway, the role of vitamin

D in treatment and/or prevention of breast cancer can be more known.

Methods

Study Design and Subject Recruitment

This was an analytic observational study with a cross-sectional approach, conducted at Dr. Kariadi Central General Hospital and Diponegoro National Hospital in Semarang. Sampling was carried out from March to November 2020 by consecutive sampling method after calculating the number of samples required. Subjects of this study were suspected breast cancer patients who came to surgical outpatient clinic of Dr. Kariadi Central General Hospital and Diponegoro National Hospital, and were scheduled a biopsy/surgery for diagnosis. Inclusion criteria were women over 25 years, normal body temperature (36.5-37.5°C), newly diagnosed breast cancer by anatomical pathology examination, normal liver function tests (AST and ALT), normal kidney function tests (urea and creatinine). Meanwhile, the exclusion criteria were history of taking non-steroidal anti-inflammatory drugs (NSAID) drugs in the last 2 days, corticosteroids in the last week, consumption of phenytoin, phenobarbital, antifungal, anti-HIV, or vitamin D supplements, and currently experiencing digestive disorders. All participated subjects have given written informed consent.

Venous blood from subjects was taken before a scheduled biopsy/surgery. Basic data were collected through history taking (history of chronic disease, parity, first gestational age, duration of breastfeeding, drug use and smoking history), physical examination (temperature, blood pressure, pulse and respiratory rate), and medical record (tumor size, lymph node involvement, and metastases). Research was conducted after obtaining ethical approval (No. 473/EC/KEP-RSDK/2020) from the Ethics Commission of Dr. Kariadi Central General Hospital.

Breast Cancer Diagnosis

Breast cancer diagnosis was conducted based on the results of anatomical pathology examination. Subjects were grouped based on their tumor characteristics according to the TNM system (including tumor size, lymph node involvement, and presence of metastasis). After knowing the TNM stage, the subjects were later grouped according to National Comprehensive Cancer Network (NCCN) staging system into operable early-stage breast cancer (K1; including TNM system stage 0, I, and II), locally advanced breast cancer (K2; including TNM system stage IIIA, IIIB,

IIIC) and advanced-stage breast cancer (K3; including TNM system stage IV).(27)

25(OH)D Serum Level Test

Five mL of venous blood was taken then serum was separated and stored at -80°C until the time of examination. Measurement of 25(OH)D serum level using competitive enzyme-linked immunoassay (ELISA) (Calbiotech, El Cajon, CA, USA) that measures 25-OH Vitamin D2 and D3. Wells coated with Anti Vitamin D antibody were incubated with standards, controls, samples, and conjugate, during which a fixed amount of biotin-labeled vitamin D competes with the endogenous Vitamin D in the sample, standard, and control serum for a fixed number of binding sites on the Anti Vitamin D antibody. The conjugate would bound immunologically to the well and decreases as the concentration of Vitamin D in the specimen increases. After washing and adding fluorescent, yellow color developed. The absorbance is measured at 450 nm spectrophotometrically. Color intensity was inversely proportional to 25-OH Vitamin D level in the sample.

COX2 Serum Level Test

COX2 serum level were measured using sandwich ELISA (Elabsience, Houston, TX, USA). An ELISA plate pre-coated with an antibody specific to Human PTGS2/COX-2 were added standards and samples and combined with specific antibody. Detection antibody specific for Human PTGS2/COX-2 and Avidin-Horseradish Peroxidase (HRP) conjugate were added next. The substrate solution is added to each well. If the wells contain Human PTGS2/COX-2, they will appear yellow. The optical density (OD) is measured spectrophotometrically at 450 nm and COX2 level was proportional to the OD value.

PGE2 Serum Level Test

Prostaglandin E2 serum level was measured using competitive ELISA principle (Elabsience). An ELISA plate was pre-coated with PGE2. PGE2 in the sample or standard competes with a fixed amount of PGE2 on the solid phase to bind with Detection antibody specific to PGE2. After washing and adding conjugate, fluorescent was added and the color turns to yellow. The OD is measured spectrophotometrically at 450 nm and PGE2 level inversely related to the OD value.

Statistical Analysis

Data were analyzed by Statistical Package for the Social Sciences (SPSS) 23 (IBM Corporation, Armonk, NY, USA).

Kruskal Wallis test was used to analyze 25(OH)D, COX2, and PGE2 serum levels, then followed by Mann Whitney post-hoc test. Spearman rank test was used to analyze the correlation between 25(OH)D and COX2, 25(OH)D and PGE2, COX2 and PGE2, and 25(OH)D and breast cancer stages in this study. The p -value < 0.05 was considered as significant with 95% confidence interval.

Results

Total 75 subjects were participated in this study. The subjects were divided into 3 different groups based on the NCCN staging system, each group consist of 25 subjects. The mean age of subjects was 51.3 ± 9.1 years old (50.8 ± 9.3 years old for K1, 51.6 ± 9.9 years old for K2, and 51.4 ± 8.6 years old for K3). A total of 74 research subjects (98.9%) had history of pregnancy and breast-feeding, 47 subjects (62.7%) already have had menopause, while 70 subjects (93.3%) had history of taking hormonal contraception. The mean value of body mass index (BMI) of research subjects was 25.23 ± 3.93 kg/m^2 (BMI of K1, K2, and K3 were 25.95 ± 3.12 kg/m^2 , 25.01 ± 4.68 kg/m^2 , and 24.74 ± 3.88 kg/m^2 , respectively). The general characteristics of the research subjects was shown in Table 1.

The risk factors for breast cancer in research subjects were menopause (62.7%) and history of using hormonal contraception (93.3%). As many as 40% of the study subjects were deficient in vitamin D. Only 30.7% of the subjects had sufficient 25(OH)D serum levels. Most of the subjects in K2 and K3 had vitamin D deficiency (56% and 44%, respectively). The highest rate of vitamin D deficiency among groups was in K2 (56%), the highest rate of vitamin D insufficiency was at K3 (29.3%), and the highest rate of vitamin D sufficiency was at K1 (52%).

Analysis of differences among groups in serum 25(OH)D levels in patients with breast cancer using the Kruskal-Wallis test found a significant difference with $p=0.012$ (Table 2). Data analysis on serum PGE2 levels of K1, K2, and K3 using the Kruskal-Wallis test showed there was a significant difference ($p=0.002$). Then the analysis of serum 25(OH)D and PGE2 levels was followed by the Mann-Whitney post-hoc test (Table 3). Lower levels of serum 25(OH)D and PGE2 were found in breast cancer patients with more advanced stage.

Analysis of correlation between parameters in serum using Spearman rank test found correlation between serum 25(OH)D and PGE2 level with $r=0.306$, $p=0.008$ and between serum 25(OH)D and breast cancer group with $r=-$

Table 1. General characteristics of research subjects.

Characteristics	Value			Total (n=75)	p-value
	K1 (n=25)	K2 (n=25)	K3 (n=25)		
Age (years), mean±SD	50.8±9.3	51.6±9.9	51.4±8.6	51.3±9.1	0.954 [#]
History of pregnancy, n (%)	25 (100%)	24 (96%)	25 (100%)	74 (98.7%)	0.440 [§]
Menarche history, n (%)					0.634 [§]
<12 years old	2 (8%)	4 (16%)	4 (16%)	10 (13.3%)	
≥ 12 years old	23 (92%)	21 (84%)	21 (84%)	65 (86.7%)	
Breastfeeding history, n (%)	25 (100%)	24 (96%)	25 (100%)	74 (98.7%)	0.440 [§]
Menopause Status, n (%)	14 (56%)	17 (68%)	16 (64%)	47 (62.7%)	0.671 [†]
History of hormonal contraceptives usage, n (%)	23 (92%)	23 (92%)	24 (96%)	70 (93.3%)	0.106 [†]
< 5 years	9 (39.1%)	3 (13.0%)	5 (20.8%)	17 (24.3%)	
≥ 5 years	14 (60.9%)	20 (87%)	19 (79.2%)	53 (70.7%)	
Any cancer history, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1.000 [§]
BMI (kg/m ²), mean±SD	25.95±3.12	25.01±4.68	24.74±3.88	25.23±3.9	0.523 [#]
Vitamin D level status, n (%)					
Deficient (<20 ng/mL)	5 (20%)	14 (56%)	11 (44%)	30 (40%)	0.019* [†]
Insufficient (21-29 ng/mL)	7 (28%)	5 (20%)	10 (40%)	22 (29.3%)	
Sufficient (≥30 ng/mL)	13 (52%)	6 (24%)	4 (16%)	23 (30.7%)	

K1: operable early stage; K2: locally advanced stage; K3: advanced stage; BMI: body mass index. [#]Tested with one way ANOVA; [§]Tested with Kruskal-Wallis test; [†]Tested with Chi-Square test; **p*<0.05 was significant.

0.229; *p*=0.048 (Table 4). No correlation between serum 25(OH)D and COX2 level (*p*=0.951) and between serum COX2 and PGE2 level (*p*=0.600).

Discussion

Several meta-analyses have shown association of low 25(OH)D serum levels with a higher incidence of breast cancer.(8,28,29) A normal serum 25(OH)D level is above 30 ng/mL and is considered sufficient. The median of 25(OH)D serum level in this study was 22 ng/mL. This was lower than another study in postmenopausal women in Brazil (median 25.8 ng/mL).(23) Serum 25(OH)D levels of 27-35 ng/mL have a 12% protective effect against breast cancer, but no additional protective effect was found for serum 25(OH)D levels above 35 ng/mL.(28)

Most of breast cancer patients in this study had vitamin D deficiency (40% deficient and 29.3% insufficient). This was consistent with previous study which reported that 66.2% of patients with newly diagnosed breast cancer had vitamin D deficiency. They find that 47.9% of research subjects were insufficient and 18.2% were deficient of vitamin D.(23) Other studies in different countries also mostly show that breast cancer patients have low average of vitamin D.(11,13,14)

Several things can affect 25-hydroxyvitamin D levels. (4) The results of general data analysis showed that there was no difference in the characteristics of age (*p*=0.954) and BMI (*p*=0.523) between groups. All study subjects were not taking any known vitamin D supplements and had no renal impairment. Most of study subjects also had minimal sun exposure due to the covered clothes, heat, and air pollution. Low consumption of vitamin D supplements, and

Table 2. Serum levels of 25-hydroxyvitamin D, cyclooxygenase-2 and prostaglandin E2 in breast cancer patients of various stages.

Variable	Median (min-max)			p-value
	K1 (n=25)	K2 (n=25)	K3 (n=25)	
25(OH)D (ng/mL)	30 (13-65)	18 (5-40)	21 (7-34)	0.012*
COX2 (ng/mL)	0.83 (0.22-6.76)	0.98 (0.39-4.53)	1.06 (0.04-4.12)	0.328
PGE2 (pg/mL)	2,244 (798-13,812)	1,268 (629-9,895)	1,070 (529-4,112)	0.002*

K1: operable early stage; K2: locally advanced stage; K3: advanced stage; 25(OH)D: 25-hydroxyvitamin D; COX2: cyclooxygenase-2; PGE2: prostaglandin E2. Tested with Kruskal-Wallis test, **p*< 0.05 was significant.

Table 3. Post-hoc test of 25(OH)D and PGE2 serum levels in breast cancer patients of various stages.

Group	25(OH)D (ng/mL)		PGE2 (pg/mL)	
	Median (min-max)	p-value	Median (min-max)	p-value
K1	30 (13-65)	0.009* [†]	2244 (798-12812)	0,036* [†]
K2	18 (5-40)		1268 (629-9895)	
K1	30 (13-65)	0.023* [†]	2244 (798-12812)	0.001* [†]
K3	21 (7-34)		1070 (529-4112)	
K2	18 (5-40)	0.210 [†]	1268 (629-9895)	0.118 [†]
K3	21 (7-34)		1070 (529-4112)	

K1: operable early stage; K2: locally advanced stage; K3: advanced stage; 25(OH)D: 25-hydroxyvitamin D; COX2: cyclooxygenase-2; PGE2: prostaglandin E2; [†]Tested with Mann-Whitney post-hoc test, * $p < 0.05$ was significant.

darker skin pigment can affect serum vitamin D levels. (13,28)

Serum 25(OH)D levels on K1, K2, and K3 in this study were significantly different with $p=0.012$. Serum 25(OH)D levels of K1 were higher than K2 and K3. This was in accordance with the study conducted in postmenopausal women that lower levels of 25(OH)D are associated with more advanced breast cancer stage.(23) Another study showed that low vitamin D levels (<32 ng/mL) were found in most cases with more advanced stages, more lymph node involvement and larger tumors.(11) Locally advanced and metastatic breast cancer patients had low levels of 25(OH)D.(12)

BMI affects serum 25(OH)D levels because thicker fat tissue interferes with sunlight absorption (the precursor of 25(OH)D), degradation, and distribution of vitamin D. BMI in K2 was higher than K3, although the difference is not significant, thus can affect the serum 25(OH)D level of K2 to be lower than K3. However, 25(OH)D levels of K2 and K3 were not significantly different ($p=0.210$). It is known that one of the hormonal effects of calcitriol in breast tissue is by reducing aromatase expression through repression of aromatase promoter II and indirectly through decreased

production of PGE2 (aromatase stimulator).(30) Several studies have also shown differences in 25(OH)D levels based on the type of tumor receptor.(13,23,24)

The results of this study suggest lower serum vitamin D (25(OH)D) levels are found in more advanced tumors (K2 and K3) than early stage tumor (K1). Correlation analysis between serum 25(OH) level and stage showed a weak correlation ($r=0.229$, $p=0.048$). Low levels of vitamin D (<20 ng/mL) give a poor prognosis, about 94% have metastases and 73% die of advanced stages.(9) Measurement of serum 25(OH)D levels taken one time at breast cancer diagnosis may not reflect serum 25(OH)D levels at the onset of cancer cells or when cancer cells become more aggressive. Even though the subjects of this study had just been diagnosed with breast cancer, it could be that the cancer had been there for a long time but was not examined. This is due to the absence of national breast cancer screening and the lack of awareness about breast cancer. Early detection of breast cancer can be done through the breast self-examination.

COX2 is usually absent in normal tissues. However, aberrant expression of COX2 is found in breast cancer.(31) COX2 products such as PGE2 and cytokines (interleukin (IL)-6 and tumor necrosis factor (TNF)- α) can increase aromatase transcription and causes tumors to enlarge in estrogen receptor positive cancer type.(16) Therefore, it is expected that with the differences in serum 25(OH)D levels in this study, there will be differences in serum COX2 levels. However, this study showed that median of K1 was lower than K2 and K3, serum COX2 levels of K1, K2, and K3 were not significantly different ($p=0.328$). The serum COX2 results in this study can be influenced by the type of breast cancer receptor. COX2 expression in tumor was highest in triple negative breast cancer (TNBC) patients. (31) Activation of the HER2 oncogene increased COX2 expression in breast cancer tissue.(32) COX2 is said to

Table 4. Correlation of 25(OH)D, COX2, PGE2 serum levels in breast cancer patients.

Parameters		r	p-value
25(OH)D	COX2	0.007	0.951 [†]
25(OH)D	PGE2	0.306	0.008* [†]
COX2	PGE2	-0.061	0.600 [†]
25(OH)D	Breast cancer group	-0.229	0.048* [†]

25(OH)D: 25-hydroxyvitamin D; COX2: cyclooxygenase-2; PGE2: prostaglandin E2. [†]Tested with Spearman rank test, * $p < 0.05$ was significant.

have a connection with aromatase so that it plays a role in hormone receptor positive breast cancer.(33,34)

Increased PGE2 levels associated with increased expression of COX2.(18) In this study, there were differences in PGE2 levels between K1, K2, and K3 with $p=0.002$. Serum PGE2 levels of patients with K1 were higher than K2 and K3 ($p=0.001$ and $p=0.036$). However, the serum PGE2 levels of K2 and K3 were not significantly different ($p=0.118$). Correlation analysis between 25(OH)D and PGE2 serum levels showed weak correlation ($r=0.306$, $p=0.008$). The results of this study are different from previous study which reported serum 25(OH)D levels were negatively correlated with serum PGE2 levels.(16) A high serum 25(OH)D level should be followed by a low serum PGE2 level.(19-21) Correlation analysis between COX2 and PGE2 serum levels showed no correlation ($p=0.600$). It may be caused by different COX2 pathway from binding of arachidonic acid (AA) to PGE2 formation and PGE2 degradation in cancer cell with different receptors.(31) The highest PGE2 was found in the microenvironment of TNBC.(31)

Factors affecting COX2 and PGE2 such as fever, consumption of NSAIDs or corticosteroids at the time of sampling have been excluded through questionnaires, interviews, and confirmed in patient's medical record. However, it is still possible that the research subjects did not report consumption of over-the-counter drug. Hence, it is necessary to conduct more in-depth interviews regarding the subject's medical history which may affect the low levels of serum PGE2 in K3 and K2.

Conclusion

This research suggested that low level of vitamin D, measured by 25(OH)D serum level, associated with more advanced stage. Serum 25(OH)D levels had weak correlation with breast cancer stage and PGE2 serum level. Further studies are needed to assess inflammatory pathways influenced by vitamin D (COX2 and PGE2) with respect to tumor receptor type.

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Authors Contribution

BR and DR were involved in supervising the research, analyzing data, compiling the manuscript. TI was involved in research planning, measurements, data analysis and compiling the manuscript. All authors discussed the results, commented and approved final manuscript. None of the authors have conflict of interest.

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