









The association between serum uric acid to high density lipoprotein-cholesterol ratio and non-alcoholic fatty liver disease: the abund study

Mehmet Ali Kosekli¹ , Ozge Kurtkulagi² , Gizem Kahveci² ,
Tuba Taslamacioglu Duman² , Burcin Meryem Atak Tel² ,
Satilmis Bilgin² , Muhammed Emin Demirkol² , Gulali Aktas² *

SUMMARY

OBJECTIVE: Non-alcoholic fatty liver disease, which is characterized by lipid being deposited into hepatocytes, affects nearly one in three adults globally. Inflammatory markers were suggested to be related with hepatic steatosis. Uric acid to HDL cholesterol ratio is proposed as a novel inflammatory and metabolic marker. We aimed to compare Uric acid to HDL cholesterol ratio levels of patients with Non-alcoholic fatty liver disease to those of healthy controls and find out potential correlations between Uric acid to HDL cholesterol ratio and other inflammatory and metabolic markers of Non-alcoholic fatty liver disease.

METHODS: Patients with a diagnosis of Non-alcoholic fatty liver disease who were on clinical follow-up in our institution were enrolled in the study as the Non-alcoholic fatty liver disease group, while healthy volunteers were enrolled as the control group. The Uric acid to HDL cholesterol ratio of the groups was compared and potential correlations were studied between Uric acid to HDL cholesterol ratio and fasting blood glucose, transaminases, serum lipids (triglyceride, LDL-cholesterol), weight, and body mass index.

RESULTS: The Uric acid to HDL cholesterol ratio of the Non-alcoholic fatty liver disease (13±5%) group was significantly higher compared to the Uric acid to HDL cholesterol ratio of the control (10±4%) group ($p<0.001$). Uric acid to HDL cholesterol ratio was significantly and positively correlated with fasting blood glucose, transaminases, triglyceride, body weight, waist circumference, hip circumference, and body mass index. A ROC analysis revealed that a Uric acid to HDL cholesterol ratio level greater than 9.6% has 73% sensitivity and 51% specificity in determining Non-alcoholic fatty liver disease.

CONCLUSION: Due to the inexpensive and easy-to-assess nature of Uric acid to HDL cholesterol ratio, we suggest that elevated Uric acid to HDL cholesterol ratio levels be considered a useful tool in diagnosing hepatic steatosis.

KEYWORDS: Inflammation. Liver steatosis. Uric acid. HDL cholesterol.

¹Abant Izzet Baysal University Hospital, Department of Internal Medicine and Gastroenterology – Bolu, Turkey.

²Abant Izzet Baysal University Hospital, Department of Internal Medicine – Bolu, Turkey.

*Corresponding author: draliaktas@yahoo.com

Conflicts of interest: the authors declare there are no conflicts of interest. Funding: none.

Received on December 15, 2020. Accepted on December 24, 2020.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is characterized by lipid being deposited into hepatocytes. It affects nearly one in three adults globally, especially in developed territories. The clinical spectrum of the disease includes hepatic steatosis, steatohepatitis, fibrosis, and even cirrhosis¹. In addition to hyperlipidemia, the burden of chronic inflammatory also contributes to the pathogenesis of NAFLD². Indeed, inflammatory markers, including C-reactive protein (CRP), mean platelet volume (MPV), red cell distribution width (RDW), and mean platelet volume to platelet count ratio were suggested to be associated with hepatic steatosis³⁻⁷.

Uric acid is an end product of the metabolism of purine (adenine and guanine). High serum uric acid levels can trigger inflammation since antigen-presenting cells have been reported to sense uric acid as a cause of endogenous pro-inflammatory signal⁸. In fact, decreased uric acid levels are associated with reduced inflammatory burden⁹. Higher uric acid levels are associated with the development of various conditions that are associated with chronic low-grade inflammation, such as, type 2 diabetes mellitus, obesity, and metabolic syndrome¹⁰⁻¹². It is also associated with the control level of diabetes mellitus and correlates with glycated hemoglobin (HbA1c) levels in diabetic subjects^{13,14}. Accordingly, elevated serum uric acid levels were reported to be associated with non-alcoholic fatty liver disease in the literature¹⁵⁻¹⁷. Hepatic steatosis is suggested to be promoted by elevated serum uric acid levels¹⁸.

Uric acid to HDL cholesterol ratio (UHR) is proposed as a novel inflammatory and metabolic marker in recent research studies. It has higher sensitivity and specificity compared to other criteria of metabolic syndrome in diagnosing the disease¹⁹. Moreover, HbA1c and fasting plasma glucose (FPG) levels of type 2 diabetic patients were significantly and positively correlated with serum uric acid levels²⁰. It is also considered to be related with cardiac conditions²¹. In addition, high UHR levels were associated with increased risk of NAFLD in a study by Zhang et al²².

In the present study, we aimed to compare the UHR levels of patients with NAFLD to those of healthy controls. We also aimed to observe potential correlations between UHR and other inflammatory and metabolic markers in NAFLD.

METHODS

Study population

Patients with a diagnosis of NAFLD who were on clinical follow-up in the gastroenterology and internal medicine outpatient

clinics of our institution between January 2019 and January 2020 were enrolled in this retrospective study. Control subjects consisted of healthy volunteers that visited our institution for a routine check-up. Patients under 18 years of age, pregnant women, or patients with any other type of liver disease were not included in the study. Patients with active infection, inflammatory diseases (i.e. rheumatoid arthritis), and malignant conditions were also excluded. The local ethics committee approved the study protocol (approval number: 2020/202).

Laboratory analyses

Age, gender, height, body weight, waist circumference, and hip circumference of the subjects were obtained from the patients' files and database of the institution. The waist to hip ratio was calculated dividing the waist circumference by the hip circumference in centimeters. The body mass index (BMI) was calculated dividing the body weight in kilograms by the height in meters squared. Cigarette smoking, alcohol drinking, and physical exercise history of the subjects were also recorded. Fasting blood glucose (FBG), fasting insulin, aspartate and alanine transaminases (AST and ALT), gamma-glutamyl transferase (GGT), uric acid, total cholesterol, LDL cholesterol, HDL cholesterol, and serum triglyceride of the subjects were also obtained and recorded. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following equation: (FBG x fasting insulin)/405. Insulin resistance was considered to be present when HOMA-IR was greater than 2.5. UHR was obtained dividing serum uric acid levels by HDL-cholesterol levels. General characteristics and laboratory variables of the study groups were compared.

Statistical analyses

Statistical analyses were conducted with statistic software (SPSS 15.0 for Windows, IBM Co., Chicago, IL, USA). Distribution of the variables among study groups was analyzed with Kolmogorov-Smirnov test. Variables with normal distribution were compared using independent samples t-test and these variables were expressed as mean±standard deviation (SD). On the other hand, variables without normal distribution were compared using the Mann Whitney-U test and these variables were expressed as median (min–max). Chi-square test was used to compare categorical variables among study groups. Correlation between study variables was analyzed with Pearson's correlation test. UHR sensitivity and specificity in selecting NAFLD patients were analyzed with a receiver operating characteristic (ROC) curve. When p-value was lower than 0.05, it was considered statistically significant.

RESULTS

Once subjects who did not meet the inclusion criteria were excluded, a total of 117 subjects, 60 patients with NAFLD and 57 healthy volunteers, was enrolled in the study. The median ages of the NAFLD and control groups were 49 (27–81) years and 46 (18–73) years, respectively ($p=0.19$). Thirty-three out of 60 subjects (55%) in the NAFLD group were men and 27 (45%) were women, while 27 out of 57 subjects (47%) in the control group were men and 30 (53%) were women ($p=0.41$).

The height ($p=0.94$), waist to hip ratio ($p=0.25$), and HDL cholesterol ($p=0.06$) of the study and control groups were not significantly different.

The body weight ($p<0.001$), BMI ($p<0.001$), waist circumference ($p<0.001$), hip circumference ($p<0.001$), fasting insulin ($p<0.001$), FBG ($p<0.001$), AST ($p=0.001$), ALT ($p=0.001$), GGT ($p=0.003$), triglyceride ($p<0.001$), total cholesterol ($p=0.002$), LDL cholesterol ($p=0.04$), uric acid ($p<0.001$), and HOMA IR ($p<0.001$) levels of the NAFLD

group were significantly higher than those of the control group. Table 1 shows the general characteristics and laboratory data of the study cohort.

The rates of smokers ($p=0.72$), alcohol drinkers ($p=0.12$) and subjects that exercise regularly ($p=0.52$) were not statistically different between NAFLD and control groups.

The UHR of the NAFLD ($13\pm 5\%$) group was significantly higher compared to the UHR of the control ($10\pm 4\%$) group ($p<0.001$).

In a correlation analysis, UHR was significantly and positively correlated with FBG ($r=0.23$, $p=0.01$), ALT ($r=0.20$, $p=0.03$), triglyceride ($r=0.4$, $p<0.001$), body weight ($r=0.39$, $p<0.001$), waist circumference ($r=0.4$, $p<0.001$), hip circumference ($r=0.22$, $p=0.02$), and BMI ($r=0.29$, $p=0.002$).

In a ROC analysis, a UHR level greater than 9.6% has 73% sensitivity and 51% specificity in determining NAFLD (Figure 1).

Table 1. General characteristics and laboratory data of the study population.

	NAFLD group	Control group	p
Sex	Men (%)	33 (55)	0.41
	Women (%)	27 (45)	
	Mean \pm SD		
UHR (%)	13 \pm 5	10 \pm 4	<0.001
Uric acid (mg/dL)	5.6 \pm 1.3	4.6 \pm 1	<0.001
LDL cholesterol (mg/dL)	123 \pm 37	107 \pm 41	0.04
Total cholesterol (mg/dL)	208 \pm 44	182 \pm 43	0.002
	Median (Min–Max.)		
Height (cm)	168 (130–184)	167 (140–195)	0.94
Weight (kg)	84 (63–120)	68 (46–105)	<0.001
BMI (kg/m ²)	30.1 (25–45)	25 (17.3–35)	<0.001
Hip circumference (cm)	110 (90–157)	100 (75–126)	<0.001
Waist circumference (cm)	103 (85–140)	88 (59–102)	<0.001
Waist to hip ratio (%)	0.9 (0.8–1.1)	0.9 (0.6–1)	0.25
Fasting insulin (uIU/mL)	14.3 (7–64)	8.6 (3.1–17.5)	<0.001
FBG (mg/dL)	99 (80–127)	91 (69–99)	<0.001
AST (U/L)	23 (11–266)	18 (9–157)	0.001
ALT (U/L)	28 (8–160)	18 (6–111)	0.001
GGT (U/L)	26 (9–180)	17 (7–177)	0.003
Triglyceride (mg/dL)	160 (53–414)	95 (31–455)	<0.001
HDL cholesterol (mg/dL)	45 (26–71)	47 (28–103)	0.06
HOMA-IR	3.34 (1.1–14)	1.8 (1–4.7)	<0.001

NAFLD: non-alcoholic fatty liver disease; UHR: uric acid to HDL cholesterol ratio; BMI: body mass index; FBG: fasting blood glucose; AST: transaminases; ALT: transaminases; GGT: gamma-glutamyl transferase; HOMA-IR: homeostasis model assessment of insulin resistance.

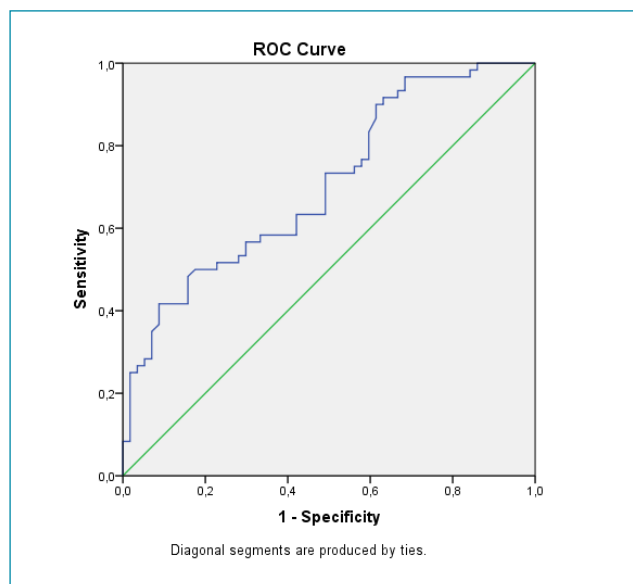


Figure 1. The ROC curve of uric acid to HDL cholesterol ratio in determining non-alcoholic fatty liver disease.

DISCUSSION

The present study showed that UHR is significantly increased in subjects with NAFLD compared to the healthy population. Moreover, UHR has significant positive correlation with other determinants of NAFLD, such as, BMI, waist circumference, hip circumference, blood glucose, ALT, and triglyceride levels. Finally, the present study demonstrated that increased UHR has high sensitivity and considerable specificity in selecting NAFLD subjects.

Uric acid is an end product of the metabolism of purine and is associated with a variety of chronic conditions. Elevated serum uric acid levels were suggested to be linked with type 2 diabetes mellitus and hypertension²³. Indeed, the authors showed that 1 mg/dL increase in serum uric acid levels increases the risk of incident hypertension 1.2 fold²⁴. In another study, it has been claimed that high uric acid levels predicted the development of type 2 diabetes mellitus²⁵. A meta-analysis in type 2 diabetic subjects suggested that increased uric acid levels were an independent marker of vascular complications and mortality in this population²⁶. The risk of microvascular complications of type 2 diabetes mellitus is increased in subjects with high uric acid levels and low total bilirubin blood levels²⁷. The combination of uric acid and HDL cholesterol has been proposed as a novel and more sensitive marker of metabolic and inflammatory conditions. UHR has been shown to be higher in metabolic syndrome and suggested to have greater sensitivity and specificity than any other criteria used to select subjects with metabolic syndrome¹⁹. Since hepatic steatosis was

associated with metabolic syndrome²⁸, a similar increase in the UHR in subjects with hepatic steatosis could be expected. In 2020, the authors reported elevated UHR levels in subjects with non-alcoholic fatty liver disease compared to controls²². However, since the study population consisted of subjects with a BMI lower than 24kg/m², this association was only applied for lean adults. In the present study, the BMI of the subjects with hepatic steatosis was significantly higher than the BMI of control subjects. Additionally, UHR was significantly correlated with BMI in the study population.

Increased UHR was reported in other conditions as well. Higher UHR has been reported in patients with coronary artery fistula compared to control subjects with normal coronary arteries²¹. Furthermore, in a recent study, elevated UHR was reported in poorly controlled diabetic subjects compared to well-controlled diabetic subjects and non-diabetic controls²⁰. UHR was significantly and positively correlated with waist circumference, body weight, body mass index, fasting glucose, and HbA1c levels in a study mentioned in the literature²⁰. Similarly, we reported that UHR was positively correlated with FBG, body weight, BMI, and waist circumference. In addition, we found a positive correlation between UHR and ALT, triglyceride, and hip circumference.

UHR is calculated dividing serum uric acid levels by HDL cholesterol and is an inexpensive, easy-to-assess tool. Therefore, it could be measured repeatedly during the follow-up of subjects with hepatic steatosis. Elevated serum uric acid levels are associated with hepatic steatosis, as reported in a Chinese study²⁹. Furthermore, the authors reported decreased HDL cholesterol levels in subjects with non-alcoholic fatty liver disease³⁰. Thus, uric acid to HDL cholesterol ratio could be a better predictor of hepatic steatosis. In the present study, despite uric acid and UHR levels were significantly increased in patients with hepatic steatosis compared to healthy controls, the HDL cholesterol of the study subjects was not statistically different.

Our study confirmed that UHR could be a marker of hepatic steatosis, and due to its inexpensive and easy-to-assess nature, it might also be useful to follow the treatment of the disease. However, our study did not answer whether elevated UHR in hepatic steatosis begins to decrease after lifestyle modification or medical treatment of the subjects with liver steatosis. A prospective study, rather than a retrospective report, could answer this question.

The present study has two limitations. First, the retrospective design, which could make the results of the study difficult to interpret. Second, a relatively small study population. However, to the best of our knowledge, this is the first study in the literature that reported both a significant association between UHR and hepatic steatosis, and a

significant correlation between UHR and other metabolic risk factors of liver steatosis.

CONCLUSION

We suggest that elevated UHR be considered an indicator of hepatic steatosis in otherwise healthy subjects. Since obtaining UHR by simply dividing serum uric acid levels by HDL cholesterol levels is easy and inexpensive, UHR may be useful to diagnose and follow subjects with hepatic steatosis.

AUTHORS' CONTRIBUTIONS

MAK: Conceptualization, Writing – Original Draft, Writing – Review & Editing. **OK:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **BMAT:** Conceptualization, Data Curation, Writing – Original Draft, Writing – Review & Editing. **GK:** Conceptualization, Data Curation, Writing – Original Draft, Writing – Review & Editing. **GA:** Conceptualization, Writing – Original Draft, Writing – Review & Editing. **MED:** Data Curation. **TTD:** Data Curation, Writing – Original Draft. **SB:** Writing – Original Draft

REFERENCES

- Hijona E, Hijona L, Arenas JI, Bujanda L. Inflammatory mediators of hepatic steatosis. *Mediators Inflamm* 2010;2010:837419. <https://doi.org/10.1155/2010/837419>
- Pawlak M, Lefebvre P, Staels B. Molecular mechanism of PPAR α action and its impact on lipid metabolism, inflammation and fibrosis in non-alcoholic fatty liver disease. *J Hepatol* 2015;62:720-33. <https://doi.org/10.1016/j.jhep.2014.10.039>
- Kosekli MA, Erkus E, Kocak MZ. Mean platelet volume to platelet ratio as a promising marker of hepatosteatosis. *Experimental Biomedical Research*. 2018;1(2):55-9. <https://doi.org/10.30714/j-ebr.2018237497>
- Targher G, Bertolini L, Scala L, Zoppini G, Zenari L, Falezza G. Non-alcoholic hepatic steatosis and its relation to increased plasma biomarkers of inflammation and endothelial dysfunction in non-diabetic men. Role of visceral adipose tissue. *Diabet Med* 2005;22(10):1354-8. <https://doi.org/10.1111/j.1464-5491.2005.01646.x>
- Aktas G, Alcelik A, Tekce BK, Savli H, Uyeturk U, Kurt M, et al. Mean platelet volume and red cell distribution width in hepatosteatosis. *Natl J Med Res*. 2013 [cited on September 15, 2013];3(3):264-6. Available from: <https://www.bibliomed.org/?mno=44249>
- Abdel-Razik A, Mousa N, Shabana W, Refaey M, ElMahdy Y, Elhelaly R, et al. A novel model using mean platelet volume and neutrophil to lymphocyte ratio as a marker of nonalcoholic steatohepatitis in NAFLD patients: multicentric study. *Eur J Gastroenterol Hepatol*. 2016;28:e1-9. <https://doi.org/10.1097/MEG.0000000000000486>
- Khoury T, Mari A, Nseir W, Kadah A, Sbeit W, Mahamid M. Neutrophil-to-lymphocyte ratio is independently associated with inflammatory activity and fibrosis grade in nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol*. 2019;31(9):1110-5. <https://doi.org/10.1097/MEG.0000000000001393>
- Shi Y, Evans JE, Rock KL. Molecular identification of a danger signal that alerts the immune system to dying cells. *Nature*. 2003;425(6957):516-21. <https://doi.org/10.1038/nature01991>
- Haryono A, Nugrahaningsih DAA, Sari DCR, Romi MM, Arfian N. Reduction of serum uric acid associated with attenuation of renal injury, inflammation and macrophages m1/m2 ratio in hyperuricemic mice model. *Kobe J Med Sci*. 2018;64(3):E107-14. PMID: 30666040
- van der Schaft N, Brahimaj A, Wen KX, Franco OH, Dehghan A. The association between serum uric acid and the incidence of prediabetes and type 2 diabetes mellitus: the rotterdam study. *PLoS One*. 2017;12(6):e0179482. <https://doi.org/10.1371/journal.pone.0179482>
- Ali N, Perveen R, Rahman S, Mahmood S, Rahman S, Islam S, et al. Prevalence of hyperuricemia and the relationship between serum uric acid and obesity: A study on Bangladeshi adults. *PLoS One* 2018;13(11):e0206850. <https://doi.org/10.1371/journal.pone.0206850>
- Jeong J, Suh YJ. Association between Serum Uric Acid and Metabolic Syndrome in Koreans. *J Korean Med Sci*. 2019;34(48):e307. <https://doi.org/10.3346/jkms.2019.34.e307>
- Duman TT, Kocak MZ, Atak BM, Erkus E. Serum uric acid is correlated with HbA1c levels in type 2 diabetes mellitus. *Exp Biomed Res*. 2018;1(1):6-9. <https://doi.org/10.30714/j-ebr.2018136918>
- Atak BM, Duman TT, Kocak MZ, Savli H. Serum uric acid level is associated with type 2 diabetes mellitus and diabetic regulation. *Exp Biomed Res*. 2018;1(4):135-9. <https://doi.org/10.30714/j-ebr.2018443416>
- Darmawan G, Hamijoyo L, Hasan I. Association between Serum Uric Acid and Non-Alcoholic Fatty Liver Disease: A Meta-Analysis. *Acta Med Indones* 2017;49(2):136-47. PMID: 28790228
- Abbasi S, Haleem N, Jadoon S, Farooq A. Association of non-alcoholic fatty liver disease with serum uric acid. *j ayub med coll abbotabad*. 2019;31(1):64-6. PMID: 30868786
- Zheng X, Gong L, Luo R, Chen H, Peng B, Ren W, et al. Serum uric acid and non-alcoholic fatty liver disease in non-obesity Chinese adults. *Lipids Health Dis*. 2017;16(1):202. <https://doi.org/10.1186/s12944-017-0531-5>
- Lanaspa MA, Sanchez-Lozada LG, Choi YJ, Cicerchi C, Kanbay M, Roncal-Jimenez CA, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. *J Biol Chem*. 2012;287(48):40732-44. <https://doi.org/10.1074/jbc.M112.399899>
- Kocak MZ, Aktas G, Erkus E, Sincer I, Atak B, Duman T. Serum uric acid to HDL-cholesterol ratio is a strong predictor of

- metabolic syndrome in type 2 diabetes mellitus. *Rev Assoc Med Bras* (1992). 2019;65(1):9-15. <https://doi.org/10.1590/1806-9282.65.1.9>
20. Aktas G, Kocak MZ, Bilgin S, Atak BM, Duman TT, Kurtkulagi O. Uric acid to HDL cholesterol ratio is a strong predictor of diabetic control in men with type 2 diabetes mellitus. *Aging Male*. 2020;23(5):1098-102. <https://doi.org/10.1080/13685538.2019.1678126>
 21. Mansiroglu AK, Cekici Y, Sincer I, Gunes Y. Serum uric acid and uric acid to HDL-cholesterol ratio in coronary artery fistulas. *Annals of Medical Research*. 2019;26(12):2771-5. <https://doi.org/10.5455/annalsmedres.2019.08.479>
 22. Zhang YN, Wang QQ, Chen YS, Shen C, Xu CF. Association between serum uric acid to hdl-cholesterol ratio and nonalcoholic fatty liver disease in lean chinese adults. *Int J Endocrinol*. 2020;2020:5953461. <https://doi.org/10.1155/2020/5953461>
 23. Mortada I. Hyperuricemia, type 2 diabetes mellitus, and hypertension: an emerging association. *Curr Hypertens Rep*. 2017;19(9):69. <https://doi.org/10.1007/s11906-017-0770-x>
 24. Bjornstad P, Laffel L, Lynch J, El Ghormli L, Weinstock RS, Tollefsen SE, et al. Elevated serum uric acid is associated with greater risk for hypertension and diabetic kidney diseases in obese adolescents with type 2 diabetes: an observational analysis from the treatment options for type 2 diabetes in adolescents and youth (TODAY) study. *Diabetes Care*. 2019;42(6):1120-8. <https://doi.org/10.2337/dc18-2147>
 25. Katsiki N, Papanas N, Fonseca VA, Maltezos E, Mikhailidis DP. Uric acid and diabetes: Is there a link? *Curr Pharm Des*. 2013;19(27):4930-7. <https://doi.org/10.2174/1381612811319270016>
 26. Xu Y, Zhu J, Gao L, Liu Y, Shen J, Shen C, et al. Hyperuricemia as an independent predictor of vascular complications and mortality in type 2 diabetes patients: a meta-analysis. *PLoS One*. 2013;8(10):e78206. <https://doi.org/10.1371/journal.pone.0078206>
 27. Ren Y, Gao L, Guo X, Huo X, Lu J, Li J, et al. Interactive effect of serum uric acid and total bilirubin for microvascular disease of type 2 diabetes in China. *J Diabetes Complications*. 2018;32(11):1000-5. <https://doi.org/10.1016/j.jdiacomp.2018.09.002>
 28. Calcaterra V, Brambilla P, Maffè GC, Klersy C, Albertini R, Introzzi F, et al. Metabolic syndrome in Turner syndrome and relation between body composition and clinical, genetic, and ultrasonographic characteristics. *Metab Syndr Relat Disord*. 2014;12(3):159-64. <https://doi.org/10.1089/met.2013.0075>
 29. Wang N, Rao JJ, Dong H, Qi JP. [The application of proton magnetic resonance spectroscopy and computerized tomography in evaluating nonalcoholic fatty liver disease]. *Zhonghua Gan Zang Bing Za Zhi*. 2008;16(7):528-31. Chinese. PMID: 18647533
 30. Krishan S. Correlation between non-alcoholic fatty liver disease (NAFLD) and dyslipidemia in type 2 diabetes. *Diabetes Metab Syndr*. 2016;10(2Suppl1):S77-81. <https://doi.org/10.1016/j.dsx.2016.01.034>

