Concise report

The effect of the systemic inflammatory response, as provoked by elective orthopaedic surgery, on serum uric acid in patients without gout: a prospective study

Jenna L. Waldron¹, Helen L. Ashby¹, Cyrus Razavi¹, Osmond L. Thomas², Sanjiv Chugh², Shreeram Deshpande², Clare Ford¹ and Rousseau Gama¹,³

Abstract

Objective. Acute gout is associated with a decrease in serum uric acid (SUA) that is considered to be in response to acute inflammation but it may be a feature of gout itself. We, therefore, aimed to investigate the effect of the acute systemic inflammatory response (SIR) on SUA concentrations in subjects without gout.

Methods. SUA and urinary excretion of uric acid (UA) (expressed as fractional excretion of UA; FEua%) were measured in 30 patients before and 48 h after elective knee or hip surgery. The SIR was assessed by measuring serum CRP and urine microalbumin excretion [expressed as the albumin-creatinine ratio (ACR)] before and after surgery in the same patients.

Results. The mean (s.d.) serum CRP increased following surgery [5.0 (5.5) vs 116.0 (81.2) mg/l; P < 0.0001] as did urine ACR [0.85 (1.03) vs 2.10 (2.60) mg/mmol; P = 0.004], SUA decreased following surgery [312 (64) vs 282 (82) μmol/l; P = 0.0033] but FEua% was unchanged [6.4 (2.3) vs 7.3 (3.3)%; P = 0.1726].

Conclusion. The SIR is associated with a decrease in SUA concentrations in normouricaemic patients without gout. The decrease in SUA concentrations is not due to increased urinary excretion of UA. This study supports the notion that the decrease in SUA during acute gout is due to the associated SIR rather than gout per se.

Key words: uric acid, systemic inflammatory response, CRP.

Introduction

Serum uric acid (SUA) concentrations decrease during an acute gouty attack [1, 2], but the reason for this finding remains unclear. It has been suggested that the decrease in SUA during an acute attack of gout is due to the systemic inflammatory response (SIR) resulting in increased urinary uric acid (UA) excretion [1], but it is possible that the decrease in SUA is a feature of gout per se. The effect of SIR on SUA in patients without gout has not been studied before. Therefore, we prospectively investigated the effect of the SIR, as provoked by elective orthopaedic surgery, on SUA and urinary UA excretion in subjects without gout and normal SUA.

Methods

Patients

Patients undergoing elective hip or knee surgery were recruited from those attending orthopaedic outpatient clinics. Exclusion criteria included hyperuricaemia, gout, renal impairment, medications known to affect UA metabolism (including diuretics, cytotoxic drugs, salicylates, allopurinol and probenecid), post-operative infection and post-operative blood transfusion. Patients gave informed written consent to participate in this study, which was approved by the Black Country Research Ethics Committee.

Resting blood and urine samples were collected into gel tubes (Sarstedt Monovet 4.7 ml, Z GEL, Sarstedt, Numbrecht, Germany) and plain universal specimen
Results are represented as mean (S.D.).

**Table 1** Biochemical results in 30 patients before and 48 h after elective knee or hip surgery

<table>
<thead>
<tr>
<th>Analyte</th>
<th>Pre-operative</th>
<th>Post-operative</th>
<th>Reference range</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP, mg/l</td>
<td>5.0 (5.5)</td>
<td>116.0 (81.2)</td>
<td>1-6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urine ACR, mg/mmol</td>
<td>0.85 (1.03)</td>
<td>2.10 (2.60)</td>
<td>0-3.4</td>
<td>0.0040</td>
</tr>
<tr>
<td>SUA, μmol/l</td>
<td>312 (64)</td>
<td>282 (82)</td>
<td>100-490</td>
<td>0.0033</td>
</tr>
<tr>
<td>FE_{ua}, %</td>
<td>6.4 (2.3)</td>
<td>7.3 (3.3)</td>
<td></td>
<td>0.1726</td>
</tr>
<tr>
<td>Serum creatinine, μmol/l</td>
<td>76 (15)</td>
<td>78 (24)</td>
<td>60-120</td>
<td>0.4633</td>
</tr>
</tbody>
</table>

Results are represented as mean (s.d.).

Containers (SSI 30 ml, polypropylene, International Scientific Supplies Ltd, Bradford, UK), respectively, before and 48 h after surgery. Serum was separated within 60 min. Separated serum and urine were aliquotted and frozen at −80°C until analysed in a single batch.

**Analytical methods**

UA (uricase enzyme method), creatinine (kinetic Jaffé method), CRP (immunoturbidimetry) and urine albumin (immunoturbidimetry) were measured using reagents on the MODULAR P analyser (Roche Diagnostics GmbH, Mannheim, Germany).

Respective intra-assay coefficients of variation are for SUA 0.5% at 342 μmol/l, urine UA 1.0% at 1.59 mmol/l, serum creatinine 0.7% at 148 μmol/l, urine creatinine 1.1% at 5.39 mmol/l, serum CRP 2.5% at 5.8 mg/l and urine albumin 1.3% at 24.9 mg/l.

The fractional excretion of UA (FE_{ua}) was calculated as a percentage using the formula: [(urinary UA/SUA) × (serum creatinine/urinary creatinine)] × 100. Urine microalbumin was corrected for urine flow rate by expression as the albumin-creatinine ratio (ACR).

**Statistical analysis**

The Kolmogorov and Smirnov method was used to assess normality of data. Raw urine ACR data were non-parametric but were normally distributed following logarithmic transformation. All other data were parametric. Paired t-test was used to assess the significance of differences between raw data or, in the case of urine ACR, logarithmically transformed data. Pearson’s linear correlation was used to assess the significance of association between variables. Data processing and statistical analyses were performed using GraphPad Instat version 3.00 for Windows 95 (GraphPad Software, San Diego, CA, USA). Data (including pre-transformed urine ACR data) are expressed as mean (s.d.).

**Results**

We studied 30 patients (17 females), average age 64.9 (8.7) years. Twenty-five patients had OA and five patients had RA. Other known comorbidities included diabetes (two patients), ischaemic heart disease (one patient), hypertension (eight patients), hyperlipidaemia (five patients), hypothyroidism on thyroxine replacement (one patient) and epilepsy (one patient). The pre-operative and post-operative biochemical data are shown in Table 1. In summary, serum CRP and urine ACR increased (P < 0.0001 and P < 0.005, respectively) following surgery, whereas SUA decreased (P < 0.005). Serum creatinine and the FE_{ua} were similar before and after surgery. There were no meaningful correlations, and in particular the percentage change in FE_{ua} did not correlate with the percentage change in SUA (r = 0.2965, P = 0.1116).

**Discussion**

SUA decreased following elective knee and hip surgery. The post-operative increase in serum CRP and urine ACR confirms that an SIR was provoked solely by surgery, since none of the patients developed post-operative infection or other acute inflammatory disease, including gout. The decrease in SUA was therefore associated with an SIR. These results support the notion that it is the inflammatory response to acute gout, rather than the intrinsic characteristic of gout itself, that may be responsible for the decrease in SUA, and may explain why up to 49% of people may have normal SUA during an acute attack of gout [1-3].

The mechanism for the decrease in SUA during an SIR remains unclear. It has been hypothesized that acute gouty attacks may be accompanied by UA diuresis, perhaps due to inflammation-induced corticosteroid release [4, 5]. Urano and colleagues [1] reported that in acute gout, the percentage change in SUA correlated with the percentage change in FE_{ua}. They therefore suggested that the mechanism of decreased SUA might be due to an increase in urinary excretion of UA, as FE_{ua} is a marker of UA excretion [1]. In our study, the percentage change in SUA did not correlate with the percentage change in FE_{ua}, and there was no significant change between pre- and post-operative FE_{ua}. We therefore have found no evidence to support the hypothesis that the decrease in SUA as a result of the SIR is due to increased urinary excretion of UA.

There are other possible alternative mechanisms for the decrease in SUA during the SIR. UA is an antioxidant that during inflammation scavenges free radicals to produce urate-radical products [6, 7]. Circulating UA may therefore be consumed in the free radical reactions generated by SIR, leading to a decrease in SUA levels. Alternatively, the decrease in SUA may be associated with an increase in UA catabolism [8].

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In conclusion, we report a decrease in SUA during an SIR in patients without gout and normal SUA. These results support the notion that the decrease in SUA during acute gout is due to the associated SIR rather than gout per se. The mechanism of the decrease in SUA during an SIR remains unclear.

Rheumatology key messages
- SUA decreases during an SIR in patients without gout.
- Decreased SUA during acute gout is due to the SIR rather than gout per se.

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J.L.W. researched the literature, recruited patients, took consent, collected samples, helped supervise the study, analysed samples, analysed the data and wrote the first draft. H.L.A. and C.R. researched the literature, recruited patients, took consent and collected samples. H.L.A. also designed and supervised the study. O.L.T., S.D., S.C., C.F. and R.G. contributed to the data. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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