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# Hyperlipoproteinaemia in primary gout: hyperlipoproteinaemic phenotype and influence of alcohol intake and obesity in Japan

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SUMMARY Serum lipoprotein profiles were investigated in 108 male patients with primary gout before treatment to elucidate the prevalence of each individual phenotype of coexisting hyperlipoproteinaemia and pathogenic factors responsible for it. The mean serum triglyceride (TG) and total cholesterol (TC) levels in the patients with gout were 2·10±0·14 mmol/l and 5·26±0·10 mmol/l (mean±SEM) respectively, which were significantly higher ($p<0·01$ and $p<0·05$ respectively) than the levels in age matched controls without gout (1·30±0·07 mmol/l and 4·77±0·08 mmol/l respectively). Serum high density lipoprotein cholesterol (HDL-C) values were slightly decreased in patients with gout compared with controls (1·24±0·08 mmol/l *v* 1·40±0·03 mmol/l, $p<0·05$). Hyperlipoproteinaemia was seen in 61 patients (56%), of whom patients with type IIa, IIb, and IV hyperlipoproteinaemia formed 13, 15, and 69% respectively. Thus the prevalence of type IV hyperlipoproteinaemia was high in primary gout as compared with primary hyperlipoproteinaemia (69% *v* 43%, $p<0·01$). The independent and relative influences of clinical data of the patients upon the concentrations of serum lipids were assessed by stepwise multiple regression analysis. Two major predictors of serum TG level were alcohol intake ($p<0·01$) and serum uric acid level ($p<0·05$). The most significant predictive variable was alcohol intake, but its influence was judged to be small ($r^2=0·067$). None of the other variables, including obesity index, had any significant influence. The relationships between any of these variables and serum TC or HDL-C levels were not significant. In addition, serum lipid levels were investigated in patients with neither obesity (defined as 120% or more of ideal body weight) nor a history of alcohol intake. Their serum TG and TC concentrations were also significantly higher than the respective control levels. Thus hyperlipoproteinaemia in primary gout is unlikely to be secondary to excess alcohol intake or obesity, or both. Instead, it may result from genetic factors such as a combined hyperlipidaemic trait.

Key words: type IV hyperlipoproteinaemia, alcohol ingestion, combined hyperlipidaemia.

Recently, several investigators reported that the prevalence of coronary heart disease (CHD) was so high in primary gout as to effect its prognosis in Western countries.[1–4] Even in Japan, where CHD is less frequently found than in Western countries, its prevalence has been on the increase, so that it is becoming a major cause of death in gouty patients.

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Although a raised serum uric acid (SUA) has been shown in a few reports[5 6] to have direct bearing upon the development of atherosclerosis, the precise mechanism is still unknown. Therefore, it seems important to assess the impairment of serum lipoprotein metabolism as a major risk factor for CHD, i.e., an increase in serum cholesterol level and a decrease in high density lipoprotein cholesterol (HDL-C) concentration, in gouty patients. The close relation of hypertriglyceridaemia with hyperuricaemia or gout has been reported by several

investigators,[7-12] but the significance of serum lipoproteins, the form in which lipids circulate, has not been well documented in primary gout.

Moreover, the mechanism of development of hyperlipidaemia in primary gout is controversial. A number of investigations suggested that it might be due to excessive alcohol intake and obesity.[11 13] However, no direct evidence supporting this has been presented. In addition, previous studies have dealt with small or heterogeneous populations.[12 14]

In the present study we used a relatively large and homogeneous group of 108 untreated patients with primary gout, whose lipoprotein phenotypes were identified by means of polyacrylamide gel disc electrophoresis, and tried to clarify whether hyperlipoproteinaemia in primary gout is consequent upon essential factors or secondary to alcohol intake or obesity.

## Subjects and methods

### SUBJECTS

The subjects used in this study were 108 male patients with primary gout, 877 normouricaemic males with primary hyperlipoproteinaemia, and 92 normouricaemic healthy male controls. The patients with gout were selected from the population of 198 patients with primary gout referred to our clinic. They had received no medication for hyperuricaemia or hyperlipoproteinaemia for at least six months before the study. Of the 90 patients excluded, two patients had overt diabetes mellitus and the remaining 88 were under treatment for hyperuricaemia or hyperlipoproteinaemia, or both. All the gouty patients met the criteria for definite or classical gout.[12] Their ages ranged from 24 to 85 years (mean±SEM 45±1 years), and the duration of the disease was from one to 28 years (mean 8·3±0·7 years). Their fasting plasma glucose concentrations were below 110 mg/dl (6·11 mmol/l).

The 877 age matched normouricaemic patients with primary hyperlipoproteinaemia, who ranged in age from 22 to 78 years (mean 47±1 years), were from the population attending our clinic for hyperlipoproteinaemia.

The 92 male controls, whose ages ranged from 25 to 78 years (mean 44±1 years), were randomly selected. They were judged normal in terms of physical findings, SUA, serum electrolyte levels, renal profiles, and liver function tests.

Measurement of serum lipids and lipoproteins was performed twice with an interval of two weeks before treatment for hyperuricaemia and repeated regularly during the treatment in patients with primary gout. Mean values were used. In the other groups the baseline values were determined only once. The gouty patients did not undergo strict calorie restriction during the study, and their mean body weight showed no significant change during the treatment.

### METHODS

Venous blood was sampled via an antecubital vein from 9.00 am to 11.00 am after an overnight fast. Serum was separated promptly by a low speed centrifugation and kept at 4°C. Serum total cholesterol (TC) and triglyceride (TG) concentrations were determined by enzymatic methods[15 16] with commercial kits (Kyowa Medex Co., Tokyo, Japan). Serum HDL-C was measured by the polyanion-metal precipitation method[17] with heparin-calcium as the precipitation agent. The classification of hyperlipoproteinaemic phenotypes recommended by the World Health Organisation[18] was based on the lipoprotein profile, including the pattern of polyacrylamide gel disc electrophoresis.[19] In addition to serum uric acid, total protein, albumin, inorganic calcium, inorganic phosphorus, and glucose, renal profiles (sodium, potassium, chloride, creatinine, urea nitrogen), and liver function tests (serum aspartate aminotransferase, γ-glutamyltransferase, lactate dehydrogenase, alkaline phosphatase) were determined by the autoanalyser technique (Toshiba TBA-880 and AHS Japan NOVA 5+5).

Ideal body weight (IBW) was obtained from the 'weight for height chart' published by the Ministry of Health and Welfare, Japan. The information about alcohol consumption (g/day) and cigarette smoking (cigarettes/day) was obtained by a questionnaire. Daily alcohol intake was given as millilitres beer/day. This was converted into the net content of alcohol. All the subjects were given detailed information about the study, and informed consent was obtained from all of them.

### STATISTICAL ANALYSIS

Results were expressed as mean values with one standard error of mean (mean±SEM). Student's *t* test was used to evaluate the significance of differences between the means in the groups. The significance of differences in frequency of individual hyperlipoproteinaemic phenotypes was analysed by the $\chi^2$ test with Yates's correction. Correlation coefficients (r) were determined by linear regression analysis and multiple regression analysis.

## Results

The clinical features of the subjects are shown in Table 1. There was no significant difference between the patients with primary gout and the normal

controls with respect to age, obesity index, alcohol intake, or smoking. The mean SUA level was 0·54±0·01 mmol/l (mean±SEM) in the untreated gouty patients (gout group). The serum TG and TC values were higher in the gout group than in the control group ($p<0·01$ and $p<0·05$ respectively). The HDL-C levels were slightly but significantly decreased in the gout group ($p<0·05$). Of the 108 patients with gout, 61 had hyperlipoproteinaemia, classified by its phenotypes as follows: eight patients (13%) with type IIa, nine (15%) with IIb, 42 (69%) with IV, and two (3%) with V (Table 2). The frequency of type IV hyperlipoproteinaemia was significantly higher ($p<0·01$) and that of type IIa significantly lower ($p<0·01$) than the corresponding frequencies in a large population of patients with primary hyperlipoproteinaemia in the Osaka area, Japan.

Table 1 *Clinical features and serum lipid concentrations*

| | *Patients with gout* | *Controls* |
|---|---|---|
| Number of subjects | 108 | 92 |
| Age (years) | 45±1 | 44±1 |
| % IBW | 117±1 | 113±1 |
| SUA (mmol/l) | 0·54±0·01** | 0·32±0·02 |
| Serum triglyceride (mmol/l) | 2·10±0·14** | 1·30±0·07 |
| Serum total cholesterol (mmol/l) | 5·26±0·10* | 4·77±0·08 |
| HDL cholesterol (mmol/l) | 1·24±0·08* | 1·40±0·03 |
| Alcohol intake (g/day) | 28±3 | 30±4 |
| Cigarette consumption (cigarettes/day) | 10±1 | 12±2 |

Values are expressed as mean±SEM.
*$p<0·05$; **$p<0·01$.

The gout group included 75 drinkers and 68 obese men with 120% of IBW or more. To determine whether or not hypertriglyceridaemia in the patients with primary gout occurred independently of alcohol intake or obesity, or both we performed two analyses. Firstly, stepwise multiple regression analysis was performed using various factors that might possibly affect serum TG level, including alcohol consumption, %IBW, age, cigarette consumption, blood pressure, SUA, serum creatinine, blood urea nitrogen (BUN), γ-glutamyltransferase (GGT), and serum aspartate aminotransferase (serum AST). The results obtained are presented in Table 3. Among these factors the greatest predictor of serum

Table 2 *Phenotypes of hyperlipoproteinaemia (HLP) in the patients with primary gout*

| | *Prevalence of HLP* | *I* | *IIa* | *IIb* | *III* | *IV* | *V* |
|---|---|---|---|---|---|---|---|
| Gout | | | | | | | |
| Untreated (108) | 56 | 0 | 13* | 15 | 0 | 69* | 3 |
| Treated (88) | 45 | 0 | 12* | 16 | 0 | 72* | 0 |
| Total (196) | 50 | 0 | 12* | 16 | 0 | 70* | 2 |
| Primary HLP | | | | | | | |
| Male (877) | 100 | 0·2 | 30·2 | 21·2 | 2·9 | 42·9 | 2·6 |

Values are expressed as percentages. Numbers of the subjects are given in parentheses.
*$p<0·01$ (*v* primary HLP).

Table 3 *Stepwise regression analysis of serum triglyceride levels on selected independent variables (108 untreated gouty men)*

| *Variable* | *Regression coefficient* | *Standard regression coefficient* | *Standard error* | *Student's t value* | *p Value* | *Multiple regression coefficient* |
|---|---|---|---|---|---|---|
| Alcohol | 1·212 | 0·258 | 0·0938 | 2·755 | <0·01 | 0·258 |
| SUA | 16·032 | 0·166 | 0·0929 | 2·340 | <0·05 | 0·307 |
| BUN | −3·391 | −0·180 | 0·0919 | 2·191 | <0·05 | 0·349 |
| Tobacco | 0·945 | 0·114 | 0·0917 | 1·998 | <0·05 | 0·366 |
| % IBW | 0·894 | 0·0940 | 0·0917 | 1·838 | NS | 0·377 |
| Serum AST | −1·404 | −0·131 | 0·0913 | 1·779 | NS | 0·398 |
| GGT | 0·688 | 0·229 | 0·0903 | 1·797 | NS | 0·429 |
| dBP* | 0·414 | 0·0398 | 0·0907 | 1·681 | NS | 0·431 |
| sBP* | −0·973 | −0·146 | 0·0908 | 1·611 | NS | 0·439 |
| Age | 0·483 | 0·0426 | 0·0912 | 1·527 | NS | 0·440 |
| Cr* | −20·715 | −0·0515 | 0·0916 | 1·452 | NS | 0·441 |

*dBP=diastolic blood pressure; sBP=systolic blood pressure; Cr=serum creatinine.

TG concentration was alcohol intake. However, only 6·7% of the variability in serum TG level could be accounted for by changes in alcohol intake ($r^2$=0·067). The other independent predictors of TG concentration were SUA (p<0·05), BUN (p<0·05), and cigarette consumption (p<0·05). Of particular interest was the absence of a significant correlation between the TG level and %IBW after adjustment for the following factors: alcohol intake, SUA, BUN, and cigarette consumption. The same analysis was performed to ascertain possible relationships of these parameters with serum TC and HDL-C levels, but no significant relationships were observed.

Secondly, serum lipid concentrations were investigated in the 23 gouty patients who neither consumed alcohol nor were obese (defined as 120% or more of IBW). Even in these patients the serum TC and TG levels were higher than those in age matched controls (TC 5·54±0·34 mmol/l *v* 4·77±0·08 mmol/l, p<0·05; TG 1·76±0·34 mmol/l *v* 1·30±0·07 mmol/l, p<0·05 respectively). The HDL-C concentration in these patients was slightly lower than that in normal controls, but this did not reach statistical significance (1·32±0·05 mmol/l *v* 1·40±0·03 mmol/l respectively). Of these 23 patients, 11 showed hyperlipoproteinaemia. The phenotype pattern of hyperlipoproteinaemia was as follows: two patients with type IIa, four with type IIb, and five with type IV. This pattern resembled that in the gout group as a whole. This finding suggests that alcohol intake and obesity were not essential for the occurrence of hypertriglyceridaemia in patients with primary gout.

The changes in serum lipoprotein profiles during treatment with antihyperuricaemic agents were also investigated. We were able to perform a follow up study in 81 patients. The follow up periods ranged from one to 58 months (mean±SEM 12±1). Thirty one of these patients were treated with allopurinol, 25 with probenecid, and the rest with a combination of both drugs. On medication the SUA level was significantly decreased from the baseline level of 0·54±0·01 mmol/l to 0·34±0·01 mmol/l (p<0·001). In contrast, there was no significant change in serum TG, TC, and HDL-C values during the treatment. The changes in hyperlipoproteinaemic phenotype are summarised in Table 4. Of the 48 hyperlipoproteinaemic cases followed up, the phenotype changed from one of IIa, IIb, and IV to another in eight cases during the treatment. Two patients with type V hyperlipoproteinaemia changed to type IV after the cessation of alcohol intake. Forty six patients showed no change in phenotype.

## Discussion

This study showed raised serum TC and TG levels, decreased HDL-C values, and a high frequency of type IV hyperlipoproteinaemia in patients with primary gout. There is considerable evidence to support the association of gout with hypertriglyceridaemia. Several studies have suggested that the hypertriglyceridaemia might be caused by alcohol intake or obesity, or both, which are common in gouty patients.[11 13] However, there has been no adequate evidence of the necessity of these factors for the development of hypertriglyceridaemia in patients with primary gout. The present study showed that alcohol intake did affect serum TG levels but was not essential for the occurrence of hypertriglyceridaemia. In addition, adiposity was not an independent predictor of a rise of serum TG concentration or the occurrence of hypertriglyceridaemia in patients with primary gout, after adjustment for alcohol ingestion, SUA, BUN, and smoking. Although Naito and Mackenzie[12] also noticed that the serum TG concentration was higher in gouty patients having no history of drinking than that in controls, they investigated only 30 patients, including individuals on medication. Raised levels of serum TG in non-drinking gouty patients were also reported by Nishida *et al*,[20] who, however, did not consider the influence of obesity. In contrast, we

Table 4 *Change of the phenotype of hyperlipoproteinaemia during administration of antihyperuricaemic agents*

| | | *Post-treatment phenotype* | | | | |
|---|---|---|---|---|---|---|
| | | *IIa* | *IIb* | *IV* | *V* | *Normo-LP†* |
| Pretreatment phenotype | IIa | 2* | 0 | 2** | 0 | 2 |
| | IIb | 0 | 3 | 3 | 0 | 2 |
| | IV | 1 | 2 | 21 | 0 | 8 |
| | V | 0 | 0 | 2 | 0 | 0 |
| | Normo-LP | 1 | 0 | 12 | 0 | 20 |

Each value represents the number of patients, for example, whose hyperlipoproteinaemic phenotype was type IIa at pre- and post-treatment period (*), or whose phenotype changed from type IIa to type IV (**).
†Normo-LP=normolipidaemia.

studied a relatively large and homogeneous gouty population.

The mechanism of development of hypertriglyceridaemia in gout is still obscure. However, at least the possibility that hypertriglyceridaemia might develop as a direct consequence of an increase of SUA concentration is unlikely since the improvement of hyperuricaemia by allopurinol or probenecid was not accompanied by a change of serum TG or TC levels in our gouty patients. This agrees with the observation of Dunn and Moses[21] that SUA levels did not correlate with serum TG levels in healthy male subjects. It remains largely unknown whether hypertriglyceridaemia or type IV hyperlipoproteinaemia is due to the impaired catabolism of TG rich lipoproteins such as chylomicrons and very low density lipoproteins (VLDL) or to their overproduction by the liver. Gibson *et al*[22] concluded that an impairment of catabolism did not exist in gouty patients as they failed to show delayed clearance of exogenously injected Intralipid. In contrast, Naito and Mackenzie[12] concluded that the availability of apolipoprotein C-II, which activates hydrolysis of TG rich lipoproteins by lipoprotein lipase, was reduced, though no direct evidence has been shown. Recently, Kodama *et al*[23] investigated the activity of lipoprotein lipase in gouty patients and concluded that it did not differ between gouty patients and control subjects. It is unlikely, therefore, that the catabolism of TG rich lipoproteins is impaired in gout. Consequently, the overproduction of TG rich lipoproteins in the liver appears to be the cause of hyperlipoproteinaemia in gout. If this is the case there must be a close correlation between the production of uric acid and that of TG rich lipoproteins. In this study we failed to show a metabolic link between the overproduction of uric acid and that of TG rich lipoproteins because most of our gouty patients had combined type hyperuricaemia with both overproduction and disturbed urinary secretion of uric acid when judged from the ratio of uric acid clearance to creatinine clearance, and we could not determine the pure production rate of uric acid.

Furthermore, the changes from one of the three phenotypes of hyperlipoproteinaemia (IIa, IIb, and IV) to another during the follow up suggested the association of a familial combined hyperlipidaemic gene with primary gout. This trait was proposed by Goldstein *et al*,[24] and the metabolic basis of this hyperlipoproteinaemia is said to be the overproduction of apolipoprotein B, which is a structural protein of VLDL and low density lipoproteins. This hyperlipoproteinaemia is characterised by the alterability of its phenotype (IIa, IIb, and IV).

In conclusion, we propose that hyperlipoproteinaemia in primary gout is unlikely to be secondary to excess alcohol intake or obesity, or both, and, instead, it may be associated with essential factors, at least in some patients with primary gout. In addition, the hyperlipoproteinaemia in primary gout may be due to the overproduction of TG rich lipoproteins rather than to the impairment of their catabolism. Our data suggested that it could be attributed to combined hyperlipidaemia in some gouty patients, though the detailed mechanism still remains to be elucidated.

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**References**

1 Beard J T II. Serum uric acid and coronary heart disease. *Am Heart J* 1983; **106:** 397–400.
2 Yano K, Rhoads G G, Kagen A. Epidemiology of serum uric acid among 8000 Japanese-American men in Hawaii. *J Chronic Dis* 1977; **30:** 171–84.
3 Halpern M J, Perecia Mignel M S. Uric acid and coronary heart disease. *J Am Geriatr Soc* 1974; **22:** 86–7.
4 Kohn P M, Prozan G B. Hyperuricemia—relationship to hypercholesterolemia and acute myocardial infarction. *JAMA* 1959; **170:** 1909–13.
5 Fessel W J. High uric acid as an indicator of cardiovascular disease. Independence from obesity. *Am J Med* 1980; **68:** 401–4.
6 Jacobs D. Hyperuricemia as a risk factor in coronary heart disease. *Adv Exp Med Biol* 1979; **76B:** 231–6.
7 Feldman E B, Wallace S L. Hypertriglyceridemia in gout. *Circulation* 1964; **29:** 508–13.
8 Berkowitz D. Blood lipid and uric acid interrelationship. *JAMA* 1964; **190:** 120–2.
9 Darlington L G, Scott J T. Plasma lipid levels in gout. *Ann Rheum Dis* 1972; **31:** 487–9.
10 Mielants H, Veys E M, DeWeerdt A. Gout and its relation to lipid metabolism. I. Serum uric acid, lipid, and lipoprotein levels in gout. II. Correlations between uric acid, lipid, and lipoprotein levels in gout. *Ann Rheum Dis* 1973; **32:** 501–9.
11 Gibson T, Grahame R. Gout and hyperlipidaemia. *Ann Rheum Dis* 1974; **33:** 298–303.
12 Naito H K, Mackenzie A H. Secondary hypertriglyceemia and hyperlipoproteinaemia in patients with primary gout. *Clin Chem* 1979; **25:** 371–5.
13 Grahame R, Scott J T. Clinical survey of 354 patients with gout. *Ann Rheum Dis* 1970; **29:** 461–9.
14 Wiedmann E, Rose H G, Schwartz E. Plasma lipoproteins, glucose tolerance and insulin response in primary gout. *Am J Med* 1972; **53:** 299–307.
15 Allain C C, Poon L S, Chan C S G, Richmond W, Fu P C. Enzymatic determination of serum cholesterol. *Clin Chem* 1974; **20:** 470–5.
16 Tiffany K O, Morton J M, Hall E M, Garrette A S Jr. Clinical evaluation of kinetic enzymatic fixed time and integral analysis of serum triglyceride. *Clin Chem* 1974; **20:** 476–81.
17 Burstein M, Scholnick. Lipoprotein-polyanion-metal interactions. *Adv Lipid Res* 1973; **11:** 68–108.

18 Beaumont J L, Carlson L A, Cooper G R, Fejear Z, Fredrickson D S, Strasser T. Classification of hyperlipidemias and hyperlipoproteinemias. *Bull WHO* 1970; **43:** 891–908.
19 Narayan K A, Narayan S, Kummerow F A. Disc electrophoresis of human serum lipoproteins. *Nature* 1965; **205:** 246–8.
20 Nishida Y, Akaoka I, Nishizawa T, Yoshimura T. Hyperlipidaemia in gout. *Clin Chim Acta* 1975; **62:** 103–6.
21 Dunn J P, Moses C. Correlation of serum lipids with uric acid and blood sugar in normal males. *Metabolism* 1965; **14:** 788–92.
22 Gibson T, Kilbourn K, Horner I, Simmonds H A. Mechanism and treatment of hypertriglyceridaemia in gout. *Ann Rheum Dis* 1979; **38:** 31–5.
23 Kodama T, Murase T, Itakura H, Akanuma Y, Takaku F, Nishida Y. Post heparin plasma lipoprotein lipase and hepatic triglyceride lipase activities in patients with primary gout. *Clin Chem* 1983; **29:** 2124–5.
24 Goldstein J L, Schrott H G, Hazzard W R, *et al.* Hyperlipidemia in coronary heart disease. II. Genetic analysis of lipid levels in 176 families and delineation of a new inherited disorder, combined hyperlipidemia. *J Clin Invest* 1973; **52:** 1544–68.