Bangladesh Med J. 2022 Sept; 51(3)
DOI: https://doi.org/10.3329/bmj.v51i3.70173

Original Article

Association of Serum Uric Acid and Liver Enzymes in Adults at Tertiary Level Hospital in Bangladesh

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Abstract

The level of serum uric acid (SUA) has been linked to metabolic syndrome, diabetes, and cardiovascular disease. The purpose of this study was to evaluate the relationship between SUA and serum liver enzymes in a Bangladeshi adult population. This cross-sectional study was conducted among apparently healthy adults aged >18 years, from March 2019 to February 2020 at the Department of Biochemistry, Sir Salimullah Medical College (SSMC), Dhaka. SUA, liver enzymes, lipid profile and other biochemical markers were measured in the collected samples by using standard methods. All statistical analyses were performed by using SPSS version 22.0 software and p<0.05 was considered statistically significant. A total of 140 subjects were selected and blood sample were collected for biochemical analysis. Among them 70 were male and 70 were female. Serum uric acid (SUA), Alanine transaminase (ALT), Aspartate aminotransferase (AST) and Gamma-glutamyl transferase (GGT) levels were significantly (p<0.001) higher in male than female group. Pearson's correlation analysis showed that there were significant positive correlation between SUA and serum ALT, AST, GGT (p<0.001). However, it also showed significant positive correlation between SUA and total cholesterol (TC), triglycerides (TG), low density lipoprotein cholesterol (LDL-C), while negative correlation was found between SUA and high density lipoprotein cholesterol (HDL-C) (p<0.001). The role of SUA in the prediction of elevated liver enzymes showed area under the ROC Curve (AUC) 0.839 for ALT, 0.848 for AST and 0.809 for GGT respectively. SUA is positively related with ALT, AST, GGT in adults. More prospective studies are needed to clarify the complex relationship between SUA and liver enzymes in the general population.

Keywords: *Serum uric acid (SUA), ALT, AST, GGT, lipid profile.*

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INTRODUCTION

Alanine aminotransferase (ALT), aspartate amino-transferase (AST) and gamma glutamyl transferase (GGT) are the liver enzymes which comprise liver function tests. Among them ALT is the most specific marker of liver function, but AST and GGT are the less specific markers because they are present in other tissues.[1] Serum uric acid (SUA) is the major end product of the purine metabolism and the level of SUA is maintained by the balance between SUA production and excretion.[2] Intracellularly uric acid can act as a pro-oxidant inducing the release of inflammatory mediators and growth factors.[3,4] Uric acid has been shown to contribute to lipoprotein oxidation and inflammation which are thought to play vital roles in the development and progression of Non-alcoholic fatty liver disease (NAFLD).[5,6] Hyperuricemia has been linked to both MetS and cardiovascular disease.[7,8] The SUA was increased in most NAFLD patients which was an independent risk factor for NAFLD. Therefore, increased SUA may play the role of linking NAFLD with MetS.[9,10]

Serum biomarkers especially alanine aminotransferse (ALT) levels are sensitive in detection of hepatocyte injury in both obese and non-obese patients. ALT levels are related to Metabolic syndrome (MetS), diabetes mellitus, cardiovascular disease and nonalcoholic fatty liver disease (NAFLD). It was evident that in asymptomatic individuals

with mild elevations of ALT and AST, 98% had liver disease commonly fatty liver disease. High aminotransferase levels even within reference range are associated with the components of metabolic syndrome that was observed in a study. Furthermore, Serum uric acid (SUA) is significantly elevated in cardiovascular disease, diabetes mellitus, Metabolic syndrome (MetS) and is also considered as important risk factor for development of NAFLD. Evidence suggests that elevated SUA levels and increased activity of liver enzymes GGT and ALT (and to a lesser extent AST) are also associated with the development of Metabolic syndrome (MetS) and nonalcoholic fatty liver disease (NAFLD). This statement is supported by some studies conducted worldwide. It was reported that hyperuricemia and SUA even in the reference range are associated with elevated serum ALT in healthy Chinese adults. However, there is limited study on the association of SUA with serum AST and GGT among healthy adults in abroad.

ALT is a specific marker of liver inflammation and hepatocellular injury.[11] As, ALT is closely associated with fatty deposition in the hepatocytes, it is commonly considered as a surrogate marker for nonalcoholic fatty liver disease (NAFLD)[12,13]. Elevated ALT is related to a range of health outcomes such as metabolic disorders and cardiovascular diseases (CVD).[14] Recent studies showed that NAFLD is closely associated with obesity, hypertension, dyslipidemia, glucose intolerance, metabolic syndrome (MetS), as well as cardiovascular events[9]. Thus, NAFLD is considered to be a hepatic consequence of metabolic diseases[10]. Like ALT, AST levels were also elevated with MetS in several cross-sectional studies.[12,15] Thus, elevated AST also might be a risk factor for MetS. However, epidemiological studies suggest that elevated levels of GGT, another liver enzyme, predict subsequent development of several metabolic disorders such as hypertension, diabetes and MetS.[16,17] Some authors have speculated that visceral fat could play a role in the association of GGT with metabolic abnormalities and this enzyme could be considered as a reliable marker of visceral fat deposition.[18]

In our country, there is no report on the association of hyperuricemia and elevated liver enzymes in general adults. Consequently, this cross-sectional study was designed to investigate the relationship between SUA levels and liver enzymes (ALT, AST and GGT) in these adult subjects.

Furthermore, increasing evidence has suggested that not only hyperuricemia but also SUA within the reference range showed a positive correlation with the components of MetS.[19] A number of cross-sectional studies have shown that GGT is correlated positively with serum uric acid.[20,21] Therefore, the proposed study was designed to evaluate the association between serum uric acid and liver enzymes (ALT, AST and GGT) in the Bangladeshi adults.

MATERIALS AND METHODS

Study settings and Study population

This cross-sectional study was conducted from 1st March, 2019 to 29th February, 2020 at the Department of Biochemistry, SSMC, Dhaka, Bangladesh. The study was conducted on 140 subjects (70 males and 70 female). Apparently healthy people of 30 to 59 yrs were included in the study. These subjects were selected from the attendants accompanying the patients attending the outpatient department of SSMC and Mitford Hospital. Study population included both male and female categorized into four quartiles including hyperuricemia on the basis of SUA level. Inclusion criteria: (i) Healthy adults with age range of 30- 59 years (ii) Both genders. Exclusion criteria: (i) Subjects with DM and renal failure. (ii) Those taking anti-hypertensive, anti-diabetic, lipid-lowering and hypouricemic drugs. (iii) Chronic liver disease such as cirrhosis, liver cancer, viral hepatitis, autoimmune hepatitis and taking hepatotoxic drug (iv) Alcoholism.

Anthropometric data collection

Height was measured (without shoes) by measuring instrument and taken to the nearest centimeters. Body weight was measured in light clothing and without shoes. Weight was recorded in Kilogram. Body mass index (BMI) was calculated as weight in Kilogram divided by height in meter square.[10] Blood pressure was measured three times at 2 minutes' interval in a sitting position after at least 5 minutes of rest in a quiet room by using of manual sphygmomanometer with appropriate cuff. The mean of three BP measurements was calculated and used in all analyses. Before collecting specimen, each patient was interviewed and relevant information was recorded systematically in a pre-designed standard data sheet and then data was checked and edited.

Study Procedure

Apparently healthy subjects were selected from the attendants accompanying the patients attending the outpatient department of SSMC and Mitford Hospital, Dhaka. These subjects were recruited following history, physical examination and routine baseline biochemical

investigations. Ethical permission was taken from the Ethical Review Committee of SSMC. After proper counseling about aim, objectives, risk and procedure of the study were explained in details to all participants. Only voluntary candidates were recruited as research participants. They had the freedom to withdraw themselves from the study at any stage. Written informed consent was taken from all participants. Socio- demographic as well as other relevant data were taken and recorded in the data collection sheet with a prefixed questionnaire. A blood sample was collected for biochemical variables to be measured.

Blood Collection and Laboratory analysis

Each participant's overnight fasting blood sample, which included about 5 mL, was taken for biochemical evaluations. Serum uric acid (SUA), fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), liver enzymes, and alanine aminotransferase were all measured in the blood biochemical studies. Alkaline phosphatase (ALP), gamma-lutamyl transferase (GGT), aspartate aminotransferase (AST), and ALT. Serum Kinetic techniques were used to determine the liver enzyme activity, and other biochemical parameters were examined by conventional colorimetric techniques. A biochemistry analyzer was used to measure the biochemical parameters. Biochemical tests were done in the Biochemistry laboratory of SSMC, Dhaka.

Operational definitions

- **Elevated liver enzymes** defined as ALT >45 U/L in male and >34 U/L in female; AST >35 U/L in male and >31 U/L in female; GGT >55 U/L in male and >38 U/L in female[22].
- **Hyperuricemia** was defined according to sex-specific SUA levels: SUA >7.0 mg/dL for male and >6.0 mg/dL for female[23].

Statistical analysis

Continuous variables were expressed as mean values and standard deviation (SD), whereas categorical variables were described as frequencies and percentages. Data with skewed distribution (SUA, ALT, AST and GGT) were log-transformed and then used for subsequent statistical analyses; the result was back-transformed to produce geometric means which were reported. SUA levels were divided into quartiles including hyperuricemia. Statistical methods followed were unpaired students' t-test, Analysis of variance (ANOVA) test where indicated. Bonferroni test was performed to show the difference in between different categories of SUA level. Pearson's correlation was performed to analyze the relation between SUA level and liver enzymes as well as between SUA and lipid profile. Multiple linear regression was performed to determine the relation between dependent and independent variables of interest after adjusting for other potentially confounding independent variables. We used the area under the receiver-operating characteristic curve (AUC) and 95% confidence intervals (CIs) to assess the predictive ability of serum uric acid levels to assess the risk for elevated liver enzymes. All statistical analyses were performed by using SPSS version22.0 software and $p<0.05$ was considered statistically significant.

RESULTS

In this study, a total of 140 subjects were selected. Among them 70 were male and 70 were female.

Table I showed the baseline characteristics of study subjects. The mean (±SD) age of male was 44.43±7.32 years and that in female was 42.80±6.92 years. It also showed that there was no statistically significant difference regarding age between two groups. In case of BMI, no significant difference was observed in between two groups. The mean (±SD) SBP in mmHg was significantly higher in male than female (130.83±12.08 vs 125.71±13.89, $p<0.05$). The mean (±SD) DBP in mmHg (87.50±9.66 vs 82.93±9.80, $p<0.01$) also showed significant difference between male and female.

Table- I: Baseline characteristics of study subjects (n=140)

Variables	All subjects (n=140)	Male (n=70)	Female (n=70)	*p*-value
Age (years)	43.62±7.15	44.43±7.32	42.80±6.92	0.175
BMI (kg/m^2)	24.11±2.86	24.51±2.87	23.71±2.81	0.099
SBP (mmHg)	128.27±13.22	130.83±12.08	125.71±13.89	<0.05
DBP (mmHg)	85.21±9.96	87.50±9.66	82.93±9.80	<0.01

Results were expressed as mean±SD. Unpaired student's t-test was performed to compare between group means.

Table II contains the mean±SD of the biochemical parameters. Serum uric acid (SUA), ALT, AST and GGT levels were significantly (p<0.001) higher in male than female group. Analysis of lipid profile showed that TC (p<0.05) and LDL-C (p<0.05) level were significantly higher in male than female subjects whereas HDL-C (p<0.01) was significantly lower in male than female group. However, in cases of TG and FPG no significant difference was observed in between groups.

Table- II: Biochemical parameters of study subjects (n=140)

Biochemical parameters	All subjects (n=140)	Male (n=70)	Female (n=70)	p-value
FPG (mmol/L)	5.34±1.11	5.45±1.16	5.22±1.04	0.228
*SUA (mg/dl)	4.94±1.35	5.46±1.33	4.49±1.32	<0.001
*ALT (U/L)	29.51±1.33	33.88±1.32	25.70±1.26	<0.001
*AST (U/L)	27.54±1.32	31.62±1.29	24.55±1.27	<0.001
*GGT (U/L)	35.48±1.46	43.65±1.42	29.51±1.34	<0.001
TC (mg/dl)	193.86±21.97	198.30±23.04	189.43±20.03	<0.05
TG (mg/dl)	157.01±26.09	160.14±21.15	153.89±30.06	0.157
HDL-C (mg/dl)	39.93±4.38	38.90±4.08	40.96±4.46	<0.01
LDL-C (mg/dl)	125.80±12.60	128.09±13.21	123.51±11.61	<0.05

Results were expressed as mean±SD and *geometric mean±SD.
Unpaired student's t-test was performed to compare between group means.

Table III (a) states the characteristics of study subjects categorized by serum uric acid (SUA) level. Participants in the higher quartiles of SUA and hyperuricemia showed an increasing pattern of age as well as BMI, SBP and DBP. Serum biochemical parameters such as ALT, AST, GGT, TC, TG, LDL-C and FPG all intended to increase from lowest to highest quartiles of SUA and hyperuricemic subgroup while HDL-C intended to decrease from lowest to highest quartiles of SUA and hyperuricemic subgroup (p<0.001).

Table- III (a): Characteristics of subjects categorized by SUA level in all subjects (n=140)

Variables	Quartiles of normal serum uric acid (SUA)				Hyperuricemia (n=18)	*p*-value
	Q1 (n=26)	Q2 (n=32)	Q3 (n=34)	Q4 (n=30)		
*SUA (mg/dl)	3.34±1.14	4.20±1.08	4.97±1.09	6.05±1.08	8.28±1.15	<0.001
Age (years)	37.54±5.85	39.75±5.61	44.06±5.60	48.50±5.53	50.33±4.70	<0.001
BMI (kg/m^2)	21.47±2.73	23.36±2.34	24.15±2.42	25.21±1.98	27.38±1.63	<0.001
SBP(mmHg)	118.65±12.37	122.19±10.77	127.50±12.51	135.93±7.45	141.67±9.39	<0.001
DBP(mmHg)	77.69±8.63	80.94±8.93	87.79±7.41	88.50±8.00	93.33±10.85	<0.001
FPG (mmol/L)	4.67±0.96	5.05±0.99	5.17±0.75	5.55±0.65	6.78±1.37	<0.001
*ALT (U/L)	23.44±1.34	26.91±1.29	29.51±1.26	33.88±1.20	39.81±1.16	<0.001
*AST (U/L)	21.88±1.38	25.70±1.25	27.54±1.27	32.36±1.16	37.15±1.16	<0.001
*GGT (U/L)	25.12±1.49	31.62±1.41	36.31±1.33	44.67±1.26	50.11±1.22	<0.001
TC (mg/dl)	178.42±21.50	183.47±14.89	190.18±12.88	205.60±14.75	222.06±22.10	<0.001
TG (mg/dl)	135.85±12.28	146.13±21.69	160.29±32.52	169.37±15.41	180.17±16.12	<0.001
HDL-C (mg/dl)	42.73±3.69	41.81±3.37	40.50±4.16	37.43±3.65	35.61±3.11	<0.001
LDL-C (mg/dl)	115.69±11.83	120.97±10.61	124.32±9.16	133.60±8.60	138.78±10.36	<0.001

Results were expressed as mean±SD and *geometric mean±SD.
ANOVA test was performed to compare all the variables between normal SUA and hyperuricemia.

Table III (b) presents the multiple comparison in between different categories of SUA level in all subjects. Significant difference was observed between the subgroups of Q1 vs Q3, Q1 vs Q4, Q1 vs hyperuricemia and Q2 vs Q4, Q2 vs hyperuricemia as well as Q3 vs hyperuricemia for all three liver enzymes (ALT, AST, GGT).

Table- III (b): Post-hoc analysis of serum ALT, AST and GGT for comparison in between different categories of SUA level in all subjects (n=140)

	Serum ALT (U/L) *p*-value	Serum AST(U/L) *p*-value	Serum GGT(U/L) *p*-value
Q1 vs Q2	1.000	0.566	0.521
Q1 vs Q3	<0.05	<0.05	<0.05
Q1 vs Q4	<0.001	<0.001	<0.001
Q1 vs Hyperuricemia	<0.001	<0.001	<0.001
Q2 vs Q3	0.996	1.000	1.000
Q2 vs Q4	<0.05	<0.05	<0.01
Q2 vs Hyperuricemia	<0.001	<0.001	<0.001
Q3 vs Q4	0.423	0.075	0.055
Q3 vs Hyperuricemia	<0.001	<0.001	<0.01
Q4 vs Hyperuricemia	0.116	0.090	1.000

Data were log transformed.
Bonferroni test was performed for multiple comparison in between different categories of SUA.

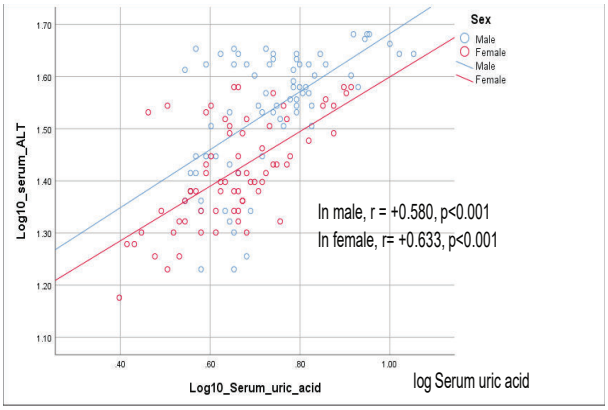

Figure- 1: *Scatter diagram showing correlation between log SUA and log serum ALT in male and female subjects*

Figure 1 illustrates the correlation between log SUA and log serum ALT in male and female subjects. It was evident that the two variables were positively and significantly (p<0.001) correlated in both genders.

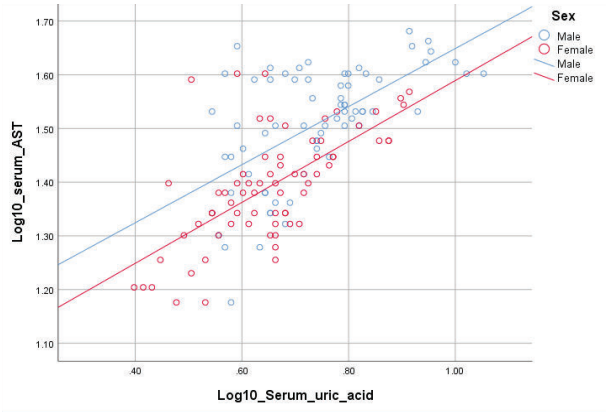

Figure- 2: *Scatter diagram showing correlation between log SUA and log serum AST in male and female subjects*

Figure 2 showing correlation between log SUA and log serum AST in male and female subjects. It was evident that the two variables were positively and significantly (p<0.001) correlated in both genders.

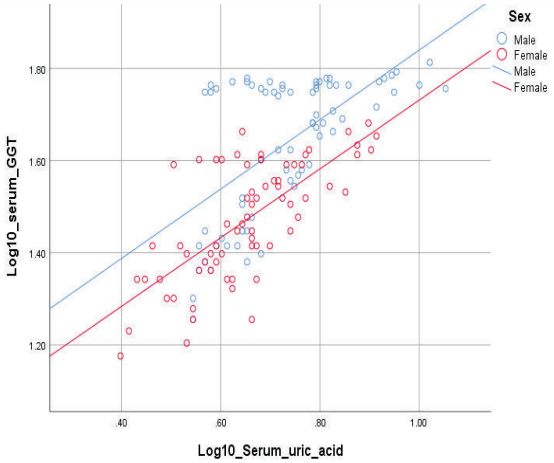

Figure- 3: *Scatter diagram showing correlation between log SUA and log serum GGT in male and female subjects*

Figure 3 showing correlation between log SUA and log serum GGT in male and female subjects. It was evident that the two variables were positively and significantly (p<0.001) correlated in both genders.

Table IV presents the role of SUA in the prediction of elevated liver enzymes in all subjects. AUC of SUA for ALT was found to be 0.839 (95% CI: 0.759-0.918) at cutoff point of 1.55 with a sensitivity of 77.8% and specificity of 73.8%. AUC of SUA for AST was found to be 0.848 (95% CI: 0.772-0.925) at cutoff point of 1.53 with a sensitivity of 77.8% and specificity 74.6%, while in case of GGT AUC of SUA was found to be 0.809 (95% CI: 0.723-0.894) at cutoff point of 1.62 with a sensitivity of 83.3% and specificity of 68.9%.

DISCUSSION

In this study it was observed that there was no significant age difference between male and female subjects. However, it was not consistent with the study done by Yang et al[23] who found a significant age difference between two groups. The study showed that BMI did not differ in between two groups. Similar results were observed by a Chinese study[24]. In this study, mean (±SD) SBP and DBP in mmHg of male differed to some extent from those of female (130.83±12.08 vs 125.71±13.89 and 87.50±9.66 vs 82.93±9.80, p<0.01). Similar observation was evident in other studies.[10,24] It was evident from the study that participants with hyperuricemia as well as those in the highest quartile (Q4) of SUA within reference range had elevated liver enzymes (ALT, AST and GGT). The data of this study also revealed that there is a stepwise increase in liver enzymes with increasing levels of SUA even within the reference range. Participants with increasing quartiles of SUA and hyperuricemia showed an increasing trend in levels of TC, TG, LDL-C, FPG as well as age, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP) except HDL-C which showed decreasing trend with increasing SUA level. Nearly similar pattern of observation was reported by two studies.[10,25] After stratification by the quartiles of SUA levels it was evident that the percentage of elevated liver enzymes (ALT, AST, GGT) were increased along with the increment of uric acid quartiles and also in hyperuricemic subgroup in subjects of both genders. However, male had a higher percentage of elevated ALT, AST and GGT than female in all of the SUA categories. Nearly similar findings were observed by some investigators.[10,24]

The present study showed that SUA was significantly and positively correlated with ALT, AST, GGT, TC, TG and

Table- IV: Diagnostic test indices and performance of SUA for predicting elevated liver enzymes in all subjects (n=140)

	AUC	Cut-off value of SUA	Sensitivity	Specificity	p-value	95% Confidence Interval	
						Lower Bound	Upper Bound
ALT	0.839	1.55	77.8%	73.8%	<0.01	0.759	0.918
AST	0.848	1.53	77.8%	74.6%	<0.01	0.772	0.925
GGT	0.809	1.62	83.3%	68.9%	<0.01	0.723	0.894

Results of ALT, AST and GGT were log transformed.
Then analyses for ROC curves were done.

LDL-C while inversely correlated with HDL-C in both genders which is consistent with other studies.[26,27] Furthermore, our data implied that increased SUA is independently associated with elevated liver enzymes (ALT, AST and GGT). A study carried out on Chinese adults by Chen et al[10] observed an association between uric acid and elevated ALT. After adjustment of multiple independent confounding variables along with SUA in multiple regression analysis where a significant independent association of SUA with liver enzymes was evident. Nearly similar observations were reported by.[10,28] Therefore, it is evident that increased SUA is associated with elevated liver enzymes. Zhang et al[29] reported that increased generation of uric acid mediated by high activity of xanthine oxidoreductase is able to accelerate the development of nonalcoholic fatty liver disease (NAFLD). Elevated uric acid induces the triglyceride accumulation by promoting the over-expression of pro-lipogenic enzymes sterol regulatory element binding proteins[30]. Evidence suggests that generation of uric acid catalyzed by xanthine oxidoreductase is accompanied by generation of reactive oxygen species. Thus, xanthine oxidoreductase induced oxidative stress lead to NAFLD development[31]. Elevated serum ALT levels are most closely related to liver fat accummulation and are commonly used as a surrogate marker for NAFLD in an epidemiological study[32]. Asymptomatic individuals with mild elevation of ALT, AST indicates the chances of liver disease, mainly NAFLD and hepatitis although AST is less specific liver enzyme[33]. A study on Framingham Offspring Heart Study demonstrated that both AST and ALT elevations up to 3 times the upper normal are associated with an increased risk for developing diabetes mellitus (DM). When restricted to normal values, only ALT was associated with incident DM. A recent cross-sectional study by Chen et al[10] found that positive relationship of elevated ALT with metabolic syndrome (MetS) was stronger than that of elevated AST. Furthermore, both NAFLD and MetS are associated with an increased risk of cardiovascular disease (CVD).[34]

GGT has been well established as a reliable marker of increased hepatic lipid content and hepatic insulin resistance by Thamer et al.[35] Both GGT and ALT have also been shown to predict the development of insulin resistance and DM stated by Vozarova et al[36]. Recent cross-sectional and longitudinal studies have found relatively independent associations between elevated serum GGT levels and hypertension or DM.[37,38] Cross-sectional studies of mostly middle-aged participants had shown linking ALT and GGT to components of the metabolic syndrome as well as T2DM and CVD.[39,40] However, it has been reported that SUA is significantly associated with hypertension, obesity, CVD, hypertriglyceridemia and hyperglycemia which may increase the risk of MetS.[41] Furthermore, SUA has been considered as an oxidative stress marker of MetS and CVD[9]. Thus, MetS has been considered to play an important role in the development or progression of NAFLD. Elevated serum uric acid levels have also been found to be associated with the development of NAFLD which can lead to cirrhosis and increased plasma activity of GGT and ALT[21]. Reason behind the pathogenesis of NAFLD appears to be insulin resistance which results lipolysis and excess deposition of fat on liver and together create inflammatory effects, oxidative stress and lead to elevate liver enzymes.[42,43] The predictive ability of SUA in the prediction of elevated liver enzymes (ALT, AST, GGT) were assessed by ROC curves. Area under the receiver operating characteristic curve (AUC) of SUA was used to identify subjects with elevated liver enzymes (ALT, AST, GGT). AUC of SUA for elevated ALT was found as 0.839 with the cut-off value of 1.55. Furthermore, AUC of SUA for elevated AST and GGT were 0.848 and 0.809 at cut-off values of 1.53 and 1.62 respectively. This observation is consistent with the finding of a study on Chinese adults conducted by Chen et al.[10] This indicates that SUA can be used as a predictor for elevated liver enzymes.

Thus, it can be concluded from the study that almost all the variables except HDL-C are increased with the increment of SUA level and hyperuricemia. Increased SUA is associated with elevated liver enzymes (ALT, AST and GGT) in adults and this association is independent of other confounding factors. This association suggests that SUA can be used as a screening test for NAFLD and other metabolic disorders.

CONCLUSIONS

Subjects in higher quartiles of SUA and hyperuricemia showed an increasing pattern of age with significantly higher BMI, SBP, DBP, FPG, ALT, AST, GGT, TC, TG, LDL-C and lower HDL-C. The variation of these parameters based on quartiles of SUA and hyperuricemia were almost similar in both genders. The percentage of adults with elevated liver enzymes increased with an increment in the SUA level in both genders while male had

a higher percentage of elevated liver enzymes than female in all SUA categories.

Pearson's correlation analysis showed positive correlation of SUA with ALT, AST, GGT, TC, TG, LDL-C and negative correlation with HDL-C among all subjects as well as in male and female subjects. In multiple regression analysis, it showed a significant independent linear association of SUA with liver enzymes (ALT, AST and GGT).

Disclosure of conflict of interest

No competing interests exist by the authors.

Statement of informed consent

"Informed consent was obtained from all participants."

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