The Correlation between Blood Pressure and Cluster Differentiation-40 Ligand (CD40l) Level

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***Abstract*- Background :** There is correlation between inflammation and hypertension. The vascular inflammation associated with hypertension could be the link between high blood pressure levels and the atherosclerotic process, which is the principal origin of cardiovascular disease. Cluster differentiation-40 ligand (CD40L) may serve as the link between the processes of thrombosis and inflammation. Recent trial has demonstrated that CD40-CD40L is critical in the pathogenesis of atherosclerosis.The roles of CD40L implicate it as a end-stage mediator of endothelial dysfunction among patients with cardiovascular disease, which is indicate CD40-CD40L system is important marker for inflammation activation and thrombosis consequence in hypertensive subjects.

Aim : Determined the correlation between blood pressure and CD40L level.

Methods : This study is observational research with cross sectional design in 30-60 years subjects. Subjects who met inclusion criteria, perform CD40L level examination. This study was conducted at internal medicine clinic Dr. Wahidin Sudirohusodo and Labuang Baji hospital Makassar from Desember 2011 until Februari 2012.

Results : From study period, 80 subjects met inclusion criteria, 38 men (47.5%) and 42 women (52.5%) with mean age 50±7 years. Mean SBP 141±25 mmHg, mean DBP 89±12 mmHg, and mean CD40L level 8,451±3,731 pg/mL. Correlation analysis between hypertension and CD40L level showed mean CD40L significantly lower in hypertensive group compared with non-hypertensive group (7,442.07 pg/mL vs 9,459.93 pg/mL, $p<0.05$). Correlation analysis between SBP and DBP with CD40L level showed negative correlation ($p<0.01$ and $p<0.001$, respectively).

Conclusión: There is negative correlation between blood pressure and CD40L level.

***Index Terms*-** Blood pressure, CD40L, Hypertension.

I. INTRODUCTION

Hypertension is blood pressure level where the risk of cardiovascular incidence in population will increase, and/or blood pressure level where medication significantly decreased cardiovascular morbidity and mortality. [1] The Seventh Report of the Joint National Committee classified hypertension as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or taking antihypertensive medication.[2]

Hypertension is major health problem because the highest prevalence of hypertension and became major risk factor for cardio-renal-cerebrovascular disease. In Indonesia, prevalence of hypertension on 2007 is 31.7%.[3] As the population ages, the prevalence of hypertension will increase even further unless broad and effective preventive measures are implemented. Recent data from the Framingham Heart Study suggest that individuals who are normotensive at age 55 have a 90 percent lifetime risk for developing hypertension.[2]

There is a correlation between hypertension and inflammation. Large scale population study already showed increased risk of cardiovascular and cerebrovascular morbidity/mortality and renal failure in hypertensive patients, even in prehypertensive population.[4] High blood pressure levels are associated with increases in circulating levels of inflammation markers which can reflect vascular inflammatory processes, suggesting that hypertension is a low-grade inflammatory process. The vascular inflammation associated with hypertension could be the link between high blood pressure levels and the atherosclerotic process, which is the principal origin of cardiovascular disease.[5]

Oxidative stress, inflammation and endothelial dysfunction are important factor in development and progression of atherosclerosis.[5] Inflammation contribute in endothelial dysfunction process, in otherwise endothelial dysfunction will lead to inflammation proccess.[6] Platelet also have a major role in inflammation and atherosclerosis process. A range of molecules, present on the platelet surface and/or stored in platelet granules, contributes to the cross-talk of platelets with other inflammatory cells during the vascular inflammation involved in the development and progression of atherosclerosis. Activated platelet in circulation also have linked in thrombosis.[7,8] Thrombosis become the leading cause of acute complication of atherosclerosis.[9] The atherosclerotic and thrombotic processes appear to be interdependent and may be integrated under the term atherothrombosis.[10]

Soluble cluster differentiation-40 (CD40) is cryptic in unstimulated platelets but is rapidly presented to the platelet surface after platelet stimulation. More than 95% of the circulating CD40 exists in platelets. Platelets express CD40 ligand (CD40L) on activation, which induces pro inflammatory changes in endothelial cells via endothelial CD40. Platelet CD40L may serve as the link between the processes of thrombosis, inflammation and atherosclerosis. Recent work has demonstrated that CD40-CD40L signaling is critical in the pathogenesis of atherosclerosis, as well as in thrombus formation and platelet aggregation.[11,12,13] Role of soluble CD40L (sCD40L)in hypertension pathohysiology and its linked between target organ damage not already know. This study aim is to

determine the correlation between blood pressure and CD40L level.

II. METHODS

This study is an observational research with cross-sectional design. The study was conducted at Internal Medicine Clinic Dr. Wahidin Sudirohusodo and Labuang Baji Hospital Makassar from Desember 2011 until Februari 2012. Population are all patients who conduct periodic checks up at Internal Medicine Outpatient Clinic Dr. Wahidin Sudirohusodo and Labuang Baji hospital Makassar. Research sample are population who met inclusion criteria, where the inclusion criteria are aged 30-60 years old, non-hypertensive and hypertensive patients (according to JNC 7 criteria, that never, taking or stop anti-hypertensive medication for 1 months), non diabetes and no impaired renal function, not consuming NSAIDs, BMI < 23 kg/m^2 and willing to participate the study.

Blood pressure was measured with sphygmanometer. Measurements were performed in a sitting position with right arm placed on the table. Korotkoff sounds 1 rated as SBP and Korotkoff 5 as DBP. Blood pressure was measured 3 times, the first measurements were excluded, the average of 2 times last measurement of blood pressure is taken as the value of the subject. Non-hypertensive group are normotension (SBP <120 mmHg or DBP <80 mmHg) and prehypertension (SBP ≥ 120-139 mmHg or DBP 80-89 mmHg). Hypertensive group are first degrees hypertension (SBP ≥ 140-159 mmHg or DBP ≥ 90-99 mmHg) and second degrees hypertension (SBP ≥ 160 or DBP ≥ 100 mmHg).

Sampling was done by consecutive sampling until the desired number of samples is reached. A blood sample taken as many as 10 ml. Taken in the fossa cubiti area and send to the Prodia Laboratory Clinic. CD40L levels is CD40L levels in blood serum samples were measured with quantitative techniques Sandwich Enzyme Immunoassay and the reaction is read using 530 reader that is expressed in pg/mL. (Standard Interval 62.5 - 4,000 pg/mL, expected values: undetectable – 11,451 pg/mL).

The data obtained were analyzed by computer using the program Statistical Package for Social Science (SPSS) with Independent t test, Pearson correlation test dan Anova test the t test. Significant test if $p<0.05$.

III. RESULTS

From study period, 80 subjects are include in the study (38 men (47.5%)) with mean of age is 50±7 of age. Mean SBP 141±25 mmHg and mean DBP 89±12 mmHg. Mean sCD40L level 8,451±3,731 pg/mL. Variable characteristic are reported in Table 1.

Table 1. Variable Characteristic

	n	Min	Max	Mean	SD
SBP (mmHg)	80	110	220	141.08	25.196
DBP (mmHg)	80	70	133	88.71	12.018
sCD40L Level (pg/mL)	80	316	15,877	8,451.00	3,731.260

Min : Minimum, Max : Maximum, SD: Standard Deviation, SBP : Systolic Blood Pressure, DBP : Diastolic Blood Pressure

Correlation analysis between hypertension group and sCD40L level showed significant correlation between blood pressure with sCD40L level ($p<0.05$), where mean sCD40L level significantly low in hypertensive group than non-hypertensive group (7,442.07 pg/mL vs 9,459.93 pg/mL). (Table 2).

Table 2. Correlation between blood presuure and sCD40L level

Group	n	Mean (pg/mL)	SD (pg/mL)	p*
Non-hypertensive	40	9,459.93	3,193.154	**0.015**
Hypertensive	40	7,442.07	3,989.646	

SD: Standard deviation, *Independent t test.

Correlation analysis between SBP and DBP with sCD40L level showed significant negative correlation ($p<0.01$ and $p<0.001$, Pearson's correlation test), where SBP and DBP significantly higher in the lowest sCD40L level ($r = -0.508$ and $r = -0.569$) (figure 1).

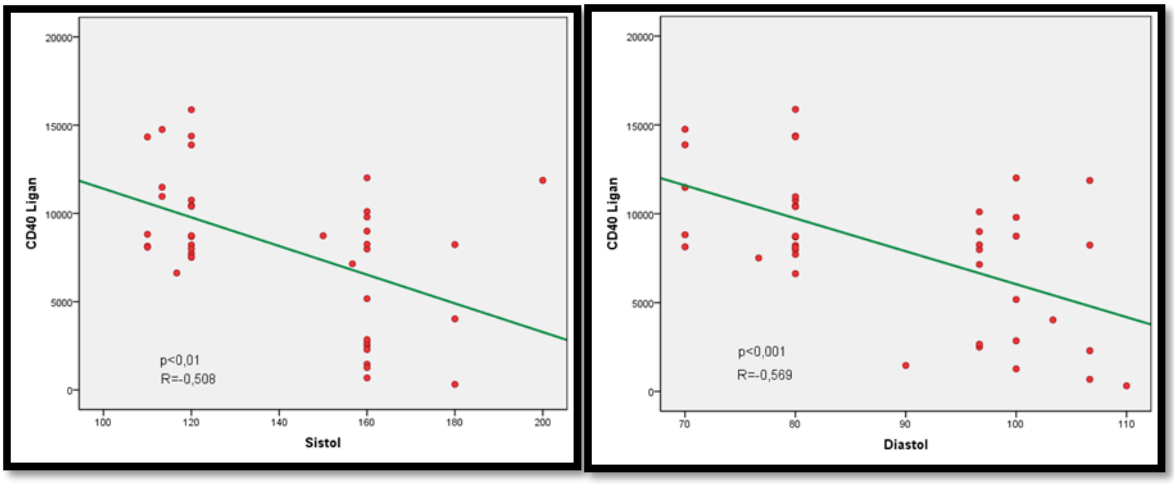

Figure 1. Correlation between SBP and DBP with sCD40L Level

IV. DISCUSSION

There is growing evidence about the association between hypertension and inflammation. Inflammation takes part in the hypertension-induced atherosclerosis. However, recent reports suggest that there is chronic low grade inflammation, which predicts future generation of hypertension in otherwise healthy populations. CD40/CD40L signaling system amplifies the endothelial cell responses to inflammation and contributes to progression of atherosclerosis. Levels of sCD40L seem to be a new predictor for future cardiovascular events in patients with high-risk atherosclerotic lesions.[14] The platelet-mediated prothrombotic and hypercoagulable state in essential hypertension may contribute to the increased risk and severity of target organ damage and atherosclerotic complications. In this context, sCD40L could be a potential molecular link between inflammation, thrombosis and essential hypertension.[15] Platelet activation and increased sCD40L have been also demonstrated in hypertensive patients.[16]

Some study showed correlation between blood pressure increments with sCD40L level. Yan et al[17] analyzed the expression of CD40 and CD40L on platelet in 20 normal controls and 150 patients with essential hypertension. Patients with essential hypertension showed a significant increase of CD40 (67.1F9.6 Mean Fluorescence Intensity, MFI) and CD40L (15.3F5.0 MFI) co-expression on platelets as well as sCD40L levels (12.8F3.9 ng/ml) compared with controls (p< 0.0001). We found that CRP levels related to CD40–CD40L system. We also observed a slight correlation between sCD40L level and blood pressure. During 3 months follow-up, patients with enhanced levels of sCD40L (N15 ng/ml) indicated a tough control of blood pressure. This study suggests that hypertension is in part an inflammatory disorder.

Using a cross-sectional approach, Patel et al[18] measured plasma concentrations of CRP, sCD40L, VEGF, and angiopoietins-1 and -2 in 147 patients with hypertension (85 with a history of CVD event/s, 62 CVD event-free) and 68 age- and sex-matched healthy controls. Concentrations of sCD40L (P = 0.039), CRP (P < 0.001), angiopoietin-1 (P < 0.001), angiopoietin-2 (P = 0.003) and VEGF (P < 0.001) were all greater amongst hypertensive patients than in controls. There were no significant differences in sCD40L and VEGF concentrations between hypertensive individuals with and without CVD events. On multiple regression analysis, sCD40L was associated with angiopoietin-2 (P = 0.01) and VEGF (P = 0.007) in hypertensive individuals, but no such associations were found within the healthy control group. In patients with hypertension, sCD40L was associated with increased circulating markers of abnormal angiogenesis (angiopoietin-2, VEGF). The interaction between sCD40L and angiogenesis may contribute to the pathophysiology of CVD in hypertension.

In this study, we found significant negative correlation between SBP and DBP with sCD40L level (p<0.01 and p<0.001), where SBP and DBP significantly higher in the lowest sCD40L level (r = -0.508 and r = -0.569). Correlation analysis between hypertension group and sCD40L level showed significant correlation between blood pressure with sCD40L level (p<0.05), where mean sCD40L level significantly low in hypertensive group than non-hypertensive group (7,442.07 pg/mL vs 9,459.93 pg/mL).

Few study showed similar results. Sonmez et al[14] investigated sCD40L levels in 30 non-obese young hypertensive men and 30 matched controls. sCD40L were not different and there were no correlations between blood pressure and sCD40L. deLemos et al[19] investigated plasma levels of sCD40L were measured in 2811 subjects from the Dallas Heart Study, a multiethnic population-based cross-sectional study. Weak but statistically significant associations were observed between sCD40L quartiles and hypertension. sCD40L was not associated with most atherosclerotic risk factors or with subclinical atherosclerosis. These findings suggest that sCD40L will not be useful as a tool to screen for the presence of subclinical atherosclerosis in the population. Penno et al[16] investigated several metabolic and vascular correlates of sCD40L levels in 90 nondiabetic never-treated essential hypertensive men. In newly diagnosed hypertensive men, sCD40L levels are inversely related to insulin sensitivity, with no correlation with blood pressure, other cardiovascular risk factors, or the degree of subclinical atherosclerosis.

The results of our study not similar with the recent hypothesis. These results might indicate lack of any inflammatory state in new onset hypertension. Increased sCD40L

levels have been associated with enhanced platelet activation in various clinical settings. Soluble CD40L has been independently associated with an increased risk of coronary and cerebrovascular events, performing better as a marker of plaque vulnerability than of plaque burden.[16] Soluble CD40L was not associated with most atherosclerotic risk factors or with subclinical atherosclerosis. These results suggest that sCD40L will not be useful as a tool to screen for the presence of subclinical atherosclerosis in the population.[19]

Yuan et al[20] investigated serum levels of CD40 and sCD40L in 328 hypertensive patients with varying degrees of organ damage. The data revealed that serum levels of CD40 were significantly greater in patients with severe, but not mild organ damage compared with patients without any organ damage. There were no significant differences in serum concentrations of sCD40L between patients with no, mild and severe organ damage. Their results indicate that upregulation of the CD40 system in hypertensive patients with certain forms of severe end-organ damage may contribute to the pro-inflammatory, pro-atherogenic and prothrombotic milieu in hypertension.

The present clinical study suffers from some limitations. First is the fact that this outpatient clinic-based study was only screening several target organ damage in subjects. Thus, the data obtained may not be readily applied to the general population. Second, the serum sCD40L levels determined in the present study are much higher than standard interval. Although differences in the preparation of blood samples, the detection techniques used and the age of the patients may have all contributed to the apparent discrepancies, a more standardized procedure should be validated for the measurement of plasma sCD40L concentrations. Third, some subjects used antihypertensive treatment is expected to slow down the pathophysiological mechanisms responsible for the activation of the CD40 /CD40L system. Further multivariate analysis using a larger patient population with better patient compliance in terms of antihypertensive drug therapy needs to be performed.

V. CONCLUSION

From this study we found negative correlation between blood pressure and sCD40L level.

REFERENCES

[1] Bakri S. Hipertensi Pada Diabetes Mellitus. Pada: Naskah lengkap pendidikan profesional berkelanjutan seri I. Makassar. 2004; p.77-90.

[2] The Seventh Report of The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC report. JAMA 2003; 289:2560-2572.

[3] Badan Penelitian dan Pengembangan Kemenkes Republik Indonesia. Riset Kesehatan Dasar (Riskesdas) 2007 Hipertensi. [Cited 2012 May]. Available from: http://www.riskesdas.litbang.depkes.co.id.

[4] Dzau VJ, Gnecchi M, Pachori AS, Morello F, Melo LG. Therapeutic Potensial of Endothelial Progenitor Cells in Cardiovascular Diseases. Hypertension 2005;46:7-18

[5] Cachofeiro V, Miana M, de las Heras N, Martin-Fernandez B, Ballesteros S, et al. Inflammation: A Link Between Hypertension and Atherosclerosis. Curr Hypertens Rev 2009; 5: 40-48.

[6] Koh KK, Han SW, Quon MJ. Inflammatory Markers and Metabolic Syndrome. J Am Coll Cardiol 2005;46:1978–85.

[7] Huo Y, Ley KF. Role of Platelets in the Development of Atherosclerosis. Trends Cardiovasc Med 2004; 14: 18-22.

[8] Flaumenhaft R. Molecular Basis of Platelet Granule Secretion. Atherioscler Thromb Vasc Biol 2003; 23:1152-1160.

[9] Davì G, Patrono C. Platelet Activation and Atherothrombosis. N Engl J Med 2007; 357:2482-2494.

[10] Corti R, Fuster V, Badimon JJ. Pathogenetic Concepts of Acute Coronary Syndromes. J Am Coll Cardiol 2003; 41: 7S-14S.

[11] Blum A. Soluble CD40 Ligand and Atherosclerosis: Linking Thrombosis and Inflammation. Haema 2006; 9(3): 361-366.

[12] Lutgens E, Lievens D, Beckers L, Donners M, Daemen M. CD40 and Its Ligand in Atherosclerosis. Trends Cardiovasc Med 2007;17:118–123.

[13] Schönbeck U, Libby P. CD40 Signaling and Plaque Instability. Circ Res 2001; 89:1092-1103.

[14] Sonmez A, Dogru T, Yilmaz MI, Ocal R, Ozgurtas T, et al. Soluble CD40 Ligand in Patients With Hypertension. Clin Exp Hypertens 2005; 8:629-634.

[15] Montecucco F, Pende A, Quercioli A, Mach F. Inflammation in The Pathophysiology of Essential Hypertension. J Nephrol 2011; 24(01): 23-34.

[16] Penno G, Pucci L, Dell'Omo G, Lucchesi D, Micolli R, et al. Soluble CD40 Ligand Level in Essential Hypertensive Men: Evidence of a Possible Role of Insulin Resistance. Am J Hypertens 2009; 22: 1007-1013.

[17] Yan JC, Ma GS, Wu ZG, Kong XT, Zong RQ, Zhan LZ. Increased level of CD40-CD40 Ligand System in Patients With Essensial Hypertension. Clin Chim Acta 2005; 355:191-196.

[18] Patel JV, Lim HS, Nadar S, Tayebjee, Hughes EA, Lip GYH. Abnormal Soluble CD40L and CRP Concentrations in Hypertension: Relationship to Indices of Angiogenesis. J Hypertens 2006; 24:117-121.

[19] de Lemos JA, Zirlik A, Schonbeck U, Varo N, Murphy SA, et al. Association Between Soluble CD40 Ligand, Atherosclerosis Risk Factors, and Subclinical Atherosclerosis: Results from The Dallas Study. Arterioscler Thromb Vasc Biol 2005; 25:2192-2196.

[20] Yuan M, Ohishi M, Raguki H, Wang H, Tao L, Ren J. Association Between Serum Levels of Soluble CD40/CD40 Ligand and Organ Damage in Hypertensive Patients. Clin Exp Pharm Physiol 2010; 37: 848-851.

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