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Association between Interleukin 10 Serum Level and Non-Alcoholic Fatty Liver Disease

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Background. *In Non-Alcoholic Fatty Liver Disease (NAFLD), there is an inflammatory process due to lipotoxicity resulting in macrophage balance imbalance in the liver. Impaired balance of liver macrophages causes IL-10 production is decline, whereas the function of IL-10 is to repair hepatocellular damage. Through this research, we will study the role of cytokines, especially IL-10 as anti-inflammatory cytokines and laboratory abnormalities, especially liver enzymes and lipid profiles in relation to the pathogenesis and development of NAFLD so that it can be a non-invasive parameter to assess NAFLD severity.*
Aim. *To determine association of serum Interleukin 10 level with NAFLD and other marker associate with NAFLD.*
Methods. *Cross-sectional study of 30 consecutive NAFLD patients who came to Adam Malik General Hospital Medan,, from May to July 2018. NAFLD was diagnosed by abdominal ultrasound. Blood glucose, total cholesterol, triglycerides, high- and low-density lipoproteins, parameters of liver function, and IL-10 were measured in each subject. Continuous variables were expressed as mean ± SD or as median (min-max); qualitative variables were presented as proportions. The Student's t test or Mann Whitney was performed when two groups were compared. Spearman's correlation results were expressed as coefficients (r) and p values. Differences were considered significant when P< 0.05. All statistical analyses were performed using the SPSS 22.*
Results. *In comparison with control group, patients with NAFLD showed increased fasting blood sugar levels (160 vs. 99 mg / dl), AST levels (27.1 vs. 20.2 U/L), ALT levels (31.5 vs. 19.3 U /L), Total Cholesterol (259 vs. 174 mg / dL), Triglycerides (175 vs. 122 mg / dL), LDL (180 vs. 88 mg /dL) while HDL levels were lower in NAFLD than controls (40 vs. 61 mg /dL). Serum IL-10 levels were lower in the NAFLD group than controls (0.71 vs. 1.45 pg / ml, p <0.001). There is a negative correlation between IL-10 and AST (r = -0.57, p <0.001), ALT (r = -0.52, p = 0.002), Triglycerides (r = -0.62, p <0.001) and LDL (r = -0.66, p <0.001)) and there is a positive correlation between IL-10 levels and HDL (r = 0.48, p = 0.004)*
Conclusion. *There were significant difference between serum IL-10 levels, Fasting blood glucose, ALT, AST, total cholesterol, triglycerides , LDL and HDL in NAFLD patients compared to controls. There were negative correlation between ALT levels, AST, total cholesterol, triglycerides, and LDL with IL-10 levels while HDL levels were positively correlated with IL-10 levels.*
Keyword: *NAFLD, Interleukin 10, AST, ALT, Lipid Profile*

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I. Introduction

Non-alcoholic fatty liver disease (NAFLD) develops rapidly into chronic liver disease in developing countries. Its prevalence is increasing rapidly throughout the world in parallel with increasing obesity and type 2 diabetes[1]. The prevalence of NAFLD in the general population is estimated 20-30% in Western countries and 15% in Asian countries[2]. In Indonesia, not much data is obtained about the prevalence or incidence of NAFLD. In a study on the rural of Jakarta, the prevalence of NAFLD was 30%, most in the middle age (37.2%)[3].NAFLD is still considered not an important clinical diagnosis. Meanwhile, about 10-30% of NAFLD has the potential for progression and develops into non-alcoholic steatohepatitis, where 25-40% of patients with non-alcoholic steatoheapatitis will develop progressive liver fibrosis and 20-30% will end up with cirrhosis[4,5]. NAFLD is made up of two components: i) evidence of fatty liver and / or steatohepatitis histologically or imaging and ii) exclusion of other causes of fatty liver, such as significant alcohol consumption, steatogenic drug use and hereditary abnormalities etc.[4]

Interleukin-10 (IL-10) is an anti-inflammatory cytokine that works to inhibit the activity of Thelper 1 (Th1), Natural Killer cells (NK) and the macrophage phenotype M1. IL-10 produced by liver macrophages or Kuppfer cell M2 phenotypes that function in maintan the liver homeostasis. The inflammatory process in

NAFLDdue to lipotoxicity, resulting in macrophage balance imbalance in the liver. Imbalance of liver macrophages causes IL-10 production decline and so its function to repair hepatocellular damage [6-9]. Therefore, the aim of this study is to determine the association of serum IL-10 levels in NAFLD patients with controls, and determine correlation of serum IL-10 levels with other laboratory markers related to NAFLD in this case the levels of transaminase enzymes and lipid profiles.

II. Material And Methods

The present study was a cross sectional study on 30 consecutive NAFLD patients who were admitted to Gastroenterology-hepatology division of the Department of Internal Medicine, Adam Malik General Hospital Medan, Indonesia. 30 patients without NAFLD weretaken as controls. This study was conducted from May 2018 to July 2018.

Inclusion criteria:

1. Men and non-pregnant women, aged ≥ 18 years.
2. Diagnosed clinically and confirmed by abdominal ultrasound. Characterized of NAFLD on ultrasound at least if two of the following findings are found: hepatorenal contrast enhancement, bright liver texture (bright liver), deep attenuation and vascular blurring.
3. Not a regular drinker of alcohol <30 gr / day for men and <20 gr / day for women.
4. Receive voluntary and written information and participation agreements to undergo physical, laboratory, radiological examinations that are known and approved by the Health Ethics Research Committee.

Exclusion criteria:

1. Patients with Hepatitis B or Hepatitis C,
2. Kidney failure (LFG <60 ml / min / 1.73 m2) and
3. Suffering from malignancy or autoimmune disease.

Control Criteria:

1. Men and non-pregnant women aged ≥ 18 years
2. Not diagnosed with NAFLD by abdominal ultrasound examination.

All subjects were taken for venous blood for routine blood tests, HBsAg, Anti HCV, ALT, AST, alkaline phosphatase, Gamma GT, total bilirubin, urea, creatinine, albumin, and fasting blood sugar, lipid profile and IL-10 serum. Serum IL-10 levels were measured using the Quantikine® ELISA Human IL-10HS KIT (R & D Systems, Inc., Minneapolis, USA. All patients gave informed consent and the study was approved by the local ethics committee.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± SD and non-normally distributed continuous variables were expressed as median (min-max); qualitative variables were presented as proportions. The Student's t test or Mann Whitney was performed when two groups werecompared. Spearman'scorrelation results were expressed as coefficients (r) and p values. Differences were considered significant when $p<0.05$. All statistical analyses were performed using the SPSS 22.0

III. Result

Basic characteristics of the subjects

A total of 60 people, divided into two groups, 30 NAFLD subjects and 30 subjects without NAFLD as controls who met the inclusion criteria. The number of male subjects in the two groups was 16 people (53.3%) and women 14 people (46.7%). The mean age in the NAFLD group was 45.93 ± 11.7 years and in the control group it was 44.8 ± 12.0 years. The disease history in subjects in the NAFLD group was 17 subjects with diabetes mellitus (56.7%), 9 subjects with dyslipidemia (30%) and 4 subjects with hypertension (13.3%). BMI was higher in the NAFLD group at 29.44 ± 2.50 kg/m^2, while in the control group it was 23.66 ± 2.63 kg/m^2. The Independent T test showed that there were significant differences in BMI between the NAFLD and control groups ($p <0.001$).

Table 1.Basic characteristics of the subjects

Characteristics	NAFLD (n=30)	Control (n=30)	p
Gender[¥]			
Male	16 (53.3)	16 (53.3)	
Female	14 (46.7)	14 (46.7)	
Age (year)	45,93±11.7	44,8±12.0	0.713
Comorbid[¥]			
Diabetes Mellitus	17(56.7)	NA	
Dyslipidemia	9(30.0)		
Hypertension	4(13.3)		
BMI (kg/m^2)	29.44±2.50	23.66±2.63	< 0,001*

Data are presented as mean ± standard deviation.[¥] Data presented as percentage. * Significant differences were estimated by means of using the Student's t test. NA :*not available*

Characteristics of subject laboratories

Table 2 shows the laboratories characteristics in the NAFLD group and control. Using Mann Whitney u test, we found a significant difference between serum IL-10 levels in NAFLD patients and control, 0.71pg/ml (0.18-1.89 pg/ml) vs. 1.45 pg/ml (0.89-2.86pg/ml) with $p < 0.001$. Serum IL-10 levels in NAFLD patients were lower than in the control group.

In this study, there was a significant difference between the NAFLD group and controls on fasting blood sugar levels, AST, ALT, total cholesterol, triglycerides, HDL and LDL. Fasting blood sugar levels in the NAFLD group were 160 mg / dl (106-240) and in the control group 99 mg / dl (88-115). AST and ALT levels were higher in NAFLD group patients. AST levels in the NAFLD group were 27.1 U / L (20-33 U/L) and the control group was 20.2 U / L (16-25 U/L). ALT levels in the NAFLD group were 31.5 U / L (22-43 U/L) and the control group was 19.3 U / L (14-25 U/L). At the lipid profile level higher levels of total cholesterol, triglycerides and LDL were found in the NAFLD group while HDL levels were higher in the control group.

Table 2.Laboratories Characteristics

Parameters	NAFLD (n=30)	control (n=30)	P
IL-10 (pg/ml)	0.71(0.18-1.89)	1.45 (0.89-2.86)	<0,001
FBG (mg/dL)	161.5(106-240)	99.0(88-115)	<0,001
AST (U/L)	27.1 (20-33)	20.2(16-25)	<0,001
ALT (U/L)	31.5(22-43)	19.3(14-25)	<0,001
Total Cholesterol (mg/dL)	259.0(232-282)	174.0(166-184)	<0,001
Triglyceride (mg/dL)	175(155-210)	122(90-142)	<0,001
HDL(mg/dL)	40(33-56)	61(58-66)	<0,001
LDL (mg/dL)	180(156-209)	88(78-100)	<0,001

Data are presented as median (min-max). FBG : Fasting Blood Glucose, AST : Aspartate Transaminase, ALT :Alanin Transaminase, HDL : High Density Lipoprotein, LDL : Low Density Lipoprotein.

Correlation of serum IL-10 levels with AST, ALT and lipid profiles

Table 3 presents the correlation between serum IL-10 levels and liver enzymes, namely AST and ALT and lipid profiles in the NAFLD patient group. By using the Spearman correlation test there was a negative correlation between serum IL-10 levels and AST and ALT with moderate correlation forces of -0.57 and -0.52 with $p < 0.01$. With the same test, there was a strong negative correlation between serum IL-10 levels and triglyceride and LDL levels, which were -0.62 and -0.66 with $p < 0.001$. Correlation of IL-10 serum with total cholesterol level was -0.35 with $p = 0.028$. The correlation of IL-10 serum with HDL levels is a positive correlation with the value of the correlation coefficient is 0.48 with $p = 0.004$.

Table 3.Correlation of serum IL-10 levels with AST, ALT and lipid profiles

Laboratories Parameters	IL-10 Serum	
	r	P
AST	-0,57	< 0,001
ALT	-0,52	0,002
Total Cholesterol	-0,35	0,028
Triglyceride	-0,62	< 0,001
HDL	0,48	0,004
LDL	-0,66	< 0,001

IV. Discussion

Nonalcoholic fatty liver disease (NAFLD) is a health problem that develops throughout the world with a wide spectrum. This disease can develop from a simple fatty liver (simple steatosis) that is non-progressive to the form of nonalcoholic steatohepatitis (NASH) which is progressive and can develop into cirrhosis. The incidence is increased in the state of obesity, hyperlipidemia and diabetes mellitus[10-12].

In this study, we found that mostly NAFLD sufferers were male(53.5%). This is in accordance with previous studies. Borai et al found that NAFLD in male was 57.4% [13]. Browning et al in the Dallas Heart Study report that the prevalence of NAFLD sufferers in men is higher about42% [14]. Kojima et al In their study in Japan found male patients by 26% compared to women at 12.7% [15]. Some longitudinal studies state that the incidence of NAFLD is lower in women due to the protective effect of the hormone estrogen on the development of NAFLD[16]. The average age of NAFLD patients in this study was 45.93 ± 11.7 years which is still classified as productive age. This age is not different from previous studies. Zahran et al in a study in Cairo reported that the average age of NAFLD patients was 48.58 ± 6.22 years [17]. Das et al reported their research in India with the mean age of NAFLD patients about 42.02 ± 9.9 years[18]. Prasetya et al reported that 93.5% of NAFLD patients in CiptoMangunkusumo Hospital were above 40 years old[19]. With aging, the liver undergoes substantial changes in structure and function associated with significant disruption of many metabolic activities and liver detoxification so that the increase in age accompanied by risk factors can increase the incidence of NAFLD[20].

The mean BMI of NAFLD patients in this study was 29.44 ± 2.50 kg/m^2, which was included in the criteria for excess weight according to WHO criteria. In the study of Zahran et al[17] and Das et al [18], the BMI of NAFLD patients was 27.9 ± 4.26 kg/m^{2}and 25.33 ± 2.44 kg/m^2. Loomis et al reported that the risk of NAFLD increased with increasing BMI[21]. Angulo and Riley et al reported that BMI is a risk factor for liver disease[22,23]. Satapathy et al reported that obesity is closely related to NAFLD where the prevalence of NAFLD in obesity is 80% [1].

Previous research states that patients with type 2 diabetes diagnosed with NAFLD are 69% -87% [4]. A meta-analysis study by Hernaez et al reported that type 2 DM patients diagnosed with NAFLD were 69% [24]. In this study, fasting blood sugar levels of NAFLD patients were significantly different from controls, about 161.5 mg / dl (106-240) vs 99.0 mg / dL (88-115). Zahran et al and Borai et al in their study also reported a significant difference between fasting blood sugar levels in the NAFLD group compared to controls ($p < 0.001$) [13,17].

In this study, total cholesterol, triglyceride, HDL and LDL levels were significantly different in the NAFLD group and controls. Where there was an increase in total cholesterol, triglycerides and LDL levels and a decrease in HDL levels in the NAFLD group compared to controls. Borai et al also reported there were significant differences between NAFLD patients and controls on total cholesterol, triglycerides, LDL and HDL levels ($p < 0.001$)[13]. Rao et al reported a significant difference between the NAFLD and control groups, increase in serum total cholesterol levels ($p < 0.05$), LDL ($p < 0.05$) and triglycerides ($p < 0.05$) and significantly decreased in HDL ($p < 0.05$)[25].

In terms of liver function tests, there were significant differences in AST and ALT levels in this study, between NAFLD groups and controls. AST levels in the NAFLD group and controls were 27.1 U / L vs. 20.2 U / L ($p < 0.001$). ALT levels between the NAFLD group and controls were 31.5 U / L vs. 19.3 U / L ($p < 0.001$). Sanyal et al in their study reported there were significant differences in ALT and AST levels in the NAFLD group and controls. AST levels in the NAFLD group of 33.3 U / L and in the control group were 26 U / L ($p = 0.016$). ALT levels in the NAFLD group were 44.2 U / L and in the control group 20.8 U / L ($p = 0.021$)[26]. Tomizawa et al in their study also reported a significant difference in AST and ALT levels in the NAFLD group and controls ($p < 0.01$). [27] AST levels in the NAFLD group and control were 38.5 ± 2.9 mg/dL vs. 12.8 ± 3.2 mg/dL. ALT levels in the NAFLD group were 44.5 ± 3.6 and in the control group 20.6 ± 4.0 mg/dL. Previous studies based on liver enzyme screening have consistently reported a lower prevalence of NAFLD (3-12%) than imaging or histological studies. Normal liver enzyme levels are found in subjects with the entire NAFLD spectrum, and therefore ALT, AST is not very useful in predicting NAFLD. Normal liver enzyme levels in NAFLD patients can make patients not aware of the existence and development of this disease[28,29]. The World Gastroenterology Organization (WGO) in its guidelines states that obesity, diabetes and ALT / AST of more than 27 IU / L are associated with high risk of developing into NASH. Metabolic syndrome, diabetes, increased ALT and AST are independent predictors of development and death in NAFLD[30].

IL-10 is an anti-inflammatory cytokine produced by Kuppfer cells in the liver. The level of IL-10 serum will decrease in chronic inflammatory conditions such as NAFLD due to the phenotypic shift of Kuppfer cells towards the M1 phenotype compared to the M2 phenotype. In this study there was a significant difference between serum IL-10 levels in NAFLD patients compared to control where IL-10 levels of NAFLD patients were lower than controls ($p<0.001$). Paredes et al in their study showed low IL-10 levels compared to controls ($p= 0.002$)[31]. Zahran et al also found IL-10 levels in NAFLD patients compared to controls were 5.59 ± 1.03 vs. 8.07 ± 1.82 ($p < 0.01$)[17]. In previous study found that treatment with IL-10 could significantly reduce TNF-α mRNA expression in the liver in rats with NAFLD[8,22]. These findings suggest that IL-10 is able to prevent liver damage and limit the effects of the inflammatory response on NAFLD.

In the correlation test in this study, it was found that there was a negative correlation between IL-10 and AST, ALT, total cholesterol, triglycerides, and LDL while with HDL levels; there was a positive correlation with serum IL-10. This is in line with the research of Zahran et al, where ALT and triglyceride levels were

negatively correlated with IL-10 levels (-0.11 and -0.59) while HDL levels were positively correlated with IL-10 (0.62). In NAFLD hepatocyte cell damage occurs due to accumulation of triglycerides in liver cells. The lower levels of IL-10 indicate the more intense inflammation in liver cells; will cause liver enzyme levels to increase[17]. The Rabelo et al study found that dyslipidemia was negatively correlated with IL-10 levels ($r = -0.36$, $p = 0.009$)[32].

NAFLD cannot consider as mild disease, because NAFLD can develop to progressive form and cause permanent liver damage. Increased inflammation and decreased anti-inflammatory cytokines characterized by decreased serum IL-10 levels, is a marker of progression of this disease. Liver enzyme levels that are still within normal limits or only slightly increased can be a gap for more aggressive treatment of NAFLD. The condition of dyslipidemia, especially hyper-triglycerides, is an independent factor in the incidence of NAFLD and need to be controlled. Through this research, it is expected that it can illustrate the role of cytokines especially IL-10 as anti-inflammatory cytokines and laboratory abnormalities, especially liver enzymes and lipid profiles in relation to the pathogenesis and development of NAFLD so that it can be a non-invasive parameter to assess NAFLD severity.

V. Conclusion

There were significant differences between serum IL-10 levels, Fasting blood glucose, ALT, AST, total cholesterol, triglycerides, LDL and HDLin NAFLD patients compared to controls. There were negative correlations between ALT levels, AST, total cholesterol, triglycerides, and LDL with IL-10 levels while HDL levels were positively correlated with IL-10 levels.

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