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Original Article

Hyperuricemia as an independent risk factor for non-alcoholic fatty liver disease (NAFLD) progression evaluated using controlled attenuation parameter-transient elastography: Lesson learnt from tertiary referral center

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ABSTRACT

Background and aim: Hyperuricemia is one of the metabolic parameter which has been considered to play an important role in non-alcoholic fatty liver disease (NAFLD). However, there is still lack of studies about association between serum uric acid with liver disease progression in NAFLD. This study aimed to know the association between hyperuricemia with moderate to severe steatosis and significant fibrosis along with other metabolic factors in NAFLD patients evaluated using Controlled Attenuation Parameter (CAP) – Transient Elastography (TE).

Methods: This is a prospective study in NAFLD patients who came to our tertiary referral center University hospital hepatobiliary outpatient's clinic. All patients underwent metabolic parameters measurement including serum uric acid level and CAP-TE examination. Cutoff value used for significant liver fibrosis ≥7 kPa and ≥285 dB/m for moderate-severe steatosis.

Results: Of 113 NAFLD patients, there were 45 patients with moderate-severe steatosis and 34 patients with significant fibrosis. Multivariate analysis showed only high level of fasting blood glucose (OR 2756; 95% CI 1.131–6.717) and low HDL level (OR 4.196, 95% CI 1.22–14.430) to be independent risk factors of moderate-severe steatosis. High level of fasting blood glucose (OR 3.98, 95% CI 1.105–14.389) and hyperuricemia (OR 2.501, 95% CI 1.095–5.714) were found to be independent risk factors for significant liver fibrosis.

Conclusion: Hyperuricemia is found to be an independent risk factor for significant liver fibrosis.

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of disease which is characterized by the accumulation of excess fat in the liver without any cause of secondary steatosis [1]. It is the most responsible cause for advanced chronic liver disease in Western countries and its prevalence also has been increasing in Asian countries [2]. NAFLD prevalence in Indonesia has been increasing from 30% in 2002 to 51% in 2015 [3]. NAFLD was previously considered to be a benign condition, but many studies have shown that simple steatosis can progress not only to steatohepatitis (NASH) [4], but also to liver cirrhosis and liver cancer [5]. Approximately around 20% of NASH progress to cirrhosis which has an increased risk in hepatocellular carcinoma (HCC) development in 15 years' time [6].

The gold standard tool in diagnosing NASH is still liver biopsy, but it is known as an invasive procedure and still unethical to do liver biopsy repeatedly in evaluating the progression of NAFLD [7]. NAFLD is not only proven to increase mortality related to liver

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disease but also to cardiovascular diseases [8], thus many non-invasive methods in evaluating liver disease progression has been developed. Recently, transient elastography (TE) with controlled attenuation parameter (CAP) is a non-invasive tools which has been proven to have a good accuracy in evaluating the degree of liver fibrosis and steatosis [7].

Hypothetically, there is a strong relationship between NAFLD and metabolic syndrome [9]. Metabolic syndrome is also known to be associated with hyperuricemia. Hyperinsulinemia can cause an increase in uric acid synthesis and decreasing its excretion [10]. Studies on NAFLD and uric acid level have frequently been done but studies on the correlation of uric acid and the histological changes in NAFLD is still lacking and still have conflicting results [11–13]. Therefore, this study aims to find the association between uric acid and other metabolic factors with the degree of steatosis and fibrosis evaluated by TE-CAP.

2. Methods

This was a prospective and cross sectional study in NAFLD patients at Cipto Mangunkusumo Hospital Hepatobiliary outpatient's clinic between 2016 and 2018 period. Study subjects were recruited consecutively. Inclusion criteria are NAFLD patients diagnosed with transabdominal USG and aged 18 years or older. Exclusion criteria are the following, (i) history of alcohol consumption, (ii) viral hepatitis infection, (iii) medication may cause liver steatosis, (iv) medication with uric acid lowering drugs, (v) stage 5 chronic kidney disease. The minimum sample size to examine the relationship of each metabolic syndrome components and hyperuricemia with moderate to severe steatosis and significant fibrosis is calculated using the formula to compare proportion of two population with independent sample: $(n = \frac{(Z\alpha\sqrt{2P(1-P)} + Z\beta\sqrt{P1(1-P1)+P2(1-P2)})2}{(P1-P2)2})$, with $\alpha = 0{,}05$ and $\beta = 90\%$.We found a total of 96 samples were required from the above equation.

Clinical evaluations, history of medications and anthropometric were carried out at the time of TE measurement. Body mass index (BMI) was calculated based on body weight in kilograms divided by the square of body height in meter. Waist circumference were measured from the line crossing umbilicus and iliac crest. Blood pressure were measured twice with 5 minutes' rest in between examination. Blood samples were taken after a minimum of 12 hours fasting to evaluate HDL, triglyceride, blood uric acid, fasting blood glucose and creatinine. Glomerular filtration rate (GFR) was estimated form the chronic kidney disease epidemiology collaboration (CKD-EPI) equation. Metabolic syndrome was diagnosed according to ATP III criteria [14]. Transient elastography (Fibroscan®) were done to evaluate the degree of steatosis and fibrosis, with TE cutoff for significant fibrosis is ≥ 7 kPa and CAP cutoff for moderate-severe steatosis is ≥ 285 dB/m [7].

Numeric variables were summarized as mean ± standard of deviation (SD) or median (min-max) if the distribution is not normal, and categorical variables as frequency and percentage. The *t*-test and chi squared test were used as appropriate. Multiple logistical regression model was used to assess factors associated with moderate-severe steatosis and significant fibrosis. Evaluated risk factors were central obesity, low HDL level, high triglyceride level, high blood pressure level and high level of fasting blood glucose level and hyperuricemia. Hyperuricemia was diagnosed when uric acid (UA) level > 7 mg/dL in men and >6 mg/dL in women [11,15]. Central obesity defined as waist circumference ≥ 90 cm in male or ≥ 80 cm in women. Low HDL level defined as a level of ≤40 mg/dL in men and ≤50 mg/dL in women or currently using lipid medication. High triglyceride level when triglyceride >150 mg/dL or currently using lipid lowering medication. High level of blood pressure defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or currently on antihypertensive medication. High level of fasting blood glucose defined as ≥100 mg/dL or currently on glucose lowering medication [14]. To avoid confounding factors, factors which affect uric acid level such as chronic kidney disease, sex and medications (statin, aspirin and bisoprolol) were analyzed using chi square test. Statistical analysis was done using SPSS version 16. This study has been approved by the University Ethics committee with no. 0208/UN2.F1/ETIK/2018.

3. Result

3.1. Patients' characteristics

There are 113 subjects who were recruited and subjects' characteristic is shown in Table 1. The majority of our subjects have type 2 diabetes, obesity and metabolic syndrome. Hyperuricemia was found in 45.5% of subjects with median uric acid 6.50 mg/dL (min-max 4.0–9.9 mg/dL). Factors which might influence uric acid level, such as male sex, medications (statin, aspirin and bisoprolol) and chronic kidney disease are distributed evenly in every group of fibrosis or steatosis. There are 20% of study subjects have an eGFR between 30 and 60 mL/min/1,73 m^2 and the rest of the subjects have normal GFR. There's no subject on diuretic, immunosuppressive agents or cytotoxic drugs.

3.2. Association between uric acid and the degree of NAFLD steatosis

Subjects in mild steatosis group have a statistically significant lower mean uric acid level when compared to moderate-severe steatosis group (6.31 mg/dL vs 6.94 mg/dL, $p = 0.03$). Univariate analysis revealed that hyperuricemia, central obesity, high level in fasting blood glucose level, low HDL level are associated with moderate-severe steatosis. But logistical regression analysis shows only low HDL level and increase in fasting blood glucose level had a significant correlation with odds ratio (OR) of 2.756 (95% CI of 1.131–6.717) and 4.196 (95% CI of 1.22–14.430) consecutively. Univariate and multivariate analysis between hyperuricemia and the degree of steatosis is shown in Table 2.

3.3. Association between uric acid and the degree of NAFLD fibrosis

Significant liver fibrosis group tend to have a higher mean value for uric acid (6.89 mg/dL vs 6.42 mg/dL) with p value = 0.145. Multivariate analysis shows that increase in fasting blood glucose level (OR 3.893; 95% CI = 1.062–13.269) and hyperuricemia (OR 2.450; 95% CI = 1.054–5.697) were independently correlated with significant fibrosis. Univariate and multivariate analysis between metabolic syndrome components and the degree of fibrosis is shown in Table 3.

4. Discussion

NAFLD is a multifactorial disease and it is known to be associated with other metabolic diseases such as obesity, diabetes mellitus and metabolic syndrome [16]. Most of the study subjects with NAFLD have BMI >25 kg/m^2, high level of fasting blood glucose, high level of blood pressure, central obesity and metabolic syndrome, but have normal HDL and triglyceride. It is thought because around 80% of the subjects are on statin medication. Besides associated with metabolic syndrome, literature data showed that hyperuricemia are associated with the incidence of NAFLD [17–20]. There are only a few studies investigate the association between

Table 1
Demographic, laboratory, and metabolic features of 113 patients with NAFLD.

Variable	Total	Mild Steatosis (n = 68)	Moderate-severe steatosis (n = 45)	Non-significant fibrosis (n = 79)	Signicant fibrosis (n = 34)
Gender					
Male	49(43.4%)	31/68	18/45	32/79	17/34
Female	64 (56.6%)	37/68	27/45	47/79	17/34
Median age in years (min-max)	58 (21–78)	57 (27–78)	53.73 (21–77)	57 (21–78)	59 (34–77)
<50 years	27 (23.9%)	14/68	13/45	20/79	7/34
≥50 years	86 (76.1%)	54/68	32/45	59/79	27/34
Mean BMI in kg/m^2 (SD)	27.47 (4.10)	26.83 (4.22)	30.54 (4.69)	27.66 (4.68)	29.80 (4.67)
BMI < 25	29 (25.7%)	24/68	5/45	22/79	7/34
BMI ≥ 25	84 (74.3%)	44/68	40/45	57/79	27/34
Mean waist in cm (SD)	99.34 (10,19)	96 (78–113)	101 (84–129)	97.53 (9.31)	101.90 (10.88)
Normal	10 (8.8%)	9/68	1/45	6/79	4/34
Central obesity	103 (91.2%)	59/68	44/45	73/79	30/34
High level of blood glucose					
No	25 (22.1%)	20/68	5/45	22/79	3/34
Yes	88 (77.9%)	48/68	40/45	57/79	31/34
High level of blood pressure					
No	36 (31.9%)	25/68	11/45	26/79	10/34
Yes	77 (68.1%)	43/68	34/45	53/79	24/34
Median triglyceride in mg/dL (min-max)	130 (48 –419)	118 (48–419)	152 (71–368)	128 (48–419)	140 (74–368)
Normal	63 (55,8%)	40/68	16/45	44/79	19/34
High level	50 (44,2%)	28/68	29/45	35/79	15/34
Mean HDL, in mg/dL (SD)	46.27 (10.0)	48.10 (9.79)	43.82 (9.96)	46.19 (9.65)	46.91(11.05)
Normal	58 (51.3%)	42/68	16/45	41/79	17/34
Low level	(48.7%)	26/68	29/45	38/79	17/34
Metabolic Syndrome					
No	24 (21.2%)	19/68	5/45	19/79	5/34
Yes	(78.8%)	49/68	40/45	60/79	29/34
Mean uric acid in mg/dL (SD)	6.56 (1.52)	6,31 (1,44)	6,94 (1,62)	6,42 (1,50)	6,89 (1,60)
Normal	61 (54.6%)	42/68	19/45	48/79	13/34
Hyperuricemia	52 (45.4%)	26/68	26/45	31/79	21/34
Statin consumption					
No	21 (18.6%)	11/68	10/45	16/79	5/34
Yes	92 (81.4%)	57/68	35/45	63/79	29/34
Bisoprolol consumption					
No	93 (82.3%)	59/68	34/45	66/79	27/34
Yes	20 (17.7%)	9/68	11/45	13/79	7/34
Aspirin consumption					
No	56 (49.5%)	38/68	18/45	39/79	17/34
Yes	57 (50.5%)	30/68	27/45	40/79	17/34
CKD eGFR >60	90 (79.6%)	54/68	36/45	62/79	28/34
eGFR < 60	23 (20.4%)	14/68	9/45	28/34	6/34

Note: BMI = body mass index, CKD = chronic kidney disease, eGFR: estimated glomerular filtration rate, HDL = high-density lipoprotein, SD = standard deviation.

Table 2
Univariate and multivariate analysis between hyperuricemia and the degree of steatosis.

Variabel	Univariat analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Central obesity	6.71 (0.82–54.95)	0.049	8.00 (0.835–76.642)	0.071
High level of blood pressure	1.66 (0.67–4.08)	0.262	–	–
High level of fasting blood glucose	3.33 (1.14–9.67)	0.022	4.196 (1.22–14.43)	0.023
Low HDL level	2.92 (1.33–6.40)	0.006	2.756 (1.131–6.717)	0.026
High trygliceride level	1.366 (0.64–2.91)	0.419	–	–
Hyperuricemia	2.211 (1.02–4.76)	0.041	1.878 (0.811–4.349)	0.141

HDL = High-density lipoprotein, OR = odds ratio.

serum uric acid level with the severity of NAFLD, and the results are still conflicting. To our knowledge, this is the first study which investigated the association of hyperuricemia with the severity of NAFLD measured by TE-CAP. TE-CAP has been validated for steatosis and fibrosis evaluation in NAFLD patients [21].

This study also takes into consideration to other factors which are usually found in NAFLD subjects where it might influence uric acid level, such as sex, antihypertensive medications, statin, antiplatelet agent, and renal impairments. Male subjects will have higher uric acid level than female subjects [22]. Chronic kidney disease will lower uric acid excretion thus plasma uric acid level will rise [23]. There are three groups of medications that are analyzed in this study, namely statin, bisoprolol and aspirin. Statin, beside its lipid lowering property, also has a significant effect in lowering plasma uric acid level [4]. Study from Ueno et all showed that diuretic, beta blocker and alpha-1 blocker might increase plasma uric acid level, while other drugs such as calcium channel blocker, ACE inhibitor, angiotensin receptor blocker (ARB) including losartan will not increase plasma uric acid level [24]. In this study a small proportion of subject taking bisoprolol, and none of them on

Table 3
Univariate and multivariate analysis between metabolic syndrome components and the degree of fibrosis.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Central obesity	0.616 (0.162–2.342)	0.485	–	–
High level of blood pressure	0.942 (0.377–2.352)	0.897	–	–
High level of fasting blood glucose	3.988 (1.105–14.389)	0.025	3.893 (1.062–13.269)	0.040
Low HDL level	1.079 (0.483–2.411)	0.853	–	–
High triglyceride level	0.992 (0.442–2.230)	0.985	–	–
Hyperuricemia	2.501 (1.095–5.714)	0.028	2.450 (1.054–5.697)	0.037

HDL = High-density lipoprotein, OR = odds ratio.

diuretic or alpha-1 blocker therapy. Other drug that can affect uric acid level is aspirin. Low dose aspirin can give rise to plasma uric acid level due to the decrease of uric acid excretion [7]. Male sex, chronic kidney disease, medication taken (simvastatin or atorvastatin, bisoprolol and aspirin) are evenly distributed among the steatosis and fibrosis groups so it won't influence the study results.

Univariate analysis shows that hyperuricemia is associated with the degree of steatosis, although there was no significant association found after adjusting for confounding factors. Even though hyperuricemia is not independently correlated with the degree of steatosis, the mean of uric acid level is significantly higher in moderate to severe steatosis group than mild steatosis. The pathogenesis of hyperuricemia leading to steatosis is still unclear and there is no study yet in human population. In vitro studies and studies in rat showed that uric acid causes triglyceride accumulation in hepatocyte by increasing the expression of lipogenic enzymes through stress in endoplasmic reticulum (ER). Uric acid also activates NADPH oxidase which resulted in ROS (reactive oxygen species) formation in mitochondria resulting in lipogenesis in liver. ROS accumulation also induces stress cascade in ER which subsequently increase the expression of lipogenic gene and the production of triglyceride [25].

Multivariate analysis from this study shows that significant fibrosis is correlated independently with hyperuricemia and high level of fasting blood glucose. This result is different from studies by Huang and Petta which found that hyperuricemia is not correlated with the degree of fibrosis but more with lobular inflammation [11,12]. Chronic inflammation activates liver stellate cell, the main source of myofibroblast in liver, and subsequently causing fibrosis [26]. Study from Sertoglu et all in 2014 suggested that hyperuricemia is associated with hepatocytes ballooning but not with fibrosis. Lobular inflammation and hepatocytes ballooning are obtained from liver biopsy data, thus is unavailable in this study. Study from Zeng et all suggested that inflammation will correlate positively with TE value. Subjects with the same fibrosis degree but with higher inflammation will have higher TE value [27]. Another study from Wong et all suggested that TE value has significant correlation with hepatocyte ballooning and lobular inflammation [28]. This different results might be due to a cross-sectional design study or because most of our subjects has more liver disease progression and NAFLD is still a dynamic process.

Mean uric acid level in significant fibrosis group was found to be higher than in non-significant fibrosis group, even though not statistically significant. Uric acid can causes pro inflammatory condition, whereas uric acid increases the expression of monocyte chemoattractant protein-1 (MCP-1) and activates NLRP3 inflammasomes. Inflammation will activates liver macrophage and cytokine secretions and ROS productions [29]. Oxidative stress will result in hepatocytes necrosis and apoptosis, and also increase the inflammation response. ROS also stimulates profibrogenesis mediator from Kupffer cell and inflammatory cells, subsequently activates stellate cells and initiates fibrosis process [30]. Uric acid can also cause the decrease of nitric oxide (NO) production and causes liver sinusoid endothelial dysfunction, which can also activates the stellate cell. Liver sinusoid is also responsible for liver cell regeneration [31]. Our study results suggest that treating hyperuricemia is might be an important thing in clinical practice to prevent liver disease progression in NASH.

The limitation of this study is that our study was a cross-sectional study and it couldn't prove the causality connection of uric acid and NAFLD. Another factors which might affect NAFLD development such as dietary intake, degree of insulin resistance (HOMA-IR), genetic polymorphism, inflammation conditions and adiponectin are also not evaluated yet, however it is not easy to obtain these data.

5. Conclusion

This study suggested that hyperuricemia is an independent risk factor for liver disease progression in NAFLD patients and it needs to take account when managing NAFLD patients.

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The authors declare there is no conflict of interest.

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