Journal of Clinical and Translational Hepatology **2024**
DOI: 10.14218/JCTH.2024.00169

Letter to the Editor

Impact of Proteinuria on Liver Enzyme Levels

David Yardeni[1], Asif Hitawala[2], Lilian Howard[3], Theo Heller[2] and Meryl Waldman[3*]

[1]Department of Gastroenterology and Liver Diseases, Soroka University Medical Center, Beer-Sheva, Israel; [2]Liver Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA; [3]Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA

Received: July 07, 2024 | **Revised:** July 07, 2024 | **Accepted:** July 07, 2024 | **Published online:** July 19, 2024

Citation of this article: Yardeni D, Hitawala A, Howard L, Heller T, Waldman M. Impact of Proteinuria on Liver Enzyme Levels. J Clin Transl Hepatol 2024. doi: 10.14218/JCTH.2024.00169.

Dear Editors,

We read with great interest the recently published article "Subnormal Serum Liver Enzyme Levels: A Review of Pathophysiology and Clinical Significance" by Youssef and colleagues.[1] While much attention is given to elevations of liver enzymes, the authors highlight clinically important, often unrecognized reasons leading to low liver enzyme levels. For example, chronic kidney disease was cited as a cause of low serum aspartate aminotransferase (AST) proportional to the progression of the disease, but the cause(s) are not well defined. Little is known about the possible influence of nephrotic syndrome (NS) on liver enzymes. NS is a kidney disorder characterized by increased permeability of the glomerular capillary wall, high-grade proteinuria (≥3.5 g/day), hypoalbuminemia (serum albumin ≤ 3.0 g/dL), hyperlipidemia, and edema. The massive urinary losses of many important plasma proteins due to NS (e.g., albumin, thyroid binding globulin, transferrin, vitamin D-binding protein, coagulation regulatory proteins) lead to decreased circulating concentrations in the blood and consequent metabolic, biochemical, and endocrine abnormalities such as hypothyroidism, vitamin D deficiency, and hypercoagulability.[2] We evaluated if NS might be another potential cause of subnormal liver enzymes, possibly due to excessive urinary losses of these enzymes or other factors. Subnormal liver enzyme tests could potentially mask clinically relevant clues to coexisting liver diseases that can cause NS (e.g., viral hepatitis[3,4]), are associated with NS (e.g., autoimmune hepatitis[5,6]), or result from hepatotoxicity from drugs used in the treatment of NS (e.g., calcineurin inhibitors, HMG-CoA reductase inhibitors). To test this hypothesis, we identified patients with a history of primary NS who had paired liver enzyme tests (analyzed in the same clinical laboratory) during active NS (ANS) and during clinical remission of NS (defined as proteinuria <350 mg/day). This allows a unique comparison of intra-individual changes in liver enzymes during two contrasting disease states, with nephrotic patients serving as their own controls. Medications known to impact liver tests (e.g., statins) had to remain unchanged at the two distinct clinical time points for patients to be included in the analysis. Of 52 patients identified with paired samples, most (71%) had primary membranous nephropathy as the cause of NS. One patient (2%) had hepatitis C infection, five (9.6%) had hypertension, and one (2%) had diabetes mellitus. Median proteinuria during ANS and remission was 6.39 g/g (4.39–10.18) and 0.19 (0.1–0.32), respectively ($p < 0.0001$). Median serum albumin during ANS was lower than in remission ($p < 0.0001$) (Table 1). Serum creatinine did not differ during ANS versus remission ($p = 0.18$). Median total bilirubin and alkaline phosphatase were lower during ANS compared to remission: 0.25 mg/dL (0.2–0.32) vs. 0.44 (0.37–0.6) ($p < 0.0001$) and 61.5 U/L (49–74) vs. 65.5 (57.7–85) ($p = 0.005$), respectively. No differences were found in the median direct bilirubin ($p = 0.07$) or in ALT ($p = 0.88$) and AST ($p = 0.1$) during ANS and remission. Median platelet count was higher ($p = 0.0001$) during ANS. Expectedly, LDL, HDL, total cholesterol, and triglycerides were elevated ($p < 0.001$) during ANS. We did not find a correlation between liver enzymes and NS-related dyslipidemia (Fig. 1), despite the known role of the liver in contributing to excess cholesterol biosynthesis during NS and the known contribution of prolonged dyslipidemia to the development of metabolic dysfunction-associated steatotic liver disease in the general population.

We acknowledge the limitations of this study. The population size was small, and the majority had kidney-limited disease due to primary membranous nephropathy with few comorbidities. This allowed for a better assessment of the impact of proteinuria alone on liver enzymes. However, these findings require validation in larger studies that include patients with different causes of nephrotic syndrome, including patients with hepatitis-associated nephrotic syndrome.

In summary, the presence of high-grade proteinuria does not appear to lead to subnormal serum liver enzyme levels. Both total bilirubin and ALP were lower during ANS compared to remission; however, the changes were minor and not clinically significant. The more hepatic-specific direct bilirubin revealed no difference, nor did ALT and AST. However, the absence of biochemical liver abnormalities may not exclude the presence of indolent liver disease, and appropriate serologic workup, radiologic imaging, and possibly liver biopsy should be considered if suspected.

[*]**Correspondence to:** Meryl Waldman, Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, USA. ORCID: https://orcid.org/0000-0001-8698-0502. Tel: +1-301-451-6990, Fax: +1-301-451-5584, E-mail: waldmanm@niddk.nih.gov

Table 1. Biochemical Lab results during active nephrotic syndrome and remission

	Number of patients*	Active nephrotic syndrome	Remission	*P*-value
Urine protein/creatinine ratio (g/g)	52 (100%)	6.39 (4.39–10.18)	0.19 (0.1–0.32)	<0.0001
Serum albumin (g/dL)	52 (100%)	2.75 (2.37–3.2)	4 (3.8–4.2)	<0.0001
Serum creatinine (mg/dL)	52 (100%)	1.17 (1.02–1.49)	1.16 (0.88- 1.46)	0.18
AST (U/L)	52 (100%)	21 (18–30.5)	20.5 (17–25.2)	0.88
ALT (U/L)	52 (100%)	20.5 (15–27.5)	20 (15–26.2)	0.96
ALP (U/L)	60 (100%)	61.5 (49–74)	65.5 (57.7–85)	0.005
Total bilirubin (mg/dL)	60 (100%)	0.2 (0.2–0.32)	0.44 (0.37–0.6)	<0.0001
Direct bilirubin (mg/dL)	60 (100%)	0.2 (0.1–0.2)	0.2 (0.2–0.2)	0.07
Total cholesterol (mg/dL)	45 (86.5%)	230 (208.5–321.7)	176 (144–209)	<0.0001
LDL (mg/dL)	45 (86.5%)	120.5 (95.5–211.5)	89 (65–119)	0.0002
HDL (mg/dL)	45 (86.5%)	67.5 (51.7–80.2)	56 (43–66)	0.0001
Triglycerides (mg/dL)	45 (86.5%)	153.5 (118.7–210)	120 (67–165)	0.0024
Platelet x100/mcL	51 (98%)	250.5 (217–332.2)	238 (195.5–284)	0.0001

*With available blood tests (paired samples in nephrotic state vs. in remission). Active nephrotic syndrome is defined as urine protein/Cr ratio ≥ 3.5 g/g; remission is defined as urine protein/Cr ratio < 0.350 g/g. Data are median and range. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Funding

This work was supported by the Intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

Conflict of interest

The authors have no conflict of interests related to this publication.

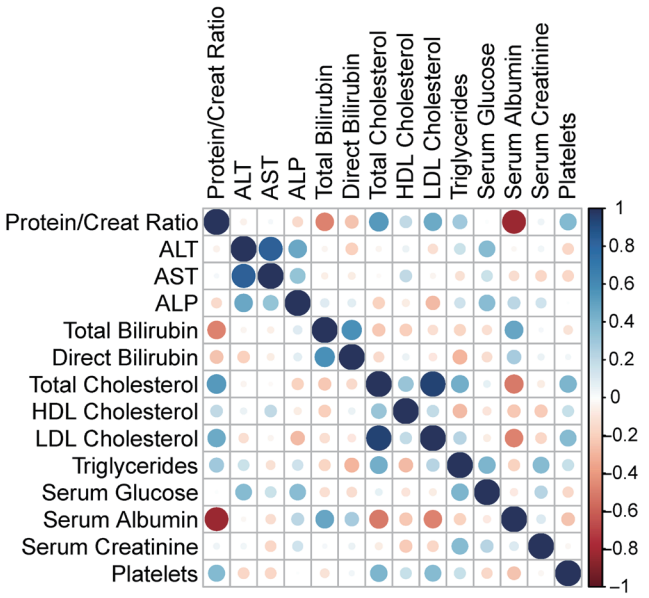

Fig. 1. Correlation plot of all evaluated tests in the cohort of NS patients. The color of the dots represents both the direction and strength of the correlation, while the size of the dots represents only the latter. AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Author contributions

DY: conceptualization, methodology, data curation, investigation, formal analysis writing original draft, writing-review & editing, visualization. AH: methodology, software, validation, formal analysis, data curation, investigation, writing-review & editing, visualization. LH: data curation, resources, investigation, writing-review and editing. TH: conceptualization, investigation, resources, supervision, funding acquisition. MW: investigation, resources, data curation, methodology, writing-review &editing, supervision, validation, project administration, funding acquisition.

References

[1] Youssef EM, Wu GY. Subnormal Serum Liver Enzyme Levels: A Review of Pathophysiology and Clinical Significance. J Clin Transl Hepatol 2024;12(4):428–435. doi:10.14218/JCTH.2023.00446, PMID:38638374.
[2] Crew RJ, Radhakrishnan J, Appel G. Complications of the nephrotic syndrome and their treatment. Clin Nephrol 2004;62(4):245–259. doi:10.5414/cnp62245, PMID:15524054.
[3] Gupta A, Quigg RJ. Glomerular Diseases Associated With Hepatitis B and C. Adv Chronic Kidney Dis 2015;22(5):343–351. doi:10.1053/j.ackd.2015.06.003, PMID:26311595.
[4] Kanduri SR, Peleg Y, Wadhwani S. Liver Disease-Associated Glomerulopathies. Adv Kidney Dis Health 2024;31(2):147–156. doi:10.1053/j.akdh.2023.11.002, PMID:38649219.
[5] Ebert EC, Hagspiel KD. Gastrointestinal and hepatic manifestations of systemic lupus erythematosus. J Clin Gastroenterol 2011;45(5):436–441. doi:10.1097/MCG.0b013e31820f81b8, PMID:21422947.
[6] Hong X, Hu S, Zhang P, Gao X, Qiao Z, Xia C, *et al*. Coexistence of primary biliary cirrhosis-autoimmune hepatitis overlap syndrome and membranous nephropathy: A case report. Clin Nephrol 2023;99(1):41–48. doi:10.5414/CN110892, PMID:36331018.