Hypertriglyceridemia in Gout

By Elaine B. Feldman, M.D., and Stanley L. Wallace, M.D.

The incidence of arteriosclerosis is reported to be greater in patients with gout than in control groups. In one study of 280 individuals with gout, 39 per cent had clinical or electrocardiographic evidence of cardiovascular disease and 45 per cent had hypertension.1 Severe involvement of the coronary or cerebral vessels and marked renal arteriosclerosis are major factors in producing death in patients with gout.2 Conversely, hyperuricemia is more frequent in patients with essential hypercholesteremia3,4 or with coronary artery disease5,6 than in normal persons. The mechanism underlying these relationships is obscure.

There has been recent emphasis on the association of hypertriglyceridemia and coronary heart disease.7 The present study was performed to evaluate the relation between the levels of circulating triglycerides and other complex lipids in patients with gout in comparison to an appropriate control group.

Material and Methods

The 34 patients with the diagnosis of gout in this study had acute episodic inflammatory arthritis. All but two were hyperuricemic (serum uric acid greater than 7.0 mg. per 100 ml.) at some time during their clinical course. Characteristic diagnostic responses were obtained upon administration of colchicine in 24 patients including the two normouricemic individuals. No patient was included as gouty in whom the diagnosis was in doubt. All patients in this study had primary gout.

Patients who met the criteria for the diagnosis of gout were also selected for the absence of recognizable clinical arteriosclerotic disease. No patient was included who at any time had had angina, coronary insufficiency, myocardial infarction, congestive heart failure, electrocardiographic changes compatible with coronary artery disease, hypertension, diabetes mellitus (hyperglycemia or glycosuria), cerebrovascular, renovascular, or peripheral vascular disease, or hypothyroidism. Patients with these disorders were excluded from this study because of the known association of alterations in serum lipids with these diseases. No patient had taken uricosuric drugs for at least 1 month prior to study, nor were any patients taking salicylates at the time of study. Diets were unrestricted. No gross dietary abnormalities were encountered.

The 34 patients with gout included 31 men and three women. Twenty-seven patients were white and seven were Negro. Six patients had both acute recurrent and chronic tophaceous gout; 28 had only acute recurrent attacks of arthritis without tophi. Five patients were significantly obese (weight more than 20 per cent above ideal weight for age and sex). Ages ranged from 28 to 79 years, with a mean age of 52 years. Two patients were less than 36 years of age; six were between the ages of 36 and 45; 12 were between 46 and 55; eight were 56 to 65; five were between 66 and 75, and one was over 75.

Laboratory studies were performed on sera obtained from patients in the morning after a 12- to 14-hour fast. Cholesterol was determined by the method of Abell, Levy, Brodie, and Kendall.8 Lipoproteins were determined by paper electrophoresis.9 Uric acid was measured by the enzymatic spectrophotometric method of Praetorius.10 Triglycerides were measured directly by Eder's modification* of the methods of Van Handel and Zilversmit11 and Carlson and Wadstrom.12 One milliliter of serum was mixed with 4 Cm. of Zeolite, extracted with 20 ml. of chloroform, and filtered. One to 3-ml. portions of filtrate were saponified with 1 drop of 2.5-per cent potassium hydroxide and 1 ml. of absolute alcohol. Two drops of 6-per cent acetic acid were added and the samples evaporated to dryness. One milliliter of 0.67 M sulfuric acid was then added. Glycerol was determined by the addition of 0.1 ml. of 0.02 M sodium periodate, 0.1 ml. of 0.2 M sodium arsenite, and 2.5 ml. of chromotropic acid reagent in turn to 0.3 ml. of the sulfuric acid solution. Readings were taken in a spectrophotometer at

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570 mg. after the reaction mixture had been heated at 100 C. for 30 minutes. Standards were solutions of tripalmitin in chloroform, 5 µg. per ml. It was unnecessary to carry an unsaponified serum aliquot through the entire procedure, since readings on such samples were almost identical to the sulfuric acid blank. All determinations were done in duplicate.

Twenty-eight healthy men were studied in a similar manner. These men were primarily husbands of clinic or hospitalized patients. Three men were significantly obese. Four men were Negro. Their diets were unrestricted. No gross dietary abnormalities were encountered. They were selected to match the gouty patients in age distribution and ranged in age from 36 to 78 years, with a mean age of 50 years. Fifteen men were from 36 to 45 years old, six were between 46 and 55, three between 56 and 65, one between 66 and 75 and three over 75.

Results

The mean serum triglyceride level in the patients with gout (142 mg. per 100 ml.) was significantly higher (p < 0.01) than the mean triglyceride level of the healthy men (100 mg. per 100 ml.) (tables 1 and 2). Hypertriglyceridemia (186 mg. per 100 ml. or more) was

Table 1

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<thead>
<tr>
<th>Age, yr.</th>
<th>Serum Lipids, Lipoproteins, and Uric Acid in Patients with Gout</th>
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<td>75</td>
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<td>67</td>
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<tr>
<td>Mean ± S.D.</td>
<td>142 ± 79</td>
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* Chronic tophaceous gout.
† Women.
Table 2

Serum Lipids, Lipoproteins, and Uric Acid in Healthy Men

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<tr>
<th>Age, yr.</th>
<th>Triglycerides mg. per 100 ml.</th>
<th>Cholesterol mg. per 100 ml.</th>
<th>a-lipoprotein % of total</th>
<th>Uric acid mg. per 100 ml.</th>
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<tr>
<td>Mean ± S.D.</td>
<td>100 ± 43</td>
<td>250 ± 45</td>
<td>18.9 ± 7.0</td>
<td>5.0 ± 1.3</td>
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</table>

Serum lipoprotein distribution did not differ significantly between the gouty patients and the healthy men. The patients with gout, α-lipoprotein averaged 16.9 per cent and β-lipoprotein plus 0-fraction 83.1 per cent. These values for healthy men were 18.9 per cent and 81.1 per cent, respectively.

Uric acid levels averaged 5.0 mg. per 100 ml. in the healthy men; two were hyperuricemic (7.0 mg. per 100 ml. or more). In the patients with gout, uric acid levels averaged 8.8 mg. per 100 ml. Five of the 34 patients with gout were normouricemic at the time of the study.

Discussion

The significantly higher serum triglyceride concentration was the only abnormality among the lipid classes observed in gouty patients compared with healthy men. This increase in...
triglycerides was noted in patients with gout despite selection to eliminate diseases known to be associated with hypertriglyceridemia. The possibility exists that the gouty patients studied had latent or subclinical atherosclerosis, and that the hypertriglyceridemia represents a manifestation of this associated disorder.

In this laboratory the mean triglyceride level reported herein for healthy men over 35 was 100 mg. per 100 ml. Other investigators noted a linear increase in triglyceride concentration with age in strictly screened normal men up to age 40. Triglyceride concentration in young men averaged 93 mg. per 100 ml. and 109 mg. per 100 ml. in older men. For this reason gouty patients were compared only to healthy men of similar ages. Similar values for triglyceride concentration in normal men (102 mg. per 100 ml.) have also been observed by others using similar methods.

No satisfactory explanations have been offered for the increased frequency of vascular complications in patients with gout. It is possible that hypertriglyceridemia and arteriosclerosis are produced by the metabolic abnormalities inherent in gout. It seems more likely, however, that these disorders are linked genetically. Hypertriglyceridemia and other types of hyperlipidemia are known to be familial, as is gout. Genetic linkage is suggested by the number of patients reported in

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**Figure 1**

Levels of serum uric acid and triglycerides in 34 patients with gout and 28 healthy men over age 35. The levels in patients with gout are represented by small stars. Levels in healthy men are represented by large dots. The lines represent the mean value for the healthy men. The limit of the vertical slightly shaded area (186 mg. per 100 ml.) represents the upper limit of normal for triglycerides. The limit of the horizontal lightly shaded area (7.0 mg. per 100 ml.) represents the upper limit of normal for uric acid. Only three values for healthy subjects fell outside the darkly shaded limits of normal for both parameters. All nine values in the unshaded area, abnormal for both parameters, were obtained in gouty patients. The correlation coefficient between uric acid and triglyceride concentrations in normal subjects was r = 0.10; in gouty patients, r = 0.05.
the literature who have had both hyperlipemia and gout.\(^5\) In a previous study, two of 26 patients with idiopathic hypercholesteremia and coronary artery disease had clinical gout, while in 10 families with hyperlipemia, one family with associated gout was observed. The lack of significant correlation between serum levels of uric acid and triglycerides in the patients with gout reported in the present study also argues against a single metabolic abnormality and inferentially in favor of genetic linkage.

The mean level of triglycerides in gouty patients, although elevated, remained within the normal range despite hypertriglyceridemia in one third of these subjects. It has to be considered that the selection of patients to eliminate those with vascular disease may have excluded from the population studied the most abnormal members. A study evaluating comparable gouty patients with coronary artery disease, and patients with coronary artery disease but without gout might provide pertinent information.

The dose-dependent relation between gene and protein (enzyme) so clearly evident in other inborn errors of metabolism has not been demonstrated for gout or hyperlipidemia. The primary expression of gene action may be many steps distant from the clinical phenomena of gout or the circulating levels of uric acid or triglycerides. It is therefore not surprising to find a lack of predictive quantitative relation between the two parameters, uric acid and triglycerides, despite the elevated mean levels of these metabolites circulating in gouty patients.

Serum cholesterol levels and lipoprotein distribution did not differ significantly between gouty patients and healthy men in the present study. Normal cholesterol values in patients with gout have been reported by some investigators,\(^5\) while others have found an incidence of hypercholesteremia as high as 50 per cent in gout.\(^8\) Some discrepancy might be explained by the influence of aging and the presence of complicating diseases in these patients. Other workers have reported an increase in \(\beta\)-lipoprotein and decrease in \(\alpha\)-lipoprotein in gouty patients.\(^9\) Again neither the normal group nor the patients with gout were characterized as to age or associated disease. Studies elsewhere\(^{21}\) and in this laboratory have indicated that serum cholesterol levels increase with age in healthy men, at least up to the fourth decade. Similarly \(\beta\)-lipoprotein cholesterol also increased with age in men.\(^22\) In another study,\(^23\) an increased atherogenic index was reported in gouty patients, with higher levels observed in tophaceous gout than in patients with acute gouty arthritis. The elevated values were observed even when results were recalculated by us excluding patients with myocardial infarction and hypertension. These alterations may be attributable to changes in triglyceride concentrations; this parameter was not measured in the study.

**Summary**

Serum triglyceride levels were significantly higher in 34 patients with gout (142 mg. per 100 ml.) in comparison to the levels in 28 healthy men over 35 years of age (100 mg. per 100 ml.). There was no significant predictive relation between levels of serum uric acid and triglycerides in either group. No significant difference in serum cholesterol levels nor lipoprotein profile was apparent between the two groups. The patients with gout had been selected to exclude any manifestations of atherosclerosis or other disease known to be associated with abnormalities in circulating lipids. The results provide support for possible linkage of genetic factors influencing uric acid and triglyceride metabolism. The presence of hypertriglyceridemia in gout may be correlated with the increased incidence of arteriosclerosis.

**References**

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