Urinary lithogenic profile of patients with non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease, ranging from pure steatosis to non-alcoholic steatohepatitis, and ultimately to liver cirrhosis.

A recent analysis of the NHANES III data[1] observed the epidemiological association between NAFLD and higher likelihood of nephrolithiasis, confirming the increased risk reported in retrospective studies[2] and in meta-analyses adjusted for comorbidities[3].

In order to study the association between NAFLD and nephrolithiasis while minimizing the confounding effect of metabolic syndrome, we investigated the impact of different degrees of NAFLD severity on potential risk factors for stone formation. This was achieved by assessing the 24h urinary profile of 42 participants enrolled at the Fondazione Policlinico A. Gemelli IRCCS, Rome, Italy, and stratified into three groups: NAFLD patients without liver cirrhosis (NLC, n=28), with liver cirrhosis (LC, n=14), and healthy individuals (HI, n=12).

NAFLD was defined as steatosis in at least 5% of total hepatocytes or by the presence of fatty liver at ultrasound evaluation. Compensated liver cirrhosis was clinically or radiologically diagnosed and only patients with a Child-Pugh A score were included. Patients with advanced chronic kidney disease (eGFR <30 mL/min/1.73 m^2), active diuretic or antibiotic treatment, alcohol abuse (>20 g/day), active neoplasia and other known causes of liver disease were excluded.

Both NLC and LC were significantly older ($p<0.001$), had higher BMI and lower eGFR than HI ($p<0.001$). Forty-six percent of NLC and 36% of LC were hypertensive, whereas the latter had significantly higher prevalence of diabetes than NLC (71% and 14%, respectively; $p<0.001$).

In this analysis, we observed that participants in the NLC group excrete less ammonium in their urine compared to HI and patients with advanced disease (LC), even after adjustment for potential confounders such as age, sex, eGFR, BMI, hypertension and diabetes (β −25.2 mmol/24h; 95% CI −46.1, −4.3; p = 0.019 and β −30.9 mmol/24h; 95% CI −48.6, −13.2; p = 0.001, respectively). The former association was confirmed when ammonium was normalized for net acid excretion, a marker of dietary acid intake, suggesting that a lower fraction of the total acid load is excreted as ammonium in NLC patients[4]. In addition, NLC participants showed higher titratable acidity (β 10.2 mEq/24h; 95% CI 0.9, 19.6; p = 0.033) and lower urine pH (β −1.16; 95% CI −1.89, −0.43; p = 0.003) compared to LC patients. This seemingly counterintuitive finding might be explained by the direct association between liver fibrosis, urine pH and urinary ammonia excretion, commonly observed in compensated liver cirrhosis.

Although, due to the high variability in the definitions, an accurate estimation of the overlap between NAFLD and metabolic syndrome is difficult to obtain, these conditions are supposed to share the underlying pathophysiological mechanism.

In the Rotterdam study each component of metabolic syndrome was linked to an higher probability of NAFLD, based on ultrasound measurement of liver steatosis[5], and a linear association between measured fat liver and sub-components of metabolic syndrome was observed[6].

Since the association between hypertension, insulin-resistance and obesity with nephrolithiasis is well established, it is without surprise that this holds true also for metabolic syndrome[7]. Indeed, the prevalence of uric acid stone disease was found to be strongly correlated with the severity of metabolic syndrome[8]. This finding was matched by the inverse association between the number of metabolic syndrome traits and urine pH[9]. Insulin resistance interferes with renal acid excretion and purine metabolism, causing unduly acidic

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urine pH coupled with reduced urinary ammonium excretion[10,11]. Thus, it could be hypothesized that the results presented here are due to the higher prevalence of metabolic syndrome in patients affected with NAFLD. However, our findings were confirmed after adjusting for multiple sub-components of the metabolic syndrome including hypertension, diabetes and BMI, hence a direct reduction in urinary ammonium excretion induced by NAFLD through distinct pathways cannot be ruled out.

Our data further suggest that urinary magnesium excretion is significantly lower in NAFLD patients without liver cirrhosis compared to healthy individuals (β −2.08 mmol/24h; 95% CI −4.08, −0.09; p = 0.041). Magnesium yields anti-lithogenic properties by reducing both aggregation and growth of calcium oxalate crystals, so that low urinary magnesium is considered a risk factor for nephrolithiasis[12]. Interestingly, an analysis of the CARDIA study observed 55% lower odds of NAFLD in the highest vs lowest quintile of dietary magnesium intake. This association was confirmed in patients without magnesium supplementation but not in supplemented subject, suggesting that higher dietary magnesium consumption could be protective against NAFLD[13]. Furthermore, insulin resistance is considered one of the main promoters of NAFLD and magnesium was found to modulate insulin secretion and sensitivity by acting on GLUT4 gene[14]. Our study supports this hypothesis by showing that the presence of hepatocellular ballooning degeneration, a histological lesion used to classify more severe cases of NAFLD, is associated with lower urinary magnesium excretion (β −4.11; 95% CI −5.99, −2.24; p = 0.001). Hence, we speculate that reduced dietary consumption of magnesium might lead to higher likelihood of both NAFLD and nephrolithiasis by worsening insulin resistance and reducing urinary magnesium excretion, with a secondary impairment of urinary ammonium excretion.

Nonetheless, Gianmoena et al. provided the first glance on molecular pathways that may explain previous epidemiological evidence, by showing increased oxalate production in mouse NAFLD hepatocytes. This observation based on animal models was confirmed in 30

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overweight children, in which urinary oxalate excretion was directly correlated to percentage of liver fat[15]. In our study, adult NAFLD patients did not have different oxalate excretion values (β −0.26; 95% CI −1.59, 1.08; $p = 0.681$), and only altered urinary ammonium and magnesium excretions were found as proposed risk factors for nephrolithiasis (Figure 1).

Our results suggest that adult non-cirrhotic NAFLD patients have a distinct urinary lithogenic risk profile characterized by reduced urinary magnesium and altered urinary ammonium excretion. Urinary magnesium excretion was found to be lower in patients with hepatocellular ballooning degeneration, providing suggestions of the possible interplay between the severity of NAFLD and a well-known risk factor for stone formation. Our findings indicate the need for further prospective studies to compare the characteristics of NAFLD patients with and without nephrolithiasis, and its incidence at different degrees of NAFLD severity to expand on the observations reported here.

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CONFLICT OF INTEREST STATEMENT

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Figure Legends

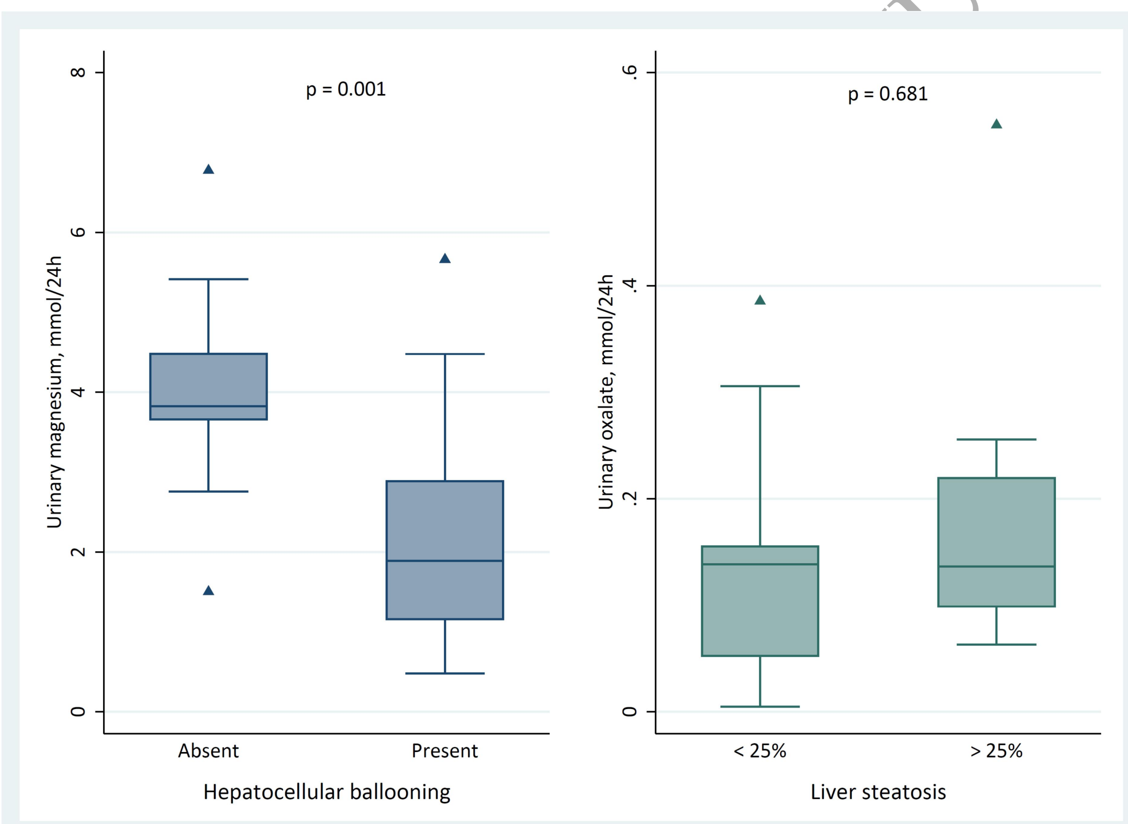

Figure 1:

Box plots of the association between liver histology scores and the main urinary risk factors for nephrolithiasis in NAFLD. Triangles are outliers.