Concise Report

Atherogenic serum lipid profile is an independent predictor for gouty flares in patients with gouty arthropathy

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Objective. Atherogenic serum lipid profile possesses pro-inflammatory properties and is associated with more active RA. While prevalent in patients with gout, whether atherogenic lipid profile is associated with gouty flares is unknown. This study aims to investigate whether atherogenic serum lipid predicts gouty flares in patients with gout.

Methods. Adult patients (age ≥21 yrs) who satisfied the 1977 ACR classification criteria for gout [19] were identified and prospectively followed between September 2006 and November 2007. Of the 100 patients, 80 were men, 65 were ethnic Chinese, 31 were Malay and the rest were Indian and Caucasian. The mean age and duration of gout (±s.d.) were 61.9 ± 14.0 and 6.6 ± 7.8 yrs, respectively. The mean serum uric acid and creatinine levels were 537.6 ± 142.8 and 173.6 ± 119.9 μmol/l, respectively. In univariate analysis, longer duration of gout, higher adjusted mean serum creatinine, lower adjusted mean fasting serum, total cholesterol and high-density lipoprotein cholesterol (HDL-C) levels were associated with gouty flares. After adjustment for potential confounders in multivariate regression models, longer duration of gout and lower adjusted mean fasting serum HDL-C level remained independently predictive of gouty flares.

Conclusions. Low serum high-density lipoprotein cholesterol level was an independent predictor for gouty flares. Whether optimizing serum HDL-C level can benefit patients with gout in terms of reducing gouty flares needs to be addressed by controlled trials.

Key words: Gout, Flares, High-density lipoprotein cholesterol, Atherogenic, Lipid profile.
corticosteroids [20]. Acute gouty flares which occurred within 2 months following initiation of ULA were not taken into account [21]. Since our patients were managed as per usual, short courses of colchicine and corticosteroids and adjustment of ULA dose were allowed during the observation period if they were indicated. This study was approved by the Institutional Review Board of our institution.

Statistical analyses

Unless otherwise specified, values are expressed as mean ± S.D. Simple descriptive statistics were used to describe demographic and clinical characteristics of our patients. Comparison of categorical data was made by the chi-square test and the Fisher’s exact test was used instead when appropriate. Comparison of continuous data was made by using the Student’s t-test and the one way analysis of variance where appropriate. Mann–Whitney U-test and Kruskal–Wallis test were used instead if the data did not follow a normal distribution or if equal variance could not be assumed. To ascertain valid estimations of outcomes with multiple observations, adjusted mean serum Cr, UA, CRP and fasting lipid levels used for analyses were derived by the area under the curve of the respective parameters over time by adding the areas of each respective block of visit intervals divided by the length of time for the whole period using the trapezium rule. The adjusted mean of these parameters is particularly suitable for this study because patients were evaluated at irregular intervals while the total duration of follow-up was similar in all patients. To minimize skewness, the frequency of gouty flares was log-transformed. Univariate linear analyses were performed to explore the relationships between frequency of gouty flares and various demographics and clinical parameters. Multiple linear regression models were constructed to identify factors predictive of gouty flares in our patients. To ascertain the validity of the multiple regression models, test of good fit and analyses of residuals were performed. Multicollinearities within the multiple regression models were detected by the tolerance test and a tolerance value >0.6 was accepted.

Statistical significance was defined as two-tailed P-value <0.05. All statistical analyses were performed by the SPSS program (Version 16.0 for Window Vista, Chicago, IL, USA).

Results

One hundred consecutive patients with gout were followed and their demographic and clinical data are summarized in Table 1. Table 2 shows the results of the regression analyses. In univariate analysis, duration of gout, higher adjusted mean serum Cr level, lower adjusted mean fasting serum TC, lower adjusted mean HDL-C and LDL-C were significantly associated with frequency of gouty flares. In multiple linear regression, duration of gout and lower adjusted mean serum HDL-C level remained predictive of gouty flares after adjustment for age, gender, ethnicity, use of allopurinol and statins, and laboratory parameters comprising the serum CRP, UA, Cr, LDL-C and TG levels. Multicollinearities were detected in three pairs of covariates. They were (i) serum TC level and serum LDL-C level [Pearson coefficient (R) = 0.926, P < 0.001], (ii) serum TC and serum HDL-C level (R = 0.388, P < 0.001) and (iii) ischaemic heart disease and aspirin use (R = 0.746, P < 0.001). To stabilize the regression model, aspirin use and serum TC level were excluded in the multivariate analyses (Table 2). In a second multivariate model that excluded ischaemic heart disease and serum LDL-C level while keeping aspirin use, serum TC level and the other covariates as in the original model, duration of gout (P = 0.007) and serum HDL-C level (P = 0.002) remained significantly associated with gouty flares.

Discussion

While higher prevalence and incidence of gout in individuals with atherogenic lipid profile have been well reported, our study demonstrates, for the first time, that low serum HDL-C level is a strong predictor of gouty flares.

Low serum HDL-C was shown to be associated with higher disease activity in a few inflammatory conditions [13–18, 22]. In a case-control study, the change of serum HDL-C level was found to be inversely associated with that of the ESR in patients with RA and the HDL-C level increased after anti-inflammatory drug treatment [22]. In a prospective study of 42 treatment-naïve patients with RA, effective control of disease activity was coupled with increments in serum HDL-C level and Apo-A1 by 21 and 23%, respectively, after disease-modifying treatment for 12 months [17]. Beyond demonstrating an association between atherogenic lipid and inflammatory arthritis, van Halm et al. [18] recently studied the lipid profile of stored blood samples from 1078 blood donors who donated blood between 1984 and 1999. It was found that the serum HDL-C level of the 79 donors who subsequently developed RA was on average 9% lower than that of the matched donors, even after adjusting for pro-inflammatory marker levels including the CRP [18]. This interesting yet important observation suggests that HDL-C might play a modulating role on inflammatory processes, as hypothesized by the authors of the study [18]. To substantiate this hypothesis, few laboratory studies demonstrated that Apo-A1 in HDL-C particles inhibits the interactions between inflammatory cells [23, 24] and suppresses IL-1- and TNF-α-driven pro-inflammatory reactions [24, 25]. Without doubt, further experiments with repeatable results are required to confirm the hypothetical link between low HDL-C and susceptibility of inflammation.

Although pathogenically distinct from RA, as alluded to above clinical observations and experiments, the putative mechanism by which HDL-C can protect against gouty flares can be postulated. During acute gout, upon recognition of the monosodium urate...
TABLE 2. Predictors for gouty flare by regression analysis

<table>
<thead>
<tr>
<th></th>
<th>Univariate</th>
<th>Multivariate</th>
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<tbody>
<tr>
<td></td>
<td>Slope (SE)</td>
<td>R</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>−0.006 (0.008)</td>
<td>−0.082</td>
</tr>
<tr>
<td>Male</td>
<td>0.139 (0.262)</td>
<td>0.054</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>−0.119 (0.195)</td>
<td>−0.074</td>
</tr>
<tr>
<td>Duration of gout, yrs</td>
<td>0.049 (0.015)</td>
<td>0.322</td>
</tr>
<tr>
<td>Duration of allopurinol use, yrs</td>
<td>0.065 (0.058)</td>
<td>−0.137</td>
</tr>
<tr>
<td>Serum CRPa, µmol/l</td>
<td>0.002 (0.001)</td>
<td>0.203</td>
</tr>
<tr>
<td>Serum UAp, µmol/l</td>
<td>0.001 (0.001)</td>
<td>0.148</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.006 (0.324)</td>
<td>0.025</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>−0.249(0.310)</td>
<td>−0.067</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>−0.142(0.501)</td>
<td>−0.034</td>
</tr>
<tr>
<td>TCa, mmol/l</td>
<td>−0.264 (0.107)</td>
<td>−0.240</td>
</tr>
<tr>
<td>LDLa, mmol/l</td>
<td>−0.369 (0.152)</td>
<td>−0.307</td>
</tr>
<tr>
<td>HDLa, mmol/l</td>
<td>−1.610 (0.435)</td>
<td>−0.350</td>
</tr>
<tr>
<td>Tgα, mmol/l</td>
<td>−0.089 (0.129)</td>
<td>−0.069</td>
</tr>
<tr>
<td>CRP, mg/l</td>
<td>0.002 (0.002)</td>
<td>0.087</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>0.127 (0.236)</td>
<td>0.054</td>
</tr>
<tr>
<td>Statin use</td>
<td>0.030 (0.234)</td>
<td>0.013</td>
</tr>
</tbody>
</table>

*Slopes for CRP, LDL, HDL, Tg, CRP, Aspirin, Statin are not statistically significant.

In summary, we found that a low fasting serum HDL-C level was predictive of more frequent gouty flares in patients with gout. The inflammation-related properties of HDL-C in gout need to be further characterized in order to explore the precise role of HDL-C in gout.

**Rheumatology key messages**
- Low serum HDL-C predicts gouty flares in gout patients even after adjustment for potential confounders.
- Like RA, HDL-C may possess anti-inflammatory properties but experiments are required to confirm this.
- It is tempting to explore, by controlled trials, whether lowering serum HDL-C reduces gouty flares.

**Disclosure statement:** The authors have declared no conflicts of interest.

**References**
Atherogenic lipid profile predicts gout flares


