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Role of Uric Acid in Chronic Liver Disease

Said Abd Elbaqy Gad, Ahmed Fathy Gomaa, Sahar Zaghloul Ghamri Mohamed *, Ayman Fathy Elsayed Mohammed

Internal Medicine department, Faculty of Medicine, Zagazig University, Egypt

***Corresponding Author: Sahar Zaghloul Ghamri Mohamed**

E-mail: Sahar.Zgg96@gmail.com

Abstract:

Chronic liver disease (CLD) represents a major global health burden, progressing through stages of inflammation, fibrosis, cirrhosis, and potential hepatic decompensation. Recent evidence suggests that serum uric acid is not only a metabolic waste product but also a biologically active molecule involved in oxidative stress, systemic inflammation, and metabolic dysregulation. Elevated uric acid levels have been linked to insulin resistance, non-alcoholic fatty liver disease (NAFLD), fibrosis progression, and hepatic steatosis. Understanding the interaction between uric acid and liver disease may help identify early biomarkers of progression and potential therapeutic targets.

Keywords: Uric acid; Chronic liver disease; NAFLD; Liver fibrosis; Hyperuricemia; Biomarkers; Metabolic syndrome.

Introduction:

An essential organ, the liver is capable of carrying out the body's metabolic, synthesis, and detoxifying processes. Numerous agents that might cause necrosis, fibrosis, and an inflammatory reaction mostly target the tissue of this organ. The liver's own function may be interrupted or diminished as a result (1).

The liver performs a variety of intricate physiological processes, such as detoxification, bile excretion, metabolism, and secretion. Known as "liver enzymes," alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are mostly found in hepatocytes and catalyzed transamination for amino acids and gluconeogenesis. Elevated serum enzyme levels are the result of liver injury, which disrupts the structure of the cell membrane and releases liver enzymes into the bloodstream (2).

Through a number of mechanisms that increase the storage of liver fat, elevated blood uric acid (SUA) levels may cause liver disease. With a global incidence of about 25%, nonalcoholic fatty liver disease (NAFLD) is currently recognized as the primary cause of liver disease and the most frequent cause of abnormal liver function (3).

Numerous investigations conducted in recent years have demonstrated a strong correlation between SUA levels and the frequency of NAFLD. According to a cross-sectional study conducted in China with 8925 participants, the risk of NAFLD rose as SUA levels rose (4). In a 4-year prospective study conducted in China, Wei et al. found that SUA levels were an independent predicted risk factor for NAFLD (5).

One hepatotoxic substance that might harm tissue is uric acid. The dosage and length of exposure to the material determine the extent and course of tissue damage. Toll-like Receptors (TLR) can identify uric acid as one of the pro-inflammatory Damage-associated Molecular Patterns (DAMPs) generated by dead cells, which can lead to an inflammatory response and liver damage (2).

A condition known as hyperuricemia is defined by an elevated level of uric acid in the blood serum. One byproduct of purine breakdown is uric acid. The liver's production of uric acid and the kidney's elimination of it both impact the amount of uric acid in the blood (2).

In every community, the prevalence of hyperuricemia tends to rise. Up until a few years ago, the percentage of adult males with hyperuricemia ranged from 25% to 30%. A meta-analysis study conducted in China revealed that the prevalence of hyperuricemia was 8.6% in women and 21.6% in men. It also discovered a correlation between the incidence of non-alcoholic fatty liver disease (NAFLD) and elevated uric acid (6).

Gouty arthritis and kidney stones are known to be caused by hyperuricemia. Hyperuricemia has also been linked in recent years to the emergence of numerous additional illnesses. Cardiovascular disease, metabolic syndrome, renal disease, and hypertension have all shown clear correlations. The underlying mechanisms include the production of systemic inflammation, oxidative stress, insulin resistance, and endothelial dysfunction by hyperuricemia (7).

It is now known that hyperuricemia contributes to systemic inflammation, insulin resistance, and oxidative stress. Therefore, it is conceivable that hepatic necro-inflammation may be related to hyperuricemia. Indeed, hyperuricemia and cirrhosis have been linked in a number of international investigations (3).

In a comparative analysis of ALT, AST, GGT, and uric acid levels in liver disorders, Benerji et al. (8) discovered a correlation between serum uric acid levels and the likelihood of hospitalization due to cirrhosis or the presence of increased serum ALT or GGT. These correlations were mostly unaffected by other established risk factors for liver disease. Their research suggests that a high level of serum uric acid may be a risk factor for the development of chronic liver disease.

An observational study by Paul et al. (9) discovered that some cases of CLD, such as autoimmune hepatitis and chronic viral hepatitis, had noticeably elevated serum uric acid levels. greater CTP scores were associated with greater uric acid levels, which were likewise associated with death. There was a link between the serum uric acid level and the CLD markers, SGOT and INR.

Serum uric acid is independently linked to the presence of non-alcoholic fatty liver disease (NAFLD) in Korean adults, and it could be a helpful supplementary metric for determining the risk of NAFLD in a clinical context. Even after controlling for other surrogate indicators of NAFLD, including AST, ALT, GGT, and CRP, these relationships persisted. An independent relationship between hyperuricemia and the degree of liver damage was demonstrated by another investigation on a cohort of patients with a histological diagnosis of nonalcoholic fatty liver disease. Specifically, they discovered that the degree of lobular inflammation and steatosis was independently correlated with hyperuricemia (7).

Of all the liver cells, hepatocytes are the most vulnerable to exposure to harmful substances. Because it can trigger cellular injury, a high blood uric acid content acts as a damage-associated molecular pattern (DAMP) in the absence of uric acid crystal formation. Injured cells emit soluble uric acid, which causes reactive oxygen species (ROS) in the mitochondria and increases inflammation. Toll-like receptor (TLR) 4 mediates the signals that trigger an immune response and raise pro-inflammatory mediators (10).

Hepatocyte damage induces the release of Monocyte Chemo-attractant Protein-1 (MCP-1), which will increase the recruitment of macrophages/ Kupffer cells and lymphocytes, and the release of pro- inflammatory cytokines, such as Interleukin-1β (IL- 1β), IL-1 and Tumor Necrosis Factor-α (TNF-α). Subsequently, the cytokines will stimulate the formation of Cyclooxygenase (COX) and activate Nuclear Factor Kappa B (NFκB) and Mitogen-activated Protein Kinase (MAPK) (10).

Numerous causative variables, including alcohol, viruses, toxic bile acids, fatty acids, medications, and immunological reaction, can cause hepatic apoptosis. Programmed cell death, or apoptosis, plays a crucial part in removing damaged cells and tissues (10).

Numerous clinical diseases, including hepatic cirrhosis and elevated levels of Alanine Aminotransferase (ALT) and Gamma-glutamyltransferase (GGT), are also brought on by hyperuricemia. Transamination reactions can be catalyzed by aminotransferase enzymes. The integrity of the liver cells is shown by the two forms of blood transaminase

enzymes, AST and ALT. The degree of damage to the liver cells may be indicated by a rise in liver enzymes. The degree of injury to liver cells increases with the levels of SGOT and SGPT enzymes (11).

Disruption of liver functioning may result in elevated SGOT and SGPT levels. When hepatocyte membrane damage occurs, the aminotransferase enzyme exits the injured cells' cytoplasm and enters the bloodstream, raising the blood's amount of the enzyme. Consequently, increased SGOT and SGPT may be a sign of liver injury (11).

Pathogen-associated Molecular Patterns (PAMPs), a signal that might cause an inflammatory response in the liver, can be triggered by uric acid. One protein that contributes to the activation of the innate immune system is called Toll-like Receptors (TLRs). As Pathogen Recognition Receptors (PRRs), TLRs are able to identify uric acid, which functions as a PAMP (12).

TNF-α, IL-β and IL-6, IFN-γ, IL-8 and MIP-2, MCP-1, and adhesion molecules like ICAM-1 and VCAM-1 are among the cytokines and proinflammatory chemokines that are generated in order to sustain the inflammation.The production of Reactive Oxygen Species (ROS) and the inactivity of Mitogen-activated Protein Kinase Phosphatase-1 (MKP-1), which causes macrophages to produce Monocyte Chemoattractant protein-1 (MCP-1), are further indications of the ongoing stimulation of inflammation by uric acid (11).

A signal that can cause an inflammatory response in the liver, uric acid is typically linked to hepatocyte death or necrosis. Damaged liver cells will go through apoptosis and create apoptotic bodies, which macrophages or nearby cells will identify and phagocytose.Through biotransformation, the liver has a strong capacity to remove harmful chemicals. The liver will have to work harder if the cleansing process exceeds its capabilities. Chronic exposure to elevated serum uric acid can eventually cause apoptosis, necrosis, and inflammation, which will harm the liver cells (12).

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