The Role of Uric Acid and Gout in the Development of Osteoporosis

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Background

- Gout is an inflammatory arthritis caused by monosodium urate crystal deposition, typically driven by hyperuricemia.
- Osteoporosis is a bone disease that develops when bone mineral density and bone mass decreases, leading to decreased bone strength.
- There are conflicting evidence on the uric acid–bone health relationship:
  - Some studies suggest uric acid may act as an antioxidant, potentially protecting bone health.
  - Gout-related chronic inflammation may promote bone resorption and *accelerate* bone loss.
- Clarifying this relationship matters clinically, as it could inform earlier osteoporosis prevention and guide urate-lowering therapy (ULT) use.
- Prior studies show mixed results and focus largely on Asian and European populations, leaving a gap in U.S.-representative data.
- This study addresses this gap by examining the association between gout, serum uric acid levels, ULT use, and indicators of bone metabolism and inflammation in U.S. adults.

Objectives

This study aimed to:

• Evaluate the association between osteoporosis, gout and hyperuricemia among U.S. adults

• Assess the influence of urate-lowering therapy (ULT) on key bone-related biomarkers and systemic inflammatory markers.

Methods

Study Design

• An observational cohort study

Study Population

• NHANES 2013–2014 and 2017–2018 cycles, a nationally representative cross-sectional survey of non-institutionalized U.S. adults.

Inclusion Criteria

• Adults ≥20 years

Parameters

- Gout & osteoporosis – self-reported physician diagnosis using NHANES questionnaire
- Uric acid – serum uric acid (SUA) classified by sex-specific cutoffs; hyperuricemia defined as ≥7.0 mg/dL (males) / ≥6.0 mg/dL (females)
- ULT use – allopurinol, febuxostat, probenecid, or colchicine-probenecid combination

Outcomes

- Osteoporosis status and bone/inflammation biomarkers: Vitamin D, Calcium, Phosphorus, ALP, CRP, and SII
- Biomarkers analyzed as both continuous and categorical (low/normal/high) variables

Statistical Analysis

- Chi-square tests – osteoporosis status and biomarkers vs. gout status, uric acid levels, and ULT use.
- Independent t-tests – ULT use vs. continuous biomarkers.
- Statistical significance: $p < 0.05$.
- Analyses performed using IBM SPSS Complex Samples to account for NHANES survey weights.

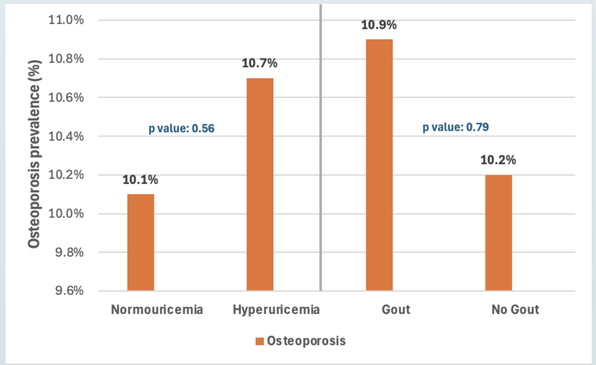
Results

Table 1: Sample Characteristics of the Study Cohort (categorical)

CHARACTERISTIC	COUNT (N)	PERCENTAGES (%)
	n= 11,338	
Age (years)		
20–39	3,641	32.1
40-64	4,891	43.1
≥65	2,806	24.7
Sex		
Male	5,460	48.2
Female	5,878	51.8
BMI		
<18.5	172	1.5
18.5- 24.9	2,834	25.0
25–29.9	3,435	30.3
30-39.9	3,365	29.7
≥40	889	7.8
Postmenopausal (women)		
Yes	1,627	14.3
Severe kidney disease		
Yes	39	0.3
HbA1c %		
< 5.7	6,079	53.6
5.7-6.4	2,986	26.3
≥ 6.5	1,345	11.9
PPI use	1,053	9.3

This table summarizes the demographic and clinical characteristics of adults included in the analytic sample. Variables presented include age distribution, sex, BMI categories, menopausal status among women, presence of severe kidney disease, HbA1c categories, and proton pump inhibitor (PPI) use.

Figure 1: Comparison of the prevalence of osteoporosis in patients with hyperuricemia vs normal uric acid levels and in gout vs. no gout



The figure compares osteoporosis prevalence between individuals with normouricemia vs. hyperuricemia and between those with gout vs. no gout. No significant differences were observed for either comparison (p = 0.564 for uric acid; p = 0.787 for gout).

Table 2: SUA Levels by Urate-Lowering Therapy (ULT) Use

ULT USE	NORMAL SUA (N) (%)	HYPERURICEMIA (N) (%)	P-VALUE
ULT	128 (80.2%)	50 (19.8%)	0.406
No ULT	874 (82.4%)	188 (17.6%)	

Normouricemia and hyperuricemia were compared between participants using urate-lowering therapy (ULT) and those not using ULT. No statistically significant difference in SUA levels was observed between groups (p = 0.406).

Results

Table 3: Continuous Biomarkers by ULT status

BIOMARKER	ULT GROUP (mean ± SE)	NO ULT GROUP (mean ± SE)	P VALUE (T test)
BONE HEALTH BIOMARKERS	n= 194	n= 11,144	
Vitamin D	86.5±4.5	71.3±1	**0**
Calcium	9.4±0.0	9.4±0.0	0.12
Phosphorus	3.6±0.0	3.7±0.0	**0.04**
ALP	76.9±2.3	71.1±0.5	**0.03**
INFLAMMATORY MARKERS			
CRP	6.1±1	3.9±0.2	0.05
SII	557.2±44.9	529.5±6.1	0.54
SUA	5.7±0.1	5.3±0.02	0.08

This table presents mean biomarker levels (± SE) for participants using urate-lowering therapy (ULT) compared with those not using ULT. ULT users had significantly higher Vitamin D and ALP levels and significantly lower phosphorus levels. They also exhibited higher CRP levels, indicating a greater systemic inflammatory burden. No significant differences were observed for calcium or SII.

Table 4: Categorical Biomarkers by ULT status

BIOMARKER	ULT GROUP (N) (%)	NO ULT GROUP (N) (%)	P VALUE (CHI SQUARE)
BONE HEALTH BIOMARKERS	n= 194	n= 11,144	
Vitamin D			**0.00**
Low Abnormal	38 (15.1%)	3025 (23.2%)	
Normal	122 (67.9%)	6718 (71.8%)	
High Abnormal	20 (17%)	425 (5%)	
Calcium			0.61
Low Abnormal	1 (0.3%)	68 (0.5%)	
Normal	173 (97.7%)	9811 (98.2%)	
High Abnormal	4 (2.1%)	156 (1.3%)	
Phosphorous			0.45
Low Abnormal	3 (0.8%)	102 (1%)	
Normal	165 (94.8%)	165 (92.2%)	
High Abnormal	10 (4.4%)	667 (6.8%)	
ALP			0.46
Low Abnormal	-	4 (0.1%)	
Normal	169(97.4%)	9903 (98.7%)	
High Abnormal	9 (2.6%)	156 (1.2%)	
INFLAMMATORY MARKERS			
CRP			**0.02**
Normal	78 (87.6%)	4430 (92.7%)	
Abnormal	22 (12.4%)	379 (7.3%)	
SII_CAT			1.00
Normal	109 (61.1%)	6500 (61.1%)	
Abnormal	69 (38.9%)	3725 (38.9%)	

This table presents biomarker categories (low abnormal, normal, high abnormal) for participants using urate-lowering therapy (ULT) compared with non-users. Significant differences were observed in Vitamin D and high-sensitivity CRP categories, with ULT users having fewer normal Vitamin D levels and a higher proportion of elevated CRP. No significant group differences were found for calcium, phosphorus, ALP, or the systemic immune-inflammation index (SII).

Discussion

Gout & Osteoporosis (Figure 1):

- Osteoporosis prevalence did not differ significantly between participants with gout and those without gout (10.9% vs 10.2%; $p = 0.79$).

Serum Uric Acid (SUA) & Osteoporosis (Figure 1):

- Hyperuricemia was not associated with osteoporosis (10.7% vs 10.1%; $p = 0.56$).

ULT & Biomarkers (Table 2&3):

- ULT use was associated with mixed effects on bone and inflammatory biomarkers.
- ULT users had higher Vitamin D, lower phosphorus, and higher ALP, possibly indicating altered bone turnover, though categorical analyses showed no consistent pattern.
- ULT users also had higher CRP levels, suggesting greater systemic inflammation. This likely reflects confounding by indication, as ULT users may have more severe gout rather than treatment-driven inflammation. Although CRP did not reach statistical significance, the finding was borderline significant and should be interpreted with caution.

Limitations

- NHANES is cross-sectional; causality cannot be established.
- ULT users likely have gout, so biomarker differences may reflect disease, not treatment.
- Diagnoses and ULT use rely on self-report, introducing recall bias and misclassification.
- The ULT subgroup is small, limiting statistical power.
- Findings may not generalize beyond the non-institutionalized U.S. population.
- Confounding variables and concomitant medications were not accounted for.
- Missing data were not addressed, which may reduce precision and accuracy.
- Biomarkers represent single time points and may not reflect long-term status.

Conclusion

- No significant association was found between osteoporosis and gout diagnosis or uric acid level.
- ULT use was associated with altered Vitamin D, ALP, phosphorus, and CRP levels, likely reflecting disease severity rather than medication effects.
- Overall, no significant association was observed between uric acid, gout, ULT use, and osteoporosis risk.

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