Cytokine Profile in Gout: Inflammation Driven by IL-6 and IL-18?

Nara Gualberto Cavalcanti\textsuperscript{a}, Cláudia Diniz Lopes Marques\textsuperscript{a}, Thiago Ubiratan Lins e Lins\textsuperscript{b}, Michelly Cristiny Pereira\textsuperscript{a}, Moacyr Jesus Barreto de Melo Rêgo\textsuperscript{b}, Angela Luzia Branco Pinto Duarte\textsuperscript{a}, Ivan da Rocha Pitta\textsuperscript{b}, and Maira Galdino da Rocha Pitta\textsuperscript{b}

\textsuperscript{a}Rheumatology Department, Hospital das Clínicas da Universidade Federal de Pernambuco (UFPE), Recife, Brazil; \textsuperscript{b}Laboratório de Imunomodulação e Novas Abordagens Terapêuticas (LINAT), Núcleo de Pesquisa em Inovação Suely Galdino (NUPIT-SG), Centro de Ciências Biológicas, Universidade Federal de Pernambuco, Recife, Brazil

ABSTRACT

Introduction: Gout is considered to be an autoinflammatory disease and the presence of monosodium urate (MSU) crystals stimulates activation of NPRL3 inflammasome and subsequently caspase-1, generating production of active IL-1\(\beta\) and IL-18. However, the association between serum cytokines levels and clinical manifestations of the disease is not yet well understood. We evaluated the serum profile of proinflammatory cytokines (IL-1\(\beta\), IL-6, IL-8, IL-17A, IL-18, IL-22, and IL-23) and described their relationship with clinical and laboratory data.

Methodology: Thirty-nine male patients with gout (GG) were assessed for clinical and laboratory variables and cytokine levels were measured by ELISA. For the purposes of comparison, 34 males with no previous history of arthritis were also included in the study (CG).

Results: Seventeen participants (43%) exhibited active arthritis on evaluation. Levels of IL-18 were significantly higher in patients in relation to the CG (\(p = 0.0013\)). No statistically significant differences were found between the GG and CG for the other measured cytokines. There was a moderate correlation between IL-18 and ESR (\(R = 0.43, p = 0.0073\)), CRP (\(R = 0.47, p = 0.0025\)), and serum levels of IL-6 (\(R = 0.36, p = 0.023\)). An association was observed between serum levels of IL-6 and the presence of tophi (\(p = 0.005\)) and deformities (\(p = 0.0008\)), as well as a correlation between this cytokine and ESR (\(R = 0.41, p = 0.011\)) and CRP (\(R = 0.48, p = 0.02\)).

Conclusions: IL-18 is associated with inflammatory activity in gout, as well as with IL-6 levels, while IL-6 is associated with clinical and laboratory activity, the presence of tophi and articular deformities, and may be a prognostic marker of this pathology.

Introduction

Gout, a chronic inflammatory disease, is considered to be the most common form of inflammatory arthritis in men over 40 years old. It is associated with sustained hyperuricemia and caused by the deposit of monosodium urate (MSU) crystals in articular and periarticular tissues (Edwards, 2011; Roubenoff et al., 1991).
It is considered to be an autoinflammatory disease whose main characteristic is activation of the innate immune system. The presence of uric acid crystals causes oligomerization and dysfunctional activity of NPRL3 inflammasome macromolecules (Martinon et al., 2002), resulting in hyperactivity of caspase-1. This process causes increased secretion of inflammatory cytokines such as IL-1β and IL-18 (Martinon et al., 2006). These cytokines, in turn, trigger a cascade of proinflammatory mediators, leading to endothelial activation and leukocyte recruitment. The main cytokines with secondary involvement in this process are IL-8 (neutrophil recruitment and activation) (Terkeltaub et al., 1991), IL-6 (amplification of the inflammatory process, possible contribution to bone damage) (Choe et al., 2011; Guerne et al., 1989; Rose-John, 2012), and TNFα (proinflammatory activation, maturation, and increased monocyte to macrophage transformation) (di Giovin et al., 1991).

The literature contains considerable experimental evidence on how molecules involved in innate immunity activation behave when stimulated by MSU, with increased production of IL-1β, IL-6, and IL-17A (Amaral et al., 2012; Conforti-Andreoni et al., 2011; Inokuchi et al., 2006; Liu-Bryan et al., 2005; Martin et al., 2009; Martin et al., 2010; Martin et al., 2011; Martinon et al., 2006; Mohamed Hachicha, 1995; Mylona et al., 2012; Nishimura et al., 1997; Ruggiero et al., 2006; Steiger & Harper, 2014; Torres et al., 2009; Urano et al., 2002). Understanding of how immunological basis of disease correlates with clinical presentation may increase the number of possible therapeutics targets, contributing to the process of developing new drugs (Mitroulis et al., 2010; Moll & Kuenmerle-Deschner, 2013; So et al., 2007; Terkeltaub et al., 2009; Tran & Edelman, 2011). However, few studies address the correlation between clinical manifestations and cytokine expression.

The objective of our study, then, was to evaluate the serum profile of cytokines (IL-1β, IL-6, IL-8, IL-17A, IL-18, IL-22, and IL-23) in patients suffering from gout and to correlate these with clinical and laboratory data, comparing the results against a group of participants without gout.

**Methods**

Clinical demographical evaluation – this was a cross-sectional, hospital-based, observational study conducted at the Hospital das Clínicas of the Federal University of Pernambuco (HC-UFPE) using a comparison group. Patients were selected based on the following inclusion criteria: aged over 18 years; diagnosed with gout according to the criteria of the American College of Rheumatology (ACR) (Wallace et al., 1977); and regular clinical follow-up conducted at our facility. Exclusion criteria were: failure to consent to the study; suffering from another clinical condition that causes hyperuricemia and/or may elevate cytokine levels, such as myeloproliferative disorders, hemolytic anemia, psoriasis, sarcoidosis, acute or chronic renal failure with creatinine clearance <30, alcohol intoxication, diabetic ketoacidosis, lactic acidosis, glycogen storage disease type I, hypo and hyperparathyroidism, or concurrent infections. The comparison group (CG) consisted of randomly selected volunteers, with no clinical history or diagnosis of gout or previous reports of arthritis, who exhibited no rheumatologic disease nor were taking immunosuppressants. Participants were exclusively male. The study was approved by the Human Research Ethics Committee of the UFPE’s Center for Health Sciences, protocol number 384250, and was developed in accordance with Declaration of Helsinki.
Participants were evaluated for the presence of comorbidities, such as *diabetes mellitus* (DM), arterial hypertension (AH), dyslipidemia (DLD), and obesity. Medications in use were recorded. The enrolled individuals were also examined for the presence of arthritis, tophi and deformities (clinically visible joint deformation not caused by soft tissue tophi). Gout attack was defined as the presence of arthritis in a patient with acute or chronic gout, and an intercritical phase as the period where a patient with a confirmed diagnosis of gout remained symptom free. After clinical assessment, blood samples were collected and the erythrocyte sedimentation rate (ESR) was measured using the Westergren method (BD bioscience), the C-reactive protein (CRP) was measured by nephelometry (normal range: <8 mg/l). We also measured the uric acid levels (Beckman Coulter – normal range: 3.5–7.2 mg/dL).

Cytokine measurement: Cytokines were measured by Sandwich ELISA (enzyme-linked immunosorbanbt assay), according to the protocol recommended by suppliers. The analyzed cytokines and their respective suppliers are as follows: IL-1β and IL-6 (BD Biosciences, San Jose, CA, USA); IL-8, IL-17A, and IL-23 (eBioscience, San Diego, CA, USA); IL-18 and IL-22 (R&D Systems, Minneapolis, MN, USA). Detection limits were: 1.95 pg/ml for IL-1β, 4.69 pg/ml for IL-6, 1.95 pg/ml for IL-8, 3.91 pg/ml for IL-17A, 46.87 pg/ml for IL-18, 15.62 pg/ml for IL-22, and 15.62 pg/ml for IL-23.

Statistical Analysis: Data values are given as median and range for non-parametric data and mean ± standard error of the mean (SEM) for data with Gaussian distribution. The Mann–Whitney test was used to determine the inter-group distribution of continuous variables for non-parametric data and the student’s t-test for parametric data. To assess the inter-group correlation, Spearman’s correlation test was used for non-parametric quantitative data and Pearson’s chi-square test for parametric data. We considered the correlation ($R_{xy}$) strength as follows: $0 < R_{xy} \leq 0.35$ = weak correlation; $0.35 < R_{xy} \leq 0.67$ = moderate correlation; $0.67 < R_{xy} \leq 1$ = strong correlation (Taylor, 1990). All tests were calculated using a significance level of 5% ($p < 0.05$). Prism software (version) 6.01 was used for analysis.

**Results**

The study included 39 male patients, with an average age of 58.2 (±1.6) years and mean disease duration of 11 (±1.9) years. The CG consisted of 34 male volunteers with an average age of 54.3 (±1.8) years. Table 1 presents the clinical and laboratory data of the sample. All gout patients were in the chronic phase of the disease (with multiple, recurrent, attacks). Near half ($n = 17$) of the patients had arthritis during investigation, with persistent clinical inflammation despite treatment (allopurinol and colchicine or low doses prednisone), while the other half ($n = 22$) had no clinical signs of arthritis. None of the individuals in the control group had arthritis or clinical conditions associated with systemic inflammation.

Although the groups were homogeneous for age and race, we observed significantly higher rates of hypertension and dyslipidemia in the GG. Thirty patients were using colchicine (all at low dosage levels) and seven were taking prednisone (maximum dose of 5 mg/d). We found no difference regarding cytokine levels among these patients compared to the patients without colchicine or prednisone, respectively.
Laboratory tests were conducted for inflammatory activity (ESR and CRP) to evaluate the degree of inflammation, indicating a significant difference for CRP between the groups. The same occurred for uric acid. Serum levels of inflammatory cytokines

Serum levels of cytokines were measured in the GG and CG as depicted in Table 2. The serum level of IL-18 in the GG was significantly higher ($p = 0.0013$) than in the CG. Analysis of the difference between cytokine distribution in the GG and CG showed no statistical significance for the other cytokines studied, according to the $p$-values provided in Figure 1.

Analysis of the correlation between serum cytokine levels and inflammatory activity tests (CRP and ESR) demonstrated a significant positive correlation with serum levels of IL-18 and IL-6 only for those in the GG (Figure 2). No linear correlation was recorded between the cytokines measured and the serum level of uric acid, although we found out that IL-18 is statistically significantly higher in patients with uric acid above the target level of 7mg/dl than in controls ($p = 0.0002$), and also than in patients with uric acid below that.

Table 1. Clinical and laboratory data for the two groups (GG and CG).

| Variable                        | GG        | %       | CG        | %       | p-value |
|---------------------------------|-----------|---------|-----------|---------|---------|
| Age in years, mean ± SEM        | 58.2 ±1.6 | 46.15   | 54.32 ±1.8| 79.41   | 0.102   |
| Ethnicity (n)                   |           |         |           |         |         |
| Brown                           | 18        | 46.15   | 27        | 79.41   |         |
| Black                           | 5         | 12.82   | 2         | 5.88    |         |
| White                           | 16        | 41.02   | 5         | 14.70   |         |
| AH (n)                          | 28        | 71.79   | 10        | 29.41   | <0.001  |
| DM (n)                          | 11        | 28.21   | 5         | 14.71   | 0.169   |
| DLD (n)                         | 25        | 64.10   | 10        | 29.41   | 0.03    |
| Obesity (n)                     | 15        | 38.46   | 9         | 26.47   | 0.283   |
| Allopurinol (n)                 | 35        | 89.74   |           |         |         |
| Colchicine (n)                  | 30        | 76.92   |           |         |         |
| Prednisone (n)                  | 7         | 17.95   |           |         |         |
| NSAI'Ds (n)                     | 7         | 17.95   |           |         |         |
| Disease duration, years, mean ± SEM | 11.0 ±1.9 | 23.1    |           |         |         |
| Deformity (n)                   | 9         |         |           |         |         |
| Tophi (n)                       | 18        | 46.2    |           |         |         |
| Arthritis (n)                   | 17        | 43.6    |           |         |         |
| No arthritis (n)                | 22        | 54.4    |           |         |         |
| ESR mm/h, median, range         | 18 (2–91) | 10 (2–45)|           |         | 0.066   |
| CRP mg/L, median, range         | 4.6 (1–110)| 2.5 (1–8.5)|           |         | 0.001   |
| Urate mg/dl, mean ± SEM         | 7.1 ± 0.3 | 5.58 ± 0.26|           |         | 0.001   |

Statistical analysis using the student’s $t$-test for parametric data and Mann–Whitney test for non-parametric data. Significance level of $p < 0.05$. SEM = Standard error of the mean.

Table 2. Serum levels of cytokines for GG and CG.

|       | IL-1β | IL-6  | IL-8  | IL-17a | IL-18* | IL-22 | IL-23 |
|-------|-------|-------|-------|--------|--------|-------|-------|
| GG (pg/ml) | 1.9   | 4.7   | 18.1  | 3.9    | 62701.0 | 71.8  | 15.6  |
|       | 1.9–46.6 | 4.7–702.6 | 1.9–702.6 | 3.9–64.5 | ±2399.0 | 15.6–273.8 | 15.6–384.7 |
| CG (pg/ml) | 1.9   | 4.7   | 27.6  | 3.9    | 52597.0 | 64.3  | 15.6  |
|       | 1.9–107.9 | 4.7–171.3 | 1.9–259.5 | 3.9–64.5 | ±1805.0 | 175.8 | 15.6–484.6 |

Median and range, except IL-18, for which mean and SEM are demonstrated. *$p < 0.005$. 

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limit and without crisis ($p = 0.0425$) – since uric acid may decrease during acute gout attacks (data provided in the supplementary information).

Evaluation of the distribution of serum cytokine levels in relation to clinical data showed an association between serum levels of IL-6 and the presence of deformities ($p = 0.0008$) and tophi ($p = 0.0053$) in the GG. There was no relationship between any other cytokines measured and these or other clinical data (age, race,
hypertension, diabetes, dyslipidemia, obesity, use of medication and duration of disease). Distributions of continuous variables were tested in the GG with active arthritis (n = 17) and in the intercritical period (n = 22). However, no association was found between the presence of arthritis and cytokine levels, although a tendency toward association between the presence of arthritis and IL-6 levels (p = 0.054) was observed.

Table 3 shows the number of patients that expressed each of the tested cytokines divided into groups according to the presence (+) or absence (−) of tophi, deformities and arthritis, respectively. Considering only the patients that had cytokine levels above the detection limit, we also found association of IL-8 and IL-23 with deformities and of IL-8 with tophi. As the number of patients with the IL-6 level above the detection limit in the

Figure 2. Correlations in the GG for IL-6 with CRP (A) and ESR (B). Correlations of IL-18 with CRP (C) and ESR (D). R = Spearman’s correlation coefficient. Significance level p < 0.05.

| Cytokine | N Above limit | Tophi (+) | Tophi (−) | p | Deformities (+) | Deformities (−) | p | Arthritis (+) | Arthritis (−) | p |
|----------|--------------|-----------|-----------|---|----------------|----------------|---|---------------|---------------|---|
| IL-1β    | (13/39)      | 4/18      | 9/21      | 0.214 | 2/9           | 11/30          | 0.231 | 7/17          | 6/22          | 0.7133 |
| IL-6     | 6/39         | 6/18      | 0/21      | **  | 5/9           | 1/30           | **  | 5/17          | 1/22          | **  |
| IL-8     | 38/39        | 17/18     | 21/21     | 0.043* | 8/9           | 30/30          | 0.042* | 16/17         | 22/22         | 0.543 |
| IL-17A   | 8/39         | 3/18      | 5/21      | 0.999 | 2/9           | 6/30           | 0.214 | 4/17          | 4/22          | 0.486 |
| IL-18    | 39/39        | 18/18     | 21/21     | 0.119 | 9/9           | 30/30          | 0.292 | 17/17         | 22/22         | 0.109 |
| IL-22    | 37/39        | 16/18     | 21/21     | 0.519 | 9/9           | 28/30          | 0.851 | 14/17         | 21/22         | 0.804 |
| IL-23    | 14/39        | 7/18      | 7/21      | 0.155 | 4/9           | 10/30          | 0.013* | 6/17          | 8/22          | 0.482 |

*Level of significance = p < 0.05. **Not possible to determine p-value.
group without tophi, deformities or arthritis was too small \( n = 0 \) or 1), it was not possible to determine \( p \) for IL-6 for these variables.

Considering the cytokine cascade, we also evaluated whether there was a correlation between the different cytokines and found only a weak association between levels of IL-18 and IL-6 \( (r = 0.3627 \text{ and } p = 0.0233) \) and IL-1\( \beta \) and IL-17A \( (r = 0.397 \text{ and } p = 0.012) \) for patients in the GG (Figure 3). No correlation was observed between interleukins in the CG.

**Discussion**

Several studies have been conducted on chronic inflammatory diseases to understand the molecular trigger of the inflammatory process and its relationship with clinical manifestations of these diseases. Few studies of gout investigate clinical data in relation to serum cytokine levels (Choe et al., 2011; Inokuchi et al., 2006; Jiang et al., 2014; Urano et al., 2002). Thus, the present study aimed to correlate clinical and laboratory characteristics typically assessed in patients suffering from gout with cytokines for which clinical data demonstrate involvement in the pathogenesis of this disease.

Our data show differences in the proportion of hypertensive and dyslipidemic individuals between the GG and CG. Individuals suffering from gout are known to have a higher prevalence of AH, given the recognized relationship between chronically high uric acid levels and higher blood pressure. There is also an association between hyperuricemia, dyslipidemia, and insulin resistance (Billiet et al., 2014; Pillinger et al., 2007). Barbaro et al. (2015) found an association between levels of IL-6, IL-1\( \beta \), and CRP (as well as IL-10 and TNF) in hypertensive patients with arterial stiffness. Jiang et al. (2014) recorded higher levels of oxidized LDL (ox-LDL) in patients with gout compared to controls, with a positive correlation between CRP, IL-6, and ox-LDL in these subjects. The question that emerges is how our results might be affected by the inter-group differences observed in relation to hypertension and dyslipidemia. Patients were therefore separated into groups according to the presence or absence of AH and DLD; however, no difference in cytokine levels was observed. Although we found a statistic correlation between SUA levels and inflammatory markers, we found no straight correlation of cytokine levels with measured SUA. In a recent interesting work, Crisan et al. found not only association of SUA levels

![Figure 3.](image-url) Correlations recorded between cytokines. \( R = \) Spearman’s correlation coefficient.
with increased production of IL-1β by PBMC’s of gout patients, but also, decreased production of IL-1 Ra (IL-1 receptor antagonist), reinforcing the proinflammatory role of uric acid (Crisan et al., 2016).

With the exception of high IL-18 levels in patients, our results showed no statistically significant difference in cytokine levels between patients and controls. The measured cytokine levels were above the average found in the literature for both the GG and CG, although there is still substantial difference in these levels among different studies, particularly when measured in those suffering from inflammatory pathologies (Choe et al., 2011; Cicuttini et al., 2005; Inokuchi et al., 2006; Jiang et al., 2014; Tsai et al., 2008; Urano et al., 2002). Several factors may be responsible for this variation: sample collection method, time between collection and processing of the sample, and differences between commercial kits of choice, which can alter the measured levels. Collection time may also be a relevant factor: recent data indicate variation in serum cytokine in accordance with circadian rhythm (Nakao, 2014). Disruption in the circadian pattern is reported in rheumatoid arthritis, with higher and more continuous cytokine production than in healthy individuals (Yoshida et al., 2014). However, there are no studies that assess whether patients with acute or chronic gout exhibit changes in basal cytokine secretion. As such, there is a need for greater standardization in collection and measuring techniques, as well as more extensive population studies to determine “normal” values for cytokines.

With respect to the serum levels of cytokines measured specifically for patients with gout, conflicting results are found in the literature, which also differ from our findings. Martin et al. (2010) recorded results similar to ours for IL-1β and IL-8 in 45 patients with gout and 46 controls. However, the authors did not assess the correlation between cytokines and patient’s clinical and laboratory data, whereas the present study found high levels IL-18 in patients in relation to controls and an correlation between IL-18 and IL-6 with inflammatory activity. Inokuchi et al. (2006) observed high IL-18, IL-6, and IL-8 levels in patients with gout suffering from arthritis, but only observed an association with inflammation using serum CRP for IL-6 and IL-8. Possibly the discrepancy involving IL-18 is an effect of the sample size, since both studies found association with manifestations of inflammation. In an experimental model of gout (air pouch model), the authors found that stimulation by monosodium urate did not increase IL-18 expression. They also found no difference in neutrophil aggregation for animals deficient in IL-18 when compared to control rats (wild type) (Inokuchi et al., 2006). However, the experimental model may not correspond to what occurs in the disease, particularly in chronic gout, when inflammatory activity is more persistent. In these cases, adaptive immunity may also play an important role. This can be indirectly inferred by the presence of T lymphocytes (CD4+ and CD8+), B cells and plasma cells in the tophi and tissue samples of patients with gout (Dalbeth et al., 2010; Lai & Zhou, 2013; Lee et al., 2011).

IL-18 is a cytokine with proinflammatory and immunoregulatory properties produced by inflammasome through activation of caspase-1. It induces the adaptive immune system by stimulating the Th1 response (Kaser et al., 2004) and, in conjunction with IL-12 or IL-15, causes interferon-γ (IFNγ) expression in activated Th1 cells. In the absence of IL-12 and IL-15, IL-18 takes on an immunoregulatory role by inducing IFNγ expression in NK cells. In association with IL-23, it also prompts Th17 response by stimulating IL-17A production by T cells (Conforti-Andreoni et al., 2011). These properties of IL-18 may be related to perpetuation of the inflammatory process, especially in chronic gout, though
further research is needed to evaluate this hypothesis. In the present study we found no association of IL-18 levels with presence of tophi or disease duration. However, we did not assess patients as to the duration of symptoms during gout attacks, which would be an interesting fact to examine in this context.

It is known that IL-1β and IL-18 share the same production source. In regard to the difference in expression of these two cytokines in our data, we point out the constitutional and continuous expression of IL-18 in peripheral blood mononuclear cells in contrast to the intermittent expression of IL-1β, triggered by stimulation. In chronic gout, continuous pain and subtle inflammation may be perpetuated by persistent activity of caspases in mononuclear cells at peripheral circulation. The occurrence of peaks of more intense localized inflammation may be a result of a local stimulation of NPRL3 by crystal precipitation (Puren et al., 1999). Another factor that may explain the lack of inter-group (GGxCG) difference regarding IL-1β expression is the fact that most patients use colchicine (76.92%), what could slow NPRL3 oligomerization, since it is reported that colchicine can at least partially inhibit the oligomerization of the NPRL3 inflammasome (Nuki, 2008). But, the main remark is still the predominantly local (intra articular) action of IL-1β or their production just at the onset of the gout attack, with subsequent rapid degradation, which would impair us to observe a raise in peripheral blood of this cytokine.

Although there is considerable experimental evidence (in animal models and cell cultures) of the correlation between high cytokine levels (particularly IL-1β and IL-6) and inflammatory activity triggered by monosodium urate, there are few clinical studies with data on the behavior of these cytokines throughout the inflammatory process in gout. The results obtained by Martin et al. (2010) were inconclusive when attempting to compare their analyses during and after the gout attack. Nevertheless, there is a substantial amount of indirect clinical evidence in relation to IL-1β. Experimental studies indicating a reduction in the inflammatory process through the use of IL-1 antagonists (anti-IL-1 antibodies and soluble receptors) raised questions as to the clinical relevance of this type of blocking (So et al., 2007; Torres et al., 2009). Clinical studies with canakinumab (anti-IL-1 antibodies), with rilonacept (IL-1 trap) and with anakinra (IL-1 receptor antagonist) demonstrated success in controlling the inflammatory process in gout, clinically corroborating the experimental results previously obtained (Chen et al., 2010; Joosten et al., 2009; So et al., 2007; Terkeltaub et al., 2009; Tran & Edelman, 2011).

For IL-22, IL-17A, and IL-23, there are no studies evaluating their levels in gout patients. Considering new data showing participation of T cells in tophi (Dalbeth et al., 2010; Lai & Zhou 2013; Lee et al., 2011) and activation of Th17 path by MUS (Conforti-Andreoni et al., 2011), and considering that IL-22 may have a role in the pathogenesis of erosion in other erosive diseases such as rheumatoid arthritis (Leipe et al., 2011) and psoriatic arthritis (Mitra, 2012), we decided to evaluate the levels of these cytokines in gout patients. We found no elevation of them and no association with clinical data. However, if we observe the levels of these cytokines only among individuals who expressed them above the detection limit, there may be some association of IL-23 and IL-8 with severity of the disease, as we found higher levels of these cytokines when looking at patients of this group with deformities (and with tophi for IL-8). These data may indicate the connection of cytokine levels with other aspects, not yet investigated, of gout immunology.
Our findings showed a significant association between IL-6 and the presence of deformities and tophi. In line with the literature, we also found a correlation between serum levels of CRP and ESR and IL-6 in patients with gout. These data is consistent with the hypothesis of IL-6 participation in the disease pathogenesis. IL-6, a proinflammatory cytokine whose production may be triggered by the exposure of synoviocytes and monocytes to uric acid, is involved in innate immunity (Guerne et al., 1989a), and is also part of the Th2 pathway in the adaptive immune system. It is as well involved in synovial activation and osteoclastogenesis regulation (Harre et al., 2011), and its association with bone damage in other inflammatory diseases is well documented. In gout, Choe et al. (2011) found a negative association between the soluble IL-6 receptor (sIL-6R) and radiographic joint damage scores, though there was no direct correlation with IL-6 levels. The author hypothesizes that these results can be explained by the fact that the evaluated patients were chronic and not experiencing gout attack at the time of their assessment. However, this raises the question of whether sIL-6R might be generating a negative feedback mechanism, thus explaining the lack of a correlation between IL-6 in these chronic patients and greater radiological joint damage.

There are indications that the dysfunctional relationship between IL-6 and its receptor in gout compromises the transition from the neutrophilic to monocytic phase of inflammation, resulting in more severe inflammation and greater probability of joint damage (Tsai et al., 2008). There are reports of association between high serum levels of IL-6 and CRP (Inokuchi et al., 2006; Urano et al., 2002), both generally correlated with a simultaneous increase in uric acid. Population studies suggest that the inflammatory component measured by increased CRP, which is associated with high levels of uric acid, is directly related to elevated IL-6 content (Lyngdoh et al., 2011; Ruggiero et al., 2007). In the general population increased serum IL-6 has been correlated with more frequent cardiovascular events and heart-related mortality (Harris et al., 1999; Kritchevsky et al., 2005). This correlation may be particularly relevant for patients with gout, since the exacerbation of inflammatory activity and high serum levels of uric acid predispose those suffering from gout to greater cardiovascular risk than the general population (Meek et al., 2014). IL-6 may have a direct role in heightened risk among these patients. However, the present study was not designed to evaluate this relationship and further research is needed to investigate this hypothesis.

We realize that this study has some limitations such as its cross-sectional design, a longitudinal study comparing the levels of cytokines in periods of crisis and intercrisis would be beneficial to better understand the cytokine role in gout inflammation. Furthermore the cytokine levels were measured in heterogeneous gout population, with differences in inflammatory status and use of medication that may have influence in inflammation process and in cytokine response to MSU. We also weren’t able to perform cytokine measurements in synovial liquid or in tophi, what would better correspond to the production of cytokines in acute gout.

In conclusion, we found significant differences in serum levels of IL-18 between patients and controls. Serum IL-6 was also related to increased ESR and CRP and was associated with the presence of tophi and deformities. Our results show a participation of IL-18 in the inflammatory process of gout, yet, for this type of study is not possible to infer to which point of the process it is related. If it’s only a late consequence of inflammation or it’s involved in the maintenance of the inflammatory process. For clarifying the role of
these cytokines in gout pathogenesis and determining if maybe there is a therapeutic role in inhibiting IL-18 further experimental studies are required. No other statistically significant associations were observed between serum levels of the evaluated cytokines and clinical or laboratory parameters of the disease. Moreover, there was no significant association between the use of gout medication and cytokine levels.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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