Preliminary report

Near-iron deficiency-induced remission of gouty arthritis

Francesco S. Facchini

Objectives. Previous evidence supports a role for iron in the pathogenesis of gout. For example, iron, when added to media containing urate crystals, stimulated oxidative stress with subsequent complement and neutrophil activation. Conversely, iron removal inhibited these responses as well as urate-crystal-induced foot pad inflammation in rats in-vivo. The objective of the present study was to investigate whether or not iron removal may improve the outcome of gouty arthritis in humans as well.

Methods. Quantitative phlebotomy was used to remove iron in 12 hyperuricaemic patients with gouty arthritis and maintain their body iron at near-iron deficiency (NID) level (i.e. the lowest body iron store compatible with normal erythropoiesis and therefore absence of anaemia).

Results. During maintenance of NID for 28 months, gouty attacks markedly diminished in every patient, from a cumulative amount of 48 and 53 attacks per year before (year –2, –1), to 32, 11 and 7 during induction (year 0) and maintenance (year +1, +2) of NID, respectively. During NID, attacks were also more often of milder severity.

Conclusions. During a 28-month follow-up, maintenance of NID was found to be safe and beneficial in all patients, with effects ranging from a complete remission to a marked reduction of incidence and severity of gouty attacks.

KEY WORDS: Gout, Arthritis, Hyperuricaemia, Oxidative stress, Near-iron deficiency.
Patients and methods

Twelve patients who satisfied inclusion criteria and agreed to participate in the current trial were studied. The study was approved by the local ethical committees, experimental procedures were in accordance with Institutional guidelines and written informed consent was obtained. All patients were hyperuricaemic, non-smokers and had a history of primary gout for >3 yr. Standard clinical criteria [10] yielding a hyperuricaemic, non-smokers and had a history of primary procedures were in accordance with Institutional guidelines participate in the current trial were studied. The study was performed monthly or bimonthly under topical anaesthesia and maintain NID was 7 and 3 ± 1, respectively, for years 0, 1 and 2. Initial body iron stores were 1.8 ± 0.6 g.

Results

The patients' clinical and demographic characteristics are shown in Table 1. Body weight and ethanol intake were unchanged. Steroids, either intra-articular or systemic, were never administered. Allopurinol average dose was 180 ± 62 mg/day, not significantly different than 24 months before starting phlebotomies (203 ± 50 mg/day). Body iron status at baseline and follow-up is also illustrated in Table 1. NID was successfully achieved within 8 ± 3 months and thereafter maintained in all patients without significant adverse reactions. The average number of phlebotomies necessary to achieve and maintain NID was 7 ± 2. 3 ± 1, 3 ± 1, respectively, for years 0, 1 and 2. Initial body iron stores were 1.8 ± 0.6 g.

TABLE 1. Demographic, biochemical and clinical data before (Year –2), at start of quantitative phlebotomy (Baseline) and after 2 yr of NID (Year +2)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Year –2</th>
<th>Baseline</th>
<th>Year +2</th>
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<tr>
<td>Age (years)</td>
<td>50 ± 6</td>
<td>52 ± 6</td>
<td>54 ± 6</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>28 ± 2</td>
<td>28 ± 2</td>
<td>29 ± 3</td>
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<tr>
<td>Gender male</td>
<td>10/12</td>
<td>10/12</td>
<td>10/12</td>
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<tr>
<td>Ethanol intake (g/day)</td>
<td>12 ± 4</td>
<td>14 ± 5</td>
<td>15 ± 6</td>
</tr>
<tr>
<td>Ferritin (µg/l)</td>
<td>287 ± 81</td>
<td>301 ± 98</td>
<td>26 ± 10*</td>
</tr>
<tr>
<td>Iron saturation (%)</td>
<td>44 ± 13</td>
<td>45 ± 12</td>
<td>13 ± 2*</td>
</tr>
<tr>
<td>MCV (fl)</td>
<td>90 ± 3</td>
<td>89 ± 4</td>
<td>80 ± 2*</td>
</tr>
<tr>
<td>Hct (%)</td>
<td>45 ± 2</td>
<td>44 ± 2</td>
<td>43 ± 1**</td>
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<tr>
<td>SUAC (mmol/l)</td>
<td>0.46 ± 0.1</td>
<td>0.50 ± 0.1</td>
<td>0.47 ± 0.1</td>
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<tr>
<td>Allopurinol use</td>
<td>11/12</td>
<td>11/12</td>
<td>11/12</td>
</tr>
<tr>
<td>Allopurinol dose (mg/day)</td>
<td>203 ± 50</td>
<td>194 ± 76</td>
<td>180 ± 62</td>
</tr>
<tr>
<td>Thiaduicret use</td>
<td>4/12</td>
<td>4/12</td>
<td>4/12</td>
</tr>
<tr>
<td>Thiaduicret dose (mg/day)</td>
<td>27 ± 18</td>
<td>30 ± 17</td>
<td>24 ± 15</td>
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*P < 0.001; **P < 0.05.
Fig. 1. Frequency distribution of cumulative attack rates during the study period.
There was a cumulative amount of 48 and 53 gouty attacks per year during the 2 yr prior to study entry (years –1 and –2); this diminished to 32, 11 and 7 attacks per year during years 0, 1 and 2, respectively. Percent changes in cumulative attack rate are shown in Fig. 1. In Fig. 2, it can be seen that the intra-individual change in the average number of gouty attack per year decreased from 6.4±3.0 to 2.0±1.0 after achievement of NID (P < 0.001). In absolute terms, 2/12 and 7/12 patients became attack-free during year 0 and the subsequent 24 months, respectively. These patients, although they continued to take allopurinol, did not require any further anti-inflammatory therapy, with either non-steroidals or colchicine. In Fig. 3 the median frequency distribution of the gouty arthritis severity score is shown before (years –2 and –1), during (year 0) and after achievement of NID in all patients (years 1 and 2).

Discussion

In the present investigation, body iron stores were lowered by means of serial venesections to the lowest values yet compatible with normal erythropoiesis (NID) and NID subsequently maintained for 28 months. NID induced either a full or partial remission of gout in all study patients that persisted for the entire period of observation. Since spontaneous remissions in the absence of obvious confounding factors (e.g. dietary changes, weight loss and medications) are unlikely, it is possible to conclude that NID prevented the relapse of the acute arthritis of primary gout in 58% of patients and markedly reduced its frequency and severity in the remaining 42%.

In former studies of iron depletion in animals, high-dose deferoxamine could mitigate, but not prevent, urate-crystal-induced foot-pad swelling, but only at high doses. Lower doses of deferoxamine had no anti-inflammatory effect [6]. Deferoxamine-mediated iron excretion decreases as body iron stores shrink [7], while during quantitative phlebotomy the kinetics of iron removal is unaffected by size of body iron stores. Therefore, when compared to those results obtained in rats treated with high-dose deferoxamine, the better outcome shown in the present study is presumably related to a greater degree of depletion of body iron stores.

The present findings were not unexpected and are in agreement with results from in-vitro studies showing the pro-inflammatory role urate crystals have when they complex iron. While soluble urate has antioxidant properties by coordinating iron in a redox-inactive form, crystalline urate binds iron loosely, permitting the crystal-bound metal to become a Fenton’s catalyst and catalyse the production of reactive oxygen species [5]. Thus, prior exposure of urate crystals to ferric iron salts markedly enhanced deoxyribose oxidation while either hydroxyl radical scavengers or deferoxamine suppressed it [5]. After iron complexation, urate crystal-mediated oxidant generation stimulated neutrophils and production of Leukotriene B4 (LTB4), a potent cytotoxin and an important chemical mediator in acute gouty attacks [11]. Metal-catalysed oxidant generation also activated complement, a further chemotactic and activating stimulus for neutrophils [12]. Ferric iron loading (of the crystals) enhanced, in a dose-dependent fashion, neutrophil chemotaxis and all related inflammatory responses while deferoxamine or hydroxyl radical scavengers suppressed them [5].

Interestingly, hyperinsulinaemia and insulin resistance also induce oxidative stress and recent data showed carbohydrate restriction, an intervention known to reduce insulin resistance and hyperinsulinaemia, was indeed quite effective in curbing the frequency of gouty attacks [13]. Iron lowering to NID markedly improves both oxidative stress [14] and insulin resistance [9] and this dual action might explain the greater effect of NID, as compared with that of carbohydrate restriction, on the incidence and severity of gouty attacks. However, neither insulin resistance nor inflammatory pathway activation were evaluated, and therefore whether similar mechanisms influenced the outcome of the present study or not is pure speculation. Nonetheless, although preliminary, the effect of NID shown is congruous with the notion that oxidative stress and gout can be promoted by increasing amounts of iron in-vitro, and prevented or blunted by use of iron chelators in-vitro, as well as in animals in-vivo [6].

There is the possibility that arthritic symptoms were not always related to re-exacerbation of gout. One limitation of the present study concerns the issue that severity assessment of gouty flares is typically based on far-from-perfect criteria. Inter-individual variability in pain threshold, in doctors’ documentation of patients’
Fig. 3. Frequency distribution of joint inflammation score (for details see methods section) during the study period. $N =$ total number of attacks.
symptoms and signs and the possibility of misdiagnosis all exist. However, the frequency of flares unequivocally decreased as documented by the overall reduction of cumulative (Fig. 1) and individual (Fig. 3) clinic appointments and such findings are hard to dispute. The issue of diagnostic accuracy is also important. Stringent diagnostic criteria, based on synovial fluid analysis, were in fact used only in 8/12 patients. However, urate crystals are not always present in acute gout. Furthermore, it was shown that iron removal was also effective in other types of experimental arthritis such as, for example, in rheumatoid [15] and adjuvant-induced arthritis, even when iron depletion was achieved by means of iron-poor diets [16]. Therefore, the fact that all patients improved, including the 1/10 possibly affected by a condition other than gout [10], indicates the likelihood that NID may lessen other types of joint inflammation as well.

At this time, it seems premature to suggest widespread use of venesections to NID as a treatment modality for gout. However, considering the growing pathogenetic importance of iron sufficiency in a variety of chronic age-related disease, from type 2 diabetes and its complications [9, 17–19], to atherosclerosis [20], chronic hepatitis C [21] and colon cancer [22] it seems obvious that, at the very least, there is an urgent need to overcome the dogmatic credence that appreciable amounts of iron should always be maintained in storage at any age and by all means.

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<th>Rheumatology</th>
<th>Key Messages</th>
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<td>1. Depletion of body iron stores to a level of NID by means of quantitative phlebotomy had a sustained beneficial effect on clinical gouty arthritis.</td>
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<td>2. During a 28-month follow-up period NID was tolerated without adverse effects. If confirmed, these results should strongly encourage NID as a cost-effective and safe therapeutic option for gouty arthritis.</td>
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Acknowledgement

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References