

Analysis of the Relationship of Serum Ferritin, Urate, and Some Hematological Parameters with Disease Activity in Gout Patients

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Abstract

Background and objectives: Gout is a type of arthritis. Acute gout is a common rheumatological disease that mostly affects first metatarsopharyngeal joint. Chronic gout is the condition that characterized by repeated episodes of acute gout. The objective of this study was to further explore the relationship between iron, ferritin, and other hematological markers with serum urate and gout.

Methods: This cross sectional study was conducted in the Department of Rheumatology of Rizgary Teaching Hospital, Erbil, and Northern Iraqi Kurdistan. A total of 85 cases were enrolled in this study, 76 males and 9 females. Their mean age (SD) was 46.6 (± 11.2) years. All participants were known to have gout and fulfilled the criteria for diagnosis of gout. Serum ferritin, C-reactive protein, Serum iron, total iron binding capacity, and serum urate level were measured in addition to renal function tests and liver function tests were measured.

Results: The mean (SD) for urate was 9.04 (± 1.16) mg/dL, 76 (89.4%) patients with high serum uric acid had high level of ferritin in the blood meanwhile; 9 patients have normal ferritin level. There was a significant positive correlation (76 out of 85 patients) between serum ferritin level and serum urate ($p < 0.005$ and $\rho = 0.237$). A positive correlation was found between C reactive protein and urate level, in contrast there was no correlation of iron level and urate level.

Conclusion: The ferritin and C reactive protein levels were significantly high among gouty patients.

Keywords: Arthritis, Ferritin, Gout, Inflammatory Markers.

Introduction: Ferritin is regarded as a storage form of iron which is a non-toxic substance.

Urate is an end result of the purine catabolism in humans.

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In some hyperuricemic patients, excess level of serum urate level ($> 6.8\text{mg/dl}$) can lead to accumulation of monosodium urate mono hydrate(MSU) crystals in the joint cavity specially meta tarsopharyngeal joint of the foot (monoarthritis) but any joint can be involved(polyarthritis specially in the female patient in post-menopausal period) with a gout arising due to an body response through the innate immune system response.¹ Urate acts as a chelator agent for the iron and thus in turn, the iron can affect the activity of the enzyme named xanthine oxidase and the production of urate.² Indeed, the ferritin has a strong relationship with the serum uric acid in both the US National Health and Nutrition Examination Survey (NHANES)³ and the China Health and Nutrition Survey⁴ with elevation in serum uric acid indicated of iron overload.⁵ Iron could precipitate the attack of gout disease by producing an inflammation which lead to formation complexes with MSU crystals, such a complex lead to stimulating oxidative stress through the generation of reactive oxygen species, and thus contributing to the granulocyte and complement activation.⁶ An improvement of the gout flares and severity after repeat blood donation in order to attain the near iron-deficient levels in hyperuricemic patients is also has a role in gout.⁷

Food is the primary source of iron, providing heme and nonheme iron through animal and plant sources, respectively. Diet is an important source of purines. Interestingly, purine-rich foods from an animal-based diet have been linked with flaring of multiple gout attacks while purine-rich foods from a

plant-based diet are not.^{8,9} These observations, combined with the other observational and intervention data, are consistent with the hypothesis that iron in purine-rich foods, e.g. red meat, could be a risk factor for gout and increase frequency.^{3,5,7}

The aim of this study is to know the association of the serum ferritin and serum iron, total iron binding capacity and other inflammatory markers with the serum urate and activity of the gouty patients.

Patients and method:

In this prospective study, 85 patients with gout were conveniently enrolled while visiting the outpatient clinic of the Department of Rheumatology at Rizgari Teaching Hospital in Erbil starting from the February 2022- August 2022, Iraqi Kurdistan Region. Verbal consent was obtained from the patients; the study was approved by Kurdistan Higher Council of Medical Specialties at December 2021. Patients were with diagnosed when fulfilling the Rome criteria of gout⁸ to be diagnosed with gout, patients must meet 2 of the following 4 criteria: a serum uric acid level $>7\text{ mg/dL}$ in men or $>6\text{ mg/dL}$ in women; the presence of tophi; the presence of MSU crystal tissues; and a history of painful joint swelling with abrupt onset and remissio Gouty patients with chronic renal failure or chronic liver disease were not included to this study. In addition, patients on steroids, non-steroidal anti-inflammatory, colchicine, iron supplements and immune suppressive drugs for the last two weeks were excluded



The enrolled patients were interviewed and clinically examined. Body mass index was calculated according to patient's height and weight. Venous blood was obtained from the patients for subsequent hematological and biochemical tests. In addition to complete blood counts, serum levels of urate, C-reactive protein (CRP), iron, ferritin, and iron binding capacity were measured using Cobas C111, Roche, Germ. Statistical analysis was done using Statistical Package for the Social Sciences (SPSS version 25). Numerical variables were expressed as mean (SD). Chi square test and Fisher's exact test were used to compare proportions.

Student's t test of two independent samples was used to compare means of two samples. A p value of ≤ 0.05 was considered statistically significant.

Results:

In this study, 85 patients with gout were studied; 76 (89.4%) were male and 9 (10.6%) were female and such a discrepancy among sex ratio related to rarity of the disease among female. Their age ranged between 26 and 69 years with a mean of 46.6 (± 11.2). Table (1) presents the patients age, gender and BMI. Acute joint swellings were observed in 56 (65.9%) patients.

Table (1): General patients' characteristics.

	No.	(%)
Age		
< 40	26	(30.6)
40-49	23	(27.1)
50-59	22	(25.9)
60-69	14	(16.5)
Mean (SD)	46.6	(11.2)
Gender		
Male	76	(89.4)
Female	9	(10.6)
BMI categories		
Normal weight (18_25)	2	(2.4)
Over-weight (26_29)	52	(61.2)
Obese (>29)	31	(36.5)
Mean (SD) (Kg/m ²)	29	(2.4)
Joint swelling		
No	29	(34.1)
Yes	56	(65.9)
Total	85	(100.0)

The laboratory parameters of the enrolled patients are illustrated in Table (2). The

means of Hb, WBC and platelets were 14.5 (± 1.7) g/dL for male and 12.1(± 1.7)



g/dL for female, for WBC $9.88 \times 10^3/\mu\text{L}$ ($\pm 2.93 \times 10^3/\mu\text{L}$) in which WBC ($>10000/\text{cubic mm}$) were regarded as leucocytosis and ($<3500/\text{cubic mm}$) as a leucopenia, and for platelets $309 \times 10^3/\mu\text{L}$ ($\pm 119 \times 10^3/\mu\text{L}$) in which platelet count ($>450000/\text{microlitre}$) were

regarded as thrombocytosis and ($<150000/\text{microlitre}$) as a thrombocytopenia. Anemia was observed in 10 (11.8%) of patients, leukocytosis was found in 34 (40%) of patients, and thrombocytosis was noted in 22 (25.9%) of patients.

Table (2): Laboratory parameters of gouty patients.

	No.	(%)
Hemoglobin		
Low	10	11.8
Normal	69	81.2
High	6	7.1
Mean (SD) (g/dL)	14.5	1.7
WBC		
Normal	51	60.0
High	34	40.0
Mean (SD) ($\times 10^3/\mu\text{L}$)	9.88	2.93
Platelets		
Normal	63	74.1
High	22	25.9
Mean (SD) ($\times 10^3/\mu\text{L}$)	309.9	119
CRP		
Normal	9	10.6
High	76	89.4
Mean (SD) (mg/L)	52	100
Ferritin		
Normal	9	10.6
High	76	89.4
Mean (SD) (ug/L)	743.8	254.4
Iron		
Normal	63	74.1
High	22	25.9
Mean (SD) (mg/dL)	121.4	46.7
TIBC		
Low	5	5.9
Normal	77	90.6
High	3	3.5
Mean (SD) (ug/dL)	309	97.1
Total	85	100.0



The mean serum ferritin level was 743.8 ug/L; 76 patients (89.4%) had elevated serum ferritin level. There was a positive

correlation between serum uric acid level and serum ferritin ($r=0.237$; $p=0.029$) as shown in Table (3) and Figure (1).

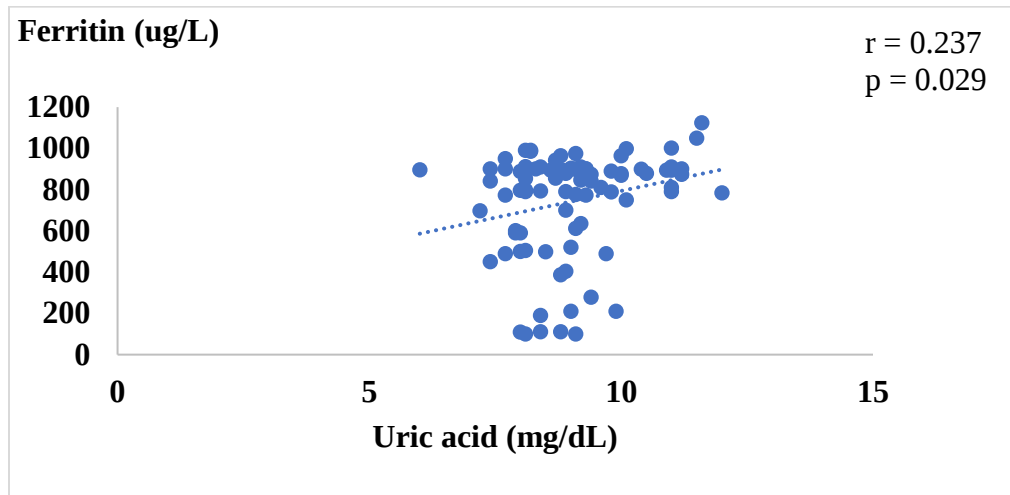


Figure (1): Correlation between serum urate and serum ferritin

There was a significant correlation between CRP and serum uric acid as shown in Figure (2) and Table (3).

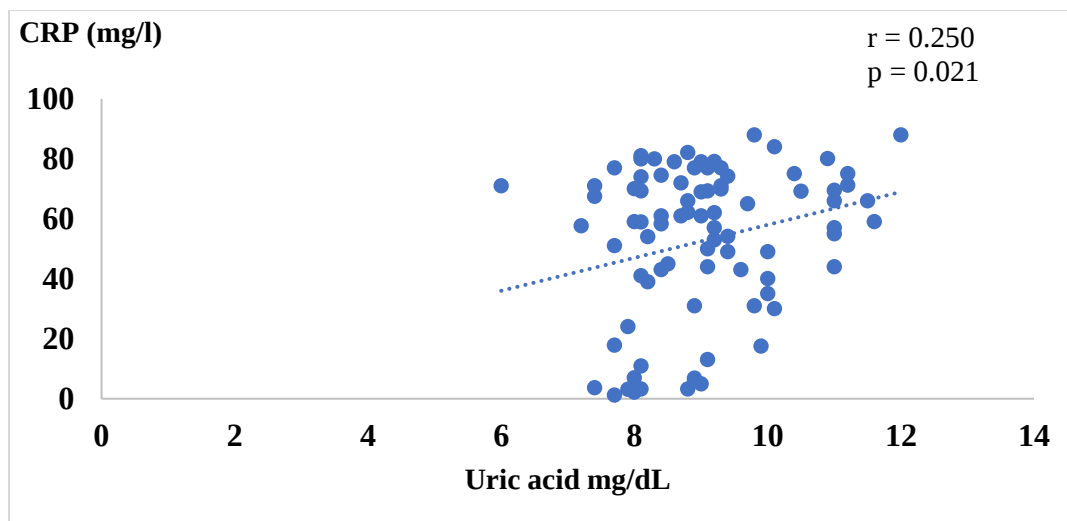


Figure (2): Shows correlation between serum urate and CRP level



Table (3) shows the association of serum uric acid with iron, ferritin and TIBC. There was no significant association

between serum urate and serum iron and TIBC. A significant association was noted with serum ferritin and CRP level.

Table (3): Correlation between serum uric acid with iron, ferritin and TIBC.

	r	(p)
CRP	0.250	0.021
Ferritin	0.237	0.029
Iron	0.094	0.392
TIBC	0.056	0.613

No significant association was detected between uric acid levels and transferrin saturation ($p = 0.304$). Table (4).

Table (4): Transferrin saturation by uric acid levels.

	Transferrin saturation				
	Low	Normal	High		
Uric acid	No. (%)	No. (%)	No. (%)	Total	P*
Low	0 (0.0)	0 (0.0)	1 (100.0)	1 (100.0)	
Normal	0 (0.0)	1 (100.0)	0 (0.0)	1 (100.0)	0.304
High	2 (2.4)	70 (84.3)	11 (13.3)	83 (100.0)	
Total	2 (2.4)	71 (83.5)	12 (14.1)	85 (100.0)	

It is evident in the figure that there was no significant correlation between uric acid

values and transferrin saturation% values ($r = -0.022$, $p = 0.839$).

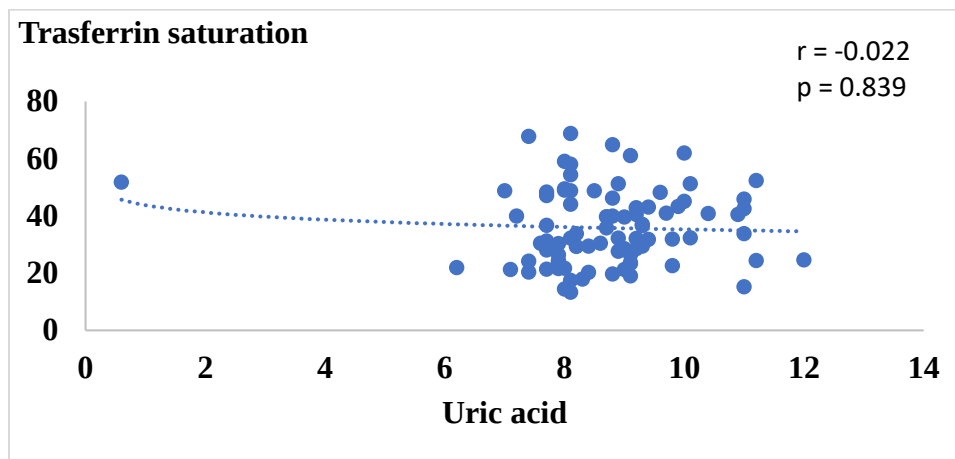


Figure (3). Correlation between serum uric acid and transferrin saturation.

Discussion:

Gout is a common hyperuricaemic metabolic condition that leads to painful inflammatory arthritis and a high comorbidity burden, especially cardiometabolic-renal conditions, including hypertension, myocardial infarction, stroke, obesity, hyperlipidemia, type 2 diabetes mellitus and chronic kidney disease.¹⁰ Ferritin is an acute phase reactant and is potentially higher in any infective or inflammatory process, making its careful interpretation necessary in such situations.¹¹

In the current study, 76 (89.4%) cases were male while 9 (10.6%) were female; this is because gout is more common among males.¹² The hematological parameters of Hb level, WBC count, and platelet count showed no significant differences among gouty patients. Two cases (2.4%) had normal BMI (BMI 18-24), 52 (61.2%) others were overweight (BMI 25-29), and 31 (36.5%) cases were obese (BMI > 30). There was no statistically significant correlation between BMI and serum uric acid (p value = 0.563, $r = -0.064$). This is contrary

to the result of a previous study done by Hutchinson who reported a significant relation between BMI and serum urate level.¹³

In this study we found that 76 (89.4%) cases have a high serum ferritin and the remaining 9 (10.6%) cases had normal serum ferritin; this result is in accordance with other studies done by Alenezi and Fatima.^{14, 15} The relationship between serum ferritin and uric acid predicts hyperuricemia since the ferritin level acts as an acute inflammatory marker and also it may reflect the iron stored level in gouty patients with excess iron level so such association related to the inflammatory process and excess iron level. Such an increase of the uric acid level with an elevation of the ferritin level may reflect a response of the host to diminish the oxidative stress presented by available metal as the uric acid assumes the empty or loosely bound coordination sites of the iron to diminish electron transport and subsequent oxidant generation. It is recognized that urate react with an iron molecule forming a



molecule that resist oxidative stress and then inhibit iron metabolism, so lead to decrease metabolism of iron through such oxidative enzymes.¹⁶

In the current cohort, 76 (89.4%) patients with gout had high CRP level; there was a positive correlation between uric acid level and CRP level. ($p = 0.021$, $r = 0.25$). This result agrees with previous studies done by Badir and Onat.^{17, 18} The higher level of CRP among gouty patients is regarded as an inflammatory marker which shows a relationship between serum uric acid and CRP.¹⁹

No relation between serum iron and TIBC were found with serum uric acid. This is contrary to two previous studies done by Khan and Ghio who showed a high serum iron among gouty patients.^{20, 21} The explanation for our result may be related to inducing inflammatory cascade that led to reduce iron level.²²

In this study we found that 71 gouty patients(83.5%) have normal transferrin saturation, 12 gouty patients(14.1%) have high transferrin saturation and 2 gouty patients(2.4%) have low transferrin saturation, there was a non-significant association between transferrin saturation and serum uric acid (p value_0.304) this is in contrary to Jeremy who showed a relationship between transferrin saturation and uric acid which may be related to the inflammatory cascade activation which lead to low iron level and in turn low transferrin saturation.²³

Conclusion:

There was a significant association between serum ferritin and CRP among gouty patients. Serum ferritin had a role in gout flare.

Conflict of interest:

None.

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