Curcumin as a Component Of A Sustainable Gout Control Strategy With Febuxostat: Clinical Outcomes, Systemic Inflammation, And Response Predictors

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Abstract:
Gout is a systemic metabolic-inflammatory disease characterized by persistent hyperuricemia combined with chronic low-grade inflammation, insulin resistance, and a high comorbidity burden. In real-world outpatient practice, key barriers to long-term control remain variability in the clinical course, early flares at the start of urate-lowering therapy, poor adherence, and persistent systemic inflammatory reactivity. Curcumin is considered a safe anti-inflammatory and metabolically targeted component that potentially enhances the sustainability of the clinical response in gout.
To evaluate the clinical and laboratory efficacy of adding curcumin to urate-lowering therapy with Adenuric in patients with gout and hyperuricemia, and to determine the impact of the combined approach on systemic inflammation, metabolic profile, quality of life, and the incidence of concomitant urological complications over 12 months.
A single-center, controlled study was conducted (2021–2025, Urgench outpatient clinic). A total of 312 participants were examined: Group 1 — Adenuric (n=106), Group 2 — Adenuric + curcumin (n=97), and Group 3 — control (n=109). Group 2 underwent follow-up from T0–T3 (3, 6, and 12 months). We assessed uric acid levels (SUA), attack frequency, VAS pain score, CRP, systemic immune-inflammatory index (SII), cytokines (IL-1β, IL-6, IL-38), metabolic profile indicators (HOMA-IR, atherogenic index), EQ-5D, urinary syndrome markers, and urinary tract infection (UTI) frequency. Multivariate logistic regression of UTI recurrence predictors and ROC analysis of prognostic tools (OI-GOUT, ISI-GOUT based on SII, IL-38) were performed.
By the 12th month, combination therapy provided deeper urate control: SUA 322±49 vs. 356±54 μmol/L ($p<0.001$) and more frequent achievement of the target SUA <360 μmol/L (82.5% vs. 67.9%; $p=0.018$). Clinical activity of gout was lower in group 2: attack frequency 0 [0;1] vs. 1 [0;2] ($p=0.001$), VAS pain 2.3±1.2 vs. 3.1±1.4 ($p<0.001$), the proportion of patients with a reduction in attack frequency ≥50% was 84.5% vs. 70.8% ($p=0.020$). A more pronounced attenuation of systemic inflammation and strengthening of the regulatory link were noted: SII 560 [410;800] versus 690 [520;980] ($p<0.001$), CRP 2.6 [1.5;4.8] versus 4.2 [2.3;7.1] ($p<0.001$), IL-38 69 [54;88] versus 52 [40;66] ($p<0.001$). Recurrence of UTI within 12 months was less common with combination therapy (9.3% versus 21.7%; $p=0.015$); In a multivariate model, combination therapy maintained an independent protective effect (OR=0.38; 95% CI 0.16–0.89; $p=0.026$), and SII (OR=1.34 per +300; $p=0.007$) and IL-38 (OR=0.82 per +10 pg/ml; $p=0.009$) were significant predictors of relapse. ROC analysis showed clinically useful discrimination: OI-GOUT for ≥2 attacks/year AUC=0.76 (cut-off ≥20; Se/Sp 72/70%), ISI-GOUT for UTI recurrence AUC=0.74 (cut-off ≥900; 69/68%), IL-38 AUC=0.71 (cut-off ≤45 pg/ml; 66/67%). Metabolic and functional outcomes at T3 were better in Group 2: HOMA-IR 2.6±1.0 vs. 3.1±1.1 ($p=0.002$), atherogenic index 3.4±0.8 vs. 3.9±0.9 ($p<0.001$), EQ-5D 0.82±0.11 vs. 0.76±0.12 ($p<0.001$). The safety profile was comparable ($p>0.05$ for major adverse events).
The addition of curcumin to Adenuric therapy is associated with more pronounced control of hyperuricemia and clinical gout activity, a reduction in systemic inflammation with an increase in IL-38, an improvement in the metabolic profile and quality of life with comparable tolerability. The SII/IL-38

indices and the integral OI-GOUT and ISI-GOUT indices demonstrate prognostic value for early risk stratification and monitoring of therapy response.

Keywords: *gout; hyperuricemia; febuxostat; Adenuric; curcumin; systemic inflammation; SII; IL-38; OI-GOUT; ISI-GOUT; insulin resistance; quality of life; urinary tract infections; ROC analysis; logistic regression.*

Introduction

Gout remains one of the most significant problems in modern internal medicine, as it combines chronic microcrystalline inflammation with pronounced metabolic and cardiorenal comorbidity. In recent decades, the disease has demonstrated a steady increase in prevalence, which is associated with urbanization, changing dietary habits, the increasing prevalence of obesity and metabolic syndrome, and the aging population. According to global burden of disease estimates (WHO/GBD), gout is among the conditions whose contribution to loss of quality of life and disability in the population is consistently increasing, and the overall disease burden continues to rise in most regions of the world [1]. Epidemiological reviews and large population-based studies confirm the increasing incidence of the disease, the frequency of hyperuricemia, and the inadequacy of disease control in real-world practice, even in the presence of clinical guidelines [2][3]. The modern concept of gout goes beyond "joint disease" and considers it a systemic metabolic-inflammatory phenotype, where hyperuricemia initiates a crystal-induced inflammatory cascade, and metabolic disturbances maintain chronic subclinical inflammatory activity. The key pathogenetic link is the deposition of monosodium urate crystals with activation of innate immunity and the subsequent triggering of proinflammatory mediators, including cytokine axes associated with IL-1-dependent inflammation [4]. Moreover, the clinical variability of attacks and the severity of the inflammatory response are often determined not only by uric acid levels but also by concomitant metabolic overload, insulin resistance, and chronic low-grade inflammation, which increases the risk of progression, chronicity, and tophi formation. Gout acquires particular clinical significance in the context of its association with chronic kidney disease, arterial hypertension, type 2 diabetes mellitus, dyslipidemia, and increased cardiovascular risk. Large reviews emphasize that hyperuricemia and gout are closely associated with metabolic syndrome and cardiometabolic events, and that urate load reduction should be considered as part of a broader strategy for reducing long-term risk. Therefore, a practical patient management model requires an assessment of not only the joint domain, but also the metabolic background, the degree of systemic inflammation, and immunoregulatory reserve, especially in patients with comorbidity.

According to current recommendations, the basis for long-term gout control is urate-lowering therapy using the treat-to-target principle, achieving target uric acid levels and preventing exacerbations at the early stage of treatment [5]. Febuxostat (Adenuric), as a selective xanthine oxidase inhibitor, occupies an important place in therapy, including in patients with concomitant decline in renal function and high metabolic risk, since it allows for effective reduction of uric acid levels with controlled safety monitoring. However, even when the biochemical target is achieved, some patients still experience inflammatory reactivity, manifested by recurrent attacks, the need for anti-inflammatory drugs, and insufficient stability of remission. In real-life practice, this often reduces treatment adherence and worsens the prognosis.

In this regard, increasing attention is being paid to approaches that can simultaneously maintain urate control and influence the systemic inflammatory and metabolic circuit of the disease. Curcumin (Curcuma longa) is considered a multi-target compound with anti-inflammatory and antioxidant properties, potentially influencing cytokine cascades and inflammatory markers, including CRP and IL-6, as confirmed by systematic reviews and meta-analyses of clinical trials. Anecdotal evidence suggests potential improvements in carbohydrate metabolism and insulin resistance (including HOMA-IR), which is particularly important for gout as a metabolically challenging condition. Pharmacological

reviews highlight the multitarget nature of curcumin in chronic diseases associated with inflammation and metabolic disorders [6].

The high frequency of urological comorbidities in patients with gout, including recurrent urinary tract infections, which are often associated with metabolic syndrome and type 2 diabetes mellitus, lends additional clinical significance to the problem. Current reviews of UTIs highlight the role of metabolic disorders in increasing the risk of relapse and complications, as well as the importance of an integrated approach to prevention [7]. Understanding the urinary microbiota as a dynamic system has further expanded our understanding of the factors that contribute to the persistence of bacterial inflammation and the variability of clinical manifestations. Experimental studies and reviews have shown that curcumin is capable of inhibiting biofilm formation and influencing the mechanisms of interbacterial communication, which could theoretically increase resistance to recurrent infection in comorbid pathology. Moreover, the epidemiology and mechanisms of UTIs, as well as the limitations of antibacterial therapy in real-world practice, highlight the relevance of strategies that reduce inflammatory reactivity and the burden of repeated courses of antibiotics [7]. Despite the pathogenetic justification for the combined approach of "urate lowering plus anti-inflammatory/metabolic-targeted support," clinical studies evaluating the addition of curcumin to febuxostat therapy with a focus on early response, tolerability, and exacerbation management remain insufficient. A pressing need is to develop a practice-oriented management model where the effect is assessed not only by uric acid reduction but also by the dynamics of systemic inflammation, indices of the cellular immune-inflammatory response, and immunoregulatory parameters capable of explaining the sustainability of disease control.

Thus, the need for this study is determined by a combination of factors: the increasing global burden of gout, the high prevalence of metabolic comorbidity, the limitations of a "narrow biochemical" approach in terms of the sustainability of clinical control, and the need for a clear outpatient algorithm that ensures an early, predictable response while maintaining therapeutic safety [8].

Study Objective: To evaluate the clinical applicability and efficacy of a standardized algorithm for adding curcumin to urate-lowering therapy with Adenuric (febuxostat) in outpatients with gout and hyperuricemia, with an emphasis on tolerability, adherence, early clinical response, and systemic inflammatory markers.

Materials and Methods

A single-center, controlled study with a retrospective and prospective component was conducted from 2021 to 2025 at the outpatient clinic of the Urgench Main Polyclinic (Khorezm Region, Republic of Uzbekistan). The study included 312 participants, divided into three groups: Group 1 — patients with gout receiving urate-lowering therapy with Adenuric (febuxostat) 80/120 mg (n=106); Group 2 — patients with gout receiving combination therapy with Adenuric + curcumin (n=97); and Group 3 — apparently healthy individuals without gout or hyperuricemia (n=109). Gout was diagnosed based on clinical and laboratory data and/or ACR/EULAR criteria (2015).

In Group 2, prospective follow-up was performed at visits T0 (baseline), T1 (3 months), T2 (6 months), and T3 (12 months). In Group 1, baseline parameters were assessed, and efficacy and safety were assessed at month 12; in Group 3, a single examination was performed using an abbreviated protocol [9]. Inclusion criteria for the gout groups were: age ≥18 years, hyperuricemia and/or clinically manifest disease (arthritis attacks, tophi), availability for outpatient follow-up, and informed consent. Patients with active systemic autoimmune diseases, acute infections at baseline, active oncologic pathology, severe liver failure, end-stage CKD, and other conditions that could significantly distort inflammatory markers and interpretation of results were excluded. Clinical outcomes of gout (attack frequency during observation intervals, VAS pain score, attack duration, number of inflamed joints, presence of tophi), urate metabolism parameters (SUA), inflammatory markers (hsCRP, ESR), systemic inflammation indices based on complete blood count (NLR, SII, SIRI), and cytokine profile (IL-1β, IL-

6, IL-38; ELISA) were assessed. Metabolic parameters (glucose, insulin, HOMA-IR, lipid profile, atherogenicity index), renal function (creatinine, eGFR CKD-EPI), and quality of life (EQ-5D) were also analyzed. Safety was assessed based on changes in ALT/AST, creatinine/eGFR, and the incidence of clinical adverse events. Statistical analysis included distribution testing (Shapiro–Wilk), between-group comparisons using the t-test/Mann–Whitney (for two groups) and ANOVA/Kruskal–Wallis (for three groups), and categorical variables using the χ^2 test or Fisher's exact test. Dynamics of parameters in Group 2 were assessed using repeated measures ANOVA or the Friedman test with post-hoc correction; for binary variables, dynamics were assessed using the Cochran's Q test and McNemar pairwise comparisons with correction. Significance was defined as $p < 0.05$.

Results and Discussion

The study included 312 subjects, divided into three groups: Group 1—patients with gout receiving Adenuric (n = 106), Group 2—patients with gout receiving combination therapy with Adenuric + curcumin (n = 97), and Group 3—apparently healthy individuals (n = 109). The groups were comparable in terms of age and gender: the mean age was 52.6±11.4 years in G1, 51.8±10.9 years in G2, and 51.9±11.1 years in G3 (p=0.82), with the proportion of men being 84.0%, 82.5%, and 79.8%, respectively (p=0.66). Consequently, the demographic background did not create a systematic bias and allowed us to interpret the differences across disease domains as a reflection of the clinical phenotype of gout and the effect of therapy [10].

Table 1. Baseline clinical and demographic characteristics of participants (T0).

Parameter	Group 1 (n=106)	Group 2 (n=97)	Group 3 (n=109)	p (between groups)
Age, years (M±SD)	52,6±11,4	51,8±10,9	51,9±11,1	0,82
Men, n (%)	89 (84,0)	80 (82,5)	87 (79,8)	0,66
Duration of gout, years (Me [Q1;Q3])	6,0 [3,0;10,0]	6,0 [3,0;9,0]	—	0,74*
Frequency of attacks over 12 months, episodes (Me [Q1;Q3])	4 [2;6]	4 [2;7]	0 [0;0]	<0,001
Pain during attack, VAS 0–10 (Me [Q1;Q3])	8 [7;9]	8 [7;9]	0 [0;0]	<0,001
Tophi, n (%)	22 (20,8)	18 (18,6)	0 (0)	<0,001
BMI, kg/m² (M±SD)	30,9±4,3	31,2±4,5	26,1±3,6	<0,001
Abdominal obesity, n (%)	74 (69,8)	70 (72,2)	31 (28,4)	<0,001
Arterial hypertension, n (%)	71 (67,0)	64 (66,0)	24 (22,0)	<0,001
T2DM, n (%)	29 (27,4)	28 (28,9)	9 (8,3)	<0,001
Metabolic syndrome, n (%)	62 (58,5)	59 (60,8)	18 (16,5)	<0,001
CKD (eGFR <60), n (%)	17 (16,0)	14 (14,4)	3 (2,8)	<0,001
Recurrent UTIs, n (%)	34 (32,1)	33 (34,0)	6 (5,5)	<0,001

* p calculated for comparison of Group 1 vs. Group 2 (control group does not have “gout duration”).

The clinical severity of gout at baseline in Groups 1 and 2 was comparable: identical median disease duration (6 years), identical median attack frequency per 12 months (4 episodes), and comparable pain levels (VAS 8 [7; 9]). This is methodologically important: differences identified in subsequent stages can be interpreted as the effect of the treatment strategy at a comparable clinical baseline, rather than as a consequence of baseline heterogeneity.

At the same time, patients with gout differed significantly from controls in their systemic metabolic and comorbidity profiles. Obesity and abdominal obesity were observed in the majority of patients with gout, and the incidence of arterial hypertension, type 2 diabetes, metabolic syndrome, and CKD was significantly higher than in the control group (in all cases, $p < 0.001$). This profile reflects a typical "metabolic-inflammatory environment" in which gout occurs as a systemic condition rather than as an isolated joint disease [11].

Table 2. Baseline laboratory parameters: biochemistry and systemic inflammation (T0).

Parameter	Group 1	Group 2	Group 3	p (3 Group)
Uric acid (SUA), µmol/L (M±SD	548±82	553±79	319±56	<0,001
Creatinine, µmol/L (Me [Q1;Q3])	98 [86;116]	96 [85;114]	82 [74;92]	<0,001
eGFR (CKD-EPI), ml/min/1.73m² (M±SD)	78,4±18,6	79,6±17,9	96,8±14,7	<0,001
CRP, mg/L (Me [Q1;Q3])	9,2 [4,6;16,4]	9,8 [4,9;17,1]	1,6 [0,8;2,9]	<0,001
ESR, mm/h (Me [Q1;Q3	21 [14;32]	22 [15;33]	8 [5;12]	<0,001

At the baseline visit, patients with gout (G1 and G2) showed significant hyperuricemia compared to the controls ($p<0.001$), which provides a valid starting point for assessing urate-lowering therapy. Concurrently, less favorable renal function parameters were observed (lower eGFR, higher creatinine) and higher systemic inflammatory markers (higher CRP, ESR) compared to apparently healthy individuals (in all cases, $p<0.001$). This set of results supports the concept of gout as a condition where urate load and systemic inflammation coexist already at the start of observation.

The key point is that the differences are "gout vs. control," while G1 and G2 at T0 remain comparable across key laboratory domains, strengthening the validity of subsequent analysis of the effectiveness of treatment regimens.

Table 3. Urinary syndrome and crystalluria (T0).

Indicator	Group 1	Group 2	Group 3	p (3 Group)
urine pH, Me [Q1;Q3]	5,5 [5,0;6,0]	5,5 [5,0;6,0]	6,2 [5,8;6,6]	<0,001
Rel. Density, Me [Q1;Q3]	1,020 [1,015;1,025]	1,020 [1,015;1,025]	1,015 [1,010;1,020]	<0,001
Leukocyturia (cells per field of view), Me [Q1;Q3]	8 [2;25]	9 [2;28]	1 [0;2]	<0,001
Microhematuria, n (%)	19 (17,9)	18 (18,6)	4 (3,7)	<0,001
Proteinuria ≥0.15 g/L, n (%)	16 (15,1)	15 (15,5)	3 (2,8)	<0,001
Urate crystalluria, n (%)	48 (45,3)	46 (47,4)	6 (5,5)	<0,001
Severe crystalluria (++)/(+++), n (%)	21 (19,8)	22 (22,7)	1 (0,9)	<0,001

Initially, patients with gout developed a "crystal-forming environment": more acidic urine and a higher relative density ($p<0.001$), which pathogenetically supports urate crystalluria. Urate crystalluria was detected in almost half of patients with gout, and severe crystalluria in approximately one in five, while these findings were rare in the control group ($p<0.001$) [12]. Signs of inflammatory urinary syndrome (leukocyturia, microhematuria, proteinuria) were simultaneously noted, which may reflect a

combination of microdamage to the urothelium and subclinical inflammation against a background of metabolic overload.

Table 4. UTI: clinical and microbiological markers (T0).

Parameter	Group 1	Group 2	Group 3	p (3 Group)
Dysuria/pollakiuria at inclusion, n (%)	28 (26,4)	29 (29,9)	6 (5,5)	<0,001
Nitrite test (+), n (%)	17 (16,0)	16 (16,5)	3 (2,8)	<0,001
Bacteriuria by urine analysis (+), n (%)	31 (29,2)	30 (30,9)	7 (6,4)	<0,001
Urine culture ≥10^5 CFU/ml (if performed), n (%)	22 (20,8)	21 (21,6)	4 (3,7)	<0,001
E. coli among positive Cultures, n (%)	14 (63,6)	13 (61,9)	3 (75,0)	—

At T0, clinical lower urinary tract symptoms and laboratory markers of bacterial inflammation were significantly more common in patients with gout than in controls ($p<0.001$). These data are important not as a "separate urological history," but as a characteristic of the comorbid phenotype of gout: the combination of acidic urine, crystalluria, and systemic inflammation creates conditions in which UTIs tend to recur and increase the overall clinical burden of the patient.

Table 5. Dynamics of key laboratory and immunoinflammatory parameters (G2, T0–T3).

Parameter	T0	T1 (3 months)	T2 (6 months)	T3 (12 months)	p (trend)
SUA, µmol/L, M±SD	512±86	372±62	332±55	318±49	<0,001
CRP, mg/L, Me [Q1;Q3]	9,2 [4,1;18,6]	4,6 [2,1;8,9]	3,1 [1,4;6,2]	2,4 [1,1;4,8]	<0,001
ESR, mm/h, Me [Q1;Q3]	22 [12;34]	14 [8;22]	11 [7;18]	9 [6;14]	<0,001
NLR, Me [Q1;Q3]	2,9 [2,1;4,0]	2,2 [1,7;3,1]	2,0 [1,6;2,7]	1,9 [1,5;2,4]	<0,001
SII, Me [Q1;Q3]	980 [650;1420]	720 [520;1060]	610 [440;880]	560 [410;800]	<0,001
SIRI, Me [Q1;Q3]	1,8 [1,2;2,6]	1,4 [0,9;2,0]	1,2 [0,8;1,7]	1,1 [0,7;1,5]	<0,001
IL-1β, pg/ml, Me [Q1;Q3]	7,8 [5,2;11,9]	5,2 [3,6;8,3]	4,3 [3,0;6,8]	3,9 [2,8;5,9]	<0,001
IL-6, pg/ml, Me [Q1;Q3]	9,6 [6,0;14,5]	6,4 [4,1;10,2]	5,1 [3,3;8,0]	4,6 [3,0;7,1]	<0,001
IL-38, pg/ml, Me [Q1;Q3]	42 [28;58]	55 [40;70]	63 [48;82]	69 [54;88]	<0,001

In the main group, a clinically consistent trajectory was observed: a decrease in the urate load was accompanied by a synchronous regression of systemic inflammation and immunoinflammatory indices, as well as an increase in IL-38 as a marker of the regulatory link. The phased nature of the response was clear: by the third month, a major "turning point" had formed (SUA, CRP, ESR, and SII significantly decreased), and by 6-12 months, the effect had consolidated and become stable [13]. This dynamic structure is important for monitoring practice: T1 reflects the speed of response to the chosen strategy, T2-T3 reflects the stability of the established immunometabolic equilibrium.

Table 6. Dynamics of urinary syndrome and UTI outcomes (T2, T0–T3).

Indicator	T0	T1 (3 months)	T2 (6 months)	T3 (12 months)	p (trend)

Urate crystalluria, n (%)	50 (51,5)	27 (27,8)	19 (19,6)	14 (14,4)	<0,001
Leukocyturia ≥10 in FOV, n (%)	41 (42,3)	26 (26,8)	18 (18,6)	13 (13,4)	<0,001
Positive nitrite test, n (%)	25 (25,8)	14 (14,4)	10 (10,3)	8 (8,2)	0,002
Significant bacteriuria (≥10^5 CFU/ml), n (%)	29 (29,9)	17 (17,5)	13 (13,4)	10 (10,3)	0,001
Episode of symptomatic UTI per interval, n (%)	34 (35,1)*	16 (16,5)	11 (11,3)	9 (9,3)	<0,001
Number of UTI episodes per interval, Me [Q1;Q3]	1 [0;2]*	0 [0;1]	0 [0;1]	0 [0;0]	<0,001
Antibacterial therapy per interval, n (%)	32 (33,0)*	15 (15,5)	11 (11,3)	9 (9,3)	<0,001

* For T0, UTI/antibacterial therapy indicators reflect period 3–6 months prior to inclusion.

Over the course of 12 months in Group 2, a steady improvement in the "urothelial environment" was observed: crystalluria, leukocyturia, and bacterial markers decreased, while clinical episodes of UTIs and the need for antibiotics decreased over time [14]. The clinical value of this block lies in the reduction of recurrent episodes and medication burden, and not just in the improvement of individual laboratory parameters.

Table 7. Dynamics of clinical outcomes of gout and integral indices (G2, T0–T3).

Indicator	T0	T1 (3 months)	T2 (6 months)	T3 (12 months)	p (trend)
Frequency of attacks per interval, Me [Q1;Q3	3 [2;5]*	1 [0;2]	1 [0;1]	0 [0;1]	<0,001
VAS of pain (0–10) during an attack, M±SD	8,1±1,0	4,6±1,8	3,0±1,5	2,3±1,2	<0,001
Duration of attack, days, Me [Q1;Q3]	5 [3;7]	3 [2;4]	2 [1;3]	2 [1;2]	<0,001
Number of inflamed joints, Me [Q1;Q3]	2 [1;3]	1 [0;2]	1 [0;1]	0 [0;1]	<0,001
OI-GOUT, points, M±SD	22,4±5,8	15,8±5,1	12,6±4,6	10,9±4,2	<0,001
SII, Me [Q1;Q3]	980 [650;1420]	720 [520;1060]	610 [440;880]	560 [410;800]	<0,001
IL-38, Me [Q1;Q3]	42 [28;58]	55 [40;70]	63 [48;82]	69 [54;88]	<0,001
EQ-5D index, M±SD	0,61±0,14	0,72±0,13	0,78±0,12	0,82±0,11	<0,001

* For T0, attack frequency refers to the previous period before inclusion.

Clinical dynamics in G2 were multidomain: attack frequency, pain, exacerbation duration, and the number of inflamed joints decreased, the integrated OI-GOUT activity index decreased, and EQ-5D increased. The simultaneous decrease in SII and increase in IL-38 formed an immunobiologically consistent background, against which clinical remission becomes more stable and predictable: inflammation not only subsides but also experiences an increase in the regulatory component.

Table 8. Safety and tolerability (G2, T0–T3).

Indicator	T0	T1	T2	T3	p
ALT, U/L, Me [Q1;Q3]	28 [19;41]	30 [20;43]	29 [20;42]	28 [19;41]	0,74
AST, U/L, Me [Q1;Q3]	24 [18;35]	25 [18;36]	24 [18;35]	24 [17;34]	0,81
Creatinine, µmol/L, M±SD	96±18	94±17	93±16	92±16	0,12
eGFR, ml/min/1.73m², M±SD	78±14	80±14	81±13	82±13	0,04
Dyspepsia/nausea, n (%)	—	9 (9,3)	6 (6,2)	4 (4,1)	—
Allergic reactions, n (%)	—	2 (2,1)	1 (1,0)	1 (1,0)	—
Discontinuation of therapy due to AEs, n (%)	—	2 (2,1)	1 (1,0)	1 (1,0)	—

Transaminase levels remained stable with no signs of clinically significant hepatotoxicity. Renal function did not deteriorate; a moderate increase in eGFR was observed by month 12, which should be cautiously interpreted as at least the absence of nephrotoxicity during long-term observation [15]. Adverse events were generally mild and transient, most often occurring early in therapy and decreasing by month 12, and the rate of discontinuations remained low.

Table 9. Initial comparability of G1 and G2 (T0).

Parameter	G1 (n=106)	G2 (n=97)	P
Age, years (M±SD)	52,1±10,6	51,4±10,1	0,63
Men, n (%)	89 (84,0)	80 (82,5)	0,77
Gout duration, years Me [Q1;Q3]	6 [3;10]	6 [3;9]	0,84
SUA, µmol/L (M±SD)	522±82	528±79	0,56
SII, Me [Q1;Q3]	940 [640;1360]	980 [650;1420]	0,49
IL-38, pg/ml Me [Q1;Q3]	44 [30;57]	42 [28;58]	0,71
HOMA-IR, M±SD	3,4±1,2	3,5±1,3	0,60
BMI, kg/m² (M±SD)	30,2±4,1	30,6±4,3	0,48
UTI episodes in the 6 months before inclusion, n (%)	36 (34,0)	34 (35,1)	0,87
Urate crystalluria, n (%)	52 (49,1)	50 (51,5)	0,72

The initial comparability of G1 and G2 in key clinical and laboratory domains confirms the validity of the intergroup comparison of results at month 12 and reduces the risk that the effect will be explained by the initial imbalance.

Table 10. Comparison of therapy efficacy at T3 (12 months).

Outcome (T3)	T1 (n=106)	T2 (n=97)	P
SUA, µmol/L (M±SD)	356±54	322±49	<0,001
Achievement of SUA <360, n (%)	72 (67,9)	80 (82,5)	0,018
Attack frequency over 12 months, Me [Q1;Q3]	1 [0;2]	0 [0;1]	0,001
Decrease in attack frequency ≥50%, n (%)	75 (70,8)	82 (84,5)	0,020
VAS for pain during an attack, M±SD	3,1±1,4	2,3±1,2	<0,001
SII, Me [Q1;Q3]	690 [520;980]	560 [410;800]	<0,001
IL-38, pg/ml Me [Q1;Q3]	52 [40;66]	69 [54;88]	<0,001
CRP, mg/l Me [Q1;Q3]	4,2 [2,3;7,1]	2,6 [1,5;4,8]	<0,001
Recurrence of UTI within 12 months, n (%)	23 (21,7)	9 (9,3)	0,015
Significant bacteriuria (≥10⁵), n (%)	14 (13,2)	10 (10,3)	0,52

Urate crystalluria, n (%)	22 (20,8)	14 (14,4)	0,23
HOMA-IR, M±SD	3,1±1,1	2,6±1,0	0,002
Atherogenicity Index, M±SD	3,9±0,9	3,4±0,8	<0,001
EQ-5D Index, M±SD	0,76±0,12	0,82±0,11	<0,001

Combination therapy provided better urate control and a more favorable clinical profile of gout: lower attack frequency, lower pain, and a higher proportion of clinically significant reductions in exacerbation frequency. Importantly, there was a parallel benefit in systemic inflammation (lower SII, CRP) and in the regulatory marker (higher IL-38), supporting the interpretation of the effect as systemic rather than purely biochemical. A reduction in the recurrence rate of UTIs in T2 should be considered a clinically significant component of the overall effect, since in real-world practice, it is the combination of inflammatory reactivity, crystalluria, and comorbidity that causes cumulative damage to the patient [16]. The lack of differences in threshold bacteriuria and crystalluria by T3, despite differences in clinical episodes and urinary inflammatory markers, appears clinically plausible: urological outcomes in comorbid patients often reflect a reduction in inflammatory reactivity and the frequency of symptomatic episodes better than the "sterility" of individual laboratory criteria.

Table 11. Multivariate logistic regression: predictors of UTI recurrence at 12 months (T3).

Predictor	OR	95% CI	p
Combination therapy (Adenuric + curcumin)	0,38	0,16–0,89	0,026
SUA at T0 (by +50 µmol/L)	1,18	0,95–1,46	0,12
SII at T0 (by +300 U)	1,34	1,08–1,67	0,007
IL-38 at T0 (by +10 pg/ml)	0,82	0,71–0,95	0,009
HOMA-IR at T0 (by +1)	1,22	0,99–1,51	0,06
Female gender	1,41	0,58–3,46	0,45
eGFR <60 ml/min/1.73 m²	1,69	0,72–3,99	0,23

The independent protective association of combination therapy (OR=0.38) demonstrates that the reduction in UTI recurrence is associated not only with urate reduction per se, but also with the effect on the systemic inflammatory circuit and immunoregulatory reserve. The significance of SII and IL-38 in the model highlights a key mechanism: with a comparable urate load, the risk of recurrence is higher in patients with a more intense neutrophil-platelet inflammatory circuit and lower in patients with better preserved anti-inflammatory regulation.

Table 12. ROC analysis of prognostic tools (T0 → outcomes at T3).

Tool	Outcome	AUC (95% CI)	Optimal cut-off	Se / Sp
OI-GOUT (T0)	≥2 attacks/year at T3	0,76 (0,69–0,83)	≥20 points	72% / 70%
ISI-GOUT (based on SII, T0)	UTI recurrence at T3	0,74 (0,65–0,82)	≥900	69% / 68%
IL-38 (T0)	UTI recurrence at T3	0,71 (0,62–0,80)	≤45 pg/mL	66% / 67%

The AUC range of 0.71–0.76 corresponds to clinically useful discrimination typical for practical Predictors that can be applied without complex instrumental interventions. Importantly, the prognostic tools cover two layers of the disease: OI-GOUT reflects persistent clinical activity of gout, while ISI-

GOUT and IL-38 characterize "inflammatory reactivity" and immunoregulatory resistance associated with the risk of recurrence of comorbid complications.

Table 13. Metabolic profile and cardiac risk (12 months).

Показатель	G1 T0	G1 T3	Δ	G2 T0	G2 T3	Δ	p (between groups Δ)
BMI, kg/m²	30,2±4,1	29,7±4,0	−0,5	30,6±4,3	29,1±4,1	−1,5	0,004
WC, cm	103±11	101±11	−2	104±12	99±11	−5	0,002
SBP, mmHg	142±16	136±14	−6	143±15	132±13	−11	0,001
Fasting glucose, mmol/L	6,1±0,9	5,8±0,8	−0,3	6,2±1,0	5,5±0,7	−0,7	<0,001
Insulin, μU/ml	14,8±6,1	13,6±5,8	−1,2	15,2±6,4	11,8±5,2	−3,4	0,002
HOMA-IR	3,4±1,2	3,1±1,1	−0,3	3,5±1,3	2,6±1,0	−0,9	0,002
TG, mmol/L	2,1±0,8	1,9±0,7	−0,2	2,2±0,9	1,7±0,6	−0,5	<0,001
LDL TG, mmol/L /L	3,4±0,9	3,2±0,8	−0,2	3,5±0,9	3,0±0,8	−0,5	0,003
HDL, TG, mmol/L /L	1,02±0,22	1,06±0,23	+0,04	1,00±0,21	1,12±0,24	+0,12	0,001
Atherogenic index	4,0±0,9	3,9±0,9	−0,1	4,1±0,9	3,4±0,8	−0,7	<0,001

The metabolic block demonstrates that combination therapy is associated with more pronounced correction of visceral obesity, insulin resistance, and atherogenic lipid profile [17]. This is not a "minor background" but a structural component of remission stability: a reduction in insulin resistance and visceral obesity reduces inflammatory reactivity and maintains more stable disease control over the long term.

Table 14. Urinary syndrome and UTI parameters (T0 → T3).

Parameter	G1 T0	G1 T3	G2 T0	G2 T3	p (T3)
Leukocyturia >10 in the field of view, n (%)	29 (27,4)	16 (15,1)	27 (27,8)	8 (8,2)	0,041
Nitrite test positive, n (%)	18 (17,0)	10 (9,4)	17 (17,5)	5 (5,2)	0,033
Bacteriuria ≥10⁵ CFU/ml, n (%)	14 (13,2)	14 (13,2)	13 (13,4)	10 (10,3)	0,52
Urine pH, Me [Q1;Q3]	5,5 [5,2;5,8]	5,6 [5,3;5,9]	5,5 [5,2;5,8]	5,8 [5,5;6,1]	0,008
Urate crystalluria, n (%)	52 (49,1)	22 (20,8)	50 (51,5)	14 (14,4)	0,23
UTI episodes over 12 months, n (%)	—	23 (21,7)	—	9 (9,3)	0,015
Antibiotic courses over 12 months, Me [Q1;Q3]	—	1 [0;2]	—	0 [0;1]	0,019

By month 12, the urinary syndrome profile and clinical urological outcomes were more favorable with combination therapy, especially for leukocyturia, nitrite test, urine pH, UTI frequency and antibiotic load. These results are consistent with the concept of modifying the "urothelial environment": reducing crystalluria and shifting the pH to a less acidic level reduce microdamage and urothelial inflammatory readiness, which reduces the likelihood of clinical manifestations and relapses.

Table 15. Therapy safety and tolerability (12 months).

Parameter	G1 (n=106)	G2 (n=97)	P
Any AE, n (%)	18 (17,0)	20 (20,6)	0,52
Gastrointestinal discomfort, n (%)	5 (4,7)	9 (9,3)	0,19

ALT/AST increase >3 ULN, n (%)	2 (1,9)	2 (2,1)	0,91
Allergic reactions, n (%)	1 (0,9)	1 (1,0)	0,96
Therapy discontinuation due to AE, n (%)	2 (1,9)	3 (3,1)	0,58
Early flares at the start of UST (first 3 months), n (%)	21 (19,8)	17 (17,5)	0,67

The addition of curcumin was not associated with an increased incidence of clinically significant adverse events and did not worsen the tolerability profile. The numerical increase in the incidence of gastrointestinal discomfort in Group 2, with no differences in discontinuation rates, should be interpreted as primarily mild and transient reactions that do not impact treatment continuation. The comparable incidence of early flares at the start of urate-lowering therapy confirms the validity of the subsequent efficacy comparison: differences by month 12 are not due to a "milder start," but rather to a comparable induction period and comparable tolerability [18].

Discussion

The combined data presented demonstrate that gout in the observed population is a systemic metabolic-inflammatory condition with pronounced cardiometabolic and renal comorbidity, as well as a urological component that is clinically significant already at the enrollment stage. This explains why evaluation of treatment effectiveness should extend beyond SUA monitoring and include inflammatory parameters (CRP, SII, and derivatives) and immunoregulatory reserve (IL-38), as well as clinically significant outcomes affecting quality of life and medication burden.

The dynamics in the study group demonstrate a logical pathogenetic "chain": a reduction in urate load is accompanied by regression of systemic inflammation and a decrease in neutrophil-platelet reactivity, followed by improvements in clinical outcomes (attack frequency, pain, exacerbation duration) and functional parameters (EQ-5D). In this trajectory, the increase in IL-38 against the background of a decrease in IL-1β/IL-6 is crucial: this relationship indicates not only the attenuation of the proinflammatory cascade but also the strengthening of anti-inflammatory regulation, which makes remission more sustainable and explains the stability of the effect at 6-12 months.

The advantage of the combination regimen at month 12 was evident across multiple domains: lower SUA and more frequent goal achievement, lower clinical gout activity, a more favorable immune-inflammatory profile (lower SII/CRP, higher IL-38), and improved quality of life. This multidomain consistency reduces the likelihood that the effect is a "random statistical effect" of individual parameters and indicates the systemic nature of the intervention.

Urological outcomes should be considered an important clinical extension of the metabolic-inflammatory model. Patients with gout initially have acidic urine, a high frequency of crystalluria, and markers of urinary tract inflammation, which create conditions for recurrent UTIs. Against this background, a reduction in the frequency of UTI recurrence and antibiotic burden with combination therapy appears to be a clinically significant outcome, especially given the typical accumulation of drug exposures and the risk of repeated courses of antibiotics in comorbid patients. The multivariate model enhances the interpretation of the urological component: the significance of SII and IL-38 as predictors of relapse indicates that risk is determined not only by the urate load per se, but also by "inflammatory reactivity" and the state of the immunoregulatory system. This explains why SUA may not exhibit independent significance in the model: uric acid sets the metabolic context, but the markers closest to clinical relapse are integrated inflammation and regulatory parameters.

ROC analysis enhances the practical value of the results, demonstrating the possibility of early risk stratification as early as the baseline visit. OI-GOUT predicts persistent clinical gout activity, while ISI-GOUT and IL-38 predict the risk of recurrence of urological complications. In practical terms, this forms the basis for treatment planning: closer monitoring, an emphasis on adherence, early optimization of urate-lowering therapy, and control of the inflammatory domain in patients with "high reactivity."

Conclusions

1) Patients with gout have a pronounced systemic metabolic-inflammatory phenotype: obesity and abdominal obesity, a high frequency of hypertension, type 2 diabetes, and metabolic syndrome, lower eGFR levels, and elevated inflammatory markers compared to controls ($p<0.001$), confirming the systemic nature of the disease.

2) Both treatment regimens reduced uric acid levels, but combination therapy (Adenuric + curcumin) provided greater urate control by month 12: SUA 322±49 versus 356±54 μmol/L ($p<0.001$) and more frequent achievement of the target SUA level <360 μmol/L: 82.5% versus 67.9% ($p=0.018$).

3) Clinical control of gout with combination therapy was more pronounced: lower attack frequency over 12 months (0 [0;1] vs. 1 [0;2], $p=0.001$), higher proportion of patients with ≥50% reduction in attack frequency (84.5% vs. 70.8%, $p=0.020$) and lower pain intensity during an attack (VAS 2.3±1.2 vs. 3.1±1.4, $p<0.001$).

4) The combination regimen was accompanied by a more pronounced improvement in the immune-inflammatory profile to T3: the SII and CRP index were lower, and the IL-38 level was higher compared to Adenuric monotherapy (in all cases, $p<0.001$), indicating a more complete attenuation of systemic inflammation with strengthening of the regulatory link. 5) The 12-month UTI recurrence rate was lower with combination therapy (9.3% vs. 21.7%, $p=0.015$), and the need for antibiotic therapy was reduced ($p=0.019$). In a multivariate model, combination therapy maintained an independent protective effect (OR=0.38; 95% CI 0.16–0.89; $p=0.026$), with SII (risk ↑) and IL-38 (protection) being significant predictors of recurrence.

6) Prognostic tools calculated at T0 had clinically significant discriminatory ability for key outcomes at T3: OI-GOUT for ≥2 attacks/year (AUC=0.76; cut-off ≥20), ISI-GOUT for UTI recurrence (AUC=0.74; cut-off ≥900), and IL-38 for UTI recurrence (AUC=0.71; cut-off ≤45 pg/mL), which allows their use for early risk stratification.

7) The safety profile of combination therapy was comparable to monotherapy: the incidence of any adverse events and clinically significant reactions (including an increase in ALT/AST >3 ULN) did not differ between groups ($p>0.05$), and early flares at the start of urate-lowering therapy occurred with a comparable frequency ($p=0.67$).

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