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# Serum apoprotein A1 levels are inversely associated with disease activity in gout

## From a southern Chinese Han population

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**Abstract**

To analyze the alteration of lipid profile and inflammatory markers in the serum of patients with gouty arthritis (GA), the levels of serum lipid profile, C-reactive protein (CRP), and erythrocyte sedimentation rates (ESRs) were measured in the serum of 69 gout patients, 35 patients with rheumatoid arthritis (RA), 23 patients with ankylosing spondylitis (AS)/spondyloarthropathy (SpA), and 25 patients with osteoarthritis (OA). The serum levels of apoprotein A1 (Apo-A1) were significantly decreased in patients with gout when compared with RA, AS/SpA, and OA patients. The serum levels of CRP were significantly increased in gouty patients when compared with RA, AS/SpA, and OA patients. Furthermore, the serum levels of ESR were significantly increased in patients with gout compared to patients with OA. Correlation analysis indicated that the levels of Apo-A1 were negatively correlated with serum ESR and CRP ($r=-0.475$, $P<.001$; $r=-0.380$, $P=.001$, respectively) in the patients with GA. Taken together, this study gives us a better understanding of the relationships between serum lipid profile and inflammatory markers in gout patients.

**Abbreviations:** Apo-A1 = apoprotein A1, AS = ankylosing spondylitis, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, GA = gouty arthritis, HDL = high-density lipoprotein, IL-1β = interleukin-1β, OA = osteoarthritis, RA = rheumatoid arthritis, SpA = spondyloarthropathy, UA = uric acid.

**Keywords:** Apo-A1, gout, inflammatory markers, serum lipid

## 1. Introduction

Gout is a disease characterized by sudden burning pain and swelling in a joint, and this clinical manifestation of joint can be self-resolution in a few days. The defective metabolism of uric acid (UA) leads to monosodium urate (MSU) crystal formation in gout patients.[1–3] Deposition of MSU in the joints and periarticular stimulates the tissue resident macrophage to secrete the interleukin-1β (IL-1β), which recruits the lots of neutrophils to the joint. In addition, MSU also stimulates neutrophils to produce IL-1β, leading to a rapidly inflammatory response. These cytokines and inflammatory cells form a complex network, leading to an enhanced inflammatory response.[4]

Inflammatory markers including C-reactive protein (CRP) and erythrocyte sedimentation rates (ESRs) could elevate in different levels when inflammation happens. The acute episode of gout is often accompanied by unbearable pain. The acute gout usually happens in some conditions such as metabolic syndrome, high serum UA levels, high seafood intake, low dairy and caffeine intake, and so on.[5–7] There are other triggering factors of gouty flares including noncompliance of urate-lowering agents, trauma, starvation, surgery, drugs that affect serum UA level, and consumption of purine-rich foods and beverages.[8–11] However, some people who do not have the above factors still suffer from varying frequencies of gouty flares.

Whether or not there are other factors contributing to gouty flares, people with dyslipidemia have higher prevalence and incidence of gout.[12,13] Apoprotein A1 (Apo-A1), primarily synthesized by hepatocytes and enterocytes,[14] is the main part of high-density lipoprotein (HDL), which gives it more pleiotropic antiatherosclerosis effect. In addition to the effect of cholesterol efflux, the second main feature is its anti-inflammatory property.[15] However, reports about the relationship between the level of serum Apo-A1 and the inflammatory markers in gout patients are rare. In this study, we measured the levels of serum lipid profile, CRP, and ESR in gout patients to better understand the relationships between serum lipid profile and inflammatory markers in gout patients.

## 2. Materials and methods

### 2.1. Patients

All of the patients were Han Chinese, selected from inpatient department of rheumatology and Clinical Immunology during

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years February 2015 to September 2016 in The First Affiliated Hospital of Xiamen University, Fujian, China. Diagnostic criteria were completed for each of the recruited patients according to the American College of Rheumatology (ACR), gouty arthritis (GA) (ACR 1997), rheumatoid arthritis (RA) (revised ACR 2010), ankylosing spondylitis (AS) (ACR 1984), spondyloarthropathy (SpA) (ACR2009), osteoarthritis (OA) (ACR 1986, 1990). The GA subjects (n = 69, mean age 52.9 ± 12.3 years) including the attack of GA with tophi patients (n = 25, mean age 53.9 ± 7.5 years) and GA without tophi patients (n = 44, mean age 52.3 ± 14.4 years), GA with lithangiuria patients (n = 14, mean age 49.6 ± 9.3 years) and GA without lithangiuria patients (n = 55, mean age 53.7 ± 12.9 years), RA (n = 35, mean age 56.1 ± 9.6 years), AS or SpA (n = 23, mean age 43.3 ± 13.5 years), and OA (n = 25, mean age 61.0 ± 6.5 years) were collected. None of the patients had cerebral vascular diseases, heart disease, hypertension, diabetes, impaired glucose tolerance, abnormal liver function, and thyroid dysfunction. In addition, any evidence of systemic infection due to bacteria, fungus, and virus in all patients must be excluded.

### 2.2. Ethics statement

The study was approved by institutional Ethics Committee of The First Affiliated Hospital of Xiamen University. The written informed consents were obtained from all the participants. All protocols were followed with Guidelines of Ethics Committee of The First Affiliated Hospital of Xiamen University.

### 2.3. Methods

Five milliliter venous blood was taken from all patients in the morning without having breakfast. Within 4 hours, the serum was separated, and the biochemical parameters including UA, lipids, liver and kidney function, and blood glucose were measured. The levels of ESR were measured by Widmanstaten natural sedimentation method. The levels of CRP were measured by the latex-enhanced immune transmission turbidimetric method.

### 2.4. Statistics

Quantitative data are expressed as mean ± standard deviation. The differences between the groups were compared using the independent sample *t* test and analysis of variance. The association between serum lipid levels and inflammatory markers was tested based on Spearman rank correlation. All the data were analyzed using SPSS13.0 (SPSS Inc., Chicago, IL) statistical software and considered significant at a *P* value <.05.

## 3. Results

### 3.1. Serum lipids in gout patients

The serum levels of triglyceride (TG) were significantly increased in patients with gout compared to patients with RA (Table 1, $P < .05$). The serum levels of free fatty acid (FFA) were significantly increased in patients with gout compared to patients with RA and patients with AS/SpA (Table 1, $P < .05$). The serum levels of total cholesterol (TC) were significantly decreased in patients with gout compared to patients with OA (Table 1, $P < .05$). The serum levels of high-density lipoproteincholesterol (HDL-C) were significantly decreased in patients with gout compared to patients with RA and patients with OA (Table 1, $P < .001$). The serum levels of Apo-A1 were significantly decreased in patients with gout compared to patients with RA, AS/SpA, and OA (Table 1, $P < .001$, $P = .008$, and $P < .001$). The serum levels of Apo B were significantly increased in patients with gout compared to patients with AS/SpA (Table 1, $P < .05$). The levels of low-density lipoproteincholesterol (LDL-C) and lipoprotein were not significantly different between the 4 groups (Table 1).

### 3.2. ESR and CRP levels in gout patients

The serum levels of CRP were significantly increased in patients with gout compared to patients with RA, patients with AS/SpA, and patients with OA (Table 1, $P < .001$, $P = .001$, and $P < .001$). The serum levels of ESR were significantly increased in patients with gout compared to patients with OA (Table 1, $P < .001$). The

**Table 1**

**The levels of UA and lipid profile in each group (mean ± standard deviation).**

| Parameters | GA | RA | AS/SpA | OA | Normal reference value |
|---|---|---|---|---|---|
| Total (male/female) | 69 (67/2) | 35 (8/27) | 23 (17/6) | 25 (2/23) | – |
| Age, y | 52.9 ± 12.3 | 56.1 ± 9.6 | 43.3 ± 13.5 | 61.0 ± 6.5 | – |
| Duration of disease, y | 10.8 ± 8.1 | 12.1 ± 13.2 | 8.5 ± 8.3 | 6.4 ± 7.9 | – |
| BMI, kg/m$^2$ | 23.7 ± 3.4 | 22.0 ± 2.4 | 22.3 ± 2.9 | 23.1 ± 3.5 | 18.5–24.9 |
| ESR, mm/h | 53.6 ± 33.5 | 43.5 ± 31.2 | 39.8 ± 33.1 | 11.8 ± 5.7* | F 0–20/M 0–15 |
| CRP, mg/L | 61.4 ± 71.9 | 17.8 ± 19.5* | 26.5 ± 26.2* | 1.4 ± 1.1* | 0–3 |
| UA, μmol/L | 490.9 ± 132.4 | 243.1 ± 77.1* | 291.3 ± 95.4* | 282.9 ± 55.4* | 88–430 |
| TG, mmol/L | 1.8 ± 2.0 | 1.1 ± 0.5** | 1.1 ± 0.8 | 1.7 ± 1.3 | 0.5–1.7 |
| Apo-B, g/L | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.0 ± 0.2** | 1.2 ± 03 | 0.6–1.1 |
| FFA, μmol/L | 492.6 ± 209.6 | 383.9 ± 191.6** | 382.3 ± 140.6** | 463.8 ± 211.1 | 129–769 |
| TC, mmol/L | 4.8 ± 1.1 | 4.9 ± 1.3 | 4.4 ± 1.0 | 5.4 ± 0.9** | 2.8–5.6 |
| LDL-C, mmol/L | 3.0 ± 1.1 | 3.0 ± 0.9 | 2.8 ± 0.7 | 3.3 ± 0.7 | 2.07–3.36 |
| Lipoprotein, mg/L | 222.2 ± 276.5 | 252.1 ± 197.8 | 240.8 ± 287.5 | 237.6 ± 253.3 | 0–300 |
| HDL-C, mmol/L | 1.0 ± 0.3 | 1.3 ± 0.4* | 1.1 ± 0.2 | 1.4 ± 0.3* | 1.1–1.7 |
| Apo-A1, g/L | 1.0 ± 0.2 | 1.4 ± 0.4* | 1.2 ± 0.3* | 1.5 ± 0.3* | 1.1–1.6 |

*P* values were obtained from the statistical comparisons among the study groups. *t* tests were used for comparisons between 2 groups. Statistical significance was accepted for *P* values <.05. F and M indicates female and male, respectively. AS = ankylosing spondylitis, Apo-B = apolipoprotein B, BMI = body mass index, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FFA = free fatty acid, GA = gouty arthritis, HDL-C = high-density lipoproteincholesterol, LDL-C = low-density lipoproteincholesterol, OA = osteoarthritis, RA = rheumatoid arthritis, SpA = spondyloarthropathy, TC = total cholesterol, TG = triglyceride, UA = uric acid.

*$P < .05$ and **$P < .01$, as compared with GA group.

**Table 2**

**The levels of lipid profile in GA (tophi)/(no tophi) group and GA (lithangiuria)/(no lithangiuria) group (mean ± SD).**

| Parameters | GA (tophi)/(no tophi) | | GA (lithangiuria)/(no lithangiuria) | |
|---|---|---|---|---|
| | GA (tophi) | GA (no tophi) | GA (lithangiuria) | GA (no lithangiuria) |
| Total (male/female) | 25 (24/1) | 44 (43/1) | 14 (14/0) | 55 (53/2) |
| Age, y | 53.9 ± 7.5 | 52.3 ± 14.4 | 49.6 ± 9.3 | 53.7 ± 12.9 |
| Duration of disease, y | 14.8 ± 7.4 | 8.5 ± 7.7* | 10.9 ± 5.7 | 10.7 ± 8.7 |
| BMI, kg/m$^2$ | 23.2 ± 3.2 | 24.0 ± 3.5 | 24.1 ± 3.8 | 23.6 ± 3.4 |
| ESR, mm/h | 62.8 ± 30.9 | 48.4 ± 34.2 | 57.4 ± 31.7 | 52.6 ± 34.2 |
| CRP, mg/L | 63.2 ± 88.3 | 60.3 ± 61.9 | 58.0 ± 55.9 | 62.2 ± 75.9 |
| UA, μmol/L | 574.0 ± 112.6 | 443.7 ± 119.8* | 526.1 ± 161.3 | 482.0 ± 124.2 |
| TG, mmol/L | 2.9 ± 3.0 | 1.2 ± 0.6** | 2.7 ± 3.9 | 1.6 ± 1.2 |
| FFA, μmol/L | 450.2 ± 194.3 | 516.7 ± 216.3 | 431.5 ± 227.9 | 508.2 ± 204.0 |
| Apo-B, g/L | 1.2 ± 0.3 | 1.1 ± 0.3 | 1.1 ± 0.2 | 1.2 ± 0.3 |
| CRE, μmol/L | 92.6 ± 25.2 | 85.8 ± 23.9 | 90.7 ± 13.6 | 87.7 ± 26.5 |
| TC, mmol/L | 4.9 ± 0.9 | 4.8 ± 1.3 | 4.9 ± 1.3 | 4.8 ± 1.1 |
| LDL-C, mmol/L | 2.7 ± 1.1 | 3.2 ± 1.1 | 2.8 ± 1.5 | 3.1 ± 1.0 |
| Lipoprotein, mg/L | 247.4 ± 312.9 | 207.8 ± 256.2 | 230.6 ± 229.1 | 220.0 ± 289.1 |
| HDL-C, mmol/L | 1.0 ± 0.2 | 1.0 ± 0.3 | 0.9 ± 0.2 | 1.0 ± 0.3 |
| Apo-A1, g/L | 1.0 ± 0.2 | 1.0 ± 0.3 | 1.0 ± 0.3 | 1.0 ± 0.2 |

*t* tests were used for comparisons between 2 groups. Statistical significance was accepted for *P* values <0.05. Apo-A1 = apoprotein A1, Apo-B = apolipoprotein B, BMI = body mass index, CRE = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FFA = free fatty acid, GA = gouty arthritis, HDL-C = high-density lipoproteincholesterol, LDL-C = low-density lipoproteincholesterol, TC = total cholesterol, TG = triglyceride, UA = uric acid.

*$P < .05$ and **$P < .01$, as compared with GA (tophi) group.

serum levels of ESR were not significantly different among GA, AS or SpA, and RA (Table 1).

### 3.3. The levels of uric acid, lipid profile, and inflammatory markers in GA (tophi)/(no tophi) group and GA (lithangiuria)/(no lithangiuria) group

The serum levels of duration of disease, TG, and UA were significantly increased in patients with gout (tophi) compared to patients with gout (no tophi) ($P = .001$, $P = .012$, and $P < .001$). The serum levels of UA, lipid profile, and inflammatory markers were not significantly different between lithangiuria and no lithangiuria groups (Table 2).

### 3.4. The relationship between serum lipid levels and inflammatory markers in gout patients

Correlation analysis indicated that the levels of Apo-A1 were negatively correlated with serum ESR and CRP ($r = -0.475$, $P < .001$; $r = -0.380$, $P = .001$, respectively) in the gout patients (Fig. 1). However, the levels of TG, TC, FFA, HDL-C, LDL-C, lipoprotein, and Apolipoprotein B (Apo-B) were not correlated with the inflammatory markers in gout patients (Table 3).

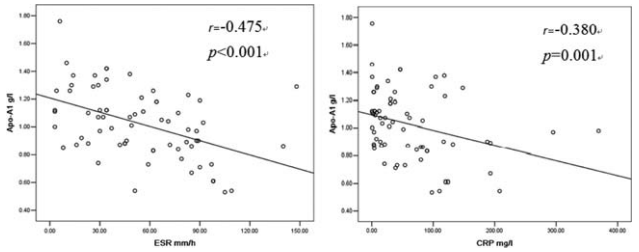


**Figure 1.** Correlation between serum lipid levels and inflammatory markers in gout patients. The association between Apo-A1 level and inflammatory markers in gout patients was tested based on Spearman rank correlation. The data were performed by using SPSS13.0 statistical software. $P < .05$ was considered as statistically significant.

## 4. Discussion

It is well known that dyslipidemia is prevalent in patients with gout, whether there is a relationship between the levels of serum lipid and the inflammatory markers in gout patients remains unknown. Here, we demonstrated that the serum levels of Apo-A1 were significantly decreased in patients with gout when compared with RA, AS/SpA, and OA patients ($P < .001$, $P = .008$, and $P < .001$). Although the number of patients in this study is small, correlation analysis indicated that the levels of Apo-A1 were negatively correlated with serum ESR and CRP ($r = -0.475$, $P < .001$; $r = -0.380$, $P = .001$, respectively) in the patients with GA. However, the levels of TG, TC, FFA, HDL-C, LDL-C, lipoprotein, and Apo-B were not correlated with the inflammatory markers in gout patients.

In line with our result here, Apo-A1 was also observed to exert an anti-inflammatory property in inhibiting lymphocyte cells' migration through decreasing the expression of adhesion

**Table 3**

**The relationship between serum lipid levels and inflammatory markers in gout patients.**

| Parameters | ESR | | CRP | |
|---|---|---|---|---|
| | *r* | *P* | *r* | *P* |
| Serum Cr, μmol/L | −0.007 | .957 | −0.057 | .64 |
| Serum UA, μmol/L | −0.124 | .309 | −0.236 | .051 |
| TC, mmol/L | −0.177 | .146 | −0.168 | .166 |
| TG, mmol/L | −0.053 | .666 | −0.138 | .257 |
| LDL-C, mmol/L | −0.081 | .506 | −0.008 | .95 |
| HDL-C, mmol/L | −0.183 | .133 | −0.092 | .453 |
| Apo-B, g/L | −0.011 | .931 | −0.030 | .805 |
| Lipoprotein, mg/L | 0.194 | .110 | 0.104 | .394 |
| FFA, μmol/L | −0.098 | .423 | 0.014 | .907 |

Correlations between serum lipids expression and inflammatory markers in the gout patients were analyzed by Spearman test. *P* value <.05 was accepted as statistically significant. Apo-B = apolipoprotein B, Cr = creatinine, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, FFA = free fatty acid, HDL-C = high-density lipoproteincholesterol, LDL-C = low-density lipoproteincholesterol, TC = total cholesterol, TG = triglyceride, UA = uric acid.

molecules, such as vascular cell adhesion molecule-1 and intercellular adhesion molecule-1.[16] When compared with stable status, a significantly lower serum level of Apo-A1 was observed in systemic inflammatory response syndrome patients with an exacerbated state. Interestingly, a specific blocking antibody to Apo-A1 was proved to interfere with the inhibitory action of HDL.[17] These data suggest a regulatory role acted by Apo-A1 in inflammation. Furthermore, the release of IL-1β by T-cell-stimulated monocytes was prohibited by Apo-A1 in vitro. However, the role of Apo-A1 in modulating the cell–cell contact inhibition remains unknown.[18]

In comparison with the pretreatment levels, increased serum HDL and Apo-A1 levels were observed in active RA patients with an effective treatment.[19] Gout is a chronic inflammatory disease induced by the MSU and characterized by recurrent attacks of acute joint inflammation.[20] Several mechanisms have been proposed for the induction of joint inflammation by the MSU crystals, such as the production of oxygen radicals and complement.[21–23] Furthermore, proinflammatory cytokines and chemokines induced by MSU crystals have also been suggested to play an important role in the development of gout.[24,25] Remarkably, the expression of IL-1β, which is the critical proinflammatory cytokine in the pathogenesis of gout,[26–28] was shown to decrease in the presence of Apo-A1. Although the exact mechanisms of action are not fully elucidated yet, Apo-A1 might affect cells interactions.[29] In addition, gout has historically been considered a male disease, and the estrogen/androgen balance determines the synthesis of Apo-A1 in the liver; it is essential to find out whether the hormonal environment could modulate the Apo-A1 function.[30] In this study, although estrogens as well as androgens inhibit the production of IL-1β and tumor necrosis factor-α on monocyte–macrophages, androgens can antagonize estrogen-stimulated liver to produce Apo-A1.[30] Previous studies showed the level of estrogen in gout patients is usually lower than RA, OA, and AS/SpA patients, which might explain why the gout usually occurs in postmenopausal women. Interestingly, gout patients with low level of estrogen exerted a lower serum levels of Apo-A1. Our study proved this opinion that with lower level of Apo-A1, the role of anti-inflammatory is impaired in gout and produces more serious inflammation reaction in gout. Furthermore, our study also indicated that the serum levels of CRP were significantly increased in patients with gout compared to patients with RA, patients with AS/SpA, and patients with OA ($P < .001$, $P = .001$, and $P < .001$). The pain intensity of gout arthritis in acute phase episode is very serious beyond RA, AS/SpA, and OA.

In conclusion, Apo-A1 plays a protective role in inflammatory reaction and might be a predictor for severity of gout and therapeutic target. As the incidence of the population of gout usually have lower estrogen, the hormonal environment may exert a role in anti-Apo-A1 antibodies production. The degree of inflammatory activity of gout arthritis in acute phase episode is more serious than the other noninfective inflammatory arthritis. However, there are several limitations to this study. First, it was a single-center and retrospective study. Second, the number of cases of this study was very small, which might result in statistical bias. Therefore, the animal model and clinical investigation need to be explored in further studies.

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