ORIGINAL ARTICLE

ASSOCIATION OF SERUM URIC ACID WITH METABOLIC DYSFUNCTION ASSOCIATED STEATOTIC LIVER DISEASE IN PATIENTS PRESENTING TO TERTIARY CARE HOSPITAL/ URIC ACID AND MASLD

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ABSTRACT

Background: Elevated uric acid, an end product of purine metabolism is associated with non-alcoholic fatty liver disease and its progression. It has been linked with diabetes, hypertension, CKD, gout, cardiovascular diseases and dyslipidemias.

Objectives: Metabolic dysfunction associated liver disease is on rise, due to changing dietary and socioeconomic patterns and has become global health issue. Elevated uric acid impacts frequency and severity of fatty liver Our objective is to explore the association of serum uric acid with metabolic dysfunction associated liver disease.

Methods: This cross-sectional study was conducted at Pakistan Railway Hospital in Medical and Radiology department from 1st Jan to 30th June, 2025. We enrolled 200 patients with MASLD, diagnosed on ultrasound with fatty liver graded to mild, moderate and severe categories. Demographic details, physical examination findings, comorbidities and relevant laboratory findings were entered on structured proforma.

Results: In this study majority were female (63%) and mean age of patients was 48+19 years. About 47.5% had mild fatty liver, 34% and 28.5% had moderate and severe fatty liver respectively. Elevated uric acid levels were seen in 75% patients with highest levels were observed in patients with severe fatty liver (7.62 vs. 5.89 vs. 4.75 P<0.001). Serum uric acid showed strong correlation with fatty liver index FLI (r=0.493, P<0.001) and moderate correlation with FIB-4 score (r=0.261, P <0.001). Life style factors like processed diet, lack of exercise, poor periodontal health are significant contributor to hyperuricemia.

Conclusion: Hyperuricemia has significant prevalence among patients with MASLD and demonstrated association with steatosis and fibrosis in liver.

Key words: fructose, obesity, uric acid, hepatic steatosis, non-alcoholic fatty liver disease

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INTRODUCTION

Elevated uric acid, an end product of purine metabolism is associated with non-alcoholic fatty liver disease and its progression. It has been linked with diabetes, hypertension, CKD, gout, cardiovascular diseases and dyslipidemias[1]. Serum uric acid is standalone risk factor as for each 1 mg increase in level, the risk of NAFLD increases by 21%[2]. Uric acid levels correlate with grades of liver lobule

inflammation, fibrosis and liver enzyme elevation. Hyperuricemia is significant risk of fatty liver even in the absence of obesity and equally affects all ages, race, gender and socioeconomic status[3, 4].

MASLD (previously called as NAFLD) is major health concern around the globe with prevalence of 30.1%[5]. It characterized by more than 5% fat buildup in the hepatocytes in the absence of other etiologies and alcohol consumption. It not only leads to cirrhosis and hepatocellular carcinoma but also multiple extra hepatic manifestations.

Dietary changes especially high consumption of fructose in processed food and sugar sweetened beverages has been linked to elevated uric acid, fatty liver and metabolic syndrome. Fructose, unlike glucose is metabolized only in liver and processed to uric acid as it blocks the production of ATP and at the same time it also promotes synthesis of triglycerides and suppress oxidation of fatty acid. Moreover, it impairs insulin signaling in liver thus enhancing insulin resistance and weight gain. Uric acid is an antioxidant but higher levels induce inflammation, oxidative stress and disrupt lipid metabolism thus promoting liver steatosis and progression to fibrosis. It also enhances insulin resistance by precipitating in pancreatic islets and suppressing endothelial nitric oxide synthase. Insulin resistance in turn increases uric acid level by increasing its synthesis and reducing its excretion in self-perpetuating vicious cycle [6, 7].

MASLD prevalence in Pakistan is 30%[8] and data on frequency of hyperuricemia is variable in different studies as no nationwide study is available. Recent study from Faisalabad found it to be 31%, while from Karachi, 56.6% had hyperuricemia in patients with NAFLD[9, 10]. Serum uric acid is cost effective, non- intrusive and valuable marker for predicting fatty liver. As its level increases likelihood of fatty liver increases even when lower cutoff 4.75 mg/dl was used[11]. Liver biopsy gives reliable information about fat accumulation and fibrosis but is associated with risks. Non-invasive markers like fatty liver index (FLI), FIB-4 have been used for diagnosis and staging of steatosis and fibrosis. They have demonstrated consistent reliability and accuracy in various studies.

Changing life style and consumption of high fructose diet has greatly affected metabolic health leading to obesity epidemic and chronic systemic diseases. Both consumption of real food and physical activity have crucial role in prevention and treatment. By increasing the understanding of healthcare professional about the disease and utility of serum uric acid as diagnostic or prognostic marker for prediction and monitoring the course of disease will reduce this global disease.

We aim this study was to find out frequency of hyperuricemia and its association with NAFLD applying FLI and FIB-4 score to assess relation with liver fibrosis.

METHODS

This study was carried out at Pakistan Railway Hospital Rawalpindi from 1st Jan 2025 to 30th June 2025 in medical and radiology department. It was a descriptive cross sectional study. Patients with MASLD between 18-75 years of age were included by non-probability consecutive sampling after informed consent and ethical approval from Riphah International University. Chronic liver disease patients due to viral infection like HCV, HBV, Wilson disease, haemochromatosis, autoimmune hepatitis, drugs and alcohol were excluded. Patients taking drugs influencing serum uric acid level like thiazide diuretic, frusemide, allopurinol, pyrazinamide, cyclosporine, Tacrolimus were also excluded. After detailed history and physical examination including BMI calculation and abdominal circumference measurement, venous sample were sent for complete blood count (CBC), HbA1c, serum uric acid, serum bilirubin, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), γ -glutamyl transferase, alkaline phosphatase (ALP), blood urea, serum creatinine, serum total cholesterol, Triglyceride, low density lipoprotein (LDL-C), and high density lipoprotein(HDL-C).

MASLD was diagnosed in patients with fatty liver having one out of five metabolic risk factors. Abdominal ultrasound was done using Min-dray machine with 2-7 MHz frequency probe by experienced radiologist and graded into mild (slight increase in echogenicity), moderate (brighter echogenicity with some blurring of vessel margins) and severe (hyper echoic liver with difficult visualization of internal structures) fatty liver categories according to standard radiologic criteria[12].

Serum uric acid level of 5mg/dl for male and 4 mg/dl for female was taken as cut off as these thresholds are regarded optimal for maintaining good metabolic profile[11]. Liver enzyme reference range for ALT was 25U/L for male and 17U/l for female[13]. For serum AST cutoff was 15-37 U/L, γ- glutamyl transferase > 40 U/L, serum triglyceride ≥ 150 and HDL-C ≤ 40mg/dl in males and ≤ 50mg/dl in female were taken as significant.

Fatty liver index (FLI) was applied to assess the likely hood of liver steatosis. A value above 60 indicates high probability of fatty liver[14].

$$FLI = (e^{0.953\times\log e(\text{triglycerides})+0.139\times BMI+0.718\times\log e(GGT)+0.053\times \text{waistcircumference}-15.745})/ (1 + e^{0.953\times\log e(\text{triglycerides})+0.139\times BMI+0.718\times\log e(GGT)+0.053\times \text{waistcircumference}-15.745}) \times 100.$$

FIB-4 was utilized for assessment of hepatic fibrosis[15].

$$\text{Fib-4} = (\text{Age [years]} \times \text{AST [IU/L]})/ (\text{platelet count } (\times 10^9/\text{l}) \times \text{ALT [IU/L]}^{1/2}$$

A higher cut off >3.25 was used for identification of fibrosis. Statistical data was analyzed using SPSS 24. Categorical variables like presence or absence of steatosis, fibrosis and gender were calculated as frequency and percentages. Continuous variables like age, ALT, HbA1c were expressed as mean ± standard deviation. We used Pearson correlation analysis to see the interconnection between serum uric acid and other clinical and biochemical parameters.

RESULTS

Out of 200 patients with MASLD enrolled in the study 126 were female and 74 males between 18 and 75 years and mean age was 48 ± 19. Frequency of hyperuricemia was 75%. Hyperuricemia showed positive correlation with liver enzyme ALT, Gamma GT, dyslipidemia.

Table 1: Serum uric acid levels and severity of liver disease

Severity of NAFLD	Number of patients	Mean serum uric acid level	P value
Mild	95(47.50%)	4.95±1.63	<0.001
Moderate	68 (34%)	5.89 ± 1.78	
Severe	37 (28.50%)	7.62± 1.91	
Total	200		

Table2: Serum uric acid with clinical and biochemical parameter correlation

Parameter	Correlation coefficient r	P value
Age	0.008	-0.089
Gender	0.021	0. 091
Hypertension	0.296	0.000
HbA1c	0.301	0.000
ALT U/L	0.198	0.003
AST U/L	0.150	0.019
Ɣ- GTU/L	0.410	0.000
Triglyceride mg/dl	0.351	0.000
Total cholesterol mg/dl	0.219	0.000
LDL-C mg/dl	0.119	0.000
HDL-C mg/dl	-0.280	0.000
BMI Kg/m^2	0.310	0.000
FLI	0.493	0.000
FIB-4	0.261	0.000

Table3: Comparison of hyperuricemia with associated factors

Sr. No.	Underlying conditions	Hyperuricemia Yes 75%	Hyperuricemia NO 25%	P value
Age	Age <50 years	60	35	
	Age > 50 years	50	35	
Gender	Women	100	26	
	Men	50	24	
Hypertension	Yes	60	35	
	No	39	66	<0.001
Diabetes mellitus	Yes	46	40	0.01
	No	60	12	
NAFLD Severity	Mild	75	20	<0.001
	Moderate	50	18	
	Severe	25	12	
Obesity	Yes	75	35	<0.001
	No	45	45	
Cardiovascular diseases	Yes	38	20	0.14
	No	90	40	
Processed diet	Yes	140	20	<0.001
	No	21	19	
Sugar sweetened beverages	Yes	120	25	<0.001
	No	30	25	
Tooth loss	Yes	146	24	<0.001
	No	16	14	
Reduced frequency of brushing	Yes	138	36	<0.001
	No	14	12	
Walking <30 min/day	Yes	120	30	<0.001
	No	20	30	

DISCUSSION

Hyperuricemia was seen in 75% of MASLD patients. A variable prevalence of hyperuricemia in NAFLD has been reported in literature. The prevalence of hyperuricemia was 45%% vs.16.8% in healthy population[16]. Rising serum uric acid exhibited linear relationship with fatty liver [17]. About 56.6% patients with severe NAFLD had hyperuricemia while patients with NAFLD having CKD 57.3% had hyperuricemia[18].

Higher prevalence of hyperuricemia is related to changing dietary and lifestyle patterns. In our study 88% gave history of processed food intake especially sugar sweetened beverages. Fructose is direct precursor of uric acid and increases insulin resistance[6]. We found 73% participants had reduced physical activity. Similar result reported by other studies[19]. This risk can be reduced by consumption of healthy diet and regular moderate exercise. Obesity especially abdominal is a risk factor for fatty liver and hyperuricemia. Majority of our patients had higher BMI as seen with previous studies [3,7,10].

We observed higher prevalence of periodontal disease in our patients with 71% gave history of tooth loss due to dental caries with 82% brushed their teeth once a day, 10% brushed twice a day and 8% 2-3 times/week. Periodontitis is significant risk factor for NAFLD and its severity. Hyperuricemia is potential direct and indirect positive contributor by causing oxidative stress and promoting inflammation.[20, 21, 22]

Elevated uric acid level even in normal range has been linked with risk of NAFLD and escalating levels are independent predictor of heightened risk. Level increased with severity of fatty liver in our study and result matched with other studies. Serum uric acid intensifies insulin resistance by various mechanism including impairing insulin signaling and direct damage to pancreatic islets.[4, 7, 10]

Higher uric acid prevalence was observed in patients with comorbid hypertension may be due to close complex inter relationship as part of metabolic syndrome. Similarly, patients with diabetes have higher prevalence of hyperuricemia and level correlated with severity of NAFLD suggesting its potential role in progression toward cirrhosis in the presence of diabetes. We also noted presence of other diseases like ischemic heart disease, congestive cardiac failure, gout and stroke contributing to increase risk and severity of hepatic steatosis and fibrosis. [1, 10, 23].

We found higher serum uric acid in patients with elevated ALT, a marker of hepatic inflammation and damage which may help in early identification of disease. Hyperuricemia correlated with hypertriglyceridemia in our patients. Similarly, we found low HDL-C, which helps in removing liver fat by reverse cholesterol transport and low level of HDLC reduces this efflux thus promoting hepatic steatosis [10, 17, 24].

We studied the prevalence of fibrosis in our study using FIB-4 score and its correlation with hyperuricemia turned out to be moderately significant. Fibrosis is an important predictor of prognosis so early detection using non-invasive score is prudent. Advanced age, comorbid hypertension, diabetes, obesity and male gender increase the risk of fibrosis [7, 10, 3, 4]. While Korean study found no correlation with fibrosis.[24]

The correlation between hyperuricemia and hepatic steatosis was found to be significant, with 83% of patients showing fatty liver index > 60, suggesting strong relation with steatosis rather than fibrosis.

Results of our study highlight importance life style intervention in MASLD by healthy diet, exercise, oral health care as well as the need for novel therapeutic interventions to reduce uric acid levels to prevent steatosis and fibrosis in the liver.

CONCLUSION

Hyperuricemia has significant prevalence among patients with MASLD and demonstrated association with steatosis and fibrosis in liver.

ETHICAL APPROVAL

Ethical approval of article was granted by the Institutional Review Committee of Islamic International Medical College vide reference No. Appl. # Riphah /IRC/ 25/1012 dated 21 January, 2025.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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AUTHOR'S CONTRIBUTIONS

SK: Study design, data collection, review of literature
KF: Study design, manuscript writing, data collection
FF: Data collection statistical analysis
SF, FZS: Study design, statistical analysis , review of literature
AA: manuscript writing, data collection
All Authors: Approval of the final version of the manuscript to be published

REFERENCES

1. Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, et al. Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-Analysis of Prospective Studies. J Clin Endocrinol Metab. 2015; 100(11):4198-207. doi: 10.1210/jc.2015-2527. Epub 2015 Aug 26. PMID: 26308292.
2. Yen PC, Chou YT, Li CH, Sun ZJ, Wu CH, Chang YF, et al. Hyperuricemia Is Associated with Significant Liver Fibrosis in Subjects with Nonalcoholic Fatty Liver

Disease, but Not in Subjects without It. J Clin Med. 2022; 11(5):1445. doi: 10.3390/jcm11051445. PMID: 35268536; PMCID: PMC8911142.

3. Sun Q, Zhang T, Manji L, Liu Y, Chang Q, Zhao Y, ey al. Association between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease: An Updated Systematic Review and Meta-Analysis. Clin Epidemiol. 2023; 15:683-693. doi: 10.2147/CLEP.S403314. PMID: 37305378; PMCID: PMC10252946.
4. Younossi ZM, Golabi P, Paik JM, Henry A, Van Dongen C, Henry L. The global epidemiology of nonalcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH): a systematic review. Hepatology. 2023; 77(4):1335-1347. doi: 10.1097/HEP.0000000000000004. Epub 2023 Jan 3. PMID: 36626630; PMCID: PMC10026948.
5. Russo E, Leoncini G, Esposito P, Garibotto G, Pontremoli R, Viazzi F. Fructose and Uric Acid: Major Mediators of Cardiovascular Disease Risk Starting at Pediatric Age. Int J Mol Sci. 2020; 21(12):4479. doi: 10.3390/ijms21124479. PMID: 32599713; PMCID: PMC7352635.
6. European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines on the management of metabolic dysfunction-associated steatotic liver disease (MASLD). J Hepatol. 2024; 81(3):492-542. doi: 10.1016/j.jhep.2024.04.031. Epub 2024 Jun 7. PMID: 38851997.
7. Fan J, Wang D. Serum uric acid and nonalcoholic fatty liver disease. Front Endocrinol (Lausanne). 2024; 15:1455132. doi: 10.3389/fendo.2024.1455132. PMID: 39669496; PMCID: PMC11635646.
8. Shahid R, Hussain M, Ghori MU, Bilal A, Awan FR. Association of hyperuricemia with metabolic syndrome and its components in an adult population of Faisalabad, Pakistan. Nutr Metab Cardiovasc Dis. 2024; 34(6):1554-1558. doi: 10.1016/j.numecd.2024.03.017. Epub 2024 Mar 16. PMID: 38664128.
9. Kuwabara M, Hisatome I, Niwa K, Bjornstad P, Roncal-Jimenez CA, Andres-Hernando A, et al. The Optimal Range of Serum Uric Acid for Cardiometabolic Diseases: A 5-Year Japanese Cohort Study. J Clin Med. 2020; 9(4):942. doi: 10.3390/jcm9040942. PMID: 32235468; PMCID: PMC7231289.
10. Festi D, Schiumerini R, Marzi L, Di Biase AR, Mandolesi D, Montrone L, et al. Review article: the diagnosis of non-alcoholic fatty liver disease -- availability and accuracy of non-invasive methods. Aliment Pharmacol Ther. 2013; 37(4):392-400. doi: 10.1111/apt.12186. Epub 2012 Dec 20. PMID: 23278163.
11. Chen YL, Li H, Li S, Xu Z, Tian S, Wu J, et al. Prevalence of and risk factors for metabolic associated fatty liver disease in an urban population in China: a cross-sectional comparative study. BMC Gastroenterol. 2021; 21(1):212. doi: 10.1186/s12876-021-01782-w. PMID: 33971822; PMCID: PMC8111711.
12. Wang M, Wang M, Zhang R, Zhang L, Ding Y, Tang Z, et al. 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. doi: 10.7717/peerj.13022. PMID: 35265397; PMCID: PMC8900609.
13. Haroon A, Askari S, Haroon A, Sohail Z. Frequency and Association of Hyperuricemia in Non-alcoholic fatty liver disease patients: Still a neglected combination? Pak J Med Sci. 2025; 41(4):1058-1065. doi: 10.12669/pjms.41.4.10333. PMID: 40290262; PMCID: PMC12022593.
14. Golmohammadi S, Tavasoli M, Asadi N. Prevalence and Risk Factors of Hyperuricemia in Patients with Chronic Kidney Disease and Non-Alcoholic Fatty Liver. Clin Exp Gastroenterol. 2020; 13:299-304. doi: 10.2147/CEG.S253619. PMID: 32903892; PMCID: PMC7445503.
15. Zhang T, Gan S, Ye M, Meng G, Zhang Q, Liu L, et al. Association between consumption of ultra-processed foods and hyperuricemia: TCLSIH prospective cohort study. Nutr Metab Cardiovasc Dis. 2021; 31(7):1993-2003. doi: 10.1016/j.numecd.2021.04.001. Epub 2021 May 7. PMID: 34119375.
16. Heredia NI, Zhang X, Balakrishnan M, Daniel CR, Hwang JP, McNeill LH, et al. Physical activity and diet quality in relation to non-alcoholic fatty liver disease: A cross-sectional study in a representative sample of U.S. adults using NHANES 2017-2018. Prev Med. 2022; 154:106903. doi: 10.1016/j.ypmed.2021.106903. Epub 2021 Dec 1. PMID: 34861339; PMCID: PMC8724407.
17. Chen Y, Yang YC, Zhu BL, Wu CC, Lin RF, Zhang X. Association between periodontal disease, tooth loss and liver diseases risk. J Clin Periodontol. 2020; 47(9):1053-1063. doi: 10.1111/jcpe.13341. Epub 2020 Jul 20. Erratum in: J Clin Periodontol. 2021 Apr;48(4):615. doi: 10.1111/jcpe.13422. PMID: 32621350.
18. Yamamoto K, Ikeya T, Okuyama S, Fukuda K, Kobayashi D. Association between the Frequency of Daily Toothbrushing and Development of Nonalcoholic Fatty Liver Disease. Dig Dis. 2021; 39(6):646-652. doi: 10.1159/000514930. Epub 2021 Feb 3. PMID: 33535206.
19. Chen Y, Lu P, Lin C, Li S, Zhu Y, Tan J, et al. Hyperuricemia and elevated uric acid/creatinine ratio are associated with stages III/IV periodontitis: a population-based cross-sectional study (NHANES 2009-2014). BMC Oral Health. 2024; 24(1):1389. doi: 10.1186/s12903-024-05173-x. PMID: 39548474; PMCID: PMC11566428.
20. Lin Y, Feng X, Cao X, Miao R, Sun Y, Li R, et al. Age patterns of nonalcoholic fatty liver disease incidence: heterogeneous associations with metabolic changes. Diabetol Metab Syndr. 2022; 14(1):181. doi: 10.1186/s13098-022-00930-w. PMID: 36443867; PMCID: PMC9706887.

21. Caussy C, Aubin A, Loomba R. The Relationship between Type 2 Diabetes, NAFLD, and Cardiovascular Risk. Curr Diab Rep. 2021; 21(5):15. doi: 10.1007/s11892-021-01383-7. PMID: 33742318; PMCID: PMC8805985.
22. Kasper P, Martin A, Lang S, Kütting F, Goeser T, Demir M,et al. NAFLD and cardiovascular diseases: a clinical review. Clin Res Cardiol. 2021; 110(7):921-937. doi: 10.1007/s00392-020-01709-7. Epub 2020 Jul 21. PMID: 32696080; PMCID: PMC8238775.
23. Jaruvongvanich V, Ahuja W, Wirunsawanya K, Wijarnpreecha K, Ungprasert P. Hyperuricemia is associated with nonalcoholic fatty liver disease activity score in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Eur J Gastroenterol Hepatol. 2017; 29(9):1031-1035. doi: 10.1097/MEG.0000000000000931. PMID: 28639970.
24. Yoneda M, Thomas E, Sumida Y, Imajo K, Hyogo H, Fujii H, et al. Uric acid levels decrease with fibrosis progression in patients with nonalcoholic fatty liver disease. Clin Biochem. 2014; 47(12):1138-9. doi: 10.1016/j.clinbiochem.2014.04.026. Epub 2014 May 4. PMID: 24797484.
25. Tricò D, Caprio S, Rosaria Umano G, Pierpont B, Nouws J, Galderisi A, et al. Metabolic Features of Nonalcoholic Fatty Liver (NAFL) in Obese Adolescents: Findings from a Multiethnic Cohort. Hepatology. 2018; 68(4):1376-1390. doi: 10.1002/hep.30035. PMID: 29665034; PMCID: PMC6173637.
26. Yuan H, Yu C, Li X, Sun L, Zhu X, Zhao C, et al. Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-Analysis of Prospective Studies. J Clin Endocrinol Metab. 2015; 100(11):4198-207. doi: 10.1210/jc.2015-2527. Epub 2015 Aug 26. PMID: 26308292.