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Inflammatory–metabolic burden and its correlates in patients with gout: a case–control study

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ABSTRACT

Aims: To evaluate cumulative advanced glycation end product accumulation measured by skin autofluorescence (AGE-SAF) in patients with gout and to investigate its associations with inflammatory burden, renal function, metabolic parameters, and the C-reactive protein–albumin–lymphocyte (CALLY) index.

Methods: This cross-sectional case–control study included 45 patients with gout and 45 age- and gender-comparable healthy controls. AGE accumulation was assessed noninvasively using skin autofluorescence (AGE-SAF). Demographic, clinical, inflammatory, metabolic, and renal variables were recorded. Correlation analyses, subgroup comparisons, receiver operating characteristic (ROC) analysis, false discovery rate (FDR)-corrected analyses, and multivariable linear regression models were performed.

Results: Patients with gout had significantly higher AGE-SAF levels than healthy controls (2.46±0.69 vs. 1.83±0.24 AU, $p<0.001$). AGE-SAF correlated positively with age, annual attack frequency, serum creatinine, and C-reactive protein levels, and inversely with estimated glomerular filtration rate (eGFR), albumin, and the CALLY index. After FDR correction, these associations remained significant. In multivariable analyses, higher CRP levels and lower eGFR independently predicted higher AGE-SAF values. Patients with impaired renal function and hypertension exhibited significantly higher AGE-SAF levels. In an exploratory ROC analysis, AGE-SAF showed discrimination between patients with gout and healthy controls (AUC 0.846, 95% CI 0.765–0.927).

Conclusion: Patients with gout exhibited increased cumulative AGE accumulation measured by skin autofluorescence. The associations of AGE-SAF with inflammatory burden, renal dysfunction, and lower CALLY index values suggest that AGE-SAF may serve as a complementary biomarker reflecting cumulative inflammatory–metabolic burden in gout. Prospective longitudinal studies are warranted to validate these findings and determine their clinical significance.

Keywords: Gout, advanced glycation end products, skin autofluorescence, inflammation, renal function, CALLY index

INTRODUCTION

Gout is a chronic inflammatory crystal arthropathy characterized by monosodium urate crystal deposition, recurrent acute attacks, and a substantial systemic comorbidity burden.[1] Beyond episodic arthritis, gout is strongly associated with obesity, insulin resistance, hypertension, chronic kidney disease, and cardiovascular disease, suggesting that the disease may represent a complex inflammatory–metabolic disorder rather than isolated hyperuricemia alone.[1,2] Persistent low-grade inflammation, oxidative stress, endothelial dysfunction, and metabolic dysregulation are increasingly recognized as potential contributors to the broader systemic manifestations of gout.[3] Furthermore, urate-mediated oxidative stress and inflammasome activation may contribute to endothelial injury and chronic inflammatory signaling pathways involved in long-term tissue damage and cardiometabolic complications.

Advanced glycation end products (AGEs) are heterogeneous molecules generated through nonenzymatic glycation and oxidation reactions involving proteins, lipids, and nucleic acids.[4] AGE accumulation is accelerated under conditions characterized by chronic inflammation, oxidative stress, aging, renal dysfunction, and metabolic abnormalities.[5] Through activation of the receptor for advanced glycation end products (RAGE), AGEs may further enhance oxidative stress, vascular stiffness, endothelial dysfunction, and chronic inflammatory signaling.[6] Consequently, cumulative AGE burden has been proposed as a biomarker that may reflect long-term inflammatory and metabolic stress across several chronic diseases.[5,6] Nevertheless, AGE accumulation measured by skin autofluorescence (AGE-SAF) is influenced by multiple metabolic and renal factors and therefore should

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be interpreted as a marker of cumulative systemic burden rather than disease-specific inflammation alone.

AGE-SAF provides a practical and noninvasive method for estimating tissue AGE deposition.[7] Elevated AGE-SAF levels have been reported in diabetes mellitus, renal dysfunction, and chronic inflammatory conditions,[8-12] suggesting that AGE-SAF may reflect cumulative systemic stress rather than disease-specific inflammatory activity.

In parallel, composite inflammatory–nutritional indices have attracted increasing interest as accessible biomarkers reflecting multidimensional systemic involvement. The CRP–albumin–lymphocyte (CALLY) index integrates inflammatory, nutritional, and immunologic status into a single composite parameter.[13] Although initially developed in oncologic settings as a prognostic biomarker, recent studies suggest that the CALLY index may also have relevance in chronic inflammatory rheumatic diseases.[14,15] In primary Sjögren's syndrome, CALLY index levels were associated with disease activity and immunonutritional status.[14] Likewise, in ankylosing spondylitis, lower CALLY index values were associated with greater systemic inflammatory stress rather than patient-reported disease activity.[15] Because gout is characterized by concomitant inflammatory, metabolic, renal, and cardiovascular disturbances, multidimensional composite indices such as the CALLY index may provide broader systemic information than isolated inflammatory markers alone.

Therefore, the present study aimed to evaluate AGE-SAF levels in patients with gout and to explore their relationship with inflammatory, metabolic, renal, and immunonutritional parameters, particularly the CALLY index.

METHODS

This single-center, cross-sectional case–control study was conducted at the Department of Rheumatology, Bursa City Hospital, Bursa, Turkiye. The study was designed and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Consecutive patients attending routine outpatient follow-up visits were screened for eligibility. Healthy controls were recruited from hospital staff and community volunteers. Demographic, clinical, laboratory, and skin autofluorescence measurements were collected using standardized procedures during routine clinical evaluations and study visits. The study protocol was approved by the Bursa City Hospital Clinical Researches Ethics Committee (Date: 03.06.2026, Decision No: 9). Written informed consent was obtained from all participants prior to enrollment. The study was conducted in accordance with the principles of the Declaration of Helsinki. Following ethics committee approval, eligible patients and healthy controls were prospectively enrolled in the study, and AGE-SAF measurements were performed according to the predefined study protocol. Clinical and laboratory variables were obtained from routinely collected clinical data and existing medical records generated as part of standard clinical care; no additional blood sampling or laboratory testing was performed specifically for research purposes.

Adult patients aged between 18 and 80 years who fulfilled the 2015 American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) classification criteria for gout were eligible for inclusion. All patients were regularly followed at the rheumatology outpatient clinic and provided written informed consent before participation. Patients with active infection, active malignancy, pregnancy, breastfeeding, severe dermatological conditions affecting skin autofluorescence measurements, or inability to provide informed consent were excluded. Healthy controls were recruited from hospital staff and community volunteers without known chronic comorbidities, gout, or inflammatory rheumatic disease and without evidence of active infection at the time of assessment. Laboratory parameters were not systematically collected in the healthy control group because no additional blood sampling was performed for research purposes. Smoking and alcohol consumption were also not systematically assessed in controls. Consequently, the CALLY index could not be calculated for the control group. To reflect a real- world gout population, patients with common comorbidities such as hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, and chronic kidney disease were not excluded. A total of 45 patients with gout and 45 healthy controls were included in the final analysis.

Despite the substantial inflammatory and metabolic burden associated with gout, data regarding cumulative tissue AGE accumulation in this population remain limited. To our knowledge, no previous study has simultaneously evaluated tissue AGE accumulation and the CALLY index in patients with gout. Clarifying these relationships may improve understanding of the cumulative inflammatory–metabolic milieu associated with gout beyond conventional clinical assessment.

Demographic and clinical characteristics were recorded for all participants, including age, gender, height, weight, and body-mass index (BMI). For patients with gout, additional disease-related variables were collected, including disease duration, number of gout attacks during the previous 12 months, medication use, total medication count, and comorbidities such as hypertension, diabetes mellitus, coronary artery disease, and hyperlipidemia. Polypharmacy was defined as the concurrent use of five or more medications.

Routine laboratory measurements were performed in the central laboratory of Bursa City Hospital using automated analyzers according to the manufacturers' instructions and standard laboratory procedures. Laboratory parameters included serum creatinine, uric acid, C-reactive protein (CRP), albumin, lymphocyte count, glycated hemoglobin (HbA1c), triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and total cholesterol levels. Complete blood count parameters, including lymphocyte count, were measured using an automated hematology analyzer (Sysmex XN-9100, Sysmex Corporation, Kobe, Japan). CRP concentrations were determined by an immunoturbidimetric method using a Roche Cobas c703 analyzer (Roche Diagnostics, Mannheim, Germany). Serum

albumin was measured using the bromocresol green method. Total cholesterol and triglyceride levels were determined using enzymatic colorimetric assays, HDL cholesterol was measured by a direct polymer–polyanion method, and LDL cholesterol was measured using a direct assay on the Roche Cobas c703 platform. Serum creatinine was measured using the alkaline picrate method standardized to isotope dilution mass spectrometry (IDMS). HbA1c was measured by high-performance liquid chromatography (HPLC) using an Adams HA-8180V analyzer (Arkray Menarini, Kyoto, Japan). All laboratory analyses were performed according to the manufacturers' instructions and routine internal quality-control procedures of the central laboratory. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The triglyceride-to-HDL cholesterol ratio (TG/HDL) was calculated as a marker of metabolic risk. CALLY index was calculated using the following formula: albumin (g/L)×lymphocyte count (/μL) divided by CRP (mg/L)×10^4. Higher CALLY index values were considered indicative of a more favorable inflammatory–nutritional profile.

Tissue accumulation of AGE-SAF measured with the AGE Reader™ device (DiagnOptics Technologies BV, Groningen, The Netherlands). Measurements were performed on the volar surface of the dominant forearm according to the manufacturer's recommendations under standardized environmental conditions. All AGE-SAF measurements were performed by the same investigator (A.G.) following a predefined measurement protocol to minimize inter-observer variability. For each participant, three consecutive measurements were obtained, and the mean value was used for statistical analyses. AGE-SAF results were expressed in arbitrary units (AU).

The primary outcome of the study was the difference in AGE-SAF levels between patients with gout and healthy controls. Secondary outcomes included the associations between AGE-SAF and inflammatory markers, renal function parameters, metabolic variables, annual attack frequency, polypharmacy status, and the CALLY index.

Because data regarding tissue AGE accumulation assessed by skin autofluorescence in gout are currently scarce, the present study should be considered exploratory and hypothesis-generating. The study included 45 patients with gout and 45 healthy controls and was intended to provide preliminary evidence regarding the relationship between AGE-SAF, inflammatory burden, renal function, and the CALLY index. Confirmation of these findings in larger multicenter prospective cohorts is warranted.

Several measures were undertaken to minimize potential sources of bias. Consecutive patient recruitment was used to reduce selection bias, while healthy controls were selected from the same geographical region. AGE-SAF measurements were performed according to a standardized protocol, and the average of three consecutive measurements was used in all analyses. Potential confounding variables, including age, gender, BMI, renal function, and major cardiometabolic comorbidities, were assessed and considered during statistical analyses. Furthermore, multivariable regression models were constructed to evaluate independent associations while adjusting for clinically relevant covariates. Nevertheless, because of the cross-sectional design, residual confounding cannot be completely excluded, and causal inferences cannot be established.

Statistical Analysis

The data analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). The distribution of continuous variables was assessed using histograms, Q–Q plots, and the Shapiro–Wilk test. Normally distributed variables are presented as mean±standard deviation, whereas non-normally distributed variables are presented as median (minimum–maximum). Categorical variables are presented as frequencies and percentages. Comparisons between groups were performed using the independent-samples t-test or Mann–Whitney U test, as appropriate, while categorical variables were compared using the Chi-square test or Fisher's exact test. Correlations between continuous variables were assessed using Spearman's rank correlation coefficient. Variables demonstrating clinical relevance or significant associations in univariable analyses were entered into multivariable linear regression models to identify independent factors associated with AGE-SAF levels. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the discriminative performance of AGE-SAF for differentiating patients with gout from healthy controls. Because multiple correlation and subgroup analyses were performed, false discovery rate (FDR) correction using the Benjamini–Hochberg procedure was applied as a sensitivity analysis to reduce the risk of type I error. No participant had missing data for the primary outcome (AGE-SAF). As no formal a priori sample size calculation was performed, a post hoc power analysis was conducted for the primary outcome based on the observed difference in AGE-SAF between the gout and control groups. Using the observed group means and standard deviations (2.46±0.69 vs. 1.83±0.24 AU), the corresponding standardized effect size was Cohen's d=1.22. With 45 participants per group and a two-sided α level of 0.05, the achieved statistical power for the primary comparison was >99%. All statistical tests were two-sided, and a p value <0.05 was considered statistically significant.

RESULTS

A total of 45 patients with gout and 45 healthy controls were included in the analysis. There were no statistically significant differences between the groups regarding age (59.62±13.88 vs. 56.78±5.43 years, p=0.088), gender distribution (female/male: 20/25 vs. 22/23, p=0.833), or height (165.09±10.31 vs. 166.60±9.04 cm, p=0.597). However, patients with gout had significantly higher body weight (84.69±17.83 vs. 76.76±13.99 kg, p=0.036) and BMI values (31.13±6.51 vs. 27.56±4.12 kg/m^2, p=0.015). AGE-SAF levels were significantly higher in the gout group than in the control group (2.46±0.69 vs. 1.83±0.24 AU, p<0.001) (**Table 1**). The post hoc power for the primary AGE-SAF comparison between the gout and control groups was >99%.

Table 1. Demographic characteristics of the gout and control groups

Variable	Gout group (n=45)	Control group (n=45)	p
Age, years	59.62±13.88; 61.00 (26–80)	56.78±5.43; 55.00 (50–74)	0.088
Female/male	20/25	22/23	0.833
Height, cm	165.09±10.31; 165.00 (140–183)	166.60±9.04; 167.00 (150–182)	0.597
Weight, kg	84.69±17.83; 87.00 (47–128)	76.76±13.99; 75.00 (44–100)	0.036
BMI, kg/m²	31.13±6.51; 29.86 (20.89–45.90)	27.56±4.12; 27.97 (17.58–35.55)	0.015
AGE-SAF, AU	2.46±0.69; 2.40 (1.30–4.60)	1.83±0.24; 1.90 (1.30–2.20)	<0.001

BMI: Body-mass index, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AU: Arbitrary unit

The mean disease duration among patients with gout was 3.13±3.17 years, while the median number of gout attacks during the previous 12 months was 2 (range: 0–4). The mean total medication count was 7.04±2.96, and polypharmacy (≥5 medications) was present in 80.0% of patients. Hypertension was the most common comorbidity (86.7%), followed by coronary artery disease (35.6%), hyperlipidemia (24.4%), and diabetes mellitus (22.2%). Impaired renal function defined as eGFR <60 ml/min/1.73m² was observed in 26.7% of patients, while elevated creatinine levels (>1.2 mg/dl) and HbA1c levels (≥6.5%) were present in 28.9% and 20.0% of the cohort, respectively (Table 2).

Table 2. Clinical characteristics of patients with gout

Parameter	Patients with gout (n=45)
Disease duration, years	3.13±3.17; 2 (1–17)
Number of attacks during the last 12 months	1.51±1.01; 2 (0–4)
Total medication count	7.04±2.96; 7 (0–13)
Polypharmacy (≥5 medications)	36 (80.0%)
Diabetes mellitus	10 (22.2%)
Hypertension	39 (86.7%)
Coronary artery disease	16 (35.6%)
Hyperlipidemia	11 (24.4%)
Smoking	14 (31.1%)
Alcohol consumption	4 (8.9%)
eGFR <60 ml/min/1.73m²	12 (26.7%)
Elevated creatinine (>1.2 mg/dl)	13 (28.9%)
HbA1c ≥6.5%	9 (20.0%)

eGFR: Estimated glomerular filtration rate, HbA1c: Glycated hemoglobin A1c

The mean creatinine level in patients with gout was 1.12±0.81 mg/dl, and the mean eGFR value was 74.47±25.19 ml/min/1.73m². The mean serum uric acid level was 5.73±1.86 mg/dl. The median CRP level was 3.09 mg/L, with a wide range from 0.50 to 100.00 mg/L, indicating heterogeneous inflammatory burden. The mean HbA1c level was 5.99±0.85%, while the mean triglyceride and HDL levels were 175.42±103.94 mg/dl and 46.36±11.02 mg/dl, respectively. The mean TG/HDL ratio was 4.21±3.58. The mean CALLY index was 49.09±49.86, and the mean AGE-SAF level was 2.46±0.69 AU (Table 3).

Table 3. Laboratory characteristics of patients with gout

Parameter	Patients with gout (n=45)
Serum creatinine (mg/dl)	1.12±0.81; 0.98 (0.52–5.93)
eGFR (ml/min/1.73m²)	74.47±25.19; 77.20 (7.40–118.00)
Uric acid (mg/dl)	5.73±1.86; 5.40 (2.20–11.00)
CRP (mg/L)	8.54±16.30; 3.09 (0.50–100.00)
Albumin (g/L)	43.88±3.78; 43.50 (33.30–53.00)
Lymphocyte count (10³/μL)	2.07±0.89; 1.97 (0.50–5.80)
HbA1c (%)	5.99±0.85; 5.80 (4.50–9.61)
Triglycerides (mg/dl)	175.42±103.94; 148.00 (74.00–581.00)
HDL (mg/dl)	46.36±11.02; 48.00 (24.90–68.00)
LDL (mg/dl)	112.52±37.99; 108.00 (53.00–215.00)
Total cholesterol (mg/dl)	193.76±51.27; 181.00 (113.00–347.00)
TG/HDL ratio	4.21±3.58; 3.25 (1.25–23.33)
CALLY index	49.09±49.86; 27.50 (0.33–174.19)
AGE-SAF (AU)	2.46±0.69; 2.40 (1.30–4.60)
Total medication count	7.04±2.96; 7.00 (0.00–13.00)

eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, CALLY: C-reactive protein–albumin–lymphocyte, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AU: Arbitrary unit

Correlation analyses demonstrated significant positive correlations between AGE-SAF and age (r=0.459, p=0.002), number of attacks during the previous 12 months (r=0.387, p=0.009), serum creatinine (r=0.387, p=0.009), and CRP (r=0.497, p<0.001). In contrast, AGE-SAF showed significant inverse correlations with eGFR (r=−0.518, p<0.001), albumin (r=−0.412, p=0.005), and the CALLY index (r=−0.485, p<0.001). No statistically significant correlations were observed between AGE-SAF and disease duration (p=0.353), uric acid (p=0.788), HbA1c (p=0.207), triglycerides (p=0.123), HDL (p=0.186), LDL (p=0.584), total cholesterol (p=0.527), or the TG/HDL ratio (p=0.478) (Table 4).

Patients with hypertension demonstrated significantly higher AGE-SAF levels compared with normotensive patients (2.55±0.69 vs. 1.88±0.29 AU, p=0.013). Similarly, patients with polypharmacy had significantly elevated AGE-SAF levels compared with patients without polypharmacy (2.57±0.70 vs. 2.01±0.46 AU, p=0.040). Although AGE-SAF levels tended to be higher in patients with diabetes mellitus and frequent attacks, these differences did not reach statistical significance (p=0.193 and p=0.084, respectively). No statistically significant associations were observed between AGE-SAF levels and coronary artery disease, hyperlipidemia, HbA1c ≥6.5%, or smoking status (Table 5).

ROC analysis demonstrated that AGE-SAF had good discriminative performance for differentiating patients with gout from healthy controls, with an area under the curve (AUC) of 0.846 (95% CI: 0.765–0.927, p<0.001). The optimal cut-off value for AGE-SAF was identified as 2.30 AU, yielding a sensitivity of 62.2% and a specificity of 100.0%. Because the cut-off and performance estimates were derived from the same relatively small case–control sample without independent validation, these findings should be considered exploratory (Table 6).

Table 4. Correlation analyses between AGE-SAF and clinical/laboratory parameters in patients with gout

Parameter	Spearman r	p
Age	0.459	0.002
Disease duration (years)	0.142	0.353
Number of attacks during the last 12 months	0.387	0.009
Total medication count	0.281	0.061
Serum creatinine (mg/dl)	0.387	0.009
eGFR (ml/min/1.73m²)	-0.518	<0.001
Uric acid (mg/dl)	-0.041	0.788
CRP (mg/L)	0.497	<0.001
Albumin (g/L)	-0.412	0.005
Lymphocyte count (10³/µL)	-0.119	0.437
HbA1c (%)	0.192	0.207
Triglycerides (mg/dl)	0.233	0.123
HDL (mg/dl)	-0.201	0.186
LDL (mg/dl)	0.084	0.584
Total cholesterol (mg/dl)	0.097	0.527
TG/HDL ratio	-0.109	0.478
CALLY index	-0.485	<0.001

AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, CALLY: C-reactive protein–albumin–lymphocyte

Table 5. Comparison of AGE-SAF levels according to clinical characteristics in patients with gout

Clinical characteristic	AGE-SAF mean±SD; median (min–max)	p
Diabetes mellitus		0.193
No	2.38±0.63; 2.30 (1.3–4.6)	
Yes	2.74±0.86; 2.70 (1.7–4.6)	
Hypertension		0.013
No	1.88±0.29; 1.90 (1.3–2.3)	
Yes	2.55±0.69; 2.50 (1.4–4.6)	
Coronary artery disease		0.513
No	2.41±0.67; 2.40 (1.3–4.6)	
Yes	2.58±0.76; 2.50 (1.7–4.5)	
Hyperlipidemia		0.441
No	2.41±0.66; 2.40 (1.3–4.6)	
Yes	2.61±0.79; 2.50 (1.5–4.5)	
Polypharmacy (≥5 medications)		0.040
No	2.01±0.46; 2.00 (1.3–3.0)	
Yes	2.57±0.70; 2.50 (1.4–4.6)	
HbA1c ≥6.5%		0.776
No	2.44±0.68; 2.40 (1.3–4.6)	
Yes	2.54±0.80; 2.50 (1.7–4.5)	
Frequent attacks (≥3/year)		0.084
No	2.34±0.61; 2.30 (1.3–4.0)	
Yes	2.83±0.86; 2.80 (1.8–4.6)	
Smoking		0.236
No	2.39±0.66; 2.40 (1.3–4.6)	
Yes	2.66±0.77; 2.60 (1.5–4.5)	

AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, SD: Standard deviation, Min: Minimum, Max: Maximum, HbA1c: Glycated hemoglobin A1c

Table 6. Receiver operating characteristic (ROC) analysis of AGE-SAF for differentiating patients with gout from healthy controls

Outcome	AUC (95% CI)	Cut-off	Sensitivity	Specificity	p
Gout vs. healthy controls	0.846 (0.765-0.927)	2.30 AU	62.2%	100.0%	<0.001

AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AUC: Area under the curve, CI: Confidence interval, AU: Arbitrary unit

In the unadjusted analysis, patients with gout demonstrated significantly higher AGE-SAF levels compared with healthy controls (β=0.63, 95% CI: 0.42–0.84, p<0.001). This association remained significant after adjustment for age and gender (β=0.58, 95% CI: 0.37–0.79, p<0.001). Further adjustment for BMI slightly attenuated the association; however, AGE-SAF levels continued to be significantly higher in the gout group (β=0.46, 95% CI: 0.21–0.71, p=0.002). These findings suggest that the observed increase in AGE-SAF levels among patients with gout was not solely explained by demographic characteristics or obesity-related differences between the groups (Table 7).

Table 7. Confounder-adjusted comparison of AGE-SAF levels between patients with gout and healthy controls

Adjustment model	Adjusted β	95% CI	p
Unadjusted model	0.63	0.42 to 0.84	<0.001
Age- and gender-adjusted model	0.58	0.37 to 0.79	<0.001
Age-, gender-, and BMI-adjusted model	0.46	0.21 to 0.71	0.002

AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, CI: Confidence interval, BMI: Body-mass index

After Benjamini–Hochberg FDR correction, the correlations between AGE-SAF and CRP, eGFR, CALLY index, age, albumin, attack frequency, and creatinine levels remained statistically significant. In contrast, associations involving TG/HDL ratio, HbA1c, and uric acid levels were not statistically significant after correction for multiple testing (Table 8).

Table 8. False discovery rate (FDR)-corrected correlation analyses for AGE-SAF

Analysis	Raw p	FDR-q	Status
AGE-SAF–CRP	<0.001	0.0035	Significant
AGE-SAF–eGFR	<0.001	0.0035	Significant
AGE-SAF–CALLY	<0.001	0.0049	Significant
AGE-SAF–age	0.002	0.0075	Significant
AGE-SAF–albumin	0.009	0.0196	Significant
AGE-SAF–attack frequency	0.009	0.0287	Significant
AGE-SAF–serum creatinine	0.009	0.0287	Significant
AGE-SAF–TG/HDL	0.478	0.547	Not significant
AGE-SAF–HbA1c	0.207	0.266	Not significant
AGE-SAF–uric acid	0.788	0.788	Not significant

AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin A1c, HDL: High-density lipoprotein, TG: Triglyceride, CALLY: C-reactive protein–albumin–lymphocyte

A parsimonious multivariable linear regression model including CRP, eGFR, and age was constructed to identify factors independently associated with AGE-SAF. The overall model was statistically significant (p<0.001) and explained

40.5% of the variance in AGE-SAF levels (R^2=0.405; adjusted R^2=0.361). Higher CRP levels (B=0.015, standardized β=0.364, 95% CI: 0.005 to 0.026, p=0.006) and lower eGFR values (B=−0.009, standardized β=−0.322, 95% CI: −0.017 to −0.001, p=0.028) were independently associated with higher AGE-SAF levels. Age was not independently associated with AGE-SAF (B=0.010, standardized β=0.207, 95% CI: −0.004 to 0.025, p=0.168) (Table 9).

Table 9. Parsimonious multivariable linear regression analysis of factors associated with AGE-SAF in patients with gout

Variable	B	Standardized β	95% CI	p
CRP, mg/L	0.015	0.364	0.005 to 0.026	0.006
eGFR, ml/min/1.73 m²	−0.009	−0.322	−0.017 to −0.001	0.028
Age, years	0.010	0.207	−0.004 to 0.025	0.168

Model R^2=0.405; adjusted R^2=0.361; overall model p<0.001. AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein

In an exploratory analysis, AGE-SAF levels differed across renal function categories (Kruskal–Wallis p=0.011), with higher levels observed in patients with greater renal impairment (Table 10). Given the small number of patients in the more severe renal dysfunction categories, this finding should be interpreted cautiously.

Table 10. Exploratory comparison of AGE-SAF levels across renal function categories

Renal function category	n	AGE-SAF mean±SD; median (min–max)	p
eGFR >60 ml/min/1.73m²	33	2.34±0.60; 2.30 (1.3–4.0)	
eGFR 30–60 ml/min/1.73m²	10	2.74±0.66; 2.70 (1.8–4.2)	0.011*
eGFR <30 ml/min/1.73m²	2	3.25±1.20; 3.25 (2.4–4.1)	

* Kruskal–Wallis test. AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, SD: Standard deviation, Min: Minimum, Max: Maximum, eGFR: Estimated glomerular filtration rate

Correlation analyses demonstrated significant negative correlations between the CALLY index and age (r=−0.353, p=0.017), annual attack frequency (r=−0.383, p=0.009), CRP levels (r=−0.959, p<0.001), and AGE-SAF levels (r=−0.485, p<0.001). In contrast, positive correlations were observed between the CALLY index and albumin levels (r=0.521, p<0.001) as well as lymphocyte count (r=0.353, p=0.017). No statistically significant correlations were detected between the CALLY index and disease duration, renal function parameters, uric acid, HbA1c, lipid parameters, or TG/HDL ratio (Table 11).

To further explore whether this association persisted after accounting for age, gender, and BMI, a partial correlation analysis was performed. The inverse relationship between AGE-SAF and the CALLY index remained statistically significant after adjustment (partial r=−0.364, p=0.014), indicating that the association was not solely explained by differences in age, gender, or adiposity (Supplementary Table S1).

In an exploratory analysis, patients with lower CALLY index values had significantly higher AGE-SAF levels than those with higher CALLY index values (2.74±0.77 vs. 2.19±0.50 AU, p=0.004) and also had greater annual attack frequency.

Table 11. Correlation analyses between CALLY index and clinical/laboratory parameters in patients with gout

Parameter	Spearman r	p
Age	−0.353	0.017
Disease duration (years)	0.089	0.562
Number of attacks during the last 12 months	−0.383	0.009
Total medication count	−0.093	0.545
Serum creatinine (mg/dl)	−0.108	0.478
eGFR (ml/min/1.73m²)	0.197	0.195
Uric acid (mg/dl)	0.065	0.673
CRP (mg/L)	−0.959	<0.001
Albumin (g/dl)	0.521	<0.001
Lymphocyte count (10^3/μL)	0.353	0.017
HbA1c (%)	−0.116	0.446
Triglycerides (mg/dl)	0.168	0.269
HDL (mg/dl)	0.139	0.363
LDL (mg/dl)	0.018	0.909
Total cholesterol (mg/dl)	0.062	0.687
TG/HDL ratio	0.109	0.476
AGE-SAF (AU)	−0.485	<0.001

eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, CALLY: C-reactive protein–albumin–lymphocyte, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AU: Arbitrary unit

Supplementary Table S1. Correlation between AGE-SAF and the CALLY index before and after adjustment for age, gender, and body mass index in patients with gout

Analysis	Correlation coefficient	p
Spearman correlation (AGE-SAF vs CALLY)	-0.485	<0.001
Partial correlation (adjusted for age, gender, BMI)	-0.364	0.014

CALLY: C-reactive protein–albumin–lymphocyte, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, BMI: Body-mass index

Patients in the low-CALLY group were older, whereas renal function parameters tended to be less favorable without reaching statistical significance. No significant differences were observed in HbA1c, TG/HDL ratio, or BMI between the groups (Table 12). Differences in CRP, albumin, and lymphocyte count were not interpreted as independent findings because these variables are mathematical components of the CALLY index.

In an exploratory analysis, patients in the low-CALLY group had higher AGE-SAF levels and greater annual attack frequency than those in the high-CALLY group (Table 13).

Distribution of AGE-SAF levels in patients with gout and healthy controls.

Box plots demonstrate median values, interquartile ranges, whiskers, and individual observations. Patients with gout exhibited significantly higher AGE-SAF levels compared with healthy controls (p<0.001) (Figure 1).

In an exploratory ROC analysis, AGE-SAF showed discrimination between patients with gout and healthy controls within the present study sample, with an AUC of

Table 12. Comparison of clinical and laboratory characteristics according to CALLY index categories in patients with gout

Variable	Low CALLY group	High CALLY group	p
AGE-SAF (AU)	2.74 ± 0.77	2.19 ± 0.50	0.004
Age (years)	63.1 ± 11.9	56.2 ± 14.7	0.048
Number of attacks during last 12 months	1.9 ± 1.0	1.2 ± 0.8	0.011
CRP (mg/L)	17.6 ± 21.4	1.9 ± 1.6	<0.001
Albumin (g/L)	41.9 ± 3.6	45.7 ± 2.8	<0.001
Lymphocyte count (10^3/μL)	1.78 ± 0.74	2.34 ± 0.95	0.026
Creatinine (mg/dl)	1.25 ± 1.03	0.99 ± 0.42	0.214
eGFR (ml/min/1.73m²)	68.3 ± 27.4	80.9 ± 21.5	0.072
HbA1c (%)	6.10 ± 0.94	5.86 ± 0.73	0.318
TG/HDL ratio	4.58 ± 3.96	3.86 ± 3.21	0.441
BMI (kg/m²)	31.9 ± 6.8	30.3 ± 6.1	0.382
Polypharmacy (%)	90.9%	69.6%	0.081

(CALLY groups categorized according to the median CALLY value: 27.50), eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin A1c, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, TG: Triglyceride, CALLY: C-reactive protein–albumin–lymphocyte, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AU: Arbitrary unit, BMI: Body-mass index

Table 13. Exploratory multivariable linear regression model for CALLY index in patients with gout

Variable	B	Standardized β	95% CI	p
AGE-SAF (AU)	−18.42	−0.371	−33.85 to −2.98	0.021
Age (years)	−0.61	−0.248	−1.19 to −0.03	0.039
eGFR (ml/min/1.73m²)	0.29	0.214	−0.02 to 0.61	0.067
Number of attacks during last 12 months	−6.84	−0.236	−13.96 to 0.28	0.059
BMI (kg/m²)	−0.48	−0.063	−2.01 to 1.05	0.529
Total medication count	−1.12	−0.071	−4.37 to 2.13	0.492

Model characteristics R^2=0.382 Adjusted R^2=0.291 Overall model p=0.004. CALLY: C-reactive protein–albumin–lymphocyte, CI: Confidence interval, eGFR: Estimated glomerular filtration rate, AGE-SAF: Advanced glycation end product accumulation measured by skin autofluorescence, AU: Arbitrary unit, BMI: Body-mass index

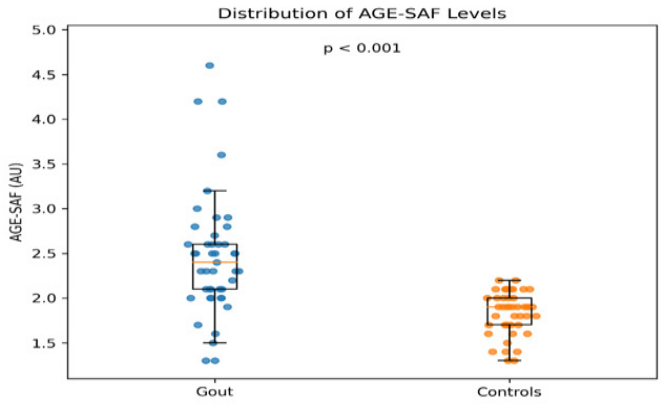


Figure 1. AGE-SAF gout vs control
AGE-SAF: Advanced glycation end product skin autofluorescence, AU: Arbitrary unit

0.846. A threshold of 2.30 AU, derived from the same dataset using the Youden index, yielded a sensitivity of 62.2% and a specificity of 100%. Because the threshold and performance estimates were derived from the same relatively small case–control sample without independent validation, these findings should be interpreted as exploratory and do not establish diagnostic utility (Figure 2).

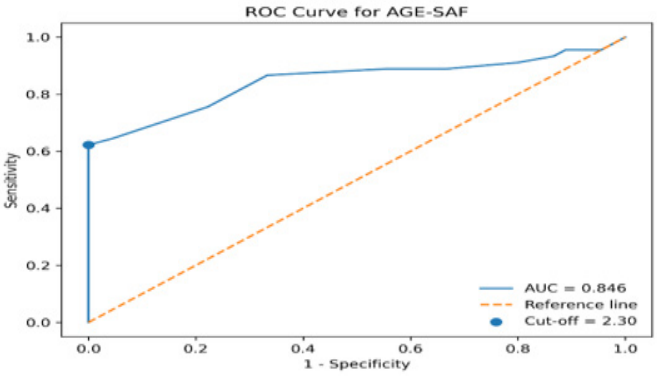


Figure 2. ROC curve
ROC: Receiver operating characteristic, AGE-SAF: Advanced glycation end product skin autofluorescence, AUC: Area under the curve

Higher AGE-SAF values were associated with lower CALLY index scores (Spearman r=−0.485, p<0.001), indicating a relationship between cumulative AGE accumulation and a less favorable inflammatory–nutritional profile. This association is illustrated in Figure 3.

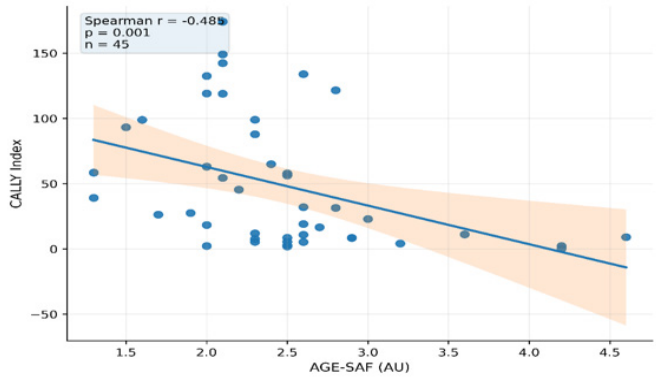


Figure 3. Association between AGE-SAF and the CALLY index in patients with gout
Scatter plot illustrating the relationship between skin autofluorescence-derived advanced glycation end product accumulation (AGE-SAF) and the C-reactive protein–albumin–lymphocyte (CALLY) index in patients with gout. Each point represents an individual participant. The solid line represents the fitted regression model, and the shaded area indicates the 95% confidence interval. Higher AGE-SAF values were associated with lower CALLY index scores (Spearman r=−0.485, p<0.001). The regression line is presented for visualization purposes only, whereas correlation coefficients were calculated using Spearman rank correlation analysis. AGE-SAF: Advanced glycation end product skin autofluorescence, CALLY: C-reactive protein–albumin–lymphocyte index, AU: Arbitrary unit

DISCUSSION

The present cross-sectional STROBE-compliant study evaluated tissue AGE-SAF in patients with gout and investigated its associations with inflammatory, renal, metabolic, and immunonutritional parameters. The principal findings were as follows: (i) patients with gout demonstrated significantly higher AGE-SAF levels than healthy controls; (ii) AGE-SAF was positively associated with inflammatory burden, annual attack frequency, and impaired renal function; (iii) lower CALLY index values were associated with higher AGE-SAF levels; (iv) CRP and eGFR remained independently associated with AGE-SAF in multivariable analyses; and (v) the association between gout and elevated AGE-SAF persisted after adjustment for age, gender, and BMI. Collectively, these findings suggest that tissue AGE accumulation may reflect the

cumulative inflammatory and metabolic burden associated with gout rather than isolated hyperuricemia alone.

Gout has traditionally been considered a crystal-induced inflammatory arthritis; however, increasing evidence supports its characterization as a complex inflammatory–metabolic disorder associated with obesity, insulin resistance, chronic kidney disease, endothelial dysfunction, and increased cardiovascular risk.[1-3] AGE–RAGE signaling has been implicated in oxidative stress and inflammatory pathways in experimental and clinical studies; however, the cross-sectional design of the present study does not allow assessment of these mechanistic or causal relationships.[6] In the present study, patients with gout demonstrated markedly higher AGE-SAF levels than healthy controls, supporting the hypothesis that cumulative AGE accumulation may represent an integrated marker of long-term inflammatory and metabolic stress in gout. Although BMI values were significantly higher in patients with gout than in healthy controls, the association between gout and elevated AGE-SAF remained significant after adjustment for age, sex, and BMI, suggesting that the observed difference in AGE-SAF may not be explained by obesity alone, although residual confounding by renal, inflammatory, metabolic, and other unmeasured factors cannot be excluded.

The observed relationship between AGE-SAF and inflammatory burden further supports this concept. AGE-SAF correlated positively with CRP and annual attack frequency, while inverse correlations were observed with serum albumin and the CALLY index. Furthermore, CRP remained independently associated with AGE-SAF in multivariable analyses. These associations may reflect links among inflammatory activity, oxidative stress, and AGE accumulation; however, the cross-sectional nature of the study precludes conclusions regarding directionality or underlying mechanisms.[4-6] Although gout attacks are episodic, many patients experience persistent low-grade inflammation between attacks, which may contribute to cumulative tissue AGE deposition over time.

Another important finding of the study was the strong relationship between AGE-SAF and renal function. AGE-SAF correlated positively with serum creatinine and inversely with eGFR, while patients with impaired renal function demonstrated significantly higher AGE-SAF levels. Moreover, eGFR remained independently associated with AGE-SAF in the adjusted regression model. Renal dysfunction is a well-recognized determinant of AGE accumulation because reduced renal clearance contributes to retention of AGE precursors and circulating AGE products.[10] Previous studies in renal disease populations have similarly demonstrated increased AGE-SAF levels among individuals with impaired kidney function.[10] Given the bidirectional relationship between gout and chronic kidney disease, the observed findings likely reflect the combined effects of inflammation, metabolic abnormalities, and impaired AGE clearance. Although age demonstrated a significant positive correlation with AGE-SAF in univariable analyses, its association did not remain statistically significant in the adjusted regression model. This finding suggests that inflammatory and renal factors may explain a substantial proportion of age-related AGE accumulation in patients with gout. Therefore, the observed increase in AGE-SAF appears unlikely to be attributable solely to chronological aging and may instead reflect the cumulative effects of disease-related inflammatory and metabolic burden.

One of the most noteworthy findings of the present study was the inverse association between AGE-SAF and the CALLY index. The CALLY index integrates inflammatory, nutritional, and immune-related components into a single composite parameter and has recently attracted attention as a multidimensional biomarker in chronic inflammatory diseases.[13,14] In the present cohort, lower CALLY values were associated with higher AGE-SAF levels, and this association remained significant after correction for multiple testing. Because CRP, albumin, and lymphocyte count are incorporated into the CALLY formula, associations between CALLY and its individual components should be interpreted cautiously. Therefore, particular attention should be paid to relationships between CALLY and external variables such as AGE-SAF, annual attack burden, renal function, and clinical characteristics. This finding indicates that the observed AGE-SAF–CALLY association persisted after adjustment for these demographic and anthropometric factors; however, it does not establish an independent biological relationship because of the mathematical dependence of CALLY on its components.

Previous studies have also suggested a potential role for the CALLY index as a marker of systemic inflammatory burden in rheumatic diseases. Bircan et al.[14] reported associations between the CALLY index and disease activity and immunonutritional status in primary Sjögren's syndrome. Similarly, lower CALLY values were associated with greater objective inflammatory burden in ankylosing spondylitis[15] and with higher attack burden and inflammatory markers in familial Mediterranean fever.[16] Although these observations provide contextual support for studying CALLY in inflammatory rheumatic diseases, differences in disease mechanisms and study populations preclude broad generalization, and the specific clinical relevance of CALLY in gout remains to be established.

Interestingly, AGE-SAF was not significantly associated with serum uric acid levels. This observation suggests that tissue AGE accumulation may reflect the long-term inflammatory and metabolic consequences of gout rather than current urate concentrations alone. Similar findings have been reported in other chronic inflammatory diseases, where AGE accumulation appears to reflect cumulative disease burden rather than isolated laboratory measurements.[11,12] This observation supports the concept that AGE-SAF may provide information complementary to conventional biochemical markers routinely used in the management of gout. Another possible explanation for the lack of association between AGE-SAF and serum uric acid is that most patients were receiving routine rheumatologic care and likely undergoing urate-lowering therapy. Consequently, a single serum uric acid measurement may not adequately reflect cumulative urate exposure over time, whereas AGE-SAF may better capture the long-term consequences of chronic inflammatory and metabolic stress. Because information regarding specific

urate-lowering therapies, treatment duration, and treatment adherence was unavailable, the potential influence of treatment-related factors on AGE-SAF could not be evaluated and warrants further investigation. Furthermore, AGE-SAF was associated with hypertension, whereas the relationship with polypharmacy did not remain significant after correction for multiple testing and should therefore be considered exploratory. These findings support the concept that AGE-SAF may function as a global indicator of cumulative cardiometabolic and inflammatory stress.

Hypertension was another factor associated with higher AGE-SAF levels, and this relationship remained significant after correction for multiple testing. Previous studies have suggested that AGE accumulation contributes to vascular stiffness, endothelial dysfunction, and adverse cardiovascular remodeling through AGE–RAGE signaling pathways.[4-6] Given the remarkably high prevalence of hypertension in the present cohort, the observed association may further support the role of AGE-SAF as a marker of cumulative cardiovascular and metabolic burden. These findings are particularly relevant because cardiovascular disease represents one of the major contributors to morbidity and mortality among patients with gout.[1-3]

Another clinically relevant observation was the tendency toward higher AGE-SAF levels among patients with polypharmacy. Although the association did not remain statistically significant after correction for multiple testing, patients receiving five or more medications demonstrated numerically higher AGE-SAF levels than those without polypharmacy. Polypharmacy is highly prevalent in gout because of the frequent coexistence of hypertension, chronic kidney disease, diabetes mellitus, obesity, and cardiovascular disease.[1-3] In the present cohort, the mean medication count exceeded seven medications per patient, and 80% of patients fulfilled the definition of polypharmacy, highlighting the substantial comorbidity burden associated with gout. Furthermore, several medications commonly prescribed in patients with gout, particularly diuretics and low-dose aspirin, may influence urate homeostasis and have been associated with an increased risk of gout flares.[1-3] Therefore, the observed relationship between AGE-SAF and polypharmacy may reflect the cumulative impact of multimorbidity, treatment burden, and chronic metabolic stress rather than medication exposure alone.

The association between AGE-SAF and annual attack frequency further supports the concept that tissue AGE accumulation may reflect cumulative disease burden. AGE-SAF demonstrated a significant positive correlation with the number of attacks during the previous year, and this association remained significant after FDR correction. Moreover, patients with lower CALLY values experienced more frequent attacks, and individuals in the low-CALLY subgroup exhibited significantly higher AGE-SAF levels than those with higher CALLY values. These findings suggest a potential biological continuum linking recurrent inflammatory activity, deterioration of inflammatory–nutritional status, and cumulative AGE accumulation. Recurrent gout attacks are characterized by intense activation of innate immune pathways, oxidative stress, and inflammatory cytokine production, all of which may contribute to AGE formation and tissue deposition over time.[4-6] In this regard, AGE-SAF may provide complementary information regarding the long-term consequences of recurrent inflammatory activity rather than merely reflecting current disease status.

From a clinical perspective, AGE-SAF should not currently be regarded as a diagnostic marker for gout or as a replacement for conventional measures such as serum urate, CRP, or renal function. Rather, its noninvasive nature and ability to reflect tissue AGE accumulation may offer complementary information regarding cumulative systemic burden,[7,8] particularly in patients with recurrent inflammatory activity, renal impairment, or cardiometabolic comorbidities.[5,10] If validated prospectively, serial AGE-SAF measurements could potentially contribute to patient stratification and longitudinal assessment of disease burden. However, whether AGE-SAF predicts clinically relevant outcomes such as future flares, renal deterioration, cardiovascular events, or treatment response remains unknown and should be evaluated in prospective longitudinal studies.

Limitations

Several limitations should be acknowledged. First, the cross-sectional design precludes causal inference regarding the relationships between AGE-SAF and inflammatory or renal parameters. Second, the study was conducted at a single center and included a relatively modest sample size, limiting the generalizability of the findings. Third, although major confounding variables were considered in multivariable analyses, residual confounding cannot be completely excluded. Fourth, AGE-SAF is influenced by multiple metabolic and renal factors and therefore should not be interpreted as a disease-specific marker of gout activity. Information regarding cumulative urate burden, monosodium urate crystal volume, duration of urate-lowering therapy, and treatment adherence was not systematically collected and therefore could not be incorporated into the analyses. In addition, laboratory parameters required to characterize renal function, systemic inflammation, and the CALLY index were not systematically available for healthy controls, and smoking and alcohol consumption were not systematically assessed in this group. Therefore, residual differences in renal, inflammatory, metabolic, or lifestyle factors between the groups cannot be excluded, and the higher AGE-SAF observed in patients with gout should not be interpreted as a gout-specific effect. Furthermore, because the CALLY index could not be calculated in controls, CALLY-related findings should be interpreted as exploratory within-cohort associations among patients with gout rather than evidence that the CALLY index differs between patients with gout and healthy individuals. The recruitment of controls from hospital staff and community volunteers may also have introduced healthy-volunteer selection bias and limited external generalizability. Finally, despite the application of FDR correction, the exploratory nature of several subgroup and correlation analyses warrants cautious interpretation.

Despite these limitations, the study also has important strengths. To our knowledge, this is among the first studies to investigate tissue AGE accumulation and its relationship with the CALLY index in patients with gout. The inclusion of healthy controls, standardized AGE-SAF measurements, detailed assessment of inflammatory, renal, metabolic, and cardiovascular parameters, and the application of multivariable and FDR-corrected analyses provide a comprehensive evaluation of cumulative disease burden in this population. Furthermore, the simultaneous evaluation of AGE-SAF, CALLY index, annual attack burden, renal function, polypharmacy, and cardiometabolic comorbidities allowed a multidimensional assessment of gout burden that has rarely been investigated previously. In addition, all AGE-SAF measurements were performed by a single trained investigator using a standardized protocol and averaged across three consecutive measurements, thereby minimizing measurement variability.

CONCLUSION

Patients with gout exhibited significantly higher tissue AGE accumulation, as measured by skin autofluorescence, compared with healthy controls. Increased AGE-SAF levels were associated with higher inflammatory burden, impaired renal function, greater annual attack frequency, hypertension, and lower CALLY index values. These findings suggest that AGE-SAF may reflect the cumulative consequences of chronic inflammation, metabolic dysregulation, renal impairment, and comorbidity burden in gout rather than current urate levels alone.

The observed inverse relationship between AGE-SAF and the CALLY index, together with the association between lower CALLY values and higher attack burden, suggests that these measures may capture different aspects of cumulative systemic burden in patients with gout. However, these exploratory associations require confirmation in larger prospective studies.

Although AGE-SAF demonstrated good discrimination between patients with gout and healthy controls in the present study, these findings should be interpreted cautiously because the study was not designed to evaluate AGE-SAF as a diagnostic tool. Rather than serving as a disease-specific diagnostic marker, AGE-SAF may provide complementary information regarding cumulative inflammatory, metabolic, renal, and cardiovascular burden in patients with gout. Future longitudinal studies are warranted to determine whether AGE-SAF predicts clinically relevant outcomes such as cardiovascular events, renal deterioration, flare frequency, treatment burden, and therapeutic response.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study protocol was approved by the Bursa City Hospital Clinical Researches Ethics Committee (Date: 03.06.2026, Decision No: 9).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights—including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: A.G., T.D.; Design: A.G., T.D.; Supervision: A.G., T.D.; Data Collection and/or Processing: A.G., T.D.; Analysis and/or Interpretation: A.G., T.D.; Literature Search: A.G.; Writing–Original Draft: A.G.; Writing–Review & Editing: T.D.; Project Administration: A.G. All authors participated in the design, execution, and analysis of the study, read and approved the final version of the manuscript.

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