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Gout and hyperlipidaemia

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An association between gout and hypertriglyceridaemia has been described by several workers (Berkowitz, 1964; Feldman and Wallace, 1964; Bluestone, Lewis, and Mervart, 1971; Darlington and Scott, 1972). The mechanism linking these two metabolic disorders remains obscure.

Obesity and excessive alcohol consumption are associated with both gout (Grimley Evans and Prior, 1968; Emmerson and Knowles, 1971) and hypertriglyceridaemia (Benedek and Sunder, 1970; Chait, Mancini, February, and Lewis, 1972), but it has not been possible previously to explain an association between the two disorders by reference to these common factors (Darlington and Scott, 1972; Wiedemann, Rose, and Schwartz, 1972). Hennecke and Südhof (1970) have suggested that fatty infiltration of the liver is associated with the hypertriglyceridaemia of gout and is responsible for the evidence of liver dysfunction reported in gouty subjects by Grahame, Haslam, and Scott (1968).

The present study attempts a further examination of the relationships between gout, fasting serum lipids, obesity, alcohol consumption, and abnormal liver function.

Method

Fasting serum triglyceride, cholesterol, and blood uric acid levels of 50 gouty subjects were compared with those of an equal number of healthy controls matched carefully for sex, age, and ponderal index (PI) (height divided by cubed root of weight) and with an equal number of subjects matched for age and sex only,

All the gouty subjects were outpatients with documented histories of recurrent acute arthritis associated with hyperuricaemia. The controls (matched and unmatched) were volunteers taking part in a health survey conducted by the Unit for Metabolic Medicine, Guy's Hospital. None had a history of gout nor other diseases which may be associated with hyperlipidaemia or hyperuricaemia.

Particular note was made of the average daily alcohol consumption of the gouty patients. Similar information about the drinking habits of the controls was obtained from a dietary questionnaire, the answers to which were verified by personal interviews where possible.

Venous blood for serum triglyceride, cholesterol, and uric acid estimations was taken after an overnight fast. In the week preceding the investigations, colchicine 0·5 mg twice a day was substituted for any blood uric acid lowering agents previously prescribed for the gouty patients. With the exception of seven gouty patients, all the investigations were conducted between the months of February and June, thus minimizing the possibility of seasonal variation of lipid or uric acid levels (Fyfe, Dunnigan, Hamilton and Rae, 1968; Goldstein, Becker, and Moore, 1972).

All serum triglyceride and cholesterol estimations were performed in the same laboratory by the methods of Cramp and Robertson (1968) and Levine and Zak (1964), respectively. Blood uric acid measurement of the gouty subjects was by an automated procedure based on the uricase digestion method of Caraway (1963). Those of the controls were performed in a different laboratory employing an automated technique, using neocuproine copper reagent (Lofland and Crouse, 1966). Investigations of the gouty patients also included estimation of serum bilirubin, alkaline phosphatase, aspartate aminotransferase, and sulphobromophthalein (BSP) retention tests. The BSP test was performed on fasting subjects by the intravenous injection of 5 mg/kg body weight BSP and withdrawal of blood from the opposite arm 45 minutes later. Measurement of BSP concentration in the serum was by the spectrophotometric method described by Seligson, Marino, and Dodson (1957). 24-hour uric acid excretion of the gouty patients was measured by the method of Caraway (1963) after a standard 3-day low-purine diet containing less than 300 mg purine daily.

Results

Details of the subjects and their mean lipid and blood uric acid values are summarized in Table I.

The mean PI of the controls not matched for obesity was significantly higher than that of the matched controls ($P < 0.0001$), i.e. they were significantly less obese.

The mean blood uric acid of the gouty patients was significantly higher than that of both control groups, and the mean of the matched controls was higher than that of the unmatched group, but not significantly so. The latter difference probably reflected the relative obesity of the matched controls.

Fasting serum triglyceride values were highest in the heavier gouty patients and there was a significant inverse correlation between triglyceride and PI ($r = 0.322$; $P < 0.02$), i.e. the more obese had higher

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Table I *Details of subjects and mean blood lipid and uric acid results*

Subjects	*Gouty*	*Controls*	
		Matched	*Unmatched*
Number (males)	50	50	50
Age (yrs) Mean Range	52·4 (26–80)	52·0 (28–80)	46·5 (28–64)
Mean ponderal index (±SD)	12·09 ± 0·56	12·06 ± 0·547†	12·55 ± 0·5†
Mean blood uric acid (mg/100 ml) (±SD)	8·94 ± 1·84*	6·00 ± 0·736*	5·756 ± 0·951
Mean serum triglyceride (mg/100 ml) (±SD)	198·3 ± 116·4‡	166·3 ± 63·86	154 ± 60·27‡
Mean serum cholesterol (mg/100 ml)	256 ± 42·8	272 ± 55·23	254 ± 50·13

† $P < 0.0001$.
* $P < 0.001$.
‡ $P < 0.05$.

serum triglyceride values (Fig. 1). There was, however, no correlation between blood uric acid and triglyceride levels of the gouty subjects ($r = 0.089$, NS).

When the mean serum triglyceride level of the gouty patients (198·3 mg/100 ml) was compared with that of their equally obese control group (166·3 mg/100 ml) a significant difference was not apparent ($t = 1.796$; $P < 0.1$), but the triglyceride value of the gouty group was significantly higher than that of the controls not matched for obesity (mean 154·6 mg/100 ml) ($t = 2.274$; $P < 0.05$).

It was still possible that the marked effect of obesity on serum triglyceride might be masking a more fundamental relationship between hyperuricaemia and serum triglyceride, and so the triglyceride values of the lean gouty patients (arbitrarily defined as those with a PI of more than 12·5) were compared with those of their matched controls. The mean serum triglyceride values of these two groups were virtually identical (Table II).

A variable effect of blood uric acid lowering agents on serum triglyceride has been suggested (Bluestone and others, 1971). In view of this, in the present study the triglyceride values of fifteen subjects who had received such treatment in the months preceding the study were compared with those who had not. Twelve patients had received allopurinol and three probenecid. Their mean serum triglyceride (223·21 mg/100 ml; SD ± 151·98) and blood uric acid (8·31 mg/100 ml; SD ± 2·27) were not significantly different from the mean triglyceride (186·74 mg/100 ml; SD ± 99·54) and uric acid (8·96 mg/100 ml; SD ± 1·47) of the 35 gouty patients who had not received these drugs.

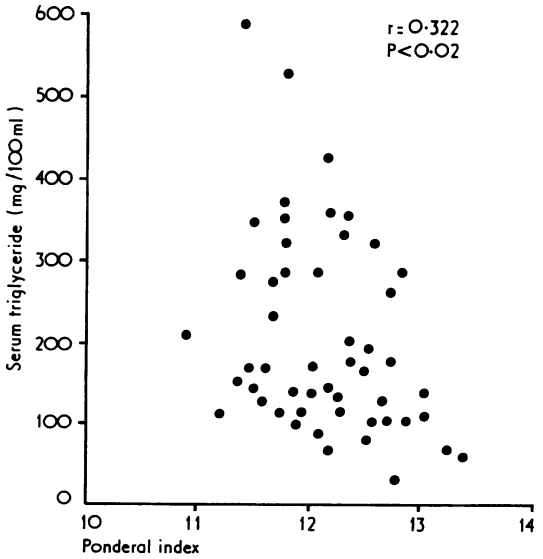

FIG. 1 *Inverse correlation between serum triglyceride and ponderal index*

Table II *Comparison of lean gouty and matched controls (ponderal index >12·5)*

Subjects	*Gouty*	*Matched controls*
Number	12	12
Age (yrs) Mean Range	52 (24–68)	51 (27–65)
Mean ponderal index (±SD)	12·79 ± 0·235	12·8 ± 0·34
Mean blood uric acid (mg/100 ml) (±SD)	9·13 ± 2·45	6·17 ± 0·58
Mean serum triglyceride (mg/100 ml) (±SD)	151 ± 90·2	147 ± 64·02

The mean serum cholesterol of the gouty patients did not differ significantly from either that of the matched or unmatched controls.

Twenty (40%) of the gouty patients drank more than 3 pints of beer, or the equivalent, daily. These patients were more obese (mean PI 11·93) than the non- or moderate drinking gouty subjects (mean PI 12·206), but the difference was not significant ($P < 0·1$). The mean triglyceride of the heavy drinkers (265·2 mg/100 ml) was significantly higher than both that of the more abstemious gouty patients (149·1 mg/100 ml) ($P < 0·0001$) and their matched controls (178·1 mg/100 ml) ($P < 0·02$) (Table III).

The mean percentage of BSP retained by the gouty patients 45 minutes after injection was 5·06 (SD ± 4·02). Sixteen subjects (32%) had retention of more than 5%. There was no correlation between heavy drinking and abnormal BSP retention (Fig. 2). Only six of the heavy drinkers had retention of more than 5% BSP. There was no correlation between the percentage of BSP and blood uric acid values ($r = 0·222$, NS) nor any correlation between BSP retention and serum triglyceride ($r = 0·011$, NS) (Fig. 3). Four patients had raised serum aspartate transaminase levels, three of whom also had abnormal BSP retention. No patient had clinical or other biochemical evidence of liver disease (Table IV).

24-hour urine uric acid estimations of the gouty

Table III *Comparison of triglyceride values of heavy and non-drinking gouty subjects and matched controls*

Subjects	*Gouty heavy drinkers*	*Obesity-matched controls*	*Gouty non- or moderate drinkers*
Number	20	20	30
Age (yrs) Mean	51	50	55
Range	(28–63)	(29–64)	(24–80)
Mean ponderal index (±SD)	11·93 (±0·527)	11·97 (±0·27)	12·206 (±0·571)
Mean fasting triglyceride (mg/100 ml) (±SD)	265·2*† (±137·3)	178·1* (±60·4)	149·1† (±73·47)

* $P < 0·02$.
† $P < 0·001$.

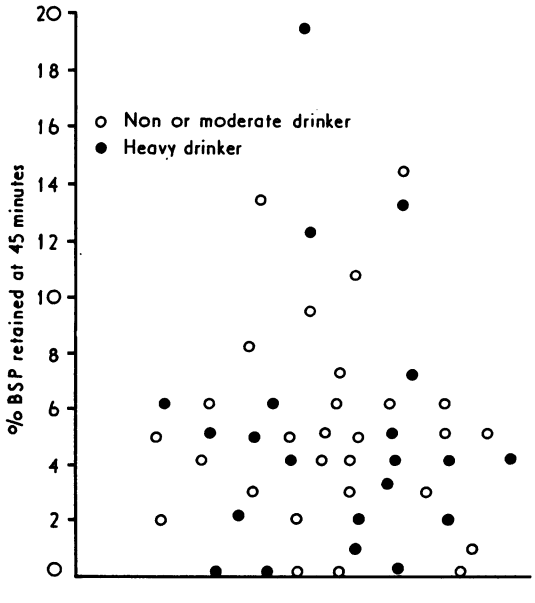

FIG. 2 *Relationship between drinking habits of gouty patients and % BSP retention at 45 minutes*

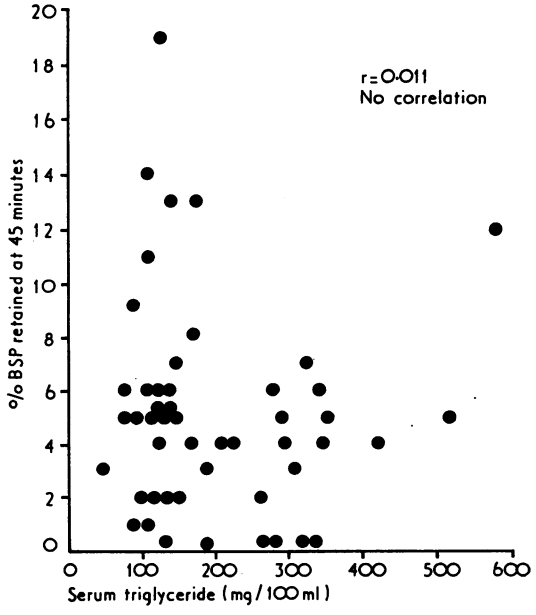

FIG. 3 *Serum triglyceride levels of gouty patients related to % BSP retention at 45 minutes*

Table IV *Gouty patients with liver enzyme abnormalities*

Aspartate amino transferase (normal < 16 I.U.)	*Per cent. BSP retained at 45 mins*	*Alcohol consumption (pints beer/day)*	*Serum triglyceride (mg/100 ml)*
22	2	>3	250
40	7	0	156
56	19	>3	132
33	6	2	122

patients revealed a mean value of 659·3 mg (SD ± 325·1). There was no correlation between uric acid excretion and triglyceride ($r = 0{\cdot}0066$, NS) (Fig. 4), nor any correlation between uric acid excretion and serum cholesterol ($r = 0{\cdot}01$, NS).

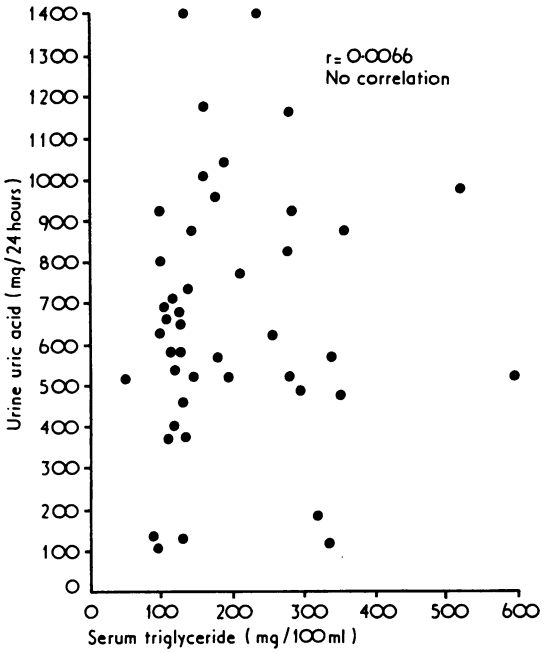

FIG. 4 *Relationship between 24-hour urine uric acid and serum triglyceride*

Discussion

Hyperlipidaemia associated with gout was well illustrated by Kuzell, Schaffarzick, Naugler, Koets, Mankle, Brown, and Champlin (1955) and there have been a number of subsequent reports relating gout with hypercholesterolaemia (Becker, 1960), hypercholesterolaemia combined with hypertriglyceridaemia (Barlow, 1968; Rondier, Truffert, Le Go, Brouilhet, Saporta, de Gennes, and Delbarre, 1970), and hypertriglyceridaemia alone (Berkowitz, 1964; Feldman and Wallace, 1964; Bluestone and others, 1971; Darlington and Scott, 1972; Mertz, Zaar, Klöpfer-Zaar, Henninges, Thieme, and Scheier, 1971).

The results of the present study confirmed the relatively high fasting serum triglyceride levels of gouty subjects compared with an unmatched group of healthy volunteers, but a similar difference between cholesterol values could not be shown.

The relevance of high serum triglyceride levels to gouty subjects has assumed importance because of the now established association between hypertriglyceridaemia and coronary artery disease (Charlson and Böttiger, 1972). The precise role of triglyceride in the pathogenesis of ischaemic heart disease remains uncertain, but its association may offer some explanation for the reported high incidence of this disease in gout sufferers (Hall, 1965).

The factors responsible for hypertriglyceridaemia in gout have not been determined. The failure to show a predictable relationship between serum uric acid and triglyceride (Feldman and Wallace, 1964), the absence of a correlation between blood uric acid and triglyceride in this study, and the absence of a concomitant reduction of triglyceride values after allopurinol treatment (Gunther and Knapp, 1970) make it unlikely that circulating uric acid has a direct influence on triglyceride levels or vice versa.

Diets with a high fat content are known to induce hyperuricaemia but this can be explained by the urate-retaining effect of ketones on the renal tubules (Scott, McCallum, and Holloway, 1964). Though dietary fats may have a very obvious effect on serum lipid levels, the very high fat diets necessary to provoke hyperuricaemia must be unusual outside the experimental situation. A similar renal mediated mechanism in the absence of a high fat diet is unlikely to explain coexisting hyperuricaemia and hypertriglyceridaemia because of the failure to show any close inverse correlation between serum triglyceride and urinary uric acid in this and other studies (Emmerson and Knowles, 1971; Darlington and Scott, 1972).

The high incidence of abnormal BSP retention in gouty patients reported by Grahame and others, (1968) could not be explained entirely by alcohol consumption, obesity, or age. Hennecke and Südhof (1970) also noted a high incidence of abnormal liver

function in gout and suggested that this and hypertriglyceridaemia may be related to fatty infiltration of the liver. However, Tremel and Pohl (1971), while confirming the frequency of liver dysfunction among gouty patients, could not show any consistent histological changes in the liver. The results of the present study revealed abnormal retention of BSP in sixteen (32%) of the gouty patients. None of the controls was subjected to this investigation and so the incidence of abnormal results reported here must be tempered with the knowledge that a proportion of healthy individuals may have retention of BSP which exceeds the conventional upper limit of normal (Zieve and Hill, 1955). It was nevertheless not possible to relate abnormal results to alcohol excess, nor was it possible to correlate the percentage of BSP retained with serum triglyceride levels. Standard liver function test abnormalities were apparent in only four patients and were associated with abnormal BSP retention in three. It may be concluded that abnormal liver function is not invariably a feature of the hypertriglyceridaemia found in gout. The cause of abnormal liver function in gouty patients awaits further elucidation.

Kuntz, Rouques, Paolaggi, and Ryckewaert (1969) reported high serum triglyceride levels in 50 patients with hyperuricaemia and noted that these subjects were also significantly heavier than the control group. Similarly, in this study the mean serum triglyceride of gouty patients was significantly higher than that of unmatched controls who were much less obese. There was, however, a significant correlation between the degree of obesity of the gouty patients and their serum triglyceride levels. This suggests that obesity may be at least a contributory factor in the aetiology of hypertriglyceridaemia accompanying gout. The absence of a significant difference between the mean fasting triglyceride levels of the gouty patients and that of the controls matched for age and PI suggests that it may be the major factor. Other studies have failed to implicate obesity in this way and it is difficult to reconcile our findings with those of Emmerson and Knowles (1971), Darlington and Scott (1972), and Wiedemann and others (1972). The observations reported here are consistent with those of Hollister, Overall, and Snow (1967), who showed that serum triglyceride is substantially dependent on the obesity factor.

The role of alcohol in the context under discussion has attracted little attention. As a cause of hypertriglyceridaemia, alcohol excess is remarkably common (Chait and others, 1972), and it is well known that alcohol consumption may be excessive in a high proportion of gout sufferers (Grahame and Scott, 1970). Gout, hyperuricaemia, and hypertriglyceridaemia occurring together after recent heavy drinking may all remit after alcohol withdrawal (Gebbie and Prior, 1967).

In the present study, twenty patients (40%) customarily drank 3 pints of beer (or equivalent) daily, and this proportion is similar to that in a much larger series of gouty subjects (Grahame and Scott, 1970). The heavy drinking patients had a significantly higher mean serum triglyceride level than that of the moderate or non-drinking gouty patients ($P < 0.001$) and than that of their matched controls ($P < 0.02$). This suggests that alcohol excess is a factor in the hypertriglyceridaemia seen in some gouty subjects. It is worth noting that though alcohol *per se* can induce hypertriglyceridaemia, all of the heavy drinkers in this series consumed mainly beer. Beer has a higher content of carbohydrate than most alcoholic beverages, the intake of which is significantly related to serum triglyceride levels (Hulley, Wilson, Burrows, and Nichaman, 1972).

The association between serum triglyceride levels, gout, obesity, and alcohol illustrated by this study have clear therapeutic implications. It remains to be seen whether abstention from alcohol, weight reduction, or even carbohydrate restriction can lower raised serum triglyceride levels accompanying gout. The results reported here indicate that these are hopeful lines of treatment which deserve further investigation.

Summary

A comparison of the fasting serum lipid levels of 50 patients with gout, 50 healthy equally obese subjects, and an equal number of healthy subjects not matched for obesity showed no difference between their mean serum cholesterol levels, and though the highest mean triglyceride level was seen in the gouty subjects, this value was not significantly different from that of the subjects matched for obesity. The subjects not matched for obesity were significantly leaner than the other two groups and their mean triglyceride was significantly lower than that of the gouty patients. A correlation between obesity and triglyceride levels was shown in the gouty subjects. These observations suggest that the high serum triglyceride values seen in gout are related to obesity.

The gouty patients who drank alcohol excessively had a mean serum triglyceride that was higher than that of their obesity-matched controls and than that of the non-drinking gouty patients. An effect of alcohol abuse is therefore another likely contributory factor to hypertriglyceridaemia accompanying gout.

No relationship could be shown between serum triglyceride and abnormal liver function, uric acid excretion, or previous drug treatment.

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