Family study of lipid and purine levels in gout patients

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SUMMARY A family study was performed to determine whether the hypertriglyceridaemia associated with gout is present in families of gout patients or due to the life style of the patient himself. The study revealed the expected hypertriglyceridaemia in gout patients; this was reflected by elevated serum levels of prebeta-lipoproteins and with reduction in the proportion of beta-lipoprotein. None of these abnormalities were seen in the first-degree relatives. Furthermore, the proportion of high-density lipoproteins was not significantly raised in gout patients.

To determine whether the hypertriglyceridaemia of gout patients occurs in their families or is simply the result of the life style of these obese, often alcohol-drinking patients who frequently originate from higher social classes¹ a family study was designed to measure lipid and uric acid levels in the blood of gout patients and their first-degree relatives and to compare them with those found in controls of the same age and sex.

Patients and methods

Pedigrees were constructed for 169 male and 11 female primary gout patients with details of age and whereabouts of all living, first-degree relatives. The patients had been diagnosed by generally accepted clinical criteria; many of them were receiving treatment for hyperuricaemia at the time of the study. Fasting blood samples were analysed to determine lipid and uric acid levels. Cholesterol was measured by a revision of the Schoenheimer-Sperry method for cholesterol determination,² triglycerides by a micro-method for direct determination,³ and electrophoretic separation of lipoproteins was performed in agarose gel by the method of Noble.⁴ Plasma urate was measured by direct ferric reduction or by absorbance change on oxidation of urate with alkaline ferricyanide.⁵

Owing to regional and ethnic variations in lipid concentrations⁶ results were compared with those

obtained by the same laboratory from 2388 control subjects of known age and sex from the same geographical area and ethnic background as the gout group, that is, from a working population in north-west London.⁷

Results

Lipid and uric acid data for gout patients, first-degree relatives, and expected values for controls at the same mean age are given in traditional units in Tables 1a and 1b.

The means and standard deviations of variables from gouty index patients and relatives when compared with controls are also expressed in standard

Table 1a Lipid and uric acid data from male gout patients and male first-degree relatives

Group	Mean and SD	n	Mean age	Expected values for controls at mean age
Male gout patients				
Cholesterol mg/dl	244.3 ± 56.4	147	56.5	234.3
Triglyceride mg/dl	212.95 ± 239.1	147	55.4	124.8
% β-Lipoprotein	45.9 ± 11.1	141	55.2	51.6
% Pre-β-lipoprotein	26.8 ± 13.4	141	55.2	21.2
% α-Lipoprotein	27.1 ± 9.6	141	55.2	27.1
Uric acid μmol/l	389.8 ± 91.1	136	55.4	360
Male relatives				
Cholesterol mg/dl	238.5 ± 48.4	69	48.1	232.7
Triglyceride mg/dl	141.8 ± 93.5	70	47.9	127.1
% β-Lipoprotein	47.7 ± 7.82	67	57.1	51.7
% Pre-β-lipoprotein	22.2 ± 10.2	67	57.1	21.0
% α-Lipoprotein	30.0 ± 7.83	67	57.1	27.6
Uric acid μmol/l	360.5 ± 67.0	64	47.9	360

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Table 1b *Lipid and uric acid data from female gout patients and female first-degree relatives*

Group	Mean and SD	n	Mean age	Expected values for controls at mean age
<i>Female gout patients</i>				
Cholesterol mg/dl	270.5 ± 91.0	4	57.3	254.1
Triglycerides mg/dl	133.8 ± 51.0	4	57.3	111.7
% β -Lipoprotein	47.1 ± 7.2	4	57.3	50.8
% Pre- β -lipoprotein	20.0 ± 4.15	4	57.3	17.9
% α -Lipoprotein	32.9 ± 5.21	4	57.3	32.5
Uric acid μ mol/l	381.1 ± 121.6	4	57.3	300
<i>Female relatives</i>				
Cholesterol mg/dl	241.8 ± 65.1	102	47.8	231.6
Triglycerides mg/dl	96.4 ± 65.7	103	47.8	97.5
% β -Lipoprotein	48.7 ± 8.17	99	46.7	50.2
% Pre- β -lipoprotein	15.3 ± 7.83	99	47.3	17.1
% α -Lipoprotein	36.2 ± 8.49	99	47.3	32.4
Uric acid μ mol/l	291.0 ± 69.0	101	48.0	270

SI conversion = cholesterol mmol/l = mg/dl $\times$ 0.0259.
Triglycerides mmol/l = mg/dl $\times$ 0.0113.

deviation units in Table 2 to eliminate the variables of age and sex. The statistical significance of differences between data from gout patients, relatives, and controls is indicated. Table 2 shows that triglyceride levels in gout patients were found to be significantly higher than in controls ($p < 0.001$). These changes were, predictably, reflected by changes in the proportion of pre- β -lipoprotein, which was also significantly higher in gout patients than in controls ($p < 0.001$). There was a significant reduction in the proportion of β -lipoprotein in gout patients when compared with controls ($p < 0.001$).

Table 3 shows that triglyceride and pre- β -lipoprotein levels in gout patients were significantly higher than in relatives ($p < 0.001$) with a significant reduction in the proportion of β -lipoprotein ($0.01 > p > 0.001$).

Table 3 shows a small but significant reduction in the proportion of β -lipoprotein in relatives when

Table 2 *Differences in mean values of variables studied between index patients and controls and first-degree relatives and controls, expressed in standard deviation units*

Variable	Index patients compared with controls	No. of subjects	First-degree relatives compared with controls	No. of subjects
Cholesterol	+0.20 ± 1.15	143	+0.25 ± 1.12*	165
Triglycerides	+0.60 ± 1.28***	143	-0.16 ± 1.18	165
% β -Lipoprotein	-0.78 ± 1.49***	142	-0.34 ± 1.18**	162
% Pre- β -lipoprotein	+0.71 ± 1.55***	142	-0.04 ± 1.07	161
% α -Lipoprotein	-0.07 ± 1.32	141	+0.27 ± 1.24*	162
Uric acid	+0.61 ± 1.44***	140	+0.05 ± 1.28	159

*0.05 > p > 0.01. **0.01 > p > 0.001. *** p = < 0.001.

Table 3 *Lipid and uric acid results from family study*

	Difference between index patients and controls	Difference between index patients and 1st-degree relatives	Difference between 1st-degree relatives and controls
	Significance	Significance	Significance
Cholesterol	NS	NS	*
Triglycerides	***	***	NS
% of β -lipoprotein	***	**	**
% of pre- β -lipoprotein	***	***	NS
% of α -lipoprotein	NS	*	*
Uric acid in males	***	***	NS
Uric acid in females	NS	*	NS

NS = not significant. *0.05 > p > 0.01. **0.01 > p > 0.001. *** p = < 0.001.

compared with control subjects ($0.01 > p > 0.001$) but no difference in triglycerides or pre- β -lipoprotein levels.

Table 3 also shows a marginal increase in the proportion of α -lipoprotein in relatives when compared with both gout patients and controls ($0.05 > p > 0.01$), but there was no significant difference between the α -lipoprotein proportions in gout patients and controls. There was no significant difference between cholesterol levels in gout patients and controls or between gout patients and relatives, but both Tables 2 and 3 show that there was a marginal increase in cholesterol levels in relatives when compared with controls ($0.05 > p > 0.01$).

As shown in Table 3, uric acid levels in male, gouty index patients were significantly higher than in controls or relatives ($p < 0.001$), despite the fact that many of them were on urate-lowering drugs. Separate analysis of female index patients must be assessed with caution in view of the small numbers concerned. Table 2 shows that the mean uric acid level in relatives was slightly greater than in controls, but this difference was very small and did not approach the significant elevation found in the study of Hauge and Harvald.⁸

The families of 35 gout patients who were found to have lipid levels (triglyceride and/or cholesterol) above the 95th centile were assessed to determine whether they constituted a particular subgroup in the family study.

First-degree relatives of hyperlipidaemic, gouty index patients had raised cholesterol levels when compared with controls (males $0.05 > p > 0.025$; females $0.02 > p > 0.01$). There were no elevations in triglyceride levels among these relatives.

Weights were measured in gout patients, relatives, and controls. There were too few female gout patients for analysis, but the weight data presented in Tables 4 and 5 were analysed and showed that male, gout patients were significantly heavier than male

Table 4 Weight data from index patients and relatives

	Range in kg	Mean weight in kg
Male index patients	57.1-126.4	82.5
Female index patients	58.4- 80.0	67.1
Male relatives	50.9-103.2	76.0
Female relatives	37.3-105.0	61.5

Table 5 Weight data from controls

	Number	Mean weight in kg	SD in kg
Male	1645	75.01	10.34
Female	743	62.98	9.35
Total	2388	71.26	10.04

relatives and controls ($p = <0.001$). The mean weight of hyperlipidaemic male gout patients was not, however, significantly heavier than the mean of the whole gouty group. This obesity may well be associated with hypertriglyceridaemia in certain male subjects and in raised triglyceride levels in the whole male gout population.

The alcohol intake of the hyperlipidaemic group varied widely, emphasising that alcohol is only one factor in inducing hyperlipidaemia but is doubtless significant in some cases.

Discussion

Many authors have noted an association between hypertriglyceridaemia and gout. For example, Darlington and Scott⁹ found significant hypertriglyceridaemia in primary gout patients when compared with matched controls ($0.01 > p > 0.001$). Berkowitz¹⁰ and Frank¹¹ found raised triglyceride levels in 52% and 84% of gout patients respectively, but this association was not seen in patients with symptomless hyperuricaemia.¹¹

In 1973 Mielants *et al.*¹² found an increase in the proportion of pre- β -lipoproteins and a reduction in the proportions of α - and β -lipoproteins in gout patients. Emmerson and Knowles¹³ demonstrated hypertriglyceridaemia in primary gout patients persisting after correction for body weight, and Darlington and Scott⁹ also described gout and hypertriglyceridaemia independent of obesity.

In 1974 Gibson and Grahame¹⁴ suggested that obesity, alcohol, or both were the main causes of hypertriglyceridaemia in gout. Gibson *et al.*¹⁵ later showed significant reductions in triglycerides in gout patients following reduction of either alcohol intake or weight, but Darlington and Scott,¹⁶ although observing some reduction in triglycerides after alcohol abstinence, did not find that this achieved statistical significance.

Elkeles and Chalmers¹⁷ raised triglyceride concentrations by infusion of fat but did not demonstrate an effect on plasma uric acid from this elevation of triglyceride. Gibson *et al.*¹⁵ also used the Intralipid tolerance test and similarly failed to demonstrate any effect either of triglyceride on uric acid levels or of hyperuricaemia on triglyceride removal.

The hypercholesterolaemia in first-degree relatives of hyperlipidaemic gouty index patients is best explained by polygenic inheritance in the same way as first-degree relatives of tall index patients tend to be taller than average. Since the hyperlipidaemia was a hypercholesterolaemia (and not a hypertriglyceridaemia such as occurs in association with gout) it was probably a finding which is unrelated to hyperuricaemia or gout itself.

Unaffected relatives of gout patients have been reported to show an increased serum level of uric acid, which is thought to be determined by polygenic factors.⁸

The results of this family study reveal hyperpre- β -lipoproteinaemia in gout patients as a whole with reduction in β -lipoprotein. These abnormalities were not seen in first-degree relatives, suggesting that the hypertriglyceridaemia associated with gout is not present in the families of gout patients but is rather due to factors in the life style of the patients.

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