Low Density Lipoprotein (LDL) values in bacterialistic sepsis patients at Haji Adam Malik Hospital Medan-Indonesia 2017

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ABSTRACT

Background: Infection and inflammation will stimulate the acute phase response (APR) activation which will cause the changes in lipid metabolism. In rodents, the infection will induce an increase in cholesterol, including LDL, whereas in the primates and humans, LDL levels will decrease or normal. As lipopolysaccharides (LPS) and cytokines will lower the total cholesterol level in primates, while in mice will increase due to the stimulation of infection enhance the cholesterol synthesis de novo, reducing the lipoprotein clearance, and lowering the cholesterol conversion into bile acid.

Aim: This study aims to determine the influence of the bacterial sepsis severity to the value of Low-Density Lipoprotein (LDL)

Methods: It was a case-control observational study which conducted from January-March 2017 to the 30 sepsis patients and 30 non-sepsis patients at Haji Adam Malik General Hospital, Medan. Data were collected by measuring LDL and PCT levels in both sepsis

and non-sepsis patients on days 0, 3, and 5 of study then was analyzed by using Mann-Whitney test to assess the relationship between them.

Results: The result showed that LDL value in sepsis group on pretreatment was $77,70 \pm 33,42$ mg / dl and increased on day 3 and 5 treatment to $83,50 \pm 38,68$ mg / dl. In the non-sepsis group, the mean value of LDL at baseline was 102.23 ± 45.90 mg/dl and increased on day 3 and 5 of treatment to 114 ± 38.58 mg/dl. Statistically, there were significant differences in LDL levels between sepsis and non-sepsis groups on the first day of treatment, day 3 and day 5 of care ($p < 0.05$). Spearman correlation test results obtained a significant negative correlation between LDL levels with sepsis degree with correlation strength is moderate ($r = -0.318$).

Conclusion: There was a significant relationship between the severity of sepsis and the LDL value in patients with sepsis.

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INTRODUCTION

Sepsis is defined as an infection (presumed or proven) accompanied by a systemic inflammatory response / SIRS (Systemic Inflammatory Response Syndrome). Severe sepsis is defined as a state of sepsis accompanied by organ dysfunction or tissue hypoperfusion. Meanwhile, septic shock is a sepsis related with hypotension (SBP <90 mmHg, or decreased $\geq$ 40 mmHg from the previous blood pressure) without any other persistent hypotension causes although it has been provided adequate fluid resuscitation. In the course of the infection process, there are significant changes in lipid metabolism and lipoprotein composition. In rodents, the infection will lead to an increase in cholesterol level, including LDL, whereas in primates and humans, the LDL levels will decline or normal.[1,2,3]

During the infection process, there are some significant changes in the lipid metabolism and lipoprotein composition. In the patients with infections, the total cholesterol, LDL, and serum triglycerides serum levels were increased, while the HDL serum level was declined which has been reported in several studies. It is related to several

mechanisms, including the reduction of TG hydrolysis, LPS and proinflammatory cytokines induces the production of free fatty acids as well as the synthesis of TG in the liver. The LDL receptor is a critical step in the lipid pathogen clearance from the circulation of sepsis, severe sepsis, and septic shock.[4,5,6,7]

Infection and inflammation induce the acute-phase response (APR) activation, which leads to the metabolism changes in lipid and lipoprotein. Plasma triglyceride levels increase from the increased of VLDL secretion as a result of adipose tissue lipolysis, fatty acid synthesis *de novo*, and suppression of fatty acid oxidation. With more severe infections, VLDL levels will decline accompanied by a decreased of lipoprotein lipase as well as apolipoprotein E in VLDL. According to the study which conducted by Khovidhunkit W (2004), there were some changes in the metabolism of cholesterol, LDL, and HDL. LPS and cytokines lowered the total cholesterol serum levels in primates, increased the cholesterol levels in mice as well as in primates, while the low level of LDL was found in rats.[2,3]

In the hospital ward at H. Adam Malik General Hospital Medan, the mortality rate due to sepsis was quite high about 520 per year. However, the true mortality rate caused by sepsis or other causes should be proved by culture that the results are not always positive. Therefore, other examinations such as procalcitonin (PCT) may be used as a marker of sepsis and to determine the relationship of the sepsis severity in which the diagnosis and management of sepsis can be more rapid and precise in reducing mortality. However, this is limited by the high cost of examination and not all health facilities are able to check procalcitonin in diagnosing sepsis.[8] Thus, the authors are interested in conducting a study to assess whether the LDL level has a relationship with sepsis/degree of severity.

METHODS

This study was conducted with case-control design at the Integrated Inpatient Wards and ICU chambers at H. Adam Malik General Hospital Medan since January-March 2017 with the approval of the ethics committee of Medical Faculty of North Sumatera University (NSU). This study was involved sepsis and non-sepsis patients as independent variables as well as Low-Density Lipoprotein (LDL) as a dependent variable. All of the patients had signed the informed consent.

The subjects of this study were sepsis patients above 17 years old, receiving information and the approval of participation in voluntary and written to undergo a physical, laboratory, as well as radiology examination known and approved by the Research Ethics Committee of the Health Division. However, the exclusion criteria for this study included" sepsis patients with the usage of lipid lowering drugs, sepsis patients with any other

comorbid such as chronic kidney disease, chronic liver disease, thyroid dysfunction, diabetes or malignancy, followed by sepsis patients with chronic inflammatory diseases such as HIV, systemic lupus erythematosus, or rheumatoid arthritis, and sepsis patients who died within 48 hours or referred to another hospital.

Procalcitonin examination was carried out with < 0.05 ng/ml as the reference value, followed by blood culture and gal with bactec 9050 as well as LDL examination of patients. Data analysis was conducted to find out the characteristic and values of LDL in the sepsis and non-sepsis infections that presented and described in the tabulation form. The sample size was 60 people, which divided into 2 groups such as 30 sepsis patients and 30 non-sepsis patients as controls. They were admitted to the inpatient integrated wards and ICU at H. Adam Malik General Hospital Medan. Data normality was carried out by Kolmogorov test and normally distributed when the P-value > 0.005. The Spearman Correlation test was conducted to determine the relationship between LDL values and the sepsis severity degree where giving significant results statistically if the P-value < 0.05. This study has obtained permission from the ethical clearance (permission to conduct research) of the Health Research Committee of Medical Faculty of North Sumatera University.

RESULTS

There were 30 sepsis and 30 non-sepsis patients treated in the inpatient integrated wards and ICU chamber at H. Adam Malik General Hospital Medan in this study. The overview of characteristic, laboratory examination results and clinical conditions of study subjects were depicted in the Tables below.

From the table above, It can be suggested that the characteristics of the study subjects of sepsis group were predominance in the 56 - 65 years age-group (30%), followed by 36-45 years age-group, and 46-55 years age-group, about 23.3% respectively. The lowest age-group of this study was 25 - 35 years old about 10%. While in the non-sepsis group, most of subjects were 46-55 years age-group (30%), followed by 56-65 years (26.7%), 36-45 years age-group (20%), and 25-35 years age-group (10%). However, there was no statistically significant difference of age group between sepsis and non-sepsis patients based on the Fisher exact test (P value > 0.05).

According to the sex group, the female gender was predominance in the sepsis group (53.3%), but the non-sepsis group mostly male gender (63.3%). There was no statistically significant difference of sex group between sepsis and non-sepsis patients from Chi-square test (P-value > 0.05).

Table 4.1 The characteristics of study subjects according to age-group and sex

Characteristic	Group		Total	P-value
	Sepsis	Non-sepsis		
Age-group (years)				
25 - 35	3 (10.0%)	3 (10.0%)	6 (10.0%)	
36 - 45	7 (23.3%)	6 (20.0%)	13 (21.7%)	0.987*
46 - 55	7 (23.3%)	9 (30.0%)	16 (26.7%)	
56 - 65	9 (30.0%)	8 (26.7%)	17 (28.3%)	
> 65	4 (13.3%)	4 (13.3%)	8 (13.3%)	
Sex				
Male	14 (46.7%)	19 (63.3%)	33 (55%)	0.194**
Female	16 (53.3%)	11 (36.7%)	27 (45%)	
Total	30 (100%)	30 (100%)	60 (100%)	

Fisher exact test Chi-square test **

Table 4.2   The distribution of bacterial species based on cultures and sources of infection from the study group

Bacterial Species	Group		Total	P-value*
	Sepsis	Non-sepsis		
Gram Positive	2 (6.7%)	3 (10%)	5 (8.3%)	
Gram Negative	15 (50%)	18 (60%)	33 (55%)	0.146
Polimicrobial	5 (16.7%)	0 (0%)	5 (8.3%)	
No infection	8 (26.7%)	9 (30%)	15 (25%)	
Source of Infection				
Lung	14 (46.7%)	16 (53.3%)	30 (50%)	
Abdomen	10 (33.3%)	7 (23.3%)	17 (28.3%)	
Urinary tract	5 (16.7%)	5 (16.7%)	10 (16.7%)	0.791
Others	1 (3.3%)	2 (6.7%)	3 (5%)	
Total	30 (100%)	30 (100%)	60 (100%)	

Fisher exact test

Table 4.3   The mean and median value of Procalcitonin (PCT) dan LDL from the study subjects

Laboratory Characteristics	N	Mean	Std. Deviation	Median	Minimum	Maximum	P-Value*
PCT_1							
Sepsis	30	20.02	20.51	18.12	0.70	102	0.0001
Non-Sepsis	30	0.74	1.24	0.25	0.04	5.87	
PCT_3							
Sepsis	30	15,97	18.03	8.64	0.27	89.10	0.0001
Non-Sepsis	30	0.48	0.81	0.17	0.04	4.07	
PCT_5							
Sepsis	30	16.82	20.73	8.85	0.31	88.64	0.0001
Non-Sepsis	30	0.36	0.84	0.04	0.04	4.07	
Laboratory Characteristics	**N**	**Mean**	**Std. Deviation**	**Median**	**Minimum**	**Maximum**	**P-Value***
LDL 1st Day							
Sepsis	30	77.70	33.418	73.50	14	196	0.01
Non-Sepsis	30	102.23	45.905	93.50	12	239	
LDL 3th Day							
Sepsis	30	80.17	32.284	84	22	173	0.001
Non-Sepsis	30	112.10	48.436	106	13	274	
LDL 5th Day							
Sepsis	30	83.50	38.676	84.50	17	243	0.0001
Non Sepsis	30	114.53	38.580	104	43	212	

Mann-Whitney test

Based on the bacteria culture in the sepsis group, the infection caused by gram-negative bacteria was predominant (50%) while the gram-positive bacteria only 6.7% and there were no infection about 26.7%. In addition, most of infection occurred in the non-sepsis group also caused by the gram-negative bacteria (60%), followed by the gram-positive bacteria (10%) as well as no infection about (30%). According to the Fisher Exact Test, there was no significant difference statistically (P-value > 0.05).

According to the source of infection, the most common infection in the sepsis group was lung infection (46%), followed by abdominal (33.3%) and urinary tract infection (16.7%). In addition, the most common infection in the non-sepsis group was also lung infection (53.3%), followed by abdominal (23.3%) and urinary tract infection (16.7%). There was no significant difference statistically for source of infection between sepsis and non-sepsis group based on the Fisher Exact Test (P-value > 0.05)

Table 4.4   The distribution of Sepsis Severity in The Sepsis Group

Sepsis Severity	Frequency	Percentage
Mild	15	50%
Severe	13	43.3%
Shock	2	6.7%
Total	30	100%

Table 4.5   The correlation of LDL level with the sepsis severity

Variable	n	r-value	P-value
LDL and sepsis severity	60	-0,318	0,013

This study suggested that the mean value of PCT for the sepsis group patients in the initial examination has reached the normal limit (< 0.05 ng/ml) about 20.02±20.51 ng/ml. This result was getting reduced from day 3 to 15.97±18.03 ng/ml, followed by day 5 become 16.82±20.75 ng/ml, as well as for the mean value of LDL in the early study was 77.70±33.42 mg/dl and getting increase from day 3 to 80.17±32.284 and become 83.50±38.68 mg/dl in the day 5. In the non-sepsis group, the mean PCT value at baseline was 0.74±1.24 ng/ml and decreased from day 3 to 0.48±0.81 ng/ml, then that value became 0.36±0.84 ng/ml in the day 5. The mean value of LDL in the non-sepsis group was found 102.23±45.90 mg/dl at baseline and increased to 112.10±48.44 mg/dl and 114±38.58 mg/dl in the day 3 and 5 respectively.

These laboratory results also explained that the PCT values in the sepsis group were higher than in the non-sepsis group, whereas the LDL values in the sepsis group were lower than in the non-sepsis group on day 1, 3, and 5.

Based on the Mann-Whitney test, the data were not normally distributed due to the P<0.05 for all PCT levels on day 1 to 5 which means there was a significant difference between the sepsis and non-sepsis groups for each PCT level. Whereas the LDL levels during treatment days 1 - 5 showed a significant difference between the sepsis and non-sepsis groups of LDL (p <0.05). According to these results, the hypothesis regarding with the relationship of the sepsis effect to the LDL value was acceptable.

According to the Table 4.4, the most of sepsis group was in mild-degree (50%), followed by severe-degree (43.3%) and shock about 6.7%.

The Spearman correlation test, due to the data was not normally distributed, indicated a significant negative correlation (r = - 0.318) between the LDL level on the first day of treatment with sepsis. It was suggested that the sepsis-degree severity increased and followed by the decrease of LDL level. So that,

the hypothesis regarding with the relationship of the LDL value with the sepsis-degree severity was acceptable.

DISCUSSION

Sepsis results from the interactions between pathogenic microorganisms and the immune system that triggers an inflammatory response/excessive and irregular inflammation which is devastating. Delayed diagnosis and treatment of sepsis lead to a worsening of illness that can cause circulatory collapse, multiple organ failures, and death.[1,9,10]

The results showed that the characteristic of the study subjects in the sepsis group was predominant in the 56-65 years old group (30%), followed by 36-45 years and 46-55 years old group (23.3%), and 25-35 years old group about 10%. Based on gender, female sex (53.3%) was more than male sex in the sepsis group. In addition, there was no statistically significant difference regarding with age and sex group in the sepsis and non-sepsis group based on Chi-square test (P > 0.05).

In the study of Gregg S Martin (2006), which conducted over 24 years from 1979 to 2002 with a total sample of 10,422,301 patients, it was found that the sepsis incidence increased in old age, and the age variable was an independent predictor of mortality.[11] Similarly, a study conducted by Nosheen Nasir (2015) in Pakistan in comparing male-sepsis-induced mortality versus female-acquired male mortality rates was found higher in men, where it was associated with higher levels of IL-6.[12]

According to the bacterial culture, it was found that most of the infection origin from gram-negative bacteria (50%) in the sepsis group, while the gram-positive bacteria accounted for 6.7%, and for the absence of bacteria about 26.7%. In addition, those results were also similar in the non-sepsis group, where the gram-negative bacteria accounted for 60%, followed by the absence of bacteria (30%), and the gram-positive bacteria about 10%. The P-value of Fisher Exact test was more than 0.05 (>0.05) where it indicated there was no statistically significant difference between the sepsis and non-sepsis group.

A study conducted by Abera Kumalo et al. (2013) in Western Ethiopia with 95 samples from March to June 2013 showed that most of the bacteria were gram-positive (53.3%), followed by gram-negative bacteria about 46.7%.[13] In contrast to the study which carried out at H. Adam Malik General Hospital where the gram-negative bacteria was predominant. This might be caused by the differences in the geographical location, epidemiological variation/ causative agents, the characteristics of patients, limited sample size, as well as the length of study.

The LDL values of the sepsis group in this study were 77.70±33.42 mg/dl at baseline and increased to 80.17±32.284 mg/dl and 83.50±38.68 mg/dl on day 3 and 5 of treatment respectively. Subsequently, the mean values of LDL of the non-sepsis group in the initial examination were 102.23±45.90 mg/dl, and it became 112.10±48.436 mg/dl and 114±38.58 mg/dl on day 3 and 5 of treatment respectively. Based on statistical analysis, there was found a significant difference of the LDL values between sepsis and non-sepsis groups either on day 1, 3, and 5 of treatment (P<0.05).

In 2011, Mitra Barati et al. conducted a comparative study of the lipid plasma concentrations in the sepsis and non-sepsis patients at ICU.[14] The results obtained the low levels of LDL and HDL but elevated triglyceride levels. Experimental studies showed that high levels of circulating cytokines would lower cholesterol levels during severe infections.

In the case of sepsis can be explained, based on the literature study, that there are significant changes in lipid metabolism and lipoprotein composition during the infection process. The infection and inflammation induce an acute-phase response (APR) which leads to some changes in the lipid and lipoprotein metabolism. Plasma triglyceride levels increase from the increased of VLDL secretion as a result of adipose tissue lipolysis, fatty acid synthesis de novo, and suppression of fatty acid oxidation. In the condition where more severe infections occurred, VLDL levels decline with a decreased of lipoprotein lipase and apolipoprotein E in VLDL. Based on a study conducted by Khovidkhunkit et al. (2004), there was a change in the metabolism of cholesterol, LDL, and HDL during infections.[3] LPS and cytokines lowered total serum cholesterol levels in primates, whereas in mice they increased the cholesterol levels but reduced the LDL levels in rats. In rats, hypercholesterolemia results from the elevated cholesterol and LDL, cholesterol conversion to bile acids, and cholesterol secretion in the bile. Some changes that take place in the proteins are critical to the HDL metabolism in reducing cholesterol-back transport and increasing cholesterol delivery to the immune cells. The oxidation of LDL and VLDL increases, while HDL becomes proinflammatory molecules. Lipoproteins will be ceramide, glucosylceramide, and sphingomyelin, where it can increase the uptake by macrophages. Thus, many changes in the lipoproteins are proatherogenic. The underlying molecular mechanisms in the decline of many proteins during APR are involved in the decrease of some hormone receptors, including peroxisome proliferator-activated receptor, liver X receptor, farnesoid X receptor, and retinoid X receptor. APR protects the host cell from harmful effects of bacteria, viruses, and parasites. However, if prolonged, some changes in the structure and function of lipoproteins will contribute to atherogenesis.[4,6,7,15]

REFERENCE

1. Artero A, Zaragoza R and Nogueira JM. Epidemiology of Severe Sepsis and Septic Shock. Severe Sepsis and Septic Shock - Understanding a Serious Killer. In-Tech. 2012:23. ISBN: 978-953-307-950-9,. Available at: http://www.intechopen.com/books/severe-sepsis-and-septic-shock-understanding-a-serious-killer/epidemiology-of-severe-sepsis-and-septic-shock

2. Badellino KO, Wolfe ML, Reilly MP, Rader DJ. Endothelial lipase is increased in vivo by inflammation in humans. Circulation. 2008; 117(5):678-85. DOI:10.1161/CIRCULATIONAHA.107.707349

3. Khovidhunkit W, Kim MS, Memon RA, Shigenaga JK, Moser AH, Feingold KR, Grunfeld C. Effects of infection and inflammation on lipid and lipoprotein metabolism: mechanisms and consequences to the host. J Lipid Res. 2004; 45(7):1169-96

4. Christ-Crain M and Muller B. Procalcitonin in bacterial infections — hype, hope, more or less?. Swiss Med Wkly. 2005; 135(31-32):451-460.

5. Van Leeuwen HJ, Heezius EC, Dallinga GM, van Striip JA, Verhoef J, van Kessel KP. Lipoprotein metabolism in patients with severe sepsis. Crit Care Med 2003; 31(5):1359-66

6. Neda Asem , Bobby B. Asem.The Many Faces of Cholesterol: How Modifications in LDL and HDL Alter Their Potential to Promote or Prevent Atherosclerosis. The UCLA USJ. 2009; 22

7. Wyllie DH, Bowler IC, Peto TE.Bacteraemia prediction in emergency medical admissions: role of C reactive protein. J Clin Pathol. 2005;58:352–356.

8. Purba DBP, Ginting F, Ginting Y. Kadar PCT sebagai marker dan hubungannya dengan derajat keparahan sepsis. Majalah Kedokteran Nusantara. 2012; 45(1): 1-6

9. Guntur AH, Setiadi S, Alwi I, Sudoyo AW, Simadibrata MK, Setiyohadi B, Syam AF,.Sepsis. Dalam Buku ajar ilmu penyakit dalam. Jilid III, Edisi VI. Interna Publishing, Jakarta. FK UI. 2014; 3(6): 692-699

10. Nasronudin. Imunopatogenesis sepsis dan prinsip penatalaksanaan. Dalam: Penyakit Infeksi di Indonesia, solusi kini dan mendatang, Airlangga University Press. 2007: 238-45.

11. Martin GS, Mannino DM, Moss M. The Effect of Age on the Development and Outcome of Adult Sepsis. Crit Care Med. 2006; 34(1):15-21.

12. Nasir N, Jamil B, Siddiqui S, Talat N, Khan FA, Hussain R. Mortality in sepsis and its relationship with gender. Pak J Med Sci. 2015; 31(5): 1201–1206.

13. Kumalo A, Kassa T, Mariam ZS, Daka D, and Tadesse AH. Bacterial Profile of Adult Sepsis and their Antimicrobial Susceptibility Pattern at Jimma University Specialized Hospital, South West Ethiopia. Health Science Journal. 2016; 10(2):3.

14. Barati M, Nazari MR, Taher MT, Farhadi N. Comparison of Lipid Profile in Septic and Non-Septic Patients, Iran J Clin Infect Dis. 2011; 6(4).

15. Kumaraswamy SB, Linder A, Akesson P, Dahlbäck B. Decreased plasma concentrations of apolipoprotein M in sepsis and systemic inflammatory response syndromes. Crit Care. 2012; 12;16(2):R60. doi: 10.1186/cc11305.