Impact of 12-week moderate intensity exercise on cardiorespiratory changes in MMP-9 and VO2max in elderly women

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Abstract - Background: Sedentary elderly lifestyle and aging can decreased the function of cardiovascular system may lead reduction of body performance. Exercise moderate intensity (EIM) can changes matrix metalloproteinase–9 (MMP-9) are decreased. MMP-9 is a potential marker the structural and function of the heart and its association with collagen degradation of blood vessel. VO_{2max} is an indicator of body performance. The aims this study was to investigate the effects of exercise moderate intensity on MMP-9 level and its relation with $VO2_{max}$ on sedentary elderly women. **Method:** The research was quasi experimental. Statistical sample included 42 sedentary elder women aged 65.86 ± 5.21 years were divided in two groups: 21 subject experimental group (EG) and 21 subject control group (CG). The exercise program is *EIM*, 3 times a week for 12 weeks, 50–85% HR_{max} during 30 minutes. The variable was examined at 0, 6 and 12 weeks. MMP-9 were measured by ELISA and predicted VO_{2max} by 6 minutes walk test (6 MWT). Data were processed by Unpaired t-test and Pearson test. **Results :** Δ MMP-9 level was significantly decreased on EG (p = 0.014) and predicted VO_{2max} was also significantly increased on EG (p = 0.000) Our data showed negative correlation between MMP-9 level and predicted VO_{2max} at 12 weeks (r = -0.224, p = 0.041). **Conclusion**: Exercise moderate intensity during 12 weeks can improve cardiovascular system and body performance through decreased of MMP-9 level and elevate of VO_{2max} in elderly.

Keywords: MMP-9, Exercise moderate intensity(EMI), VO_{2max} and Elderly women

I. INTRODUCTION

Sedentary elderly lifestyle and aging can decreased the function of cardiovascular system may lead reduction performance. Engaging in any activity such as housework, shopping, is better than living a purely sedentary lifestyle, but participating in a planned exercise program will get even more cardiovascular benefits especially for elders. Walking may be an ideal exercise for elders because it is safe, cheap, easy to do [1,2]. Aging a major risk factor the development of arterial stiffnes and cardiovascular disease. Matrix metalloproteinases (MMPs) are family of nine or more highly Zn^{++}, in the circulation are thought to modulate the activation of growth factor, cytokines and angiogenesis facilitating physiological adaptations to exercise training [3,4]. The MMP families of enzymes contribute to both normal and pathological tissue remodelling. Each MMP target a specific substrate, thus appropriate MMP must be released in a time and location- specific manner to orchestrate membrane remodelling and adaptation [5,6].

The patophysiology mechanisme underlying vascular remodeling include the processes regulate extra cellular matrix collagen [7]. In recent years, scientists have studied many biomaker of matrix remodeling that closely reflect the ongoing process of continuous matrix breakdown and synthesis [8]. MMP-9 is present in developing cardiac tissue in human and rodents, and is expressed between 16 and 18 days of embryogenesis [9,10]. Also reported to paly a significant role in neovascularization through the proteolytic degradation of the protein in basal lamina of the blood vessel and a release of the biologically active form of vascular

endothelial growth factor [11]. MMP-9 robustly increases several cardiovasculare diseases, including hypertension, atherosclerosis and myocardial infarction (MI). Human vasuclar endothelium contain several type of colllagen. Plasma MMP-9 is a type IV and V colllagen, which is found in subendothelial basement membrane. Gelatinase B or MMP-9 is secreted by a wide number of cell types, including neutrophils, macrophages and fibroblast. MMP-9 is synthetized during granulocyte differentiation in the bone marrow. In human but not rodents, neutrophil MMP-9 is covalently linked with lipocalin, which protects it from proteolytic degradation[12,15].

Hence, it has been proposed that dimished activity of MMP-9 is associated with accumulation of extracellular matrix in the resistance arteries, thereby contributing to hypertension. MMP-9 degrades the extracellular matrix (collagen type IV dan V) in normal physiology process, Higher MMP-9 concentrations was related with greater risk to a higher hypertension because these marker reflect vascular remodelling that accompanies the evalution of high blood pressure [16]. Therefore examination of arterial stiffness is an important determinant of cardiovascular risk. Elastin is main elastic component of the arterial wall and can be degraded by enzymes such as serine protease and MMP [17].

There are three general activation mechanisms of MMPs, including the pro-MMP cleavage, phosphorylation, and oxidative stressors. MMPs can also be activated by oxidative stressors such as homocysteine (Hcy), nitric oxide (NO), and hydrogen sulfide (H_2S). Hcy is a metabolite of the amino acids cysteine and methionine that activates MMPs by the extracellular signal-regulated kinase pathway [18,19]. The three MMP regulators mentioned above can give more insight on how MMP levels can be regulated in ways that can benefit the human body against diseases. Based on the previously published studies, the responses of MMPs to resistance training are more likely related to duration of exercise training. Resistance training lasting from 5 to 12 weeks may increase MMP-2 and -9 in both animal and human subjects[20], whereas acute bout of resistance training may decrease these MMPs [(21)]. The impact of aerobic exercise training on MMPs may be related to duration of exercise. In general, the long-term aerobic exercise training lasting up to 12 weeks may decrease both MMP-2 and 9 [22,23], while these MMPs increase following acute bouts of exercise [24]**.**

Aging progressively associated with high levels of oxidative biomolecules that react with free radicals causing increased damage to proteins, fats and DNA. Oxidative stress is a term of cell damage caused by an imbalance between prooxidants (RONS) and antioxidants. ROS is an oxygen-generated free radical and is most widely produced in mitochondria[25]. Increased oxidative stress due to chronic sedentary in elderly will cause oxidative damage of mitochondrial tissue especially complex I, complex II and ATP synthesis complex so that the ability of energy formation and mitochondrial matrix to produce antioxidant. Moderate intensity exercise done continuously will lead to adaptation with increased antioxidants through the formation of mitochondrial ROS [26].

Data collection VO_{2max} previous studies in Indonesia, the mean VO_{2max} elderly with sedentary lifestyle was obtained in the range of 6.73-25.103 $mLO_2.kgbb^{-1}.min^{-1}$, and after the lifestyle became more active then the average range VO_{2max} range of approximately 18.48-25.24 $mLO_2.kgbb^{-1}.min^{-1}$ [27]. VO_{2max} is an indicator of the ability to exercise aerobic exercise and daily activities optimally [2,28], One of the adaptation processes including increased antioxidant capacity marker (GPx, CAT) by activation of NRF2 and decreased oxidative stress markers among which are TBARS and malondialdehyde (MDA [29,31).

The aims this study was to investigate the effects of exercise moderate intensity 12 weeks on changes matrix metalloproteinase-9 (MMP-9) level and its relation with $VO2_{max}$ on sedentary elderly women.

II. METHODS

Material and Methods

Subjects. The research was quasi experimental (*control group pre test post test design)* study was participated by 42 subjects sedentary elderly women with age 65.86 ± 5.21 years, were divide in two groups each 21 subject experimental group (EG) and 21 subject control group (CG). Each person was selected based on inclusion were determined through interview and ADL Bartel score > 12, pedometer > 5000 step per day, is good balance and cognitive status cooperative. Physical examination (Body weight, height, blood pressure and heart rate regular 60-100 beats per minute). Drop out criteria did not discipline in research program.

Material and Equipment, consists of; sphygmomanometer, stethoscope, weigh scale, heart rate monitor, spirometer, stop watch, pulse oximeter, pedometer.

Protocol experiment. Before starting exercise, subject 5 minutes warm up and stretch and after exercise 5 minutes cooling down. Design exercise moderate intensity (50-85% HR max), three time in a week for 12 week, 30 minutes per session, type exercise aerobic walking [(31)] monitoring during period of training necessary pulse rate monitor every 10 minutes. Predicted VO_{2max} by 6 minutes walk test (6 MWT).

Study ethics. Complaint during exercise will be activity such as specific treatment until the complain loss. Subject explained about the procedure and aim the study before program. Informed consent if confirmed.

Biochemical analysis. Basal blood draws were collected at basaline at 5 minute before exercise and 24 hour after exercise via venepuncture. Blood sample centrifuged 3000 rpm for 30 minutes and plasma 1.5 ml store was frozen at -20^0 C until assay. All sample were measured MMP-9 using ELISA method and *TBARS Assay Kit*.

Statistical analysis. Data were analysed using SPSS package program version 20.0. Unpaired t-test and Pearson test compare mean Δ MMP-9 level and predicted VO2max between CG and EG at 0 and 12 weeks after exercise. All analyses were performed using SPSS 20.0

III. RESULTS

As shown in the table 1. Baseline characteristic subject no difference such as ages, weight, height, BMI, pedometer and ADL between CG and EG. ($p > 0.05$)

1. The characteristic subject

Tabel 1. Data physical and physiological characteristic subjects

Test/unit	Control group (CG) n = 21 mean ± SD	Experimental group (EG) n = 21 mean ± SD	Evaluation *p*
Age (yr)	65.29 ± 4.84	66.71 ± 4.99	0.181[a]
Body Weight (kg)	55.51 ± 12.15	56.67 ± 10.17	0.739[a]
Height (cm)	147.19 ± 4.78	150.09 ± 4.28	0.098[b]
BMI(kg.m^{-2})	25.48 ± 4.76	25.14 ± 4.36	0.811[a]
Pedometer (step)	2850.05 ± 1338.43	3448.67 ± 1231.78	0.139[a]
ADL	19.24 ± 0.76	19.47 ± 0.68	0.300[b]

[a] t- test unpaired
[b] Mann-Whitney U test
*Value $p > 0.05$ → significance differences two groups (homogen)
ADL Barthel : *activity daily living*

Table 1 summarizes the characteristic of subjects in this study. All 42 subjects between control group (CG) dan experimental group (EG) complete exercise the same treatment no difference.

2. Changes in plasma matrix metalloproteinse-9 (MMP-9)

Tabel 2. The comparison of the difference Δ variabel between Control group (CG) and Experimental group (EG)

Variabel	Control group (n=21) mean ± SD	Experimental group (n=21) mean ± SD	Evaluation p
MMP9	56.47 ± 156.49	-51.41 ± 113.47	0.015*
VO_{2maks} ($ml.kg^{-1}.min^{-1}$)	0.973 ± 3.81	3.946 ± 2.52	0.005*
BPS	-1.667 ± 7.66	-8.762 ± 8.09	0.006*
BPD	-1.571 ± 8.46	-5.143 ± 6.21	0.127
GPx (U/mg)			
0 week	284.53 ± 149.21	107.65 ± 57.67	0.000[a*]
12 weeks	231.86 ± 73.32	184.79 ± 64.73	0.015[a*]

[a] Uji Mann Whitney (nilai *p* Shapiro Wilk < 0.05)
[*]Uji t-test unpaired (p<0.05)
*value Δ = the difference absolute value between 0 and 12 weeks exercises

The result research obtain matrix metalloproteinse-9 (MMP-9), blood pressure systolic (BPS) decrease significance and prediction VO_{2max} increased significance, the subject exercise aerobic intensity moderate prolonged 12 weeks.

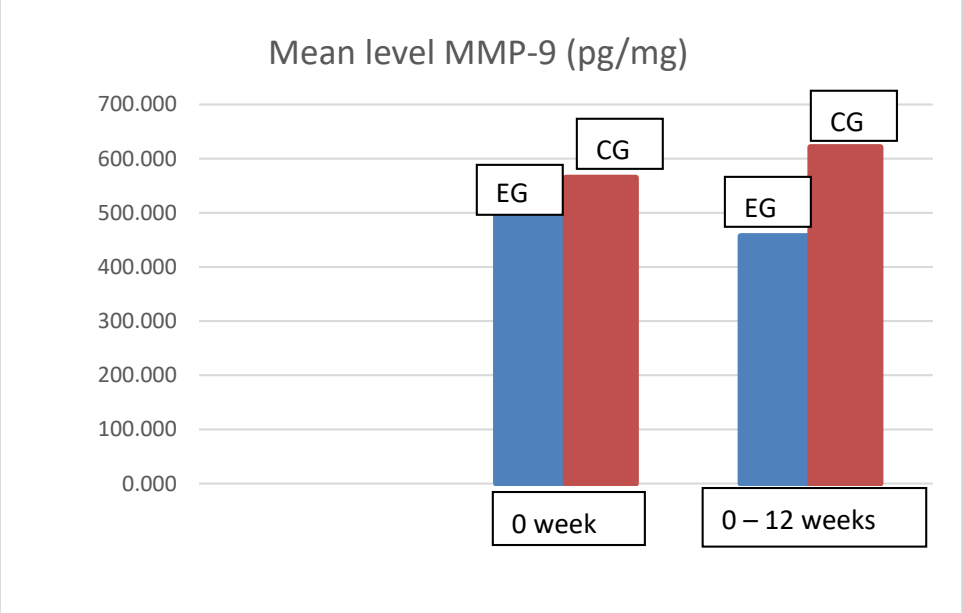

Figure 1. The comparison of the difference mean level MMP-9 between Control group (CG) and Experimental group (EG)

Then conducted a correlation between research MMP-9 and other research variable found matrix metalloproteinse-9 (MMP-9) significance negative correlated between prediction VO2max (r= - 0.311, p= 0.045), while blood pressure systolic (BPS) is correlation positive (r =0,221) and other variable no correlation. Level thiobarbiturate acid reactive substance (TBARS) in 0 weeks (1.13 ± 0.17 nmol/mL) and 12 weeks (1.05 ± 0.12 nmol/mL), difference level between 0 and 12 weeks seen a downward trend TBARS 7.08%.

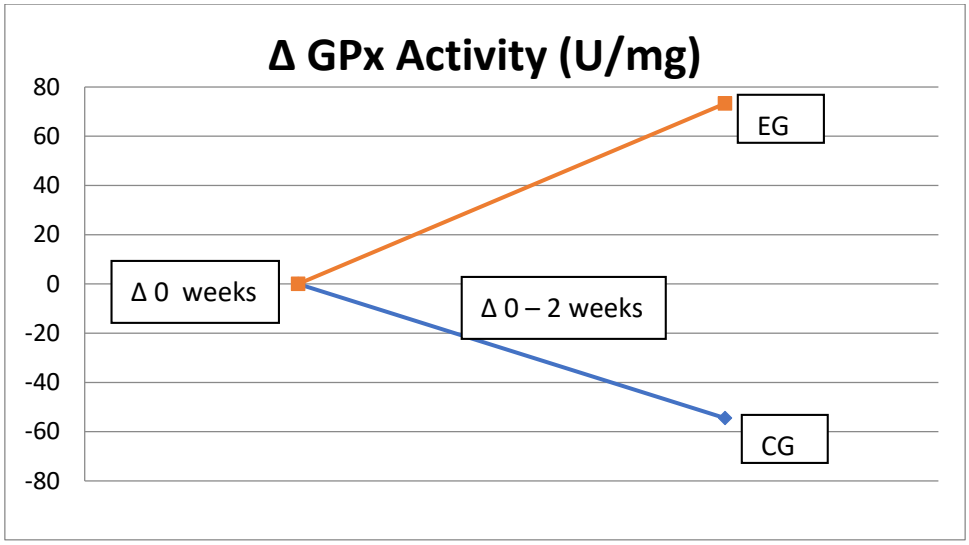

Figure 2. The comparison of the difference changes Δ GPx activity between Control group (CG) and Experimental group (EG)

The results showed a decrease in plasma GPx control group by 7.40% at week 12 while the experimental group showed a significant increase in plasma GPx activity by 40.16% after 12 weeks (start 0 weeks : 107.65 U/mg and 12 weeks: 184.79 U/mg). Because the initial data of the study did not show equality ($p < 0.05$), data processing was performed using Δ between 0 and 12 weeks of training and the percentage change. 0–12 weeks GPx activity obtained by the control gro7up was found to decrease by -52.67 U/mg and the treatment group increased by 77.14 U/mg ($p = 0.003$).

IV. DISCUSSION

The predominant exercises aerobic intensity moderate to able decreased matrix metalloproteinse-9 (MMP-9) play role degradation collagen type IV in wall endothelium blood vessel. Increased level matrix metalloproteinse-9 (MMP-9) related with hypertension due to with remodelling blood vessel [15]. Arterial stiffness is an important determinant of cardiovascular risk. Elastin is the main elastic component of the arterial wall and can be degraded by enzymes such as serine proteases and MMP. Serum MMP-9 levels associate with arterial stiffness and predict cardiovascular risk [17]. MMP-9 play a role in the formation and destabilization of plaque that are biomarker of *acute coronary syndrome*. Inhibition of MMP-9 production may lead to decreased plaque formation and decline the cardiovascular disease[32]. Our finding suggest that the decline of MMP-9 in this study represent another alternative pathway for changes in cardiovascular adaptation due to exercise in elderly. Decreased of MMP-9 improves the extracellular matrix by inhibiting the degradation of collagen tipe IV and V lamina basalis to form cardiovascular adaptation by improving the elasticity of blood vessels thereby decreasing BP in elderly. it prevent cardiovascular disease in elderly. The elevated MMP-9 level occur in CAD patients. MMP-9 can predict an increase mortality in CAD patient[33].

Free radicals can increased degradation collagen (decreased synthesis collagen) through increased activity matrix metalloproteinase-9 (MMP-9) [34]. To our study, additional measured TBARS level to know free radicals due to prolonged exercise. Apparently found a tendency to decreased TBARS level of 7.8% this indicate moderate aerobic exercise can reduce free radicals be able to affect the decrease in levels of matrix metalloproteinase-9 (MMP-9) in the body, which improve the body's circulation work. One that affect the increase in VO_{2max} is by improving the circulation to increase oxygenated blood flow in the circulation VO_{2max}.

In this study also increased the antioxidant (glutathione peroxidase) of 40.16% after 12 weeks, increased in glutathione peroxidase

signifies the improvement of mitochondrial function because it is mostly found in the mitochondrial matrix. Glutathione expression increases through nuclear factor erythroid 2 (Nrf2) activity due to the process of long-term intensity moderate aerobic exercise adaptation. The role reactive oxygen species (ROS) in activation of the transcription factor Nrf2, the master regulation of antioxidants enzymes and celullar stress resistance. Moderate-intensity aerobic exercise increases oxidative stress at optimal levels thereby increasing ROS with the optimal amount which does not cause damage to mtDNA. Glutathione peroxidase serves to counteract free radicals in the mitochondria [35]. Therefore, this type of exercise will further increase the levels of antioxidants (glutathione peroxidase) which serves to reduce the free radical formed is marked by the visible decrease in levels of TBARS week-12 exercise. Thus, the elderly is strongly encouraged to continue doing moderate intensity exercise regularly to control the production of free radicals with more optimal.

V. CONCLUSIONS

Moderate intensity aerobic exercise for 12 weeks has been show changes in matrix metalloprotein-9 (MMP-9) is decreased, play role degradation collagen in wall endothelium blood vessel. Increased level matrix metalloproteinse-9 (MMP-9) related with hypertension due to with remodelling blood vessel. Arterial stiffness is an important determinant of cardiovascular risk. Affect the decrease in levels of matrix metalloproteinase-9 (MMP-9) which improve the body's circulation work. One that affect the increase in VO_{2max} by improving the circulation to increase oxygenated blood flow in the circulation $VO_{2max.}$ Certainly the decline of MMP-9 as well as a significant correlation with predicted VO2max thus can improve cardiovascular system and increase body performance that will delay the aging process of the body.

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