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The Relationship of Vitamin D Serum Levels with The Lowering of The Left Ventricular Systolic Function in Women with Locally Advanced Breast Cancer Undergoing Doxorubicin Chemotherapy

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ABSTRACT

Chemotherapy with doxorubicin in breast cancer patients can cause cardiotoxicity and increase mortality by up to 50%. Vitamin D can cause indirect effects on decreasing heart function. This study examined the relationship of serum blood vitamin D levels with decreased left ventricular systolic function in women with locally advanced breast cancer (LBAC) undergoing doxorubicin chemotherapy. This was an analytical observational study with cross-sectional design. Data collection for vitamin D and echocardiography was performed on patients undergoing chemotherapy for one year. The data were then tested using the contingency coefficient test and regression test. This study found vitamin D deficiency in 17 persons (56.7%). On echocardiography examination, the mean left ventricular ejection fraction (LVEF) was obtained before administering neoadjuvant chemotherapy by 65.0±3, and the average LVEF after administration of neoadjuvant chemotherapy was 61.80±6.283. A total of 18 patients (60%) experienced decreased left ventricular systolic function. There was a significant relationship between vitamin D levels and decreased left ventricular systolic function (p = 0.007). There was a statistically significant relationship between vitamin D levels and decreased systolic function in women with LBAC undergoing neoadjuvant chemotherapy. The higher serum vitamin D level, the lower the decrease in left ventricular systolic function after undergoing Doxorubicin chemotherapy.

Keywords: locally advanced breast cancer, vitamin D, left ventricle ejection fraction (LVEF), doxorubicin.

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INTRODUCTION

Breast cancer most commonly affects women, although men also have the potential to be affected but the chances are very small with a ratio of 1 in 1000 (1). The incidence of breast cancer is 42.1 per 100,000 population, with an average death rate of 17 per 100,000 population in Indonesia. A total of 207 new patients with breast cancer found in Dr. Soetomo Surabaya in 1 year in 2009. More than 70% of patients who came were already in stage III and IV where around 30% aged over 55 years (2). Some risk factors for breast cancer include the use of hormonal contraceptives, such as oral contraceptives and the age of menarche (3–5).

Neoadjuvant therapy for cancer is an anticancer treatment provided before the primary treatment. The main therapy is surgery; thus, it is induction therapy. The first benefit of neoadjuvant is its ability to make tumors that cannot be operated on can be operated on or to reduce the size of advanced breast cancer. The antitumor activity of both standard therapies, thus promising to enhance personalized cancer treatment and accelerate the successful clinical development of targeted compounds (6). Although, there were affective psychopathological comorbidities affecting the quality of life of patients undergoing radiotherapy (7).

Cardiotoxicity is a major problem often occurring in the administration of doxorubicin chemotherapy (8). Doxorubicin can cause kidney damage and nephropathy causing proteinuria which can cause massive loss through urine vitamin levels from 25-OH vitamin D and 1,25-OH vitamin D. Decreased vitamin D due to doxorubicin can cause indirect effects to decrease heart function (9). Left Ventricular Dysfunction (LVD) and cause a decrease in left ventricle ejection fraction (LVEF) and lead to heart failure. The occurrence of cardiotoxicity due to doxorubicin occurring into congestive heart failure will increase mortality by up to 50%. The incidence of cardiotoxicity related to doxorubicin was reported in 9% of 2625 patients. Previous studies mention the incidence of acute cardiotoxicity due to anthracycline

chemotherapy is 14%, while the incidence of cardiotoxicity after one year of administration reaches 70%. The magnitude of this incident causes the need for increased vigilance against cardiotoxicity due to chemotherapy (10). This study aimed to analyze the relationship of serum blood vitamin D levels with decreased left ventricular systolic function in women with locally advanced breast cancer (LBAC) undergoing Doxorubicin chemotherapy at Dr. Soetomo Hospital, Surabaya.

METHODS

This was a study using a correlation test with an observational analytic study design with a cross-sectional study design by examining the relationship of serum vitamin D levels with decreased systolic function in women with LBAC undergoing neoadjuvant chemotherapy at Dr. Soetomo Hospital, Surabaya, Indonesia. The study population was female patients with LBAC undergoing one-year post neoadjuvant chemotherapy at Dr. Soetomo Hospital, Surabaya, in 2019. This study was conducted with a total of 30 research subjects. Exclusion criteria from the sample were patients with impaired kidney and liver function, patients with residual breast cancer, and patients with heart failure (EF <50). Data were tested using the contingency coefficient, while the regression test with SPSS 16.0.

RESULTS

Table 1 shows the characteristics of the study subjects. In this study, there were 30 research subjects, all of whom were female patients with an average age of 48.03±10.381 years. Doxorubicin's mean cumulative dose in this study was 298,7559±23.93, with a minimum value of 240.64 and a maximum value of 351.56. In this study, the average body surface area (BSA) of 1.5533±0.14399 was obtained with a minimum value of 1.28 and a maximum value of 1.87. To determine cardiotoxicity status, echocardiography was performed in patients to assess LVEF obtained mean before giving neoadjuvant chemotherapy at 65.0±3,582 and after giving neoadjuvant chemotherapy at 61.80 ± 6.283 with a minimum value of 40 and a maximum value of vitamin D 19.5987±6.48986.

Table 1: Characteristics of subjects

Categories	Mean	Minimum	Maximum
Age (years)	48.03±10.381	30	74
<35 years, n (%)	3 (10)		
>35 years, n (%)	27 (90)		
Cumulative dose of Doxorubicin	298.7559±23.93	240.64	351.56
BSA	1.5533±0.14399	1.28	1.87
LVEF pre chemotherapy	65.0±3.582	56	71
LVEF post chemotherapy	61.80±6.283	40	69
Serum Vitamin D levels	19.5987±6.48986	7.78	33.21

BSA: Body Surface Area; LVEF: Left Ventricular Ejection Fraction

Table 2 shows the cross-tabulation of age, time, and vitamin D category with the incidence of cardiotoxicity. In the age group >35 years, we obtained 15 persons with a decrease in LVEF. In the post-chemotherapy group for more than 13 months, 10 persons with LVEF decreased, and 1 without LVEF decreased. Of the subjects with vitamin D deficiency, 14 were obtained with a decrease in LVEF and 3 people without a decrease in LVEF. From the insufficiency group, there were 4 people with a decrease in LVEF and 7 people without a decrease in LVEF. In this study, 18 (60%) experienced decreased left ventricular systolic function after neoadjuvant chemotherapy.

Table 2: Cross-Tabulation of Age, Time and Vitamin D Category with Cardiotoxicity

Variables	Decreased LVEF	
	Yes	No
Sex		
Female	18 (60%)	12 (40%)
Age (year)	30-74*	
<35	3	0
>35	15	12
Post-Chemotherapy Period (month)	12-16*	
12-13	8	11
>13	10	1
Vitamin D Category	7.78-33.21*	
Deficiency	14	3
Insufficiency	4	7
Normal	0	2
Total	18	12

*Mininmun-maximum

Table 3 shows the results of the post-chemotherapy diagnosis after the administration of chemotherapy. From the results of echocardiography found 2 persons (6.7%) experienced left ventricular (LV) concentric remodeling, 18 persons (60%) had LV systolic dysfunction, 1 person (3.3%) LV diastolic dysfunction and pericardial effusion, 1 person (3.3%) experienced mild mitral regurgitation, 1 person (3.3%) had valvular heart disease, and 7 people (23.3%) had normal echocardiography.

Table 3: Post-Chemotherapy Diagnosis

Post-Chemotherapy Diagnosis	n	Percentage (%)
LV concentric remodeling	2	6.7%
LV sistolic dysfunction	18	60%
LV diastolic dysfunction dan pericardial effusion	1	3.3%
Mild mitral regurgitation	1	3.3%
Valvular heart disease	1	3.3%
Normal	7	23.3%

The data obtained showed in Table 4 that there was a statistically significant correlation between post-chemotherapy period (95% CI; p = 0.009) and vitamin D levels (95% CI; p = 0.002) with decreased left ventricular systolic function in women with LBAC undergoing neoadjuvant chemotherapy.

Table 4: Correlation test results

Categories	Decreased in left ventricular systolic function		*p*
	Yes (n=18)	No (n=12)	
Sex			
Female	18 (60%)	12 (40%)	
Age (years)			
<35 years	3 (10%)	0 (0%)	
>35 years	15 (50%)	12 (40%)	
Post-chemotherapy period (years)			0.009
<12	6 (20%)	6 (20%)	
13-15	12 (40%)	6 (20%)	
Vitamin D			0.002
Normal	0 (0%)	2 (6.67%)	
Insufficiency	4 (13.33%)	7 (23.33%)	
Deficiency	14 (46.67%)	3 (10 %)	

DISCUSSION

This study showed the results that there was a significant relationship between vitamin D levels with decreased left ventricular systolic function in women with LABC undergoing doxorubicin chemotherapy. The higher serum vitamin D level, the lower the decrease in left ventricular systolic function after undergoing doxorubicin chemotherapy.

This study found subjects with an average age of 48.03±10.381 years. This is not much different from previous studies reporting the average age of breast cancer patients 49 years (11,12). Characteristics of research subjects based on BSA obtained an average result of 1.5533±0.14399. The coefficient of variation in body surface area statistics of less than 10% illustrates that the study subjects had anthropometric tendencies almost the same with each other/not varied and had an impact on the administration of chemotherapy drugs which tend to be the same between research subjects. The average cumulative dose of doxorubicin in this study was 298.7559±23.93. This is in line with previous study which stating that as many as 27% of patients experienced a decrease in the left ventricular ejection fraction >10% with a cumulative dosage range of doxorubicin 300-450 mg/m^2 (13). This study found that there was no significant correlation between the cumulative dose of doxorubicin with decreased left ventricular systolic function in women with LBAC undergoing neoadjuvant chemotherapy. In this study, the majority of subjects experienced decreased left ventricular systolic function after administration of doxorubicin chemotherapy. This is consistent with a prospective study conducted in 2011 that decreased systolic and diastolic function of the heart occurred immediately after the start of chemotherapy. (14). This study showed a statistically significant correlation between post chemotherapy time levels and decreased systolic function in women with LBAC undergoing neoadjuvant chemotherapy. Another study supporting this showed early-onset chronic cardiotoxicity, such as cardiomyopathy, developing into congestive heart failure (CHF) generally appearing within one year after administration of doxorubicin therapy (15).

Vitamin D is made in the skin from sun exposure. UV-B rays from the sun hitting the skin and humans synthesize vitamin D3 are the most natural form. Humans do not make vitamin D2, and most oil-rich fish such as salmon, mackerel, and herring contain vitamin D3 (16). Digested vitamin D is introduced into the body in the form of chylomicrons absorbed into the lymphatic system and enter venous blood. Normal levels of vitamin D in human blood serum are above 75 nmol/L (30 ng/L) (16,17). Vitamin D plays an important role in various functions of the body's metabolism. In addition, it is associated with increased morbidity and mortality. Women who live in a tropical country can have vitamin D deficiency if they have sun-avoiding lifestyles, work indoors, and have a low dietary intake of vitamin D (18). Vitamin D deficiency has a relationship with the pathogenesis of cardiovascular disease. Vitamin D supplements can play a role in reducing the morbidity and mortality of cardiovascular disease. Patients with cardiovascular disease have lower vitamin D levels and vitamin D deficiency has a significant correlation with heart function (17).

The results of examination of vitamin D levels in the blood are in units of ng/mL. The levels will be divided into four categories as follows: deficiency with levels below 20 ng/mL, insufficiency with a range of 21-29 ng/mL, normal with a range of 30-54 ng/mL, and high with levels above 55 ng/mL (19,20). Low vitamin D levels play a role in the pathogenesis of congestive heart failure. Heart muscle cells have vitamin D receptors and Ca^{2+} binding proteins dependent on calcitriol. 1,25 (OH) 2-vitamin D3 stimulates Ca^{2+} channels dependent on type L stresses in heart muscle cells through stimulation of protein-mediated guanine nucleotide-binding from adenylate cyclase/cAMP/protein kinase messenger systems. Vitamin D may affect heart function, and vitamin D deficiency can play a role in the pathogenesis of DCMP (21).

Vitamin D has been hypothesized to play an essential role in reducing LV hypertrophy and functions partly through modulation of the renin-angiotensin system (RAS), which plays a crucial role in regulating the volume and blood pressure of homeostasis. Vitamin D functions as an endocrine suppressor of biosynthesis of renin, and subsequent genetic disorders from vitamin D receptors (VDR) can cause over-stimulation of RAS, causing high blood pressure and cardiac hypertrophy. Vitamin D deficiency induces myocardial hypertrophy and production and deposition of extracellular matrix in rat myocardial tissue. Mediated by matrix metalloproteinase, extracellular matrix remodeling can be involved in progressive LV remodeling, dilatation, and heart failure. In a healthy Indo-Asian population, plasma metalloproteinase levels are inversely proportional to vitamin D status. Furthermore, after one year of treatment with vitamin D, the average plasma metalloproteinase level significantly decreases. Vitamin D receptors have been detected in the heart muscle, and the specific depletion of cardiomyocytes from these receptors in knock-out mice is associated with hypertrophy of heart cells. In studies of animals, vitamin D can suppress the expression of renin and can reduce blood pressure. Vitamin D deficiency can, therefore, increase blood pressure and trigger hypertrophy of the heart muscle (22).

Further research is needed by examining vitamin D pre-chemotherapy and post-chemotherapy with a more significant number of samples and supplemental supplementation of vitamin D in locally advanced breast cancer patients who will

undergo doxorubicin chemotherapy and periodic monitoring of left ventricular function using echocardiography.

CONCLUSION

There was a significant relationship between vitamin D levels and decreased left ventricular systolic function in women with LABC who underwent doxorubicin chemotherapy. The higher serum vitamin D level, the lower the decrease in left ventricular systolic function after undergoing doxorubicin chemotherapy.

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