Gout and its relation to lipid metabolism

I. Serum uric acid, lipid, and lipoprotein levels in gout

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The relation between uric acid and lipid metabolism has been the subject of various recent studies. Harris-Jones (1957) reported that the serum uric acid level was often elevated in patients with essential hyperlipoproteinemia. Strejček and Kučerová (1968) demonstrated the incidence of gout in patients with high serum lipid levels, and the same phenomenon was observed by Berkowitz (1964), Feldman and Wallace (1964), Barlow (1966), Benedek (1967), Günther, Herbst, and Knapp (1967) and Darlington and Scott (1972). Investigations in which all the serum lipids and lipoproteins are determined in patients with gout and a control group are rare.

This paper reports the levels of serum uric acid, triglycerides, free-fatty acids (FFA), phospholipids, and total cholesterol in patients with gout and in a control group, with a comparison of the lipoprotein fractions of both groups.

Material and methods

31 patients with primary gout were assembled. The diagnosis of primary gout had been made according to the criteria of Decker, Acheson, Barry, Cobb, Mikkelsen, O'Sullivan, Rose, and Wallace (1968). There were 29 males and two females, and their ages varied from 19 to 79 yrs (mean 46).

The 31 subjects of the control group (5 females and 26 males), were all seen in the out-patients department for the treatment of minor traumatic injuries. In this group the ages varied from 18 to 75 yrs (mean 46). The age distribution of the two groups was thus closely comparable (Fig. 1).

Other concomitant disorders were excluded in all subjects. None was receiving any medication. The lipid and uric acid levels were measured after a 12-hour fast.

The serum uric acid levels were determined by the method of Caraway (1955). The triglycerides were determined after hydrolysis and saponification by the enzymatic method of Eggstein and Kreutz (1966). The free-fatty acids (FFA) were estimated by the microcolorimetric method of Novák (1965). The technique of Bartlett (1959) was used for the phospholipids. Total cholesterol was determined by the method of Sperry and Webb (1950), with extraction, hydrolysis, and precipitation on digitonine. Electrophoresis of lipoproteins was carried out as described by Chin and Blankenhorn (1968) on cellulose acetate strips (90 min. and 150 V), using a Natrium-veronal buffer (pH 8·6, ionic strength 0·075);

![FIG. 1 Age distribution of control group and patients with gouty arthritis](image-url)

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microdensitometry coloration was done with Oil Red. The pherograms were scanned with a Vitatron spectrophotometer type U.F.D.100.

Results

The frequency distribution of uric acid, triglycerides, FFA, phospholipids, and cholesterol levels and of the percentages of each lipoprotein fraction was found to be of the log normal type (Fig. 2). The log normal distribution of the data was confirmed by graphic normality tests. The statistical calculations were thus performed after log transformation of the serum levels (Tables I and II). It is important to notice that the mean value, expressed in mg./100 ml., was obtained by transformation of the m log value. The characteristics of the populations were defined by the lowest value, the 2.5th percentile, the mean level,
Table I  Serum uric acid and lipid levels in gout and in control subjects  

\[
m \log = \text{mean of logarithm of experimental data},
\]

\[
s \log = \text{standard deviation of logs},
\]

\[
sm \log = \text{standard error of the mean}
\]

<table>
<thead>
<tr>
<th>Serum levels of:</th>
<th>Group</th>
<th>Lowest value ((\text{mg./100 ml.)})</th>
<th>2.5th percentile</th>
<th>Mean value ((\text{mg./100 ml.)})</th>
<th>97.5th percentile</th>
<th>Highest value</th>
<th>(m \log)</th>
<th>(s \log)</th>
<th>(sm \log)</th>
<th>(t)</th>
<th>(P)</th>
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<td>2.52</td>
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<td>0.6353</td>
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<td>6.76</td>
<td>8.51</td>
<td>9.06</td>
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<tr>
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<td>56</td>
<td>96</td>
<td>208</td>
<td>177*</td>
<td>1.9830</td>
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<td>68</td>
<td>241</td>
<td>861</td>
<td>875</td>
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<td>0.2764</td>
<td>0.0496</td>
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<td>57</td>
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<td>297</td>
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<td>0.1048</td>
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<td>5.8</td>
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<td>0.9141</td>
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<td>5.6</td>
<td>10.5</td>
<td>19.8</td>
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<td>6.0</td>
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<td>1.1899</td>
<td>0.2068</td>
<td>0.0371</td>
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</table>

* So-called discrepant values.

Table II  Percentages of lipoprotein fractions in gouty patients and control subjects

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<th>Fraction</th>
<th>Group</th>
<th>Lowest percentage</th>
<th>2.5th percentile</th>
<th>Mean percentage</th>
<th>97.5th percentile</th>
<th>Highest percentage</th>
<th>(m \log)</th>
<th>(s \log)</th>
<th>(sm \log)</th>
<th>(t)</th>
<th>(P)</th>
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</thead>
<tbody>
<tr>
<td>(\alpha)-lipoproteins</td>
<td>Control</td>
<td>144</td>
<td>14.6</td>
<td>29.1</td>
<td>58.2</td>
<td>47.7*</td>
<td>1.4644</td>
<td>0.1506</td>
<td>0.0270</td>
<td>5.34</td>
<td>&lt;0.0005</td>
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<tr>
<td></td>
<td>Gout</td>
<td>4.2</td>
<td>7.9</td>
<td>17.5</td>
<td>38.9</td>
<td>30.1*</td>
<td>1.2453</td>
<td>0.1726</td>
<td>0.0310</td>
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<tr>
<td>Pre-(\beta)-lipoproteins</td>
<td>Control</td>
<td>0.0</td>
<td>0.0</td>
<td>6.5</td>
<td>50.8</td>
<td>26.1*</td>
<td>0.8159</td>
<td>0.4450</td>
<td>0.0799</td>
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<td>5.1</td>
<td>5.5</td>
<td>25.1</td>
<td>100</td>
<td>83.3*</td>
<td>1.3999</td>
<td>0.3295</td>
<td>0.0591</td>
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<td>(\beta)-lipoproteins</td>
<td>Control</td>
<td>39.3</td>
<td>44.0</td>
<td>58.9</td>
<td>78.8</td>
<td>77.2*</td>
<td>1.7704</td>
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<td>Gout</td>
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<td>15.6</td>
<td>44.6</td>
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<td>0.0411</td>
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</table>

* So-called discrepant values.

the 97.5th percentile and the highest value. The 2.5 percentile and the 97.5th percentile are obtained by transformation of \(m \log - 2s \log\) and \(m \log + 2s \log\). The statistical results are also shown on Tables I and II.

For some parameters, the 2.5 percentile was found to be lower than the lowest value and the 97.5th percentile higher than the highest value, because the analysed population is relatively small. We must stress that the percentiles are deduced from the characteristics of the populations and that the highest and lowest values are obtained experimentally. The so-called discrepant values are marked with an asterisk in Tables I and II.

Discussion

Our findings confirm those of Berkowitz (1966) and Günther, Knapp, and Siller (1968), who reported that the frequency distribution of the serum lipid levels is of the log normal type. Unfortunately, most other investigators who determined the serum lipid levels in gout and in normal populations did not perform frequency histograms and made their statistical calculations as if the frequency distributions were normal.

**SERUM URIC ACID**

As expected, there was a significant increase of the serum uric acid level in the group of gouty patients \((t = 7.42; \ P < 0.0005)\), although an important overlapping of the two populations is to be noticed. In fourteen gouty patients, the serum uric acid level was lower than the 97.5th percentile value of the control group and in five normal subjects the uric
acid level was found to be higher than the 2.5th percentile value of the gouty group. These data are in harmony with those found by most authors, so that we are also inclined to attribute only little value to the uric acid level in the diagnosis of gouty arthritis.

TRIGLYCERIDES
Like Berkowitz (1964), Feldman and Wallace (1964), Barlow (1966), Benedek (1967), Rondier, Truffert, Le Go, Brouilhet, Saporta, De Gennes, and Delbarre (1970), and Darlington and Scott (1972), we found a significant increase in the triglyceride level in gouty arthritis.

Previously, however, only Berkowitz (1967) and Günther and others (1968) considered the log normal frequency distribution of this parameter. The values were compared with a control group only in the first investigation.

CHOLESTEROL
We found a significant increase in the serum cholesterol level in gout. These observations confirm the findings of Barlow (1966) and Rondier and others (1970), but this increase was not observed by Berkowitz (1964), Feldman and Wallace (1964), Benedek (1967), and Darlington and Scott (1972). Only Berkowitz (1964) took the log normal frequency distribution into consideration. Günther and others (1968) reported the characteristics of the serum cholesterol level in gouty patients and emphasized the log normal distribution of this parameter. It is obvious that both the $m$ log (2.3938) and the $s$ log (0.1048) values of cholesterol in our patients were closely similar to the values (2.4377 and 0.0975) reported by these authors.

FREE-FATTY ACIDS
The free-fatty acids have been investigated by only three authors. Barlow (1966) and Darlington and Scott (1972) found a statistically significant increase of FFA in gouty patients, and Gunther and others (1968) also reported higher levels of FFA in gout but did not support their results by statistical comparison.

PHOSPHOLIPIDS
As Darlington and Scott (1972) reported, we found a significant increase of the phospholipids in gout. Rondier and others (1970), however, did not report any significant variation of the phospholipids.

Lipoproteins
We found a statistically significant increase of the pre-$\beta$-lipoproteins and a concomitant decrease of both the $\alpha$- and $\beta$-lipoproteins in gouty patients. The statistical evaluation was performed on the percentages of each lipoprotein fraction and not on the serum concentration. Feldman and Wallace (1964) did not find a variation in the lipoprotein spectrum in gout, but no separation of the pre-$\beta$-fraction from the $\beta$-fraction was possible with their electrophoresis procedure. Bluestone, Lewis, and Mervart (1971) found that the gouty patients with increased triglyceride levels also presented increased pre-$\beta$-lipoprotein fractions.

We thus found a significant increase in the triglycerides, cholesterol, FFA, and phospholipids. Furthermore, the lipoprotein spectrum is characterized by an increase in the percentage of pre-$\beta$-lipoproteins and a concomitant decrease in the $\alpha$- and $\beta$-lipoproteins. The significant increase of all lipid values clearly indicates a disturbance in the lipid metabolism in gout.

Although coincidental disturbances cannot be excluded, the existence of a direct correlation between the disturbances in the purine and the lipid metabolism seems more likely to us. We can no longer doubt that the existence of different genetic defects, causing various enzyme disturbances, is the basis of primary gout (Kelley, Rosenbloom, Henderson, and Seegmiller, 1967; Rosenbloom, Henderson, Caldwell, Kelley, and Seegmiller, 1968; Seegmiller, Klienberg, Miller, and Watts, 1968; Kelley, Greene, Rosenbloom, Henderson, and Seegmiller, 1969); Kelley, Levy, Rosenbloom, Henderson, and Seegmiller, 1968). The aetiology of primary hyperlipoproteinemia is possibly based on a similar mechanism (Fredrickson, Levy, and Lees, 1967). The correlation between the purine and lipid metabolism demonstrated in this investigation indicates the possible existence of a genetic linkage. Since a genetic disturbance in both disorders is manifested by one or more enzyme defects, we wish to postulate the existence of a close enzymatic relation between the two metabolisms. This relation could be explained by the existence of an enzyme defect in gout which also interferes with the lipid metabolism.

The discovery of such a common enzyme defect would be the key to this hypothesis. In the framework of these considerations, it is important to notice that Berkowitz (1965) and Rondier and others (1970) found a simultaneous decrease of both triglycerides and uric acid in gouty patients treated with lipid-lowering therapy. Bluestone and others (1971), on the other hand, found a decrease in triglycerides in gouty patients treated with uric acid-lowering drugs.

Finally, it appears that the determination of the lipids and lipoprotein spectrum is of great importance in cases of primary gout, both to confirm the diagnosis and to provide useful therapeutic indications.

Summary
Serum uric acid, lipid, and lipoprotein levels were determined in 31 patients with primary gout and in 31 control subjects. Since the frequency distributions of these parameters were found to be of the log normal...
type, the statistical calculations were performed after log transformation of the serum levels.

A statistically significant increase in uric acid and in all lipids was found in gouty subjects as compared to the controls. In the lipoprotein spectrum, a statistically significant increase of the pre-β-lipoproteins and a concomitant decrease of both the α- and the β-lipoproteins were found in the gouty patients. These findings clearly establish the existence of a disturbance in lipid metabolism in gout. The importance of lipid and lipoprotein determinations in cases of primary gout is emphasized.

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