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Relationship between Serum Dehydroepiandrosterone Levels and Heart Ejection Fraction in Heart Failure Patients

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ABSTRACT

Cardiovascular disease is still a serious problem in the world of health. Life expectancy after being diagnosed with heart failure is 50% and 10% for 5 and 10 years. Steroid hormones such as Dehydroepiandrosterone (DHEAS) have cardioprotective effects by inhibiting the formation of atherosclerotic plaque, pulmonary artery vasodilators, and protecting cardiomyocytes. DHEAS levels decrease with age. Decreased DHEAS levels are associated with an increased risk of cardiovascular disease. This study aimed to know the relationship between DHEAS levels in serum and ejection fractions in heart failure patients. This cross-sectional study used a sample of 34 people aged > 30 years who had been diagnosed with heart failure by a specialist in the Department of Cardiology and Vascular Medicine. The diagnosis of heart failure uses Echocardiography to determine the ejection heart fraction. DHEAS levels were taken from venous blood and examined using the CLEIA method with an IMMULITE device (Siemens Healthineers, Germany). Statistical analysis was performed by Spearman correlation test, with a significance level of $p < 0.05$. Thirty-four research subjects found that 13 patients had an ejection fraction of 40% (Heart Failure with Reduced Ejection Fraction/HFrEF), 12 patients had an ejection fraction of 41-49% (borderline) and 9 patients had an ejection fraction of $\geq 50\%$ (Heart Failure with Preserved Ejection Fraction/HFpEF). Spearman correlation test results obtained a correlation coefficient or $r=0.357$ with a value of $p=0.038$, which meant there was a significant relationship between DHEAS with ejection fraction ($p < 0.05$). The lower the DHEAS level, the ejection fraction would also be lower. Further with age, DHEAS levels get lower. The lower the DHEAS level, the lower the ejection fraction.

Keyword: Dehydroepiandrosterone, DHEAS, ejection fraction, heart failure

INTRODUCTION

Cardiovascular disease is still a serious problem in the world of health and is a frequent cause of death in developing countries. The World Health Organization (WHO) in 2017 estimates that total deaths due to cardiovascular disease have increased to 17.7 million or 31% of global causes of death.¹ Riskesdas in 2013 stated that heart failure ranks number eighth of many non-communicable chronic diseases in Indonesia with a prevalence of 0.13% based on diagnosed by a doctor and 0.3% based on a doctor's diagnosis and symptoms.²

Dehydroepiandrosterone the most abundant steroid hormone made in the adrenal cortex. The most circulating DHEA in circulation is in the form of sulfate (DHEAS). DHEAS levels decrease with increasing age in both males and females. Steroid hormones such as DHEAS have cardioprotective effects by inhibiting the formation of atherosclerotic plaque, pulmonary artery vasodilators, and

protecting cardiomyocytes. Low DHEAS level has been associated with increased risk for coronary heart disease and death in older adults. A low level of DHEAS is also associated with greater prevalence and incidence of a cardiometabolic risk factor such as high blood pressure, insulin resistance, and impaired fasting glucose level. Decreased DHEAS levels are associated with an increased risk of cardiovascular disease, morbidity due to cardiovascular disease, coronary heart disease, and atherosclerosis.^{3,4,5}

One of the diagnostic test instruments to diagnose heart failure is Echocardiography that can be used to determine the ejection fraction. This examination can be used to determine the severity of heart failure that will be related to the patient's morbidity and mortality. Implementation of Echocardiography requires experts and examination time is not short so that other investigations needed from the laboratory side are expected to help determine the severity of heart failure quickly. The relationship between DHEAS levels and heart

ejection fraction in patients with heart failure has never been studied in Indonesia, especially in East Java, so based on these considerations, the researchers wanted to know the relationship between DHEAS levels in serum and ejection fractions in heart failure patients at the Dr. Soetomo Hospital, Surabaya in the hope of checking DHEAS levels can help diagnose heart failure.

METHODS

This research was conducted from July-December 2019 using a cross-sectional design. This study used 34 samples. The samples were taken by consecutive sampling and the sample size in this study was calculated based on the sample size formula for the correlation coefficient in a single sample. Based on the above calculations, the minimum sample size required was 30 samples. All study subjects were > 30 years old and had been diagnosed with heart failure by a Cardiologist based on Echocardiography examination divided into three criteria: fraction ejection > 50% (Heart Failure with Preserved Ejection Fraction/HFpEF); 41-49% (borderline); 40% (Heart Failure with Reduced Ejection Fraction/HFrEF). All Echocardiography examinations were performed in the Integrated Cardiology Center of the Dr. Soetomo Hospital, Surabaya and all DHEAS examinations were done at the Clinical Pathology Laboratory, Dr. Soetomo Hospital. DHEAS examination used the IMMULITE instrument (Siemens Healthineers, Germany) with the Chemiluminescence Enzyme Immunoassay (CLEIA) method. Reference values for DHEAS in the Clinical Pathology Laboratory Dr.

Soetomo Hospital were 35-430 µg/dL for females and 80-560 µg/dL for males. This study used 3 mL of serum. All samples were taken during the Clinical Chemistry examination. Before being examined, the samples were stored in a refrigerator at -80°C until ready to be examined. Samples were rejected when lysed, frozen and lipemic. All samples were taken at a random time. All patients who enrolled in the study had to be over 30 years of age, diagnosed with heart failure by a Cardiologist, and willing to attend the study. This study has received approval from the Ethics Committee of Dr. Soetomo Hospital, Surabaya with number 1593/KEPK/X/2019.

Data normality test was done using the Kolmogorov-Smirnov test. Data normally distributed were expressed as mean values, while data not normally distributed were expressed as median values. The relationship between decreased serum DHEAS levels and heart ejection fraction was analyzed by conducting the Spearman correlation test if the distribution was not normal and the Pearson test if the distribution was normal. The distribution was declared normal if the p-value < 0.05.

RESULTS AND DISCUSSION

The research subjects consisted of 34 patients divided into 21 patients or 61.8% males and 13 people or 38.2% females. The mean age and Standard Deviations (SD) were 58.06 years and 9.075 years. Echocardiography examinations were carried out by the same two heart and blood vessels during the study period.

The highest DHEAS level in this study was 442 µg/dL and the lowest level was 15 µg/dL. The mean DHEAS level SD was 71.9478,336 µg/dL, with a median of 55.5. The highest ejection fraction value in this study was 65% and the lowest value was 15%. The mean value of ejection fraction (SD is 42.5911,724 with a median of 44.5).

Spearman correlation test results obtained a correlation coefficient (r) of 0.357 with a value of p=0.038, which meant there was a significant relationship between DHEAS with ejection fraction (p < 0.05). These results indicated the correlation of the lower the DHEAS level in the serum, the lower the heart ejection fraction. These results can be seen in Figure 1.

Table 1. Research sample characteristics

	n	%
Age (year)	34	
Average±SD	58.06±9.075	
Gender		
Males	21	61.8
Females	13	38.2
Echocardiography examination results		
≤ 40% (HFrEF)	13	38.2
41-49% (borderline)	12	35.3
> 50% (HFpEF)	9	26.5

Table 2. Mean value SD and median DHEAS levels and ejection fraction

	n	Mean±SD	Median (min-max)
DHEAS (µg/dL)	34	71.94±78,336	55.5 (15-442)
Ejection fraction (%)	34	42.59±11,724	44.50 (10-65)

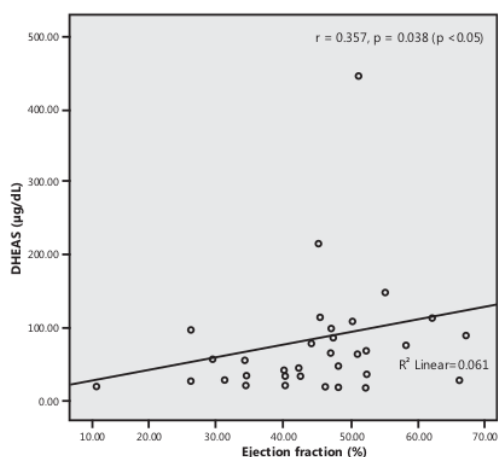


Figure 1. Correlation between DHEAS and ejection fraction

The results of the Spearman trial for DHEAS levels and age obtained a p-value of < 0.001, which meant it was associated with age and DHEAS levels ($p < 0.05$). The relationship between age and DHEAS had a negative direction with the coefficient of freedom or $r = -0.602$. The older the person was the lower the DHEAS levels in serum.

The results of this study were the same as previous studies conducted by Mancini in 50 patients aged 42–88 years old with a diagnosis of heart failure. Thirty patients with HFpEF and 20 patients with HFrEF. This study stated that DHEAS levels and age had the opposite, which meant the higher the age, the DHEAS levels will be the lower. Decreased DHEAS levels in plasma were associated with the severity of heart failure and increased oxidative levels may be related to decreased DHEAS levels in heart failure.⁷

DHEAS not only circulating at the highest concentration in blood but also displaying the most extensive decrease upon aging. There is a significant inverse association between DHEAS and cardiovascular risk, morbidity, and mortality. DHEAS reduction levels correlate with several types of age-related dysfunction including cardiovascular disease.⁸

Yeap study in 2020 amongst 4,107 males with mean baseline age 63.2 years, 873 new cases of hospitalizations or death due to heart failure. Lower DHEAS and free testosterone levels are associated with a higher incidence of heart failure in post-menopausal females and males. Older heart failure patients usually fell into the higher NYHA classification, which meant they had worse left ventricular systolic function. There are potential

effects of free testosterone and DHEAS on atherogenesis, blood pressure, and cardiac myocytes, all capable of modulating heart failure risk.⁹

DHEAS levels can be affected by chronic diseases and certain conditions. Patients with heart failure who have comorbidities in the form of diabetes mellitus or obesity are proven to have lower DHEAS levels because the condition of hyperglycemia inhibits the production of DHEAS.¹⁰ Pregnancy and oral contraception trigger a decrease in serum DHEAS levels.¹¹

Heart failure is initiated by various myocardial injuries such as myocardial infarction, myocarditis, or chronic myocardial dysfunction due to familial and metabolic cardiomyopathy, and due to chronic volume pressure due to valvulopathy, intracardiac shunt or systemic hypertension. This situation can cause cardiac fatigue due to compensatory mechanisms in the heart and peripheral circulation to maintain cardiac output. Patients with heart failure show a decreased ejection fraction on Echocardiography. Dehydroepiandrosterone is a hormone, which function is to protect the heart. Reduced levels of DHEAS in the blood will cause reduced cardiac protective hormone, which causing cardiomyocytes to be damaged more easily, facilitates platelet aggregation in the endothelium so that the risk of atherosclerosis increases, facilitates vasoconstriction of blood vessels so that the risk of systemic hypertension will increase.^{12,13}

DHEAS has not been stated to be used as an alternative laboratory examination to help diagnose heart failure. At present N-terminal B-type Natriuretic Peptide (NT-proBNP) is still considered a gold standard marker for heart failure. B-type Natriuretic Peptide (BNP) is secreted by the atria and ventricles of the heart in response to an increase in pressure on the heart wall. Normal natriuretic peptide levels in suspected heart failure patients who have not received therapy will exclude heart failure, so no Echocardiography is needed.¹⁴

The correlation value in this study is low so DHEAS has not been declared to be used as an alternative laboratory examination to assess the severity of heart failure. Low correlation values can occur because samples are not taken at the same time and researchers do not exclude the presence of chronic diseases such as hypertension or diabetes mellitus as well as pregnancy and the use of oral contraceptives.

The limitation of this study was that the researchers only looked for a relationship between the reduction in DHEAS and ejection fraction in heart

failure without excluding risk factors. The researchers did not differentiate between gender and did not take blood at the same time for each subject. DHEAS levels examination in the laboratory was not carried out on the same day as the Echocardiography examination, the baseline of DHEAS level was not known so the magnitude of the reduction was also unknown. Some of these factors may be biased in this study.

CONCLUSIONS AND SUGGESTIONS

Along with age, DHEAS levels get lower. The lower the DHEAS level, the lower the ejection fraction. Further research can be done with a larger number of samples, searching the risk factors, differentiation between gender and sampling should be done at the same time for each subject.

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