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Roles of Nonalcoholic Fatty Liver Disease and Hyperuricemia in Lifestyle-related Diseases

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Abstract

Objective: We aimed to elucidate the relationships among hyperuricemia, nonalcoholic fatty liver disease (NAFLD), and other lifestyle-related diseases.

Methods: We enrolled 420 subjects who had a complete medical check-up at Tokyo Women's Medical University between June 2016 and December 2017. Risk factors related to NAFLD or hyperuricemia were analyzed by contingency tables using multivariate logistic regression. Statistical significance was set at $p<0.05$.

Results: NAFLD was significantly related to homeostasis model assessment-insulin resistance (≥2.5) and hyperuricemia (>7 mg/dL). Central obesity and impaired fasting glucose, which are components of metabolic syndrome (MetS), were significantly associated with NAFLD. MetS was also significantly associated with NAFLD. The following were identified as risk factors for hyperuricemia: sex (male), dyslipidemia (increased low-density lipoprotein cholesterol), hyperinsulinemia, NAFLD, eGFR (<60 mL/min/1.73 m^2), and alcohol overuse. Furthermore, central obesity and dyslipidemia (decreased high-density lipoprotein cholesterol and/or high triglycerides) were significantly associated with hyperuricemia.

Conclusions: Hyperuricemia and NAFLD are related to one another, to MetS, and to other lifestyle-related diseases. Thus, effective treatment of NAFLD and hyperuricemia is vital, which requires both medication and lifestyle modification approaches.

Keywords medical check-up, hyperuricemia, nonalcoholic fatty liver disease (NAFLD), metabolic syndrome

Nonalcoholic fatty liver disease (NAFLD) is no longer considered a primary liver disease, but rather a component of metabolic syndrome, insulin resistance, and other lifestyle-related diseases (e.g., diabetes, dyslipidemia, and hypertension)[1–3]. NAFLD is common among individuals undergoing medical check-up in Japan, with an estimated prevalence of 20%–30%, which is expected to increase with increasing obesity rates[4–6]. According to a proposed pathogenetic mechanism for NAFLD—the "two-hit" hypothesis—fat accumulation in hepatocytes contributes to increased hepatic oxidative stress[7], which in turn may cause insulin resistance, thereby leading to further fat accumulation[8,9].

Hyperuricemia, whose prevalence is increasing worldwide[10], is relevant to the discussions about metabolic syndrome. Serum uric acid levels could rise because of increased uric acid synthesis, decreased uric acid excretion, or a combination of these mechanisms. Diminished uric acid excretion has been reported in patients with metabolic syndrome[11], which possibly reflects impaired renal excretion mediated by hyperinsulinemia-enhanced proximal tubular sodium reabsorption[12,13]. Reduced uric acid excretion due to this enhanced sodium reabsorption occurs in conditions such as obesity and hypertension[14], which are the two most common diseases associated with metabolic syndrome[15].

In patients with metabolic syndrome, NAFLD may represent a hepatic component of the disease, while hyperuricemia may be indicative of the disordered metabolism. Thus, in this study, we aimed to evaluate the relationship among hyperuricemia, NAFLD, and other lifestyle-related diseases.

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Methods

Study design

This retrospective cohort study was performed in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Tokyo Women's Medical University (approval date: November 1, 2018; approval number: 4967). The study cohort was from among those who visited the Department of Complete Medical Check-up at Tokyo Women's Medical University (Japan) between June 2016 and December 2017. Specifically, we included those who had a periodic check-up at the "human dry dock" (the Japanese health check-up system). Subjects with either hepatitis C or hepatitis B infections were excluded from our study.

Services delivered at the human dry dock

The periodic health check-up program at the human dry dock is comprehensive. It includes the following assessments: physical characteristics (height, body weight, and waist circumference), complete blood count, blood biochemistry, urinalysis, electrocardiography, abdominal ultrasonography, upper gastrointestinal tract barium meal or endoscopic examination, visual acuity test, tonometry, fundic examination (retinal photography), and hearing assessment. Details of the subjects' medical histories and levels of alcohol consumption were obtained by interview with a doctor.

Definition of insulin resistance

Insulin resistance was defined using the homeostasis model assessment-insulin resistance (HOMA-IR) score, which was calculated as follows: {[fasting glucose (mg/dL) × fasting insulin (μU/mL)]/405}. A score of ≥2.5 was the threshold for insulin resistance.

Definition of risk factors

We included the following eight potential risk factors: alcohol overuse (>20 g ethanol/day), hypertension (systolic blood pressure (SBP) ≥130 mmHg, diastolic blood pressure (DBP) ≥85 mmHg, and/or current drug treatment), elevated low-density lipoprotein cholesterol (LDL-C) (LDL-C ≥140 mg/dL and/or current drug treatment), hyperinsulinemia (serum insulin ≥13 μIU/mL), metabolic syndrome (diagnosed using the 2005 guidelines of the Evaluation Committee on Diagnostic Criteria for Metabolic Syndrome of Japan)[16], hyperuricemia (uric acid >7 mg/dL and/or current drug treatment), impaired renal function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), and NAFLD (fatty liver in the absence of either hepatitis C or hepatitis B infection and without alcohol consumption >20 g ethanol/day). Moreover, metabolic syndrome diagnosis required the presence of central obesity and at least two of the following: hypertension, prior treatment for hypertension and dyslipidemia, prior treatment for dyslipidemia and impaired fasting glucose (IFG), or prior treatment for diabetes mellitus. Central obesity was defined as a waist circumference ≥85 cm for men and ≥90 cm for women; hypertension, as SBP ≥130 mmHg; dyslipidemia, as serum triglycerides ≥150 mg/dL and/or high-density lipoprotein cholesterol (HDL-C) <40 mg/dL; and IFG, as glucose levels ≥110 mg/dL).

Definition of fatty liver

Fatty liver was confirmed by abdominal ultrasonography with findings of either high hepato-renal echo contrast, liver brightness, or deep attenuation. In this study, computerized tomography (CT) was not performed. In a previous study, ultrasonography enabled the diagnosis of fatty liver with high accuracy, using a total area of hepatic steatosis exceeding 20%[17]. CT and magnetic resonance imaging (MRI) only allow identification of moderate or severe fat accumulation, with the total area displaying hepatic steatosis exceeding approximately >30%[18]. Ultrasound is better than CT and MRI for simple diagnosis of hepatic steatosis[19]. Accordingly, we diagnosed fatty liver using ultrasonography in this study.

Statistical analysis

Statistical analysis was performed using IBM SPSS version 26.0 (IBM Corp., Armonk, NY). Continuous variables were expressed as means (standard deviation) per group. Statistical difference was determined by two-sided Student's *t*-tests (for equal variance) or Welch's *t*-test (for unequal variance). Non-normally distributed variables were compared by the Mann–Whitney U test. Variables reported as proportions were compared using the chi-square test. The relationships between risk factors and NAFLD or hyperuricemia were examined by multivariate logistic regression analysis, reporting odds ratios (ORs). A p value <0.05 was considered statistically significant. Moreover, variables that were included into the models were based on the existing knowledge of risk factors for NAFLD or hyperuricemia and impaired renal function. The variables considered in the models were age, sex, metabolic syndrome, HOMA-IR, and impaired renal function for NAFLD. For hyperuricemia, the variables considered in the models were age, sex, metabolic syndrome, dyslipidemia, hyperinsulinemia, alcohol overuse, and impaired renal function.

Results

Study population

We included 420 subjects. Of these, 294 were males aged 64.8 (standard deviation 12.0) years and 126 were females aged 64.2 (standard deviation 11.4) years. NAFLD and hyperuricemia were detected in 100 (23.8%) and 192 (45.7%) subjects, respectively. Overall, 25.5% of males and 19.8% of females had NAFLD, while 59.5% of males and 13.5% of females had hyperuricemia.

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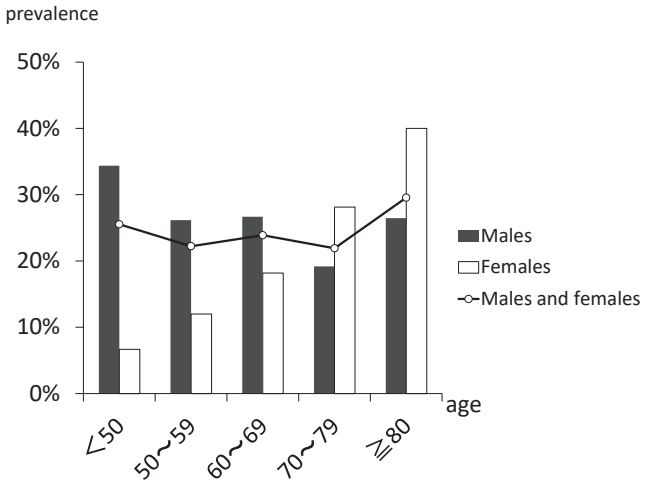

Fig. 1. Age- and Sex-Specific Proportions of NAFLD
NAFLD: nonalcoholic fatty liver disease.

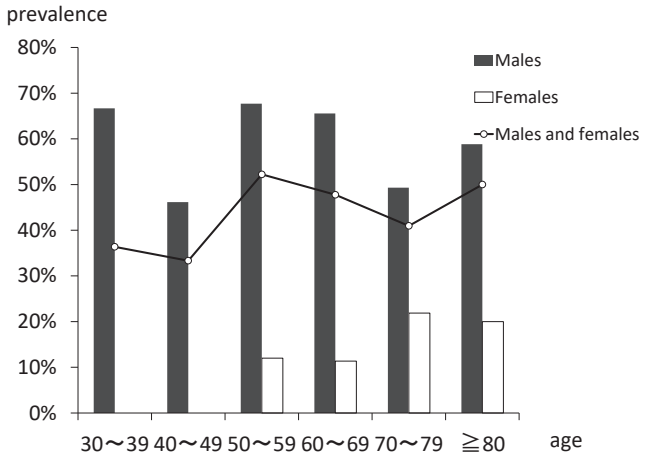

Fig. 2. Age- and Sex-Specific Proportions of Hyperuricemia

Fig. 1 shows the age- and sex-specific rates of NAFLD. The prevalence in females tended to increase gradually with age, whereas the difference in age-specific rates was not remarkable in males. **Fig. 2** shows the age- and sex-specific proportions of hyperuricemia. The prevalence in females tended to rise gradually with age after 50 years old, whereas the difference in age-specific proportion was not remarkable in males. In the study of Ozaki *et al.*[20], serum uric acid level increased after menopause in females.

Clinical characteristics and risk factors for NAFLD

Table 1 shows the clinical characteristics of 100 subjects with NAFLD (NAFLD group) and 320 without NAFLD (non-NAFLD group). Notably, SBP, DBP, triglyceride, uric acid, fasting plasma glucose, HbA1c, fasting plasma insulin, HOMA-IR, and waist circumference were significantly higher whereas HDL-C was significantly lower in the NAFLD group than in the non-NAFLD group. To identify the risk factors that were significantly associated with NAFLD, we performed a contingency table analysis between the NAFLD and non-NAFLD groups using multivariate logistic regression analysis. The analysis showed that HOMA-IR ≥2.5 (OR=2.779, p=0.001), hyperuricemia (OR=2.025, p=0.013), and metabolic syndrome (OR=1.949, p=0.015) are statistically significant risk factors for NAFLD (**Table 2**).

We further investigated which risk factors, including components of metabolic syndrome (i.e., central obesity and hypertension, central obesity and dyslipidemia, and central obesity and IFG), were significantly related to NAFLD. We performed a contingency table analysis between the NAFLD and non-NAFLD groups using multivariate logistic regression analysis. We found that, in addition to hyperuricemia (OR=2.145, p=0.007), central obesity and IFG (OR=2.039, p=0.017) are statistically significant risk factors for NAFLD (**Table 3**).

Clinical characteristics and risk factors for hyperuricemia

Table 4 shows the clinical characteristics of 192 subjects with hyperuricemia (hyperuricemia group) and 228 subjects without hyperuricemia (non-hyperuricemia group). Male sex, SBP, DBP, triglyceride, fasting plasma glucose, HbA1c, fasting plasma insulin, HOMA-IR, NAFLD, and waist circumference were significantly higher whereas HDL-C and eGFR were significantly lower in the hyperuricemia group than in the non-hyperuricemia group. To determine the risk factors that were significantly associated with hyperuricemia, we performed a contingency table analysis between the hyperuricemia and non-hyperuricemia groups using multivariate logistic regression. The analysis revealed that male sex (OR=7.375, p<0.0001), dyslipidemia (high LDL-C)(OR=1.714, p=0.030), hyperinsulinemia (OR=3.552, p=0.038), NAFLD (OR=3.640, p<0.0001), eGFR <60 mL/min/1.73 m^2 (OR=4.454, p<0.0001), and alcohol overuse (OR=2.614, p=0.001) are statistically significant risk factors for hyperuricemia (**Table 5**).

We further investigated the risk factors that were significantly related to hyperuricemia, including components of metabolic syndrome (i.e., central obesity and hypertension, central obesity and dyslipidemia (low HDL-C and/or high triglycerides), and central obesity and IFG). We performed a contingency table analysis between the hyperuricemia and non-hyperuricemia groups using multivariate logistic regression. Male sex (OR=6.724, p<0.0001), NAFLD (OR=3.632, p<0.0001), eGFR <60 mL/min/1.73 m^2 (OR=4.677, p<0.0001), alcohol overuse (OR=2.435, p=0.002), and the presence of central obesity and dyslipidemia (low HDL-C and/or high triglycerides)(OR=1.825, p=0.045) were statistically significant risk factors for hyperuricemia (**Table 6**).

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Table 1. Clinical Data of Subjects with or without NAFLD

Characteristics	Subjects with NAFLD	Subjects without NAFLD	*p* value
	Mean (Standard deviation) [Number]		
Age	64.2 (12.2) [100]	64.7 (11.7) [320]	0.718
Sex, male/female	[75/25]	[219/101]	0.197
Systoric blood pressure (mmHg)	129.6 (17.1) [100]	123.0 (17.5) [320]	0.001
Diastolic blood pressure (mmHg)	78.5 (10.9) [100]	75.4 (11.7) [320]	0.017
Total cholesterol (mg/dL)	199.4 (31.1)[100]	203.5 (35.6) [320]	0.310
LDL cholesterol (mg/dL)	120.6(26.6) [100]	116.9 (29.3) [320]	0.253
HDL cholesterol (mg/dL)	55.2 (12.7) [100]	66.2 (18.6) [320]	<0.0001
Triglyceride (mg/dL)	130.5 (67.8) [100]	111.6 (71.8) [320]	0.021
Uric acid (mg/dL)	6.1 (1.3) [100]	5.6 (1.3) [320]	0.001
FPG (mg/dL)	108.7 (16.7) [100]	104.7 (16.8) [320]	0.037
HbA1c (%)	6.2 (0.7) [100]	5.9 (0.5) [320]	<0.0001
Fasting plasma insulin (μIU/mL)	7.7 (4.6) [100]	5.0 (3.4) [320]	<0.0001
HOMA-IR	2.1 (1.4) [100]	1.3 (1.0) [320]	<0.0001
eGFR	67.6 (14.2) [100]	68.2 (14.6) [320]	0.748
Waist circumference (cm)	92.2 (8.4) [100]	84.9 (9.3) [320]	<0.0001

Results are shown as mean (standard deviation). NAFLD: nonalcoholic fatty liver disease, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model assessment-insulin resistance, eGFR: estimated glomerular filtration rate.

Table 2. Multivariate Logistic Regression Analysis of Risk Factors for NAFLD

Characteristics	Subjects with NAFLD (*n*=100)	Subjects without NAFLD (*n*=320)	Adjusted OR	95% CI	*p* value
	Number (%)				
Aging (over 60 years old)	67 (67.0)	210 (65.6)	1.121	0.662–1.900	0.670
Male	75 (75.0)	219(68.4)	0.738	0.401–1.361	0.331
Female	25 (25.0)	101 (31.6)			
HOMA-IR≥2.5	29 (29.0)	31 (9.7)	2.779	1.513–5.102	0.001
HU	60 (60.0)	132 (41.3)	2.025	1.163–3.524	0.013
eGFR<60	26 (26.0)	90 (28.1)	0.614	0.343–1.099	0.101
MetS	46 (46.0)	81 (25.3)	1.949	1.140–3.331	0.015

NAFLD: nonalcoholic fatty liver disease, OR: odds ratio, CI: confidence interval, HOMA-IR: homeostasis model assessment-insulin resistance, HU: hyperuricemia, eGFR: estimated glomerular filtration rate, MetS: metabolic syndrome.

Table 3. Further Multivariate Logistic Regression Analysis of Risk Factors for NAFLD

Characteristics	Subjects with NAFLD (*n*=100)	Subjects without NAFLD (*n*=320)	Adjusted OR	95% CI	*p* value
	Number (%)				
Aging (over 60 years old)	67 (67.0)	210 (65.6)	1.067	0.630–1.808	0.809
Male	75 (75.0)	219 (68.4)	0.704	0.380–1.303	0.264
Female	25 (25.0)	101 (31.6)			
HU	60 (60.0)	132 (41.3)	2.145	1.235–3.724	0.007
eGFR<60	26 (26.0)	90 (28.1)	0.628	0.352–1.121	0.116
Central obesity and hypertension	52 (52.0)	103 (32.2)	1.562	0.849–2.875	0.152
Central obesity and dyslipidemia (low HDL-C and/or high TG)	48 (48.0)	95 (29.7)	1.249	0.686–2.275	0.467
Central obesity and IFG	34 (34.0)	49 (15.3)	2.039	1.139–3.650	0.017

NAFLD: nonalcoholic fatty liver disease, OR: odds ratio, CI: confidence interval, HU: hyperuricemia, eGFR: estimated glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, IFG: impaired fasting glucose.

Discussion

In this study, we investigated the relationship between NAFLD and hyperuricemia with regard to metabolic syndrome. Previous studies reported that insulin resistance results in abnormal glucose metabolism in both NAFLD[21] and liver cirrhosis[22]. Supporting these reports, our study confirmed that components of metabolic syndrome (central obesity and IFG) are statistically significant risk factors for NAFLD (**Table 3**). Furthermore, HOMA-IR level ≥2.5, which is used to indicate insulin resistance, was also a statistically significant risk factor for NAFLD. Insulin resistance in the liver inhibits the glycolytic pathway, activates the pentose phosphate cycle, and thus accelerates purine

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Table 4. Clinical Data of Subjects with or without Hyperuricemia

Characteristics	Subjects with HU	Subjects without HU	*p* value
	Mean (Standard deviation) [Number]		
Age	64.5 (11.6) [192]	64.7 (12.0) [228]	0.909
Sex, male/female	[175/17]	[119/109]	<0.0001
Systoric blood pressure (mmHg)	127.2 (15.8) [192]	122.3 (18.7) [228]	0.004
Diastolic blood pressure (mmHg)	78.3 (11.9) [192]	74.2 (11.1) [228]	<0.0001
Total cholesterol (mg/dL)	201.0 (37.1) [192]	203.8 (32.4) [228]	0.418
LDL cholesterol (mg/dL)	118.8 (31.1) [192]	116.9 (26.5) [228]	0.485
HDL cholesterol (mg/dL)	58.5 (14.5) [192]	68.0 (19.4) [228]	<0.0001
Triglyceride (mg/dL)	135.3 (81.6) [192]	99.9 (56.4) [228]	<0.0001
FPG (mg/dL)	108.1 (17.0) [192]	103.7 (16.4) [228]	0.007
HbA1c (%)	6.0 (0.6) [192]	5.9 (0.5) [228]	0.008
fasting plasma insulin (μIU/mL)	6.7 (4.5) [192]	4.8 (3.0) [228]	<0.0001
HOMA-IR	1.8 (1.3) [192]	1.3 (0.9) [228]	<0.0001
eGFR	63.7 (14.9) [192]	71.6 (13.1) [228]	<0.0001
NAFLD (%)	31.3 [60/192]	17.5 [40/228]	0.001
Waist circumference (cm)	89.7 (8.4) [192]	84.0 (9.8) [228]	<0.0001

Results are shown as mean (standard deviation). HU: hyperuricemia, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FPG: fasting plasma glucose, HbA1c: hemoglobin A1c, HOMA-IR: homeostasis model assessment-insulin resistance, eGFR: estimated glomerular filtration rate, NAFLD: nonalcoholic fatty liver disease.

Table 5. Multivariate Logistic Regression Analysis of Risk Factors for Hyperuricemia

Characteristics	Subjects with HU (*n*=192)	Subjects without HU (*n*=228)	Adjusted OR	95% CI	*p* value
	Number (%)				
Aging (over 60 years old)	125 (65.1)	152 (66.7)	0.660	0.395–1.103	0.113
Male	175 (91.1)	119 (52.2)	7.375	3.948–13.776	<0.0001
Female	17 (8.9)	109 (47.8)			
Dyslipidemia (high LDL cholesterol)	121 (63.0)	109 (47.8)	1.714	1.053–2.787	0.030
Hyperinsulinemia	18 (9.4)	5 (2.2)	3.552	1.073–11.757	0.038
eGFR<60	76 (39.6)	40 (17.5)	4.454	2.504–7.924	<0.0001
MetS	83 (43.2)	44 (19.3)	1.195	0.692–2.061	0.523
NAFLD	60 (31.3)	40 (17.5)	3.640	1.915–6.920	<0.0001
Alcohol overuse	85 (44.3)	71 (31.1)	2.614	1.463–4.670	0.001

HU: hyperuricemia, OR: odds ratio, CI: confidence interval, LDL: low-density lipoprotein, eGFR: estimated glomerular filtration rate, MetS: metabolic syndrome, NAFLD: nonalcoholic fatty liver disease.

Table 6. Further Multivariate Logistic Regression Analysis of Risk Factors for Hyperuricemia

Characteristics	Subjects with HU (*n*=192)	Subjects without HU (*n*=228)	Adjusted OR	95% CI	*p* value
	Number (%)				
Aging (over 60 years old)	125 (65.1)	152 (66.7)	0.651	0.390–1.085	0.100
Male	175 (91.1)	119 (52.2)	6.724	3.618–12.497	<0.0001
Female	17 (8.9)	109 (47.8)			
eGFR<60	76 (39.6)	40 (17.5)	4.677	2.624–8.335	<0.0001
Central obesity and hypertension	96 (50.1)	59 (25.9)	1.021	0.554–1.880	0.947
Central obesity and dyslipidemia (low HDL-C and/or high TG)	93 (48.4)	50 (21.9)	1.825	1.014–3.284	0.045
Central obesity and IFG	51 (26.6)	32 (14.0)	1.091	0.592–2.011	0.781
NAFLD	60 (31.3)	40 (17.5)	3.632	1.914–6.891	<0.0001
Alcohol overuse	85 (44.3)	71 (31.1)	2.435	1.369–4.332	0.002

HU: hyperuricemia, OR: odds ratio, CI: confidence interval, eGFR: estimated glomerular filtration rate, HDL-C: high-density lipoprotein cholesterol, TG: triglyceride, IFG: impaired fasting glucose, NAFLD: nonalcoholic fatty liver disease.

synthesis and uric acid production via the liver[23,24]. Notably, insulin resistance in patients with metabolic syndrome induces compensatory hyperinsulinemia, which, in chronic cases, induces sodium reabsorption from the proximal convoluted tubules of the kidneys thereby promoting uric acid reabsorption.

Moreover, we found that central obesity and dyslipidemia (low HDL-C and/or high triglycerides), which are components of metabolic syndrome, and high LDL-C are statistically significant risk factors for hyperurice-

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mia (**Table 5** and **6**). Subjects with visceral obesity have been reported to show increased uric acid production and serum uric acid levels[25,26]. Visceral fat accumulation increases serum uric acid levels through the following mechanism: in subjects with visceral obesity, excessive free fatty acids in the portal vein stimulate the overproduction of very low-density lipoprotein, which in turn leads to hypertriglyceridemia. Hypertriglyceridemia activates the pentose phosphate cycle through the nicotinamide adenine dinucleotide phosphate pathway and consequently increases the production of uric acid[20,27].

Hyperuricemia is a mediator of proinflammatory endocrine imbalance in the adipose tissue and thus is a potential underlying factor for dyslipidemia, inflammation, and subsequent atherogenesis[28]. A previous study showed a significant positive relationship between serum uric acid levels and triglyceride, total cholesterol, and LDL-C levels, with an inverse relationship with HDL-C[29]. Concurrent dyslipidemia and hyperuricemia have also been reported[30–32]. Furthermore, we also found that hyperuricemia has a statistically significant relationship with hyperinsulinemia (**Table 5**), which is consistent with the finding of Tanabe *et al.*[33]. Hyperuricemia and insulin resistance mutually amplify each other, and both are assumed to promote arteriosclerosis.

In this study, we emphasize the need for early prevention of hyperuricemia, dyslipidemia, central obesity (visceral obesity), and hyperinsulinemia with both medication and lifestyle modification (healthy diet, exercise, and restricted drinking) to reduce the incidence of associated arteriosclerotic diseases.

Renal dysfunction was another risk factor associated with hyperuricemia (**Table 5** and **6**), which is an interesting finding given the recent evidence that uric acid is a risk factor for renal dysfunction[34]. Notably, both hyperuricemia and gout have renal dysfunction and renal stone development as complications. Some studies have shown that uric acid-lowering therapies in patients with both hyperuricemia and renal dysfunction could improve renal function[35–38].

Furthermore, we showed that the prevalence of hyperuricemia among females tended to increase gradually after the age of 50 years (**Fig. 2**). Urate resorptive transporters are important for uric acid reabsorption and urate transporter 1 is suppressed by estrogen. Thus, increased serum urate levels in postmenopausal females in our study possibly reflected the change in renal urate elimination associated with loss of female hormones[39].

In addition, we also showed that the NAFLD prevalence among females tended to rise gradually with age, whereas the rate of NAFLD in men remained almost unchanged. These results suggest an influence of female hormones on fatty liver development. Estrogen suppresses visceral fat accumulation and increases subcutaneous fat accumulation[40]. Hence, a decrease in estrogen activity may promote visceral fat accumulation, thereby resulting in fatty liver development[41].

Based on our results, hyperuricemia was a significant risk factor for NAFLD (**Table 2** and **3**), which is consistent with the available clinical evidence suggesting that hyperuricemia is significantly related to NAFLD. Lombardi *et al.*[42] reported that serum uric acid levels mainly contribute to NAFLD pathogenesis through insulin resistance[43], production of radical oxygen species[44], and activation of the Nod-like receptor pyrin domain-containing protein 3 inflammasome[45–47]. Hyperuricemia may cause insulin resistance by reducing endothelial nitric oxide bioavailability[43]. Additionally, uric acid may be produced by fructose metabolism and may induce hepatic steatosis in the liver through mitochondrial oxidative stress[48–51]. Uric acid is a strong environmental oxidant in metabolic syndrome, and hyperuricemia could stimulate nicotinamide adenine dinucleotide phosphate oxidase and directly contribute to NAFLD pathogenesis[52]. Generally, serum uric acid could regulate lipid production and facilitate the onset of metabolic disorders and NAFLD through multifaceted pathways[53].

Our data further indicated that NAFLD is an independent risk factor for hyperuricemia. However, the specific NAFLD pathogenesis inducing high serum uric acid levels remains to be clearly established. Nevertheless, inflammatory cells may infiltrate hepatic and fatty tissues, and subsequently nucleic acids may be released from hepatocytes undergoing apoptosis, which in turn produces an environment that is conducive to hyperuricemia development[54].

Hyperuricemia and NAFLD are related to one another and either of the two is related to metabolic syndrome, insulin resistance, dyslipidemia, renal dysfunction, and various lifestyle factors. On this basis, it is plausible that we should aim to treat these conditions with both medication and lifestyle advice.

Conclusion

In conclusion, hyperuricemia and NAFLD are related and both are associated with metabolic syndrome and other lifestyle-related diseases. Thus, an effective treatment of NAFLD and hyperuricemia requires both medical therapy and lifestyle changes.

Conflict of Interest

The authors have no conflict of interest to declare.

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