Journal of Muhammad Medical College
Website: jmmc.mmc.edu.pk

Original Article

Association of nonalcoholic fatty liver disease with uric acid, BMI and dyslipidemia.

Sadia Rehman [1, *] Huma Salahuddin[2], Hina Moazzam[3], Sana Ahmed[4], Shazia Junaid[5], Muhammad Farhan[6],

1: Assistant professor
Department of Biochemistry
BUHS, Karachi.

2: Assistant professor
Department of Physiology
Zia Uddin medical university
Karachi.

3: Assistant professor
Department of Physiology
BUHS, Karachi.

4: Assistant professor
Department of Biochemistry
BUHS, Karachi.

5: Physiology Lecturer; Army medical college, Rawalpindi.

6: Associate Professor
Department of Biochemistry
University of Karachi.

***=corresponding author**

dr.sadia89@hotmail.com

Abstract:

Introduction: Nonalcoholic fatty liver disease (NAFLD) is gradually recognized as a main health challenge especially in the developed countries. NAFLD comprises of a series of liver damage that may vary from simple steatotic fluctuations to nonalcoholic steatohepatitis, fibrosis and progression to cirrhosis.

Objectives: To assess the association of non-alcoholic fatty liver disease with BMI, lipid profile and serum uric acid.

Methodology: This comparative study, after approval from Ethical review Board of the Institute, was carried out at Sharif Medical city hospital, a tertiary care hospital. The 200 patients of nonalcoholic fatty liver disease (NAFLD) were selected from the medical ward, considering inclusion and exclusion criteria. For control group, subjects were recruited from local population. The obtained data was statistically analyzed using SPSS version 23.0. The parameters compared between two groups includes lipid profile, serum uric acid, diastolic and systolic blood pressure, BMI and age.

Results: Significant statistical differences were seen between the results of two groups. Mean serum uric acid found raised in study group when compared with controls. BMI along with diastolic and systolic blood pressures were seen to be elevated in NAFLD group. Dyslipidemia was also found to be present in NAFLD group.

Conclusions: The study can be concluded that raised BMI, serum cholesterol and triglycerides and uric acid are correlated with progress of the non-alcoholic fatty liver disease. These findings can be used by the physicians for early detection and prevention of the progression of NAFLD.

Keywords: uric acid, Non-alcoholic fatty liver disease, body mass index.

Introduction:

Non alcoholic fatty Nonalcoholic fatty liver disease is a medical pathologic unit gradually recognized as a main health challenge especially in the developed countries.[1] NAFLD comprises of a series of liver damage that may vary from simple steatotic fluctuations to nonalcoholic steatohepatitis, fibrosis and progression to cirrhosis.[2] NAFLD is categorized by the presence of increased triglycerides in the liver. Lipolysis produces serum free fatty acids which leads to de novo biosynthesis of hepatic triglycerides. This dietary fat along with the de novo synthesis contributes to the pathogenesis of NAFLD. Around 10–25% patients of NAFLD develop nonalcoholic steatohepatitis (NASH), the advanced type of hepatic steatosis. In genetically prone individuals, this increased lipid content exceeds the oxidative capacity leading to production of free radicals.[3] This leads to cytokine induction, lipid peroxidation, chemo attraction of inflammatory mediators, activation of hepatic stellate cell and lastly fibro genesis with fat deposition in the extracellular matrix.[4] Although, the risk for developing NAFLD in an individual increases when the body mass index (BMI) increases,

however NAFLD is also present in non-obese individuals (BMI < 30 kg m−2 in non-Asians; <27.5 kg m−2 in Asians) and in individuals having normal body weight (BMI < 25 kg m−2 in non-Asians; <23 kg m−2 in Asians).[5] According to National Health and Nutrition Examination Survey (NHANES) study conducted in 2012, the prevalence of NAFLD during 1988-1994 in lean individuals (BMI < 25 kg m−2) in the United States was 7%.[6]

Serum Uric acid (SUA) is a terminal product of catabolism of purine. High levels of serum uric acid in the body may arise due to any defect in the process of uric acid synthesis or excretion. Many previous studies found an increased activity of the enzyme xanthine oxidoreductase with NAFLD.[6] This enzyme catalyzes the main step in production of uric acid. Raised uric acid levels lead to over-expression of pro-lipogenic enzymes and sterol regulatory element-binding proteins (SREBP).[7] Both these changes lead to increased synthesis and deposition of triglycerides. NAFLD is widely considered as a hepatic complication of metabolic syndrome.[8] The oxidative properties of uric acid led to the advancement of liver injury. In NAFLD the irregularities of lipid metabolism such as increased free fatty acid uptake, lipolysis along with decreased fatty acid oxidation and deposition of triglycerides lead to buildup of lipids inside the liver cells.[9] These shifts in the metabolism of lipids are associated with an initiation of inflammatory cascade and oxidative stress along with an abnormal production of adipokines that disturb signaling pathways.[10] Many other cytokines which include Interleukin-6,interleukin-1, tumor necrosis factor-alpha, and acute phase proteins are involved in the process as explained in proteomic studies.[11] Several studies suggest that obesity and raised UA levels synergistically interacted to raise the risk of NAFLD and hypertriglyceridemia.[12]

As non-alcoholic steatohepatitis and hepatic fibrosis can progress to liver cirrhosis, early detection and timely intervention and lifestyle modification can prevent the disease from progressing. Hence detection and evaluation of predictive factors and early biomarkers of NAFLD and of its progressive forms is needed. Serum uric acid, deranged BMI and dyslipidemia are among the biomarkers which serve as early detectors of the progression and severity of hepatic damage in NAFLD. All these factors have common metabolic reactions and are linked with hepatic steatosis and metabolic syndrome, therefore proposing a likely synergistic activity.[13] During present study, we tried to find out the link of NAFLD with BMI, serum uric acid and lipid profile. Findings may prove useful, to gastroenterologists, for understanding the synergistic action of the studied biomarkers. This will help in identification of high-risk group and screening will therefore, may lead to early detection of NAFLD patients.

Methodology:

This comparative study, after approval from Ethical review Board of the Institute, was carried out at Sharif Medical city hospital Lahore from January 2018-November 2018. Sample size calculated using Open epi software using parameters from a study carried out in China.[12] Sample size (n=200) achieved using non-probability consecutive sampling technique and divided in 2 groups. The control group (group A) included 100 healthy subjects without any history of chronic illness or alcohol use. The study group (group B) included 100 non-alcoholic subjects with fatty liver disease based on the findings of ultrasound. Subjects included were of either gender between 18 to 60 years. Those with the history of drug addiction, alcohol intake and viral hepatitis were excluded. Lab investigations performed and recorded were in both groups. Hypertensive cut-off values were 140 mmHg for systolic and 90 mmHg BP for diastolic BP respectively. Anonymity of data ensured. After informed consent, blood samples were withdrawn from the subjects. Serum uric acid was estimated using the commercial sensitive quantitative fluorometric uric acid assay Kit with catalog Number STA375. The formula used for BMI calculation is; Body mass index (BMI) = Weight in kilograms (height in meter) x2. Ultrasonography is considered as a reliable and non-invasive way for the detection of abnormality in liver architecture having a sensitivity range of 82%-89% and a specificity of 93% for identification of fatty infiltration. Using ultrasonography fatty liver is identified as an echogenic organ with more echogenicity as compared to the right kidney.[13] Steatosis is graded as mild, moderate and severe. In Mild steatosis, high liver echogenicity is observed with normal intra hepatic vessels and diaphragm. In moderate steatotic change, mildly increased echogenicity with mildly obscured visualization of diaphragm is seen. In severe steatosis highly echogenic liver with poor visualization of diaphragm and intrahepatic vessels is observed along with obscured penetration. [13]

IBM SPSS version 23.0 was applied to enter and evaluate the data. Independent sample t-test was utilized to compare means between two study groups. Pearson Correlation was used to find the any relation of NAFLD with serum uric acid. p-value of less than 0.05 was taken statistically significant.

Results:

Comparison of demographic variables between two groups is shown in table 1. As evident from the table, the difference between all these variables for both groups were statistically significant ($p < 0.05$) except for total cholesterol. The Pearson correlation coefficient between NAFLD and study variables is shown in table 2. We observed positive correlation of NAFLD with SAU, BMI, total cholesterol and LDL, while we observed negative correlation of NAFLD with TG, ALT, SBP, DBP, FPG and HDL.

Table No 1: Baseline attributes of samples

Attributes	Controls (n=100)		Cases (n=100)		P value
	Mean	±SD	Mean	±SD	
Age (years)	41.9	5.4	46.6	5.8	<0.01*
BMI (kg/m^2)	25.1	1.4	32.1	5.3	<0.01*
SBP	107.6	9.0	133.5	8.4	<0.01*
DBP	66.4	8.0	76.3	7.6	<0.01*
Fasting plasma glucose	5.4	0.4	6.0	0.6	<0.01*
Triglycerides mmol/l	1.2	0.1	3.1	0.5	<0.01*
Total cholesterol	6.3	7.2	6.1	0.4	0.85
HDL	1.3	0.2	0.9	0.2	<0.01*
LDL	2.7	0.4	3.4	0.4	<0.01*
serum uric acid	236.6	39.0	355.7	40.2	<0.01*

p-*value of < 0.05 was considered significant using independent sample t test.*

Table No 2: Correlation Analysis of Studied Parameters with NAFLD (n=100)

Parameters	r-value	p-value
serum uric acid	0.80	<0.01*
BMI	0.09	0.37
Triglycerides mmol/l	-0.08	0.43
SBP	-0.10	0.28
DBP	-0.009	0.93
Fasting plasma glucose	-0.11	0.23
Total cholesterol	0.05	0.61
HDL	-0.17	0.07
LDL	0.01	0.91

P –value of < 0.05 was considered statistically significant

Discussion:

In our country fatty liver disease often remains undiagnosed due to the lack of proper screening and non-identification of risk factors that leads to progression of fatty liver disease. The aim of current study was to detect correlation of NAFLD with BMI, lipid profile and serum uric acid. Results showed that an increase in BMI is correlated with NAFLD, making obesity a predisposing factor for fatty liver disease. This association can be explained by an increase in the visceral adipose tissue along with an increase in serum triglycerides, both of these factors lead to metabolic syndrome and rise concomitantly in obesity and NAFLD.[14] Also serum uric acid showed a positive correlation, a finding in agreement with published research.[15,16] This association can be explained by the increased activity of the enzyme xanthine oxidoreductase in NAFLD patients which leads to excessive production of uric acid. These results provide a significant basis of relationship between NAFLD and raised serum uric acid.[17]

Our results showed derangement of lipid profile. Total serum triglycerides, serum cholesterol and LDL were significantly raised in NAFLD group. While serum HDL was found to be lower in this group. Many studies have revealed a connection amongst insulin resistance and NAFLD. These changes can be explained by the mechanism that insulin has antilipolytic effects and insulin resistance leads to an increase in lipolysis in the peripheral adipose tissues which causes upsurge of free fatty acids levels.[18] The higher levels of free fatty acids lead their deposition in sub cellular organelles that causes dysfunction of mitochondria and endoplasmic reticulum leading to the development of lipotoxicity.[19] Moreover the deposition of fat in blood vessels leads to atherosclerotic changes in these vessels. We found mean fasting plasma glucose raised in study group, a finding that probably indicates insulin resistance and hyperglycemic state in these patients. We observed that in NAFLD group the systolic and diastolic blood pressures were significantly raised. These findings are in agreement with published research that fatty liver disease is correlated with cardiovascular complications probably because of excessive deposition of lipids in the blood vessels[20] as increased BMI is frequently observed in patients with NAFLD. In some studies weight loss and exercise were found to have beneficial effect in minimizing the level of steatosis and decreasing BMI.[21,22] Disease spectrum of fatty liver disease is very vast. Early detection and identification of risk factors can help us to lower the disease burden. Early detection is equally important in slowing the disease progression and development of complications. Early detection of biomarkers, for example uric acid can serve as a trigger for the gastroenterologists to go for screening of fatty liver. Likewise, other predisposing factors for example obesity, raised BMI and dyslipidemia are equally important in identification of the onset of fatty liver.[23,24] Patients presenting with these risk factors must also be monitored and screened for the progress of fatty liver. The results of current study will be helpful to gastroenterologists and general practitioners for early detection of fatty liver disease. The limitations of current

study includes that it was carried out at single center and ultrasonic finding for fatty liver disease were not confirmed by liver biopsy.

Conclusion:

BMI, serum uric acid, dyslipidemia and systolic and diastolic blood pressures are related with the development of non-alcoholic fatty liver disease. Serum uric acid (SUA) has a positive association with NAFLD and can be used as an early detection biomarker. These factors can serve as triggers for the screening of NAFLD.

References:

1. Vanni E, Bugianesi E, Kotronen A, De Minicis S, Yki-Järvinen H, Svegliati-Baroni G. From the metabolic syndrome to NAFLD or vice versa?. Digestive and liver Disease. 2010 May 1;42(5):320-30. https://doi.org/10.1016/j.dld.2010.01.016.
2. Lombardi R, Pisano G, Fargion S. Role of serum uric acid and ferritin in the development and progression of NAFLD. Int. J. Mol. Sci. 2016 Apr; 17(4):548.
3. Zou, B, Yeo, YH, Nguyen, VH, Cheung, R, Ingelsson, E, Nguyen, MH (Prevalence, characteristics and mortality outcomes of obese, nonobese and lean NAFLD in the United States, 1999–2016 . J Intern Med. 2020; 288: 139– 151. https://doi.org/10.1111/joim.13069.
4. Yang H, Li D, Song X, Liu F, Wang X, Ma Q, Zhang X, Li X. Joint associations of serum uric acid and ALT with NAFLD in elderly men and women: a Chinese cross-sectional study. J. Transl. Med. 2018 ;16(1):1-0. https://doi.org/10.1186/s12967-018-1657-6.
5. Katsiki N, Mikhailidis DP, Mantzoros CS. Non-alcoholic fatty liver disease and dyslipidemia: an update. Metabolism. 2016;65(8):110923. https://doi.org/10.1016/j.metabol.2016.05.003.
6. Oral A, Sahin T, Turker F, Kocak E. Relationship between serum uric acid levels and nonalcoholic fatty liver disease in non-obese patients. Medicina. 2019;55 (9):600. https://doi.org/10.3390/medicina55090600.
7. Yang H, Li D, Song X, Liu F, Wang X, Ma Q, Zhang X, Li X. Joint associations of serum uric acid and ALT with NAFLD in elderly men and women: a Chinese cross-sectional study. J. Transl. Med. 2018;16(1):1-0. https://doi.org/10.1186/s12967-018-1657-6.
8. Portincasa P, Bonfrate L, Khalil M, Angelis MD, Calabrese FM, D'amato M, Wang DQ, Di Ciaula A. Intestinal barrier and permeability in health, obesity and NAFLD. Biomedicines. 2021;10(1):83. https://doi.org/10.3390/biomedicines10010083.
9. Ezquerro S, Mocha F, Frühbeck G, Guzmán-Ruiz R, Valentí V, Mugueta C, Becerril S, Catalán V, Gómez-Ambrosi J, Silva C, Salvador J. Ghrelin reduces TNF-α–induced human hepatocyte apoptosis, autophagy, and pyroptosis: role in obesity-associated NAFLD. The Journal of J. Clin. Endocrinol. Metab. 2019;104(1):21-37. https://doi.org/10.1210/jc.2018-01171.
10. Kasper P, Martin A, Lang S, Demir M, Steffen HM. Hypertension in NAFLD: An uncontrolled burden. J. Hepatol. 2021 ;74(5):1258-1260.
11. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M, Steffen HM. NAFLD and cardiovascular diseases: a clinical review. Clin. Res. Cardiol. 2021;110(7):921-37. https://doi.org/10.1007/s00392-020-01709-7.
12. Zhang Z, Wang J, Wang H. Correlation of blood glucose, serum chemerin and insulin resistance with NAFLD in patients with type 2 diabetes mellitus. Exp. Ther. Med. 2018 ;15(3):2936-40. https://doi.org/10.3892/etm.2018.5753.
13. Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, Clark JM. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082-90. https://doi.org/10.1002/hep.24452.
14. Tang Z, Pham M, Hao Y, Wang F, Patel D, Jean-Baptiste L, Fan L, Wang W, Wang Y, Cheng F. Sex, age, and BMI modulate the association of physical examinations and blood biochemistry parameters and NAFLD: a retrospective study on 1994 cases observed at Shuguang Hospital, China. Biomed Res. Int. 2019;2019. https://doi.org/10.1155/2019/1246518.
15. Akhtar DH, Iqbal U, Vazquez-Montesino LM, Dennis BB, Ahmed A. Pathogenesis of insulin resistance and atherogenic dyslipidemia in nonalcoholic fatty liver disease. J. clin. transl. hepatol. 2019; 7(4):362-370. 10.14218/JCTH.2019.00028.
16. Deprince A, Haas JT, Staels B. Dysregulated lipid metabolism links NAFLD to cardiovascular disease. Mol. Metab. 2020;42:101092. https://doi.org/10.1016/j.molmet.2020.101092.
17. Amor AJ, Perea V. Dyslipidemia in nonalcoholic fatty liver disease. Curr. Opin. Endocrinol. Diabetes. Obes. 2019;26(2):103-8. 10.1097/MED.0000000000000464.
18. Julián MT, Pera G, Soldevila B, Caballería L, Julve J, Puig-Jové C, Morillas R, Torán P, Expósito C, Puig-Domingo M, Castelblanco E. Atherogenic dyslipidemia, but not hyperglycemia, is an independent factor associated with liver fibrosis in subjects with type 2 diabetes and NAFLD: a population-based study. Eur Endocrinol. 2021;184(4):587-96.
19. Niederseer D, Wernly B, Aigner E, Stickel F, Datz C. NAFLD and cardiovascular diseases: epidemiological, mechanistic and therapeutic considerations. J. Clin. Med.. 2021;10(3):467. 10.3390/jcm10030467.
20. Seo YB, Han AL. Association of the serum uric acid-to-

creatinine ratio with nonalcoholic fatty liver disease diagnosed by computed tomography. Metab. Syndr. Relat. Disord. 2021;19(2):70-75. https://doi.org/10.1089/met.2020.0086.

21. Kosekli MA, Kurtkulagii O, Kahveci G, Duman TT, Tel BM, Bilgin S, Demirkol ME, Aktas G. The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the abund study. Rev. Assoc. Med. Bras. 2021 Sep 6;67:549-54. https://doi.org/10.1590/1806-9282.20201005.
22. Zhang Q, Ma X, Xing J, Shi H, Yang R, Jiao Y, Chen S, Wu S, Zhang S, Sun X. Serum uric acid is a mediator of the association between obesity and incident nonalcoholic fatty liver disease: a prospective cohort study. Front. Endocrinol. 2021;12:50.
23. Wang M, Wang M, Zhang R, Zhang L, Ding Y, Tang Z, Fan H, Wang H, Zhang W, Chen Y, Wang J. A combined association of serum uric acid, alanine aminotransferase and waist circumference with non-alcoholic fatty liver disease: a community-based study. PeerJ. 2022;10:e13022.
24. Zhang C, Song H, Yang L, Liu Y, Ji G. Does High Level of UricAcid Lead to Nonalcoholic Fatty Liver Disease. Global Journal of Digestive Disease 2018; 4: 3:7.