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The relationship between Biochemical and Immunological parameters and their effect on gout patients

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Abstract

Background: Gout is thought to be an autoinflammatory illness because monosodium urate (MSU) crystals trigger the activation of NLRP3 inflammasome, which in turn triggers caspase-1 to release active cytokines. Yet, it is still unclear how blood cytokine levels relate to the symptoms and clinical indicators of the illness. The serum levels of Interleukin-6 (IL-6), Adiponectin (ADP), C-Reactive Protein (CRP), and Uric Acid (UA) were examined, and their relationship with clinical and laboratory findings was discussed.

Methods: ELISA was used to determine the clinical, laboratory, and cytokine levels of 80 male and female gout patients (gout group). The study also included 70 individuals without a history of arthritis for comparison.

Results: On analysis, 80 out of the 150 individuals had gout arthritis. Uric Acid, IL-6, and CRP concentrations were all noticeably more prevalent in patients than in the control group ($P < 0.001$). Furthermore, ADP levels in patients were considerably lower than those of the control group ($P < 0.001$) as well. The present results were examined for age, gender, and body mass index (BMI).

Conclusion: High mean levels of UA, CRP, and IL-6, in both male and female gouty patients, as well as low mean values of ADP, were discovered when biochemical parameters were evaluated. As a result, UA, IL-6, ADP, and CRP are concluded to be significant markers for the development of gout-related comorbidities and are key gout predictors.



Introduction

Gout is a notable cause of significant public health with a direct impact on individuals' health and quality of life [1], with a prevalence ranging from 1 to 4 percent in different populations [2,3]. The pathophysiological process is characterised by high serum uric acid (sUA) concentrations, either due to reduced excretion of uric acid (70–90%) or enhanced uric acid production (10–30%) [4]. Gout is responsible for intense inflammation of joints and arthritic pain, which significantly impairs the patient's quality of life [5,6]. Gout's management is additionally complicated by a frequent co-existence of high blood pressure, cardiovascular disease, stroke, and chronic renal disease, influencing both progression of disease and choice of treatment [7].

The pathogenesis of gout is still complicated, yet it's mainly characterized by deposition of crystal monosodium urate (MSU) into joints, tendons, cartilage, and soft tissues, which evokes an inflammatory process. Hyperuricemia, indicated by a sUA level greater than 7.0 mg/dL, is the prevailing factor for gout development [8]. In experimental studies, it has been indicated that injury to a tissue causes the release of endogenous alarm signals promoting inflammation [9]. Notably, uric acid (UA) causes human mononuclear cells to release interleukins, including the inflammation-related protein interleukin-6 (IL-6) [10].

IL-6 is a cytokine that encourages inflammation and regulates the production of acute-phase proteins, all contributing to body defense against inflammation [11]. Its generation could be initiated by exposure of synoviocytes and monocytes to UA, which further accelerates the process of inflammation and even causes damage and destruction of joints and bones [12,13]. Interestingly, IL-6 has a number of characteristics that are similar to interleukin-1 (IL-1), which is also an inflammatory cytokine, such as being able to induce fever and the synthesis of acute-phase proteins [14,15].

Besides IL-6, adipokines, including adiponectin (ADP), were shown to play an important role in regulating urate levels and gout development [16,17]. Adiponectin is a cytokine produced by adipose tissue that regulates systemic inflammation, metabolism, and immune responses [18,19]. Adiponectin has been suggested by evidence to affect gout by regulating inflammation pathways and preventing the state of inflammation attendant upon hyperuricemia [20].

In addition, based on in vitro studies, UA enters vascular smooth muscle cells, triggering a pro-inflammatory response which leads to an increase in cell proliferation and production of inflammatory mediators, including CRP [21]. C-reactive protein (CRP) is among the best-characterized serum proteins used as

a measure of inflammation. It rises to 1000-fold during an inflammatory state like gout [22]. CRP is synthesized by the liver upon stimulation by cytokines, such as IL-6, and correlates with the number of joints affected by gout. CRP starts rising within 4–6 hours of the inciting inflammatory event and peaks at 48–72 hours [23].

The interaction of sUA levels with IL-6 production has been clearly established by earlier literature [24]. The available evidence implicates high uric acid levels with increased production of IL-6 by human mononuclear cells, which, in turn, augments inflammation. The relationship highlights the importance of comprehending the interaction among such biomarkers in individuals with gout.

The purpose of the present research is to assess serum concentrations of IL-6, adiponectin (ADP), CRP, and uric acid (UA) among patients with gout and examine their relationships. Second, it intends to link these biomarkers with clinical and laboratory values and contrast them with a control population without gout. Through the assessment of such biomarkers, an understanding of the pathophysiological processes of inflammation occurring with gout and hints towards potential target points for treatments can be acquired.

Methods

The investigation included the collection of 150 samples from Al-Hussein Teaching Hospital and specialty clinics, Thi-Qar, Iraq, from August 2021 until September 2022 (80 for patients with gout and 70 for controls). The age range for participants was 20–94 years in each group. For the diagnosis of the presence of gout among patients, blood samples of 150 individuals were collected, 80 of whom were diagnosed with gout and 70 were not. Every participant had a comprehensive clinical examination. Table 1 lists the participants' ages and numbers.

Groups	Age (years)	Number of patients in each group
Gout Patients	< 35 years	40
	35–49 years and	30
	50–64 years	
	> 65 years	10
Controls	20 - 44	50
	45 - 69	10
	70 - 94	10

Table 1: The age and quantity of the groups under study.

Measurements

This study used a Roche/Hitachi Cobas C311 system to detect blood uric acid levels, which automatically calculates the analyte concentration of each sample, and CRP levels were detected using CRP-LATEX (Germany–Japan) methods. Additionally, commercially available ELISA kits were utilized to assess the quantities of IL-6 and adiponectin (ADP), using kits from Sunlong Biotech and the Bioassay Technology

Laboratory (BT LAB) in accordance with the manufacturer's directions.

Results

Clinical and Characteristic Features of the Studied Groups

Figure 1A shows the current study, which includes 150 participants who were stratified for age (20-94 years) and BMI (normal weight, Overweight, and Obese). The patient group consisted of 80 individuals (57 males and 23 females), and the control group consisted of 70 healthy individuals, and their effect on all parameters was discussed.

Serum uric acid levels in healthy controls and gout patients

In Table 2, Figure 1B. According to the current findings, the mean sUA levels in gout patients were 10.23 ± 1.44 mg/dL versus 5.50 ± 1.21 mg/dL in healthy control participants, a substantially higher level ($P < 0.001$).

Comparison of CRP (Inflammatory Biomarker) levels between gout patients and healthy people

The mean serum CRP levels were 47.21 ± 36.56 mg/L and 7.25 ± 1.11 mg/L, as shown by Figure 1C and Table 2. It was observed that gout patients have a substantially greater CRP level than healthy individuals ($P < 0.001$) when comparing the two groups of people.

Immunological Analysis

Serum IL-6 levels in healthy controls and gout patients

In Table 2 and Figure 1D, mean serum IL-6 levels observed were 13.97 ± 10.11 ng/L and 5.18 ± 1.46 ng/L in patients with gout and healthy controls. It was observed that patients suffering from gout have a notably high serum IL-6 level in contrast to healthy individuals ($P < 0.001$).

Serum ADP concentrations in gout and non-gout test subjects

The mean levels of serum ADP in gout and non-gout subjects were 8.98 ± 3.0 mg/L and 16.63 ± 3.09 mg/L, as depicted in Table 2 and Figure 1E. It was observed that serum ADP in gout patients was significantly lower than that of the healthy control group ($P < 0.001$).

The Effect of Age on Studied Parameters

In the current study, the effect of the age factor was taken into account. Four age groups of participants in this study were created, as illustrated in Table 3A. By comparing patient outcomes across age groups, no considerable difference was identified.

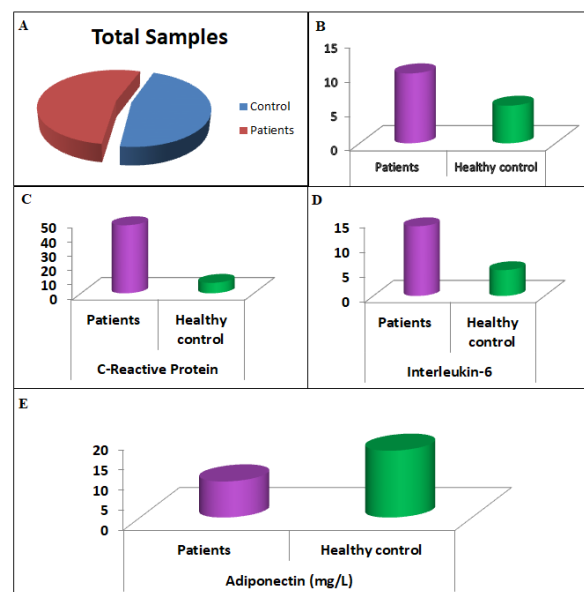


Figure 1: A: Total sample (80 patients and 70 control), B: Mean levels of parameter (UA) according to study groups, C: Mean levels of parameter (CRP) according to study groups, D: Mean levels of parameter (IL-6) according to study groups, E: Mean levels of parameter (ADP) according to study groups.

Mean ± SD and Range	Case-control comparison		P
	Patients n = 80	Healthy control n = 70	
UA (mg/dL)			
Mean ± SD	10.23 ± 1.44	5.50 ± 1.21	< 0.001 † HS
Range	7.80 - 13.40	3.50 - 7.50	
CRP (mg/L)			
Mean ± SD	47.21 ± 36.56	7.25 ± 1.11	< 0.001 † HS
Range	10.0 - 192.0	5.00 - 9.00	
Interleukin-6 (ng/L)			
Mean ± SD	13.97 ± 10.11	5.18 ± 1.46	< 0.001 † HS
Range	7.23 - 56.38	2.76 - 8.41	
Adiponectin (mg/L)			
Mean ± SD	8.98 ± 3.0	16.63 ± 3.09	< 0.001 † HS

Table 2: Mean levels of parameters UA, CRP, IL6, and ADP according to study groups.

SD: standard deviation, n: number of cases, HS: Highly significant at $P \leq 0.001$, †: independent samples t-test

Mean Levels of Parameters (UA, CRP, IL-6, ADP) according to Age Groups

The current findings demonstrate that the mean sUA levels in patients in the age range of 35 to 49 years were non-significantly higher than the mean serum uric acid levels in other groups, as shown in Table 3A, which displayed the mean sUA levels probability value to be $P = 0.910$. Mean levels of serum CRP were 48.00 ± 39.43 mg/L, 63.86 ± 60.41 mg/L, 42.14 ± 33.42 mg/L, and 44.15 ± 33.26 mg/L. Patients in the age group 35-49 years exhibited higher mean CRP concentrations compared to the rest. However, the result was not significant ($P = 0.192$). Regarding mean serum IL-6 levels, they were 21.23 ± 15.94 ng/L, 13.31 ± 9.10 ng/L, 13.60 ± 10.29 ng/L, and 13.04 ± 8.43 ng/L for patients under 35, 35-49, 50-64, and over 65 years old, respectively. Patients in the age group under 35 had

higher mean levels than those in the other age groups, but the difference was not statistically significant ($P = 0.341$). Also, mean levels of serum ADP for age groups like the previously mentioned were 8.03 ± 2.90 mg/L, 8.93 ± 2.97 mg/L, 9.44 ± 2.95 mg/L, and 8.52 ± 3.20 mg/L. Patients aged 50 to 64 had higher mean levels than other age groups, but the difference ($P = 0.585$) was not statistically significant.

The Effect of Gender on Studied Parameters

The gender factor was considered in the present research work; two gender groups of participants were created, as illustrated in Table 3B. The significant difference was determined by comparing each group's results to those of the corresponding control group.

Cytokine levels	A: Age group comparison				P value
	< 35 years n = 40	35-49 years n = 14	50-64 years n = 37	> 65 years n = 22	
UA (mg/dL)					
Mean $\pm$ SD	10.20 $\pm$ 1.63	10.43 $\pm$ 1.57	10.11 $\pm$ 1.34	10.28 $\pm$ 1.56	0.910 $\uparrow$ NS
Range	8.90 - 12.70	7.90 - 12.50	7.80 - 12.60	7.90 - 13.40	
CRP (mg/L)					
Mean $\pm$ SD	48.00 $\pm$ 39.43	63.86 $\pm$ 60.41	42.14 $\pm$ 33.42	44.15 $\pm$ 33.26	0.192 $\uparrow$ NS
Range	12.0 - 96.0	10.00 - 192.00	11.0 - 192.0	11.50 - 192.0	
Interleukin-6 (ng/L)					
Mean $\pm$ SD	21.23 $\pm$ 15.94	13.31 $\pm$ 9.10	13.60 $\pm$ 10.29	13.04 $\pm$ 8.43	0.341 $\uparrow$ NS
Range	10.19 - 50.98	7.39 - 44.08	7.23 - 56.38	7.85 - 48.19	
ADP (mg/L)					
Mean $\pm$ SD	8.05 $\pm$ 2.90	8.93 $\pm$ 2.97	9.44 $\pm$ 2.95	8.52 $\pm$ 3.20	0.585 $\uparrow$ NS
Range	5.63 - 11.11	2.71 - 12.47	4.65 - 16.80	3.22 - 16.24	
Cytokine levels	B: Male/Female comparison				P value
	Male n = 57		Female n = 23		
UA (mg/dL)					
Mean $\pm$ SD	10.23 $\pm$ 1.35		10.24 $\pm$ 1.68		0.960 $\uparrow$ NS
Range	7.90 - 13.40		7.80 - 13.20		
CRP (mg/L)					
Mean $\pm$ SD	48.37 $\pm$ 38.51		44.32 $\pm$ 38.27		0.727 $\uparrow$ NS
Range	10.0 - 192.0		11.0 - 192.0		
Interleukin-6 (ng/L)					
Mean $\pm$ SD	14.04 $\pm$ 10.88		13.77 $\pm$ 8.11		0.915 $\uparrow$ NS
Range	7.23 - 56.38		7.98 - 48.19		
ADP (mg/L)					
Mean $\pm$ SD	9.24 $\pm$ 2.84		8.35 $\pm$ 3.36		0.238 $\uparrow$ NS
Range	2.71 - 16.31		3.22 - 16.80		

Table 3: A: Frequency distribution of UA, CRP, IL-6, and ADP values by gout patient age groups, **B:** Frequency distribution of gout patients' values of UA, CRP, IL-6, and ADP by gender. n: number of cases; SD: standard deviation; $\uparrow$: independent samples t-test; S: significant at $P \leq 0.05$; NS: not significant

The frequency distribution of UA, CRP, IL-6, and ADP values in gout patients by gender

Gout patients' serum levels for a few biochemical indicators have been compared based on gender, and the results are shown in Table 3B. In terms of sUA mean levels, the current findings indicate that male patients' mean sUA levels were non-significantly lower than female patients' mean sUA levels, 10.23 ± 1.35 mg/dL and 10.24 ± 1.68 mg/dL, respectively ($P = 0.960$). Also, mean levels of serum CRP in men and women were 48.37 ± 38.51 mg/L and 44.32 ± 38.27 mg/L, respectively; although the difference was statistically nonsignificant ($P = 0.727$), male groups had higher mean levels than female groups. Whereas the mean serum IL-6 levels for male and female groups, respectively, were 14.04 ± 10.88 ng/L and 13.77 ± 8.11 ng/L. The mean values of the male and female groups were also statistically nonsignificant ($P = 0.915$). While the mean serum ADP levels for male and female

groups, respectively, were 9.24 ± 2.84 mg/L and 8.35 ± 3.36 mg/L, there was no statistically significant difference between the mean levels of the two sexes ($P = 0.238$).

The Effect of BMI on Studied Parameters

In the current study, the effect of the BMI factor was considered; three groups (normal weight, Overweight, and Obese) of participants were created, as illustrated in Table 4. By comparing the patient outcomes across these three groups, no substantial differences were identified.

Cytokine levels	BMI comparison			P value
	Normal Weight n = 28	Overweight n = 35	Obesity n = 17	
UA (mg/dL)				
Mean $\pm$ SD	9.97 $\pm$ 1.36	10.2 $\pm$ 1.57	10.3 $\pm$ 1.55	0.680 $\uparrow$
Range	7.80 - 11.80	8.10 - 13.20	7.90 - 13.40	NS
CRP (mg/L)				
Mean $\pm$ SD	49.9 $\pm$ 31.09	45.7 $\pm$ 28.62	46.9 $\pm$ 30.9	0.169 $\uparrow$
Range	11.0 - 112.0	11.5 - 103.0	10.0 - 109.0	NS
Interleukin-6 (ng/L)				
Mean $\pm$ SD	13.0 $\pm$ 9.3	13.8 $\pm$ 9.9	13.2 $\pm$ 8.8	—
Range	7.23 - 49.23	8.34 - 56.38	7.98 - 49.42	
Adiponectin (mg/L)				
Mean $\pm$ SD	8.62 $\pm$ 2.80	8.63 $\pm$ 2.69	9.46 $\pm$ 2.39	0.580 $\uparrow$
Range	2.71 - 16.67	6.49 - 14.60	7.20 - 16.80	NS

Table 4: Frequency distribution of serum UA, CRP, IL-6, and ADP in gout patients by BMI group.

Frequency distribution of (UA, CRP, IL-6, ADP) levels according to the BMI of gouty patients

As shown in Table 4, slightly increased levels of sUA in obese people were observed relative to other categories, with a probability value, $P = 0.680$. Additionally, average serum CRP values were 49.9 ± 31.09 mg/L, 45.7 ± 28.62 mg/L, and 46.9 ± 30.9 mg/L. In comparison among normal weight, overweight, and obese patients, the highest mean values were seen in normal weight patients when compared with those in other categories. The difference was not statistically significant ($P = 0.169$). For IL-6, the mean levels were 13.0 ± 3.33 ng/L, 13.8 ± 3.05 ng/L, and 13.2 ± 2.11 ng/L. In patients who were normal weight, overweight, and obese, the mean values were greater in the overweight patients than in the other groups. However, the difference ($P = 0.566$) was not statistically significant. While the average serum levels of ADP were 8.62 ± 2.80 mg/L, 8.63 ± 2.69 mg/L, and 9.46 ± 2.39 mg/L in individuals who were normal weight, overweight, and obese, respectively, the variance in mean levels across the groups was also not statistically significant ($P = 0.580$).

Discussion

Across the world, gout is a serious medical condition [25]. Gout is diagnosed based on clinical symptoms, indicators, and the findings of blood tests. In the present study, gout sufferers were assessed and categorized into age (20–90 years), gender (males and

females), and BMI groups. Many studies have examined the gender gap in gout epidemiology; however, only a small portion of gout patients were female. The vast majority of research refers to gout as a "male sickness", and most of the patients studied were men. Gout frequency in women increases after menopause; however, after the age of 60, both male and female patients with gout may experience the same incidence rate [26]. It was also discovered that men are more likely to get gout [25], which was the situation in the current study.

In the present study, Table 2 and Figure 1 showed that the patients' levels of sUA, CRP, and IL-6 were considerably higher than those of the control group ($P < 0.001$). It was also shown in Table 2 and Figure 1 that the level of ADP was considerably decreased in people suffering from gout than in the healthy control group, with $P < 0.001$. This demonstrates that blood UA and pro-inflammatory cytokines may be combined to increase the accuracy of the diagnosis of gout. One of the main causes of gout is thought to be hyperuricemia. It has been shown that all gouty patients develop hyperuricemia for at least a short while [27,28]. A strong association between levels of sUA and the likelihood of developing gout was studied in several research works [29-31]. Due to UA's low solubility, chronic hyperuricemia creates harmful crystalline urate deposits around joints, which eventually lead to gout and destroy joints by inflaming them [32]. Hence, according to the primary gout definition specified by a 1977 criteria of American Rheumatism Association, among 12 gout diagnostic markers, hyperuricemia is one of them [33]. The gout group in the current study showed significantly increased sUA levels compared to the control group. Still, it is not particular that sUA levels are always higher in gout patients. On the contrary, gout can still occur even when sUA levels are at normal levels [34]. To increase the diagnostic precision of UA, further biochemical indications must be developed immediately. Gout's pathogenesis is based on the innate immune system being activated, which results in the release of proinflammatory cytokines [35]. Serum levels of CRP and IL-6 in the patients in the current study were significantly greater than those in the control group, supporting the finding that these markers were significantly elevated in people who had acute gout attacks [36]. Although it is well known that UA crystals play a role in the etiology of gout, the current study's patients' serum ADP levels were significantly lower than those in the control group. This finding is consistent with the finding that acute gout patients had significantly lower concentrations of ADP, which can cause inflammation. Moreover, increasing blood UA levels have been linked to higher levels of proinflammatory cytokines [37,38].

These results imply that UA in combination with CRP and IL-6, two pro-inflammatory cytokines, may be a valuable tool for the identification of gout. Since rheumatoid arthritis (RA), gout and pseudogout, ankylosing spondylitis (AS), osteoarthritis (OA), and psoriatic arthritis (PsA) are the most prevalent types of inflammatory arthritis [39], finding reliable biochemical markers that can separate gout patients from those with other kinds of inflammatory arthritis is essential.

The results of comparing serum levels (UA, CRP, IL-6, and ADP) between age groups, as well as in this investigation (Table 3A), indicate that sUA values in the 35-49 age group patients were higher but not significantly so than those in other groups ($P = 0.910$). The mean serum CRP value was highest in patients in the age range of 35 to 49 compared to other groups, while the difference wasn't statistically significant ($P = 0.192$) in those under 35, 35 to 49, 50 to 64, and more than 65 years old, respectively. Furthermore, serum IL-6 levels were highest in the youngest age group (<35 years) compared to older subjects; this difference was not statistically significant ($P = 0.341$). Moreover, it was found that mean levels of serum Adiponectin were higher in patients in the 50-64 age group than in the other groups, but the difference was not statistically significant ($P = 0.585$).

The comparison of serum UA, CRP, IL-6, and ADP levels between gender groups has been carried out, and the results are shown in Table 3B. According to the current findings, the mean levels of sUA in patients who were male were not significantly lower than those in patients who were female. Mean levels of serum CRP were higher in males in comparison with females, but the difference was non-significant ($P = 0.727$). The mean levels of serum IL-6 in male groups were greater than the mean levels in female groups, although this difference was not statistically significant ($P = 0.915$). Although the difference between the mean levels of serum ADP in male and female groups was not statistically significant ($P = 0.238$), the mean levels were greater in the male group.

Finally, a comparison was made between levels of serum (UA, CRP, IL-6, ADP), with respect to BMI, as shown in Table 4. Analysis showed that obese patients had slightly higher sUA levels than other comparison groups, although this was not statistically significant ($P = 0.680$). Also, the mean levels of serum CRP in patients with normal weight had greater mean levels than the other groups, though the difference was not statistically significant ($P = 0.169$). For IL-6, the mean levels were greater in the overweight patients than in the other groups, with $P = 0.566$, which was statistically nonsignificant. The mean values of serum ADP were greater in obese patients compared to other groups,

with $P = 0.580$, which was statistically nonsignificant in normal weight, overweight, and obese patients, respectively.

According to some research, sUA levels may help swiftly identify gout from other inflammatory arthritis [40,41]. But it is not always the case because the diagnostic accuracy of gout from other inflammatory arthritis patients cannot always be achieved by only combining increased sUA levels with levels of cytokines having a proinflammatory effect. More studies must be conducted to examine other biomarkers, but not proinflammatory cytokines, to boost the identification of gout individuals from patients suffering from various forms of inflammatory arthritis.

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Author Contributions

All authors worked together in writing the manuscript and approved the final version of the manuscript

Competing Interest

The authors declare that they have no conflict of interest regarding the publication of this work.

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