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Does High Level of Uric Acid Lead to Nonalcoholic Fatty Liver Disease?

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Abstract

Nonalcoholic fatty liver disease (NAFLD) was considered as a hepatic manifestation of metabolic syndrome. Uric acid is the final metabolite of purine compounds in human. Purine metabolic disorders lead to hyperuricemia, which has a close relationship with NAFLD. Recent studies have shown that uric acid can induce NAFLD by stimulating endoplasmic reticulum stress, oxidative stress and insulin resistance. However, the relationship reported by many studies between NAFLD and hyperuricemia remains controversial. What role of UA plays in NAFLD needs further explored. This paper reviews the relationship between hyperuricemia and NAFLD in clinic and experimental animals, as well as its potential underlying mechanism.

Keywords: Nonalcohol fatty liver disease; Metabolic syndrome; Uric acid; Hyperuricemia

Abbreviations: SUA: Serum Uric Acid; NAFLD: Non-alcoholic Fatty Liver Disease; ALT: Alanine Aminotransferase; HUA: Hyperuricemia; NASH: Non-alcoholic Steatohepatitis.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is a pathological change of liver tissue, which is similar to alcoholic liver disease but has no excess alcohol abuse history [1]. In recent years, along with the increasing trend of obesity and metabolic syndrome, NAFLD has become one of the most common chronic liver diseases worldwide. The prevalence of NAFLD ranges from 20%-30% in the general population and up to 75%-100% in obese individuals [2]. Several population based epidemiological studies have indicated that the prevalence of NAFLD in China is approximately 15% among adults (6.3%-27.0%) [3]. NAFLD is possibly replacing hepatitis B as the leading cause of chronic liver disease in China [4]. The spectrum of NAFLD related diseases is increasing. With the development of the disease, it may cause liver fibrosis, liver function damage, even lead to cirrhosis and hepatocellular carcinoma [5,6]. What is the pathogenesis of NAFLD? Although the proposal of "two hits" involving insulin resistance and oxidative stress has been well accepted, the mechanism of NAFLD was thought very complex and still remained unclearly [7,8].

Uric acid is the end product of purine metabolism. Excessive purine intake, endogenous purine, and purine metabolism can lead to uric acid production. Most uric acid is excreted with urine through kidney, and the rest enters into the intestinal tract through bile duct and decomposed by intestinal bacteria. When uric acid is synthesized more than excreted, the content of uric acid elevated [9,10]. Studies have found that consuming a lot of purine and high-energy food results in metabolic syndrome (MS) [11]. Purine metabolic disorders cause hyperuricemia, which is common in central obesity, high blood triglycerides and other patients with MS [12].

NAFLD is considered one of the manifestations of MS in liver, which often coexists with other symptoms of the metabolic syndrome including central obesity, type 2 diabetes, hypertension, and hyperlipidemia [13,14]. In recent years, it is found that NAFLD patients are often accompanied with hyperuricemia [15]. A community-based study showed that the prevalence of NAFLD and hyperuricemia was 33.1% and 17.1%, and 23.5% of the NAFLD subjects had hyperuricemia [16]. More and more studies indicated that serum uric acid (SUA) might be a novel risk factor of

NAFLD, its high concentration is associated with the occurrence and progress of the disease [12,17,18]. Further research found that elevated SUA was independently associated with NAFLD regardless of insulin resistance and metabolic syndrome status, especially hypertriglyceridemia or central obesity [19-21]. However, whether elevated level of SUA during the development of NAFLD or NASH is a cause, a consequence or just a bystander remains unclear. Therefore, here we make a review on UA and NAFLD and try to elaborate their relationship.

The literature search for this review was conducted on literature published through 2000, using the PubMed and China National Knowledge Infrastructure databases. The search keywords were used: uric acid or SUA OR hyperuricemia and NAFLD/nonalcoholic fatty liver disease OR NASH/non-alcoholic steatohepatitis OR fatty liver OR liver enzymes OR liver damage.

Correlation between NAFLD and SUA

The association between uric acid and NAFLD has been demonstrated by clinical and epidemiological studies. Accumulating evidence has shown that the SUA level was an independent predictor of increased prevalence of NAFLD. In the meantime, there were also some data showing that NAFLD significantly elevated the risk of hyperuricemia. Therefore, many researchers believe that there was an interdependent relationship between NAFLD and uric acid, which has not been revealed clearly by far. The clinical studies concerning the correlation of NAFLD and SUA were listed in **Table 1.**

High level of SUA is the biomarker and risk factor of NAFLD

In the past decades, with the increasing prevalence of NAFLD, many clinical studies were carried out to investigate its related biomarker and risk factors. Recent observational studies suggest that hyperuricemia (SUA >7.0 mg/dL in men and >5.7 mg/dL in women) is a risk factor for NAFLD among people for nutrition examination in USA [22]. In a cross-sectional study, 8,925 subjects (6,008 men) with a mean age of 43 were enrolled to investigate the relationship between SUA level and NAFLD in Chinese population. The research result indicated that the level of SUA was closely related to NAFLD [23]. Liang et al. evaluated some valid biomarkers in 21,798 patients with NAFLD and found that the risk of NAFLD gradually increased with elevated SUA levels, independent of other metabolic risk factors [24]. Hu et al. studied 7,152 employees in Shanghai. The data analysis suggested that SUA level had an assistant diagnostic value for NAFLD [25]. A total of 1,948 adults (691 diagnosed with NAFLD) from Zhejiang, China was followed for 8 years to investigate risk factors for NAFLD development. After 8-year follow-up, 337 (17.30%) subjects free of NAFLD at baseline developed NAFLD with an especially greater increase in parameters including SUA, and 123 (6.31%) subjects diagnosed with NAFLD seceded with decreasing trend of SUA [26]. Furthermore, hyperuricemia was an independent risk factor of this disease, independent of gender, age, metabolic syndrome, and other clinical variables in non-diabetic Chinese men [27]. In order to compare SUA values in two racial groups in China: Uyghur, with a high prevalence of NAFLD, and Han,

Table 1 Correlation between NAFLD and SUA.

	Study Design	Study Subjects (NO.)	Relationship	References
High Level of SUA is the Biomarker and Risk Factor of NAFLD	Cross-sectional	People for Nutrition Examination Survey in USA (5,370)	SUA is risk factor of NAFLD	22
	Cross-sectional	Employees of Zhenhai Refining & Chemical Company Ltd., China (8,925)	SUA is risk factor of NAFLD	23
	Cross-sectional	People for examination survey in China (21,798)	SUA is risk factor of NAFLD	24
	Prospective cohort	participants non-NAFLD (1257); NAFLD patients (691)	SUA is risk factor of NAFLD	26
	Cross-sectional	Subjects in health examination, Uyghur (4,157) and Han (6,448)	SUA is risk factor of NAFLD	28
	Prospective cohort	Korean men (5,741)	SUA is risk factor of NAFLD	29
	Retrospective cohort	Healthy Korean subjects (4,954)	SUA is risk factor of NAFLD	30
	Cross-sectional	Subjects from 2 separate medical centers 960,455)	Association between sUA and NAFLD was significantly greater in females than in males	32
	Cross-sectional	Obese children(268)	SUA is risk factor of NAFLD	33
SUA Level is Related with Liver Damage in NAFLD	Cross-sectional	Individuals aged 20-60 who underwent blood tests for ALT and uric acid (82,608)	SUA is positively related to high ALT	35
	Cross-sectional	NAFLD patients (166)	HUA is related to liver damage	36
	Correlational	NAFLD patients (1,365)	SUA decrease with fibrosis progression	37
	Prospective cohort	NASH patients (130)	HUA is inversely correlates with liver damage	38
	Retrospective cohort	NAFLD patients (118)	SUA is related to severe histological changes	40
NAFLD Develops Hyperuric-emia	Prospective cohort	NAFLD (5,541)	NAFLD was associated with development of HUA	41
	Retrospective cohort	Middle-aged South Korean male workers (51,210.6)	Fatty liver is one risk factor of HUA	42

with a lower prevalence, Cai et al. examined SUA and clinical characteristics of melltabolic syndrome in 4,157 Uyghur and 6,448 Han subjects. They found that the prevalence of NAFLD in Uygur and Han population was 42.3% and 33.3%, the prevalence of hyperuricemia was 8.8% and 14.7% respectively, SUA was an independent risk factor in NAFLD in both Uyghurs and Han people [28]. Similarly, Ryu et al. investigated 5,741 Korean men, aged 30 - 59, finding that SUA appeared to be an independent predictor for developing ultrasonographically detected fatty liver even in normal-weight men [29]. Among 4,954 healthy Korean subjects without other risk factors enrolled in an study, the incidence of NAFLD after 5 years increased with the level of baseline SUA (5.6%, 9.8%, 16.2%, and 20.9%, respectively) [30]. One study in the USA analyzed 5,370 men and women aged 20-74 years from the Third National Health and Nutrition Examination Survey (NHANES III) (1988-1994). After adjustment, individuals with hyperuricemia were more likely to have NAFLD (OR 1.4) [22]. In another nationally representative sample of United States nondiabetic adults, elevated uric acid level is associated with ultrasound-diagnosed NAFLD independently of metabolic syndrome features [20]. In one recent systematic meta-analysis, 4 cross-sectional studies, 2 prospective studies, and 3 retrospective studies involving 55,573 participants were identified. The pooled OR of NAFLD occurrence was 1.92 comparing the highest to lowest SUA levels in a random effect model. Subgroup analysis showed that high SUA levels increased the risk of NAFLD in cross-sectional studies (OR 2.18), retrospective studies (OR 1.82), and prospective studies (OR 1.43) [31].

Furthermore, the association between SUA and NAFLD was significantly greater in females than in males. In order to detect the association between sex-specific SUA and NAFLD, one study involved both cross-sectional population consisted of 58,849 individuals who underwent a health examination and longitudinal population from 14734 initially fatty liver disease-free individuals who underwent an annual health screen Analysis. Sex-specific SUA quartiles (Q1-Q4) were defined: 330, 331-380, 381-435, and 436 mmol/L for male; 230, 231-270, 271-310, and 311 mmol/L for female. Analysis for the sex-specific subgroup showed the adjusted ORs for Q4 versus Q1 were 2.898 in female and 1.887 in male in the cross-sectional population, the HRs for the Q4 were 2.355 in female and 1.249 in male in the longitudinal population compared with Q1 [32]. The meta analysis results also demonstrated the risk of NAFLD seemed more pronounced among women (OR 1.85) than among men (OR 1.56) [31]. In addition, a cross-sectional study including 268 obese children without alcohol consuming and hepatitis B or C was consecutively conducted at an auxology clinic. After a series of index examination and data analysis, researchers finally assessed the predictors of NAFLD in obese children, which showed that SUA was the independent predictor of NAFLD [33].

To investigate whether uric acid has a causal role in the development of hepatic steatosis, a mouse model of hyperuricemia was established by feeding C57BL/6 mice for 8 weeks with the diet consisting of 2% oxonic acid and 3% uric acid (HUA). The mice showed significantly higher SUA, serum and intrahepatic triglyceride levels than chow diet-fed mice. Furthermore, the supplementation of HFD with 2% oxonic acid and 3% uric acid induced more remarkable elevation of SUA and intrahepatic triglyceride than the mice fed HFD alone [34].

SUA level is related with liver damage in NAFLD

Elevated SUA has been reported to be associated with increased mortality in 15,083 participants in the Scottish Heart Health Extended Cohort (SHHEC) Study during a median follow-up of 23 years. The high level of SUA was most associated with kidney-related death, leading to earlier mortality, especially in women [17]. Recently, studies found that increasing SUA is also associated with increasing severity of NAFLD on ultrasonography [16,20]. Individuals with hyperuricemia were more likely to have elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) (adjusted OR 1.8) [22]. In one cross-sectional study including 82,608 people, there was a significant positive dose-response association between SUA levels and the rate of elevated serum ALT. This association was maintained in all categories of gender and BMI, and was observed among patients diagnosed with NAFLD [35]. In a homogeneous cohort of biopsy-proven 166 NAFLD patients, about 20% of patients had hyperuricemia. Higher HOMA index (OR 1.219) and hyperuricemia (OR 4.906) were linked to NAFLD activity score (NAS) ≥ 5 by multiple logistic regression analysis. Hyperuricemia is independently associated with the severity of histological liver damage in NAFLD patients [36]. Thus, SUA was suggested to serve as a serum marker for liver damage.

However, it should be noted that SUA levels are mainly a product of hepatic production and renal clearance. Thus, UA may decrease with the subsequent progression of fibrosis in NAFLD patients. The SUA level in patients with cirrhosis have been recognized as decreased compared with healthy subjects. In a study enrolling a total of biopsy-proven 1,365 patients with NAFLD, hyperuricemia was found in 30.2% of the patients. The uric acid levels of NAFLD patients with severe fibrosis (Stages 3-4) significantly decreased compared to those with mild fibrosis (Stages 1-2) (P=0.0449) after adjusting for age, BMI, dyslipidemia, and diabetes [37]. Similarly, in biopsy-proven Taiwanese NASH patients with fibrosis, there was a significant inverse correlation between hyperuricemia and fibrosis stages, ranging from 48.4% of F0-1, 33.3% of F2, and 9.1% of F3-4, respectively. Normal uric acid level (OR 5.6) was one of the significant factors associated with significant fibrosis [38].

These findings are not controversial. Since most cohort studies only enrolled health subjects and moderate NAFLD, instead of end-stage liver disease, the dose-response association between SUA and NALD severity are likely concluded. A mouse NAFLD model established by feeding with a high fat diet with high cholesterol and a high sugar supplement in water for 8, 27, and 49 weeks, closely mimics progressive NAFLD covering the full spectrum of liver pathophysiologic changes characterized in human NAFLD progression. Liver triglyceride levels increased in the HFD compared to the chow diet group at all time-points. Hepatocyte ballooning positive increased and fibrosis was detectable at 27 weeks. Necrosis, lobular, portal inflammation and fibrosis

became prevalent at 49 weeks. Liver damage, assessed by serum ALT, increased from 8 weeks and more significantly at 27 weeks. However, a modest, 1.5-fold, increase in SUA level appeared at 8 weeks, while tended to decrease at 27 weeks [39]. Another retrospective study analyzed data from 118 consecutive biopsy-proven NAFLD patients showed that SUA was the independent predictor for moderate-to-severe steatosis, ballooning, NAS ≥5; not for significant and advanced fibrosis, neither for more-than-mild portal inflammation [40].

NAFLD develops subsequent hyperuricemia

Different from the above studies, a few researchers found that NAFLD could lead to elevated uric acid level, causing hyperuricemia. Xu et al. evaluated the effect of NAFLD on the development of hyperuricemia in a cohort of 5,541 patients without hyperuricemia at baseline. This follow-up study of 7 years had found that NAFLD was strongly associated with subsequent incidence of hyperuricemia. The incidence of hyperuricemia was 8.81 per 1000 person-year of follow-up in participants without NAFLD at baseline, but increased to 23.02 per 1000 person-year in participants with baseline NAFLD. Cox proportional hazards regression analyses showed that age, gender, and body mass index adjusted hazard ratio for incident hyperuricemia was 1.609 (1.129-2.294) in individuals with NAFLD [41]. Another Korean cohort study on the incidence of hyperuricemia in middle-aged South Korean male workers with a follow-up from 2002 to 2009, found that 2,496 male out of 51,210.6 person developed hyperuricemia. The regression analysis showed the risk of incident hyperuricemia by baseline level of liver function and the presence of fatty liver. Fatty liver at baseline was associated with a significantly increased risk of hyperuricemia (hazard ratio 1.13) [42]. Although there are only a few proofs indicating that NAFLD leads to hyperuricemia, this is a different point of view, which should be also taken into consideration when concerning the relation of NAFLD and UA.

Mechanism Underlying the Relationship between UA and NAFLD

Based on the clinical reports, some researchers tried to study the effect of UA on NAFLD development. Recently, concerns have been given to serum uric acid levels and development of NAFLD [43]. These studies provide new insights into the mechanisms by which uric acid stimulates fat accumulation in the liver.

UA and oxidative stress

Some studies suggested that uric acid could induce oxidative stress (OS), which plays an important role in the pathogenesis of NAFLD [44]. Zhang et al. found that high level of UA increased ROS levels and induced oxidative stress in cultured rat pancreatic β cells [45]. In adipocytes, soluble UA stimulates an increase in reactive oxygen species (ROS) production, which has been recently recognized as a major causative factor for obesity-related inflammatory endocrine imbalance [10,46]. UA increases the mRNA expression of monocyte chemotactic protein-1 (MCP-1) and decreases the mRNA expression of adiponectin. A strong positive association between serum leptin and UA has been demonstrated in both diabetic and healthy subjects. These cytokines play an important role in the pathology of NAFLD [10,46]. It was reported that the kidney damage caused by hyperuricemia was primarily due to oxidative stress, which can damage endothelial cells and lead to kidney dysfunction. In both kidneys of hyperuricemic Sprague Dawley (SD) rats injected with oxonic acid potassium salt and UA and human umbilical vein endothelial cells (HUVECs) treated with UA, the level of ROS was higher, while the expression level of catalase was lower than the control group [44]. Additionally, treating HepG2 cells with UA for 30 min strongly increased ROS levels by 6.9 fold as compared with controls [41].

Xanthine oxidase (XO), also known as xanthine oxidoreductase, is a rate-limiting enzyme that catalyses uric acid production with concomitant generation of ROS. During oxygen-dependent reactions, this enzyme generates ROS, such as superoxide anion and hydrogen peroxide [47]. A xanthine oxidase inhibitor and scavenger of free radicals, allopurinol, could prevent early alcohol-induced liver injury in rats through preventing oxidant-dependent activation of NF-kappaB [48]. Thus, UA and OS are coexisting partners promoted by XO, which played an important role in the association between NAFLD and hyperuricemia. The expression and activity of XO were significantly increased in cellular and mouse models of NAFLD [41]. Knocking down XO expression or inhibiting XO activity significantly decreases UA production and attenuates free fatty acids-induced fat accumulation in HepG2 cells [41].

UA and insulin resistance

Insulin resistance (IR) is the most important mechanism in the development of NAFLD and metabolic syndrome (MS) [49]. Plasma levels of uric acid are strongly associated with insulin resistance and NAFLD. Obese subjects with high levels of uric acid showed lower insulin sensitivity (40%), evidenced by homeostasis model assessment of insulin resistance (HOMA-IR), insulin-stimulated glucose disposal, and lower levels of oxidative stress (30%) markers, compared with obese subjects with normal uric acid concentration [50]. Studies have found that insulin can promote the renal tubular sodium and uric acid salt absorption. After improving IR, down-regulating insulin content, serum uric acid level was significantly decreased. This suggests that hyperuricemia is also an important marker for insulin resistance [50]. Meanwhile, excessive SUA can stimulate the release of inflammatory factors, promote oxidative stress, and thus contributes to aggravate insulin resistance [46]. Furthermore, hyperuricemia has deleterious effects on endothelial function and on nitric oxide bioavailability, thus causing hyperinsulinemia. Thus, it is likely that hyperuricemia and insulin resistance share a bidirectional causal effect [51,52].

Potassium oxonate was previously found to reduce the degradation of uric acid, thereby increasing uric acid level in rodents. In an acute hyperuricemia mouse model created by potassium oxonate treatment, high uric acid levels impaired glucose tolerance with insulin resistance. UA inhibited phospho-Akt (Ser473) response to insulin and increased phospho-IRS1 (Ser307) in liver, muscle and fat tissues, thereby inhibited insulin

signaling in hyperuricemia mice [53]. It was demonstrated that decreasing uric acid levels in Pound mice with allopurinol during 8 weeks significantly improves insulin resistance, which was confirmed by insulin tolerance tests [54]. For *in vitro* studies, high level of uric acid develops hepatic steatosis and insulin resistance in two hepatocyte cell lines, HepG2 and L02. UA promoted the phosphorylation of Akt and insulin receptor substrate (IRS)-1 [34]. Based on this point, UA seems to directly induce insulin resistance *in vivo* and *in vitro*.

However, when HepG2 cells were exposed to high dose of UA treatment together with N-acetylcysteine (NAC), a ROS scavenger, UA-induced IRS1 activation and Akt inhibition were blocked. The addition of NAC also blocked this hyperuricaemia-induced insulin signaling impairment in mice [53]. Another research found that uric acid induced the activation of NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome both *in vivo* and *in vitro*. Knocking down NLRP3 expression rescued uric acid-induced insulin signaling and lipid accumulation in hepatocyte [34]. Thus, it was suggested that the effect of hyperuricaemia on liver IR might be mediated through increased oxidative stress, activation of inflammasome, or other mechanisms.

UA and endoplasmic reticulum stress

Previous studies provide evidences for endoplasmic reticulum stress (ERS) induced by uric acid. After cultivation of rat glomerular mesangial cells exposed to uric acid for 24 to 48 hours, the mRNA and protein expression of glucose-regulated protein 78 (GRP78) were found up-regulated obviously [55]. ERS could induce numerous intracellular pathways leading to hepatic steatosis, insulin resistance, inflammation, and apoptosis, all of which are crucial in the pathogenesis of NAFLD [56]. One recent *in vitro* study demonstrated hepatic fat accumulation promoted by uric acid. Meanwhile, uric acid also induced ERS in cultured hepatocytes, assessed by the increase of GRP78/94, splicing of the X-box-binding protein-1 (XBP-1), phosphorylation of protein kinase RNA-like ER kinase (PERK), and eukaryotic translation initiation factor-2a (eIF-2a) [57]. An inhibitor of ERS, tauroursodeoxycholic acid (TUDCA), was found able to block lipogenesis and prevented triglyceride accumulation both in HepG2 cells and primary hepatocytes [57].

UA and the metabolism of lipid and sugar

The liver fat content was reported positively correlated with SUA (r = 0.130) in one study. Liver fat content greater than 10% was related to elevated SUA and an increased presence of hyperuricemia [16]. Uric acid might increase the risk for hepatic lipid deposition. It was demonstrated that uric acid induces triglyceride accumulation by overexpression of lipogenic enzymes, such as acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FAS), and stearoyl-CoA desaturase 1 (SCD1), via activation of SREBP-1c [57]. Energy sensor AMP activated kinase (AMPK), closely related with lipid metabolism, can stimulate lipid oxidation through activating malonyl-CoA. It also inhibits hepatic lipid synthesis through inactivating sterol responsive element binding protein (SREBP)-1c and -2, and inhibiting ACC1 activity [58,59]. Studies demonstrated that the generation of uric acid-induced uricase, could inhibit AMPK phosphorylation in fructose-exposed HepG2 cells [10].

In a randomized controlled trial, the results suggested that consumption of fructose at average level did not raise uric acid [60]. While excess fructose acutely raised serum uric acid in normal subjects [61]. Yang et al. also confirmed that high-fructose consumption could induce hyperuricemia [62]. In addition, relative epidemiological studies showed that high fructose consumption was associated with the incidence of NAFLD [54,63]. Some studies have showed that increased fructose consumption favors the increase of some molecules leading to increased fatty acid synthesis as well as uric acid. Uric acid could up-regulate fructokinase expression to accelerate fructose metabolism through activating transcription factor, carbohydrate response element binding protein (ChREBP), which led to the amplification of the lipogenic effect of fructose, via directly binding to carbohydrate response elements (ChoRE) in HepG2 cells [64]. It indicates that the uric acid produced by fructose metabolism could enhance the triglyceride-raising effects of fructose. In addition to generate triglycerides as a direct consequence of fructose metabolism, a study showed that fructose also stimulated triglyceride synthesis via a purine-degrading pathway that is triggered from the rapid phosphorylation of fructose by fructokinase. AMP enters into the purine degradation pathway through activating AMP deaminase, resulting in generation of uric acid and mitochondrial oxidants. Mitochondrial oxidative stress caused the inhibition of aconitase in the Krebs cycle, resulting in the accumulation of citrate and the stimulation of ATP citrate lyase and fatty-acid synthase leading to *de novo* lipogenesis [54].

Conclusion

Among so many studies on the relationship between NAFLD and UA, most displayed strong association between hyperuricemia and NAFLD, and SUA is independently associated with early liver histological changes. Thus, as a high risk factor, uric acid might develop as one prediction marker for the occurrence and severity of NAFLD incidences, which implies that uric acid may be a potential therapeutic target for NAFLD, especially in patients with hyperuricemia. However, the potential mechanism of how UA contribute to NAFLD pathology is far from being well clarified, and further studies are required to investigate the approach of decreasing SUA levels in NAFLD to help develop new treatment for NAFLD.

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Author Contributions

Chunlei Zhang and Haiyan Song designed and wrote the review; Lili Yang and Yang Liu contributed to collected the data; Guang Ji conceived and edited the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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