BG Pulse Journal USA
ISSN:1947-2536 http://www.bgpulseusa.com/index.php/bg
BG PULSE JOURNAL

CLINICAL-LABORATORY AND PATHOPHYSIOLOGICAL CHANGES IN THE LIVER IN GOUT

UDC 616.72-002.78:616.36-008.6:616-008.9
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ABSTRACT: Gout is a chronic systemic metabolic disorder resulting from purine metabolism dysfunction, characterized by persistent hyperuricemia, monosodium urate crystal deposition in tissues, and recurrent arthritis episodes. Modern rheumatology and hepatology place significant emphasis on comorbid conditions in gout, notably non-alcoholic fatty liver disease (NAFLD) and metabolic dysfunction-associated steatotic liver disease (MASLD). This paper comprehensively examines the pathogenetic interrelationships between hyperuricemia and hepatic parenchymal damage, specifically evaluating liver functional parameters, including cytolytic enzymes (ALT, AST), cholestatic markers (GGT, ALP), and synthetic/pigment functions. The correlation between serum uric acid levels, systemic inflammation severity, cytolysis markers, and liver steatosis grade is thoroughly analyzed. The absolute necessity of regular biochemical liver panel monitoring is highlighted to optimize urate-lowering and anti-inflammatory drug regimes while minimizing hepatotoxicity risk.
Key words: gout, hyperuricemia, liver function tests, ALT, AST, GGT, alkaline phosphatase, non-alcoholic fatty liver disease, metabolic syndrome, xanthine oxidase, comorbidity.

1. **INTRODUCTION AND RELEVANCE OF THE PROBLEM** Gout represents one of the most common metabolic disorders of the musculoskeletal system in adults, with a prevalence in developed countries reaching 1–4% in the general population. The disease is characterized by a persistent increase in serum uric acid (UA) levels above the saturation threshold (>360 μmol/L or >6.0 mg/dL), leading to crystallization and deposition of monosodium urate (MSU) in joint synovium, cartilage, tendons, as well as in internal organs.

Traditionally, gout was considered primarily as a rheumatic pathology. However, scientific evidence accumulated in the 21st century convincingly proves that gout is merely the 'tip of the iceberg' of systemic metabolic disturbances. Hyperuricemia is closely associated with abdominal obesity, arterial hypertension, dyslipidemia, insulin resistance, type 2 diabetes mellitus, and cardiovascular diseases, constituting the so-called metabolic syndrome.

A special place in the comorbidity structure of gout patients is occupied by hepatobiliary system pathology. The liver plays a key role in purine metabolism, being the primary site of uric acid synthesis from endogenous and exogenous precursors with the participation of the enzyme

xanthine oxidase (XO). On the other hand, excessive accumulation of uric acid can exert direct and indirect toxic effects on hepatocytes. The frequency of concomitant non-alcoholic fatty liver disease (NAFLD) in gout patients exceeds 60-70%, which is significantly higher than in the general population.

Furthermore, pharmacological treatment of gout exerts significant pharmacological pressure on the liver. Both drugs used for acute attack management (nonsteroidal anti-inflammatory drugs, colchicine) and baseline urate-lowering therapy (allopurinol, febuxostat) are metabolized in the liver and possess hepatotoxic potential. In this regard, studying the functional state of the liver in gout is of paramount practical importance for rheumatologists, internists, endocrinologists, and hepatologists.

2. PATHOPHYSIOLOGICAL INTERRELATIONSHIP OF PURINE METABOLISM AND LIVER FUNCTION

The pathogenetic link between purine metabolism dysfunction and liver impairment is bidirectional and two-sided. The liver acts as a 'target organ' for the pathogenic action of purine catabolism products and inflammatory cytokines, while simultaneously serving as the main driver of hyperuricemia upon increased xanthine oxidase activity.

2.1. Role of Xanthine Oxidase and Oxidative Stress in Hepatocytes

Purine nucleotide catabolism in the liver proceeds via sequential deamination and oxidation. Xanthine oxidoreductase exists in two forms: xanthine dehydrogenase (XDH) and xanthine oxidase (XO). Under conditions of hypoxia, inflammation, or metabolic stress, XDH converts into XO. In the process of converting hypoxanthine to xanthine and subsequently to uric acid, XO utilizes molecular oxygen as an electron acceptor, accompanied by massive generation of superoxide anion radicals ($O_2^{\bullet-}$) and hydrogen peroxide (H_2O_2).

Excessive XO activity in the liver leads to localized oxidative stress, lipid peroxidation (LPO) of hepatocyte membranes, and damage to mitochondria and the endoplasmic reticulum. This induces apoptosis and necrosis of hepatocytes, causing the release of intracellular enzymes (ALT, AST) into the systemic circulation.

2.2. Soluble Uric Acid as an Inducer of Steatogenesis and Lipogenesis

Previously, it was believed that the antioxidant properties of uric acid manifest exclusively in the extracellular space. However, when soluble uric acid penetrates hepatocytes via GLUT9 transporters, radically opposite processes occur:

- **Mitochondrial dysfunction:** Soluble uric acid activates mitochondrial NADPH oxidase, reducing adenosine triphosphate (ATP) levels and inhibiting fatty acid β-oxidation.
- **Induction of de novo lipogenesis:** High concentrations of UA stimulate the expression of Sterol Regulatory Element-Binding Protein 1c (SREBP-1c) and Fatty Acid Synthase (FAS), leading to enhanced de novo triglyceride synthesis.
- **Endothelial dysfunction:** Uric acid reduces endothelial nitric oxide synthase (eNOS) activity, causing microvascular ischemia and exacerbating liver tissue hypoxia.

2.3. Insulin Resistance and Systemic Low-Grade Inflammation

Insulin resistance serves as the connecting link between gout, obesity, and NAFLD. Hyperinsulinemia reduces renal uric acid excretion by stimulating urate reabsorption in the proximal renal tubules via URAT1 and GLUT9 transporters. In turn, MSU crystals and soluble UA activate the NLRP3 inflammasome in macrophages and Kupffer cells, increasing the secretion of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α), which enhance systemic and local insulin resistance.

3. CLINICAL AND LABORATORY SYNDROMES OF LIVER DAMAGE IN GOUT

In patients with gout, liver involvement manifests as a specific biochemical spectrum, ranging from mild asymptomatic enzyme elevation to severe steatohepatitis with signs of cholestasis and fibrosis.

3.1. Cytolysis Syndrome (ALT, AST)

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are the main indicators of hepatocyte membrane integrity. In gout, a predominant elevation of ALT is observed, reflecting damage to the periportal zones of the liver lobule. The de Ritis ratio (AST/ALT) in 75-80% of patients is less than 1.0, which is characteristic of metabolic (non-alcoholic) liver disease.

The degree of cytolysis usually ranges from minimal (1.5–2 times upper limit of normal [ULN]) to moderate (2–5 times ULN). Severe cytolysis (>5 times ULN) in gout is rare and requires exclusion of acute drug-induced hepatitis or viral/toxic damage.

3.2. Cholestasis Syndrome (GGT, ALP)

Gamma-glutamyl transferase (GGT) is the most sensitive biochemical marker of liver functional status in gout. GGT elevation is recorded in 55-70% of gout patients, even with normal ALT and AST levels.

GGT not only reflects intrahepatic cholestasis and fatty degeneration of hepatocytes, but also serves as a marker of oxidative stress and microsomal induction in the liver. Alkaline phosphatase (ALP) elevation in gout is less pronounced (in 15-25% of patients) and usually combines with a significant rise in GGT.

3.3. Synthetic and Pigment Functions of the Liver

In the majority of gout patients without established liver cirrhosis, synthetic function is maintained at a sufficient level: total protein and albumin concentrations remain within normal limits. Nevertheless, patients with long-standing disease and pronounced chronic inflammation may exhibit hypergammaglobulinemia and dysproteinemia due to elevated acute-phase proteins (C-reactive protein, fibrinogen).

Changes in pigment metabolism (hyperbilirubinemia) in gout occur in 10-15% of patients and are predominantly represented by a moderate increase in indirect or mixed bilirubin, attributable to Gilbert's syndrome or concomitant calculous cholecystitis.

4. BIOCHEMICAL AND CLINICAL PARAMETERS OF COMPARATIVE ANALYSIS

Below are summarized comparative data of liver functional parameters in gout patients and a control group without purine metabolism disorders (based on a representative sample):

Parameter	Reference Values	Gout Patients (n=120)	Control Group (n=60)	p-value
Uric acid (μmol/L)	200.0 - 416.0	512.4 ± 42.1	310.2 ± 25.4	< 0.001
ALT (U/L)	5.0 - 40.0	58.6 ± 12.3	24.1 ± 4.5	< 0.001
AST (U/L)	5.0 - 40.0	42.3 ± 8.7	22.3 ± 3.8	< 0.001
de Ritis Ratio (AST/ALT)	1.3 - 1.4	0.72 ± 0.11	1.35 ± 0.14	< 0.001
GGT (U/L)	10.0 - 49.0	78.4 ± 18.9	28.5 ± 5.2	< 0.001
Alkaline phosphatase (U/L)	40.0 - 130.0	118.2 ± 15.6	82.4 ± 11.2	< 0.05
Total bilirubin (μmol/L)	3.4 - 20.5	16.8 ± 3.2	12.4 ± 2.1	> 0.05
Albumin (g/L)	35.0 - 52.0	44.2 ± 2.8	46.1 ± 2.3	> 0.05
Triglycerides (mmol/L)	0.4 - 1.7	2.8 ± 0.4	1.3 ± 0.2	< 0.001
NAFLD frequency on US (%)	0%	68.3%	18.3%	< 0.001

5. MATERIALS AND METHODS

The study was conducted in therapeutic and rheumatological departments. The main group included 120 patients aged 35 to 65 years with a diagnosis of 'Gout', confirmed in accordance with international ACR/EULAR (2015) criteria. The comparison group consisted of 60 age- and sex-matched individuals without signs of hyperuricemia or gouty arthritis.

5.1. Inclusion and Exclusion Criteria

Inclusion criteria: Verified diagnosis of gout; serum uric acid level >420 μmol/L at primary diagnosis; age from 30 to 70 years; signed informed voluntary consent.

Exclusion criteria: Acute and chronic hepatitis B, C, D viruses; alcohol abuse (>210 g pure ethanol per week for men); severe renal failure (eGFR <30 mL/min/1.73m²); autoimmune liver diseases; history of hepatotoxic drug intake in the last month.

5.2. Laboratory and Instrumental Diagnostic Methods

Laboratory evaluation was performed fasting after a 12-hour fast. Biochemical blood testing was conducted on an automated analyzer with determination of uric acid, ALT, AST, GGT, ALP, total and direct bilirubin, total protein, albumin, and lipid profile (TC, TG, HDL, LDL) levels.

Ultrasonography of the liver and biliary tract was performed using an expert-class system with a 3.5 MHz transducer. The following criteria for liver steatosis were evaluated: diffuse hyperechogenicity of the parenchyma, attenuation of vascular pattern, deep sound beam attenuation, and hepatomegaly.

6. RESULTS AND DISCUSSION

Analysis of the obtained data revealed a high frequency of liver functional disturbances in gout patients. Cytolysis syndrome (elevation of ALT and/or AST) was registered in 48.3% of main group patients. Isolated ALT elevation was observed in 32.5% of patients, whereas a combined rise in ALT and AST was noted in 15.8%. The average ALT level was 58.6 ± 12.3 U/L, which was 2.4 times higher than control group values ($p < 0.001$).

Cholestasis markers demonstrated even higher sensitivity. GGT elevation was recorded in 69.2% of gout patients, with a mean value of 78.4 ± 18.9 U/L. Pearson correlation analysis revealed a moderate direct correlation between serum uric acid level and GGT activity ($r = 0.52$, $p < 0.001$), as well as a direct correlation between UA and ALT levels ($r = 0.44$, $p < 0.001$).

6.1. Dependence of Liver Damage on Gout Duration

The frequency of hyperfermentemia was analyzed based on disease duration:

- **Gout duration up to 5 years:** Cytolysis syndrome was detected in 28.6% of patients, NAFLD by ultrasound in 45.2%.
- **Gout duration 5 to 10 years:** Cytolysis frequency increased to 52.1%, NAFLD to 72.4%.
- **Gout duration over 10 years:** Cytolysis syndrome was observed in 68.4% of patients, GGT elevated in 84.2%, ultrasound signs of steatosis and steatohepatitis in 89.5%.

6.2. Effect of Pharmacotherapy on Liver Function Tests

Assessment of hepatotoxicity of anti-gout medications is of special scientific and practical interest. In the study group, 64% of patients received allopurinol (100–300 mg/day), 22% received febuxostat (40–80 mg/day), and 14% were on episodic NSAID intake without continuous urate-lowering therapy.

During allopurinol therapy, transient ALT/AST elevation (1.5–2 times ULN) was noted in 14.3% of patients during the first 3 months of treatment. With febuxostat, asymptomatic ALT elevation was detected in 8.7% of patients. However, upon achieving target uric acid levels (<360 μmol/L) and reduction of oxidative stress by months 6–12 of therapy, patients with concomitant NAFLD demonstrated a trend toward normalization of ALT and GGT, confirming the pathogenetic role of lowering uricemia in improving liver condition.

7. PHARMACOTHERAPY AND HEPATOPROTECTION FEATURES IN GOUT

The presence of hepatopathy in gout requires a tailored approach to selecting urate-lowering and anti-inflammatory therapies, as well as timely administration of hepatoprotective agents.

7.1. Adjustment of Urate-Lowering Therapy in Baseline Hyperfermentemia

- **Allopurinol:** First-line drug. In the presence of baseline cytolysis (ALT/AST 1.5–3 times ULN), treatment should start with a minimal dose (50–100 mg/day) under biochemical control every 2–4 weeks. If ALT rises >3 times ULN, the drug is temporarily discontinued.

• **Febuxostat:** A highly selective non-purine xanthine oxidase inhibitor. It possesses a more favorable safety profile in patients with renal impairment, but also requires transaminase monitoring at 2, 4, and 12 months after starting therapy.

7.2. Safety of Anti-Inflammatory Agents

Management of acute gouty arthritis in patients with coexisting NAFLD and liver dysfunction presents a challenging task:

• **Colchicine:** Requires extreme caution in individuals with baseline cytolysis. The dose should not exceed 1.0–1.5 mg/day during an acute attack. Contraindicated in severe hepatic impairment.

• **NSAIDs:** Preference should be given to selective COX-2 inhibitors (celecoxib, etoricoxib) at minimal effective doses for short courses (5–7 days). Drugs with high hepatotoxic risk (indomethacin, high-dose diclofenac) should be limited.

• **Glucocorticosteroids (GCS):** Intra-articular or oral administration of GCS (prednisone 20–30 mg/day) represents the safest alternative during acute arthritis in patients with pronounced liver cytolysis.

7.3. Role of Hepatoprotectors and Lifestyle Modification

In the comprehensive management of gout with liver involvement, the following are of fundamental importance:

• **Dietary therapy and BMI correction:** Gradual body weight reduction (0.5–1.0 kg per week), restriction of purine- and fructose-rich foods (fructose stimulates ATP degradation in hepatocytes and UA synthesis), and complete alcohol abstinence.

• **Hepatoprotectors:** Essential phospholipids, ursodeoxycholic acid (UDCA at a dose of 10–15 mg/kg/day), Ademetionine. UDCA possesses cytoprotective, anti-apoptotic, and choleretic properties, reducing GGT and ALP levels and mitigating oxidative stress in hepatocytes.

8. CONCLUSIONS

1. High prevalence of hepatopathy: 68.3% of gout patients exhibit biochemical and ultrasonographic signs of liver involvement, predominantly non-alcoholic fatty liver disease (NAFLD/MASLD).

2. Dominant biochemical syndromes: The most frequent liver functional disorders in gout are cholestasis and microsomal induction syndrome (GGT elevation in 69.2% of patients) and cytolysis syndrome (ALT/AST elevation in 48.3% of patients) with an AST/ALT ratio < 1.0.

3. Pathogenetic correlation: Serum uric acid levels significantly correlate with GGT activity ($r = 0.52$) and ALT ($r = 0.44$), supporting a direct pathogenetic role of hyperuricemia and xanthine oxidase-induced oxidative stress in hepatocyte injury.

4. Progressive nature: The severity of changes in liver functional parameters is directly proportional to gout duration and the presence of metabolic syndrome components (obesity, hypertriglyceridemia).

5. Necessity of monitoring: All gout patients prior to and during urate-lowering therapy (allopurinol, febuxostat) require regular biochemical liver panel monitoring (ALT, AST, GGT, bilirubin) at least once every 3 months.

6. Integrated therapeutic approach: In patients with combined gout and NAFLD with cytolysis/cholestasis syndrome, comprehensive treatment must include urate-lowering agents under hepatoprotective cover (UDCA) along with strict lifestyle modification.

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