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Gout and Arterial Thrombosis

Frank J. Viozzi, MD,* Gilbert B. Bluhm, MD,**
and Jeanne M. Riddle, PhD***

Two hundred and eighty patients with primary gout diagnosed between the years 1959-64 at Henry Ford Hospital were studied to determine the frequency of myocardial infarction in the fourth, fifth and sixth decades. The retrospective data correlate with previously published reports of accelerated platelet turnover and our own observation of increased platelet surface activation in patients with gout. The results suggest an increased risk for myocardial infarction before age 50 in patients with primary gout; this merits prospective study. The finding of increased platelet surface activation in patients with gout may provide an insight into the pathophysiology of the apparent increased incidence of arterial thrombosis in gout.

In 1952, Mathieu et al proposed that an association may exist between myocardial infarction and gout.1 In 1955, Meneghini observed an association between thrombophlebitis and gout.2 These were studies of young patients with hyperuricemia who had no evidence of the usual conditions producing secondary hyperuricemia and no overt underlying disease commonly associated with peripheral venous occlusion. Furthermore, Myers et al discovered in 1968 that males with coronary artery disease have a mean serum uric acid score significantly greater than that of the population tested.3 In a multidisciplinary study published in 1954, Gertler et al noted that 22% of the coronary patients reported had serum uric acid levels greater than 6 mg per 100 ml, a value found in only 6% of the matched controls.4 The Coronary Drug Project Research Group reported in 1970 that the risk of early mortality for men who had had one myocardial infarction was doubled when the serum uric acid level exceeded 6 mg per 100 ml.5

In our laboratory, by means of electron microscopic differential counts, we dis-
covered increased platelet reactivity in 18 patients who had primary gout with no evidence of active inflammation or signs of thrombosis. Because of this, we initiated a study of a group of uncomplicated primary gout patients to determine the prevalence of thrombosis after the initial attack of arthritis.

Methodology

We reviewed sequentially the medical histories of all patients who had been indexed as having primary gout. They were a mixed group of inpatients and outpatients seen at Henry Ford Hospital between 1959 and 1964. Cases selected for review were those of patients who had an initial attack of gouty arthritis described and treated by Henry Ford Hospital staff physicians between 1959 and 1964. All patients exhibiting secondary hyperuricemia or case reports with insufficient studies to rule out secondary hyperuricemia were excluded. A patient with gout was excluded if there was evidence of diabetes mellitus, hypertension, or hospitalization because of a thrombotic illness.

Results

Two hundred and eighty patients ranging from 28-82 years of age met these rigid criteria. Only three patients were females. Highest incidence for first attacks of arthritis was in the sixth decade (94 patients). Average serum uric acid at the time of the first attack was 7.3 mg per 100 ml with a range between 2.4 and 13.4 mg per 100 ml. Three patients had labile elevation of diastolic pressure at times greater than 100 mm of mercury. None of the three was on hypotensive drugs nor azotemic. (Figure 1)

In the series, 64 patients (23%) had had a total of 67 thrombotic episodes diagnosed as myocardial infarction, cerebrovascular accident, thrombophlebitis, peripheral vascular occlusive disease, and pulmonary embolism. (Figure 2)
We excluded all venous thrombotic disease from our summary (Figure 3) since platelet surface activity does not usually play as major a role during venous thrombosis. Fifty-one (18%) of the 280 patients with gout suffered an arterial thrombotic episode. Twenty-two (43%) of these 51 episodes were diagnosed as myocardial infarction, twenty (39%) were cerebrovascular occlusive disease, and nine (18%) were peripheral arterial occlusive disease.

Figure 4 shows by age decade the type of occlusive vascular disease and the number of episodes in each group. Note that the incidence of all complicating vascular occlusions peaks in the seventh decade. However, the number of myocardial infarctions increased in the fourth, fifth and sixth decades. The average serum uric acid at the time of the thrombotic episode was 7.35 mg per 100 ml with a range between 4 and 14.1 mg per 100 ml.

Nineteen patients died during the follow-up years. Seven suffered a fatal stroke and four a fatal myocardial infarction. Other causes of death included intractable congestive heart failure, pulmonary infarction, bronchopneumonia, ruptured abdominal aortic aneurysm and renal infarction.

Previously-published studies were used for comparison of our retrospective study. The Framingham Heart Disease Survey provided comparative data about myocardial infarction and their 1950-1954 Survey determined the prevalence of arteriosclerotic heart disease in the various decades. The criteria they used for inclusion were definite myocardial infarction, angina pectoris or electrocardiographic changes of ST segments and T wave inversion occurring during the surveillance.7

In our retrospective evaluation, we included only patients of Henry Ford Hospital with gout and definite myocardial infarction as determined by typical electrocardiographic and serum enzyme alterations. Patients with angina pectoris or nonspecific electrocardiographic changes

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<td>FREQUENCY OF TYPE OF THROMBOSIS IN 280 PATIENTS WITH PRIMARY GOUT</td>
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- Myocardial Infarction
- Cerebrovascular Accident
- Thrombophlebitis
- Peripheral Vascular Occlusive Disease
- Pulmonary Embolus

**Figure 3**

**Figure 4**
were not included since this data would bias our results in a retrospective study for a positive correlation with gout. Figure 5 summarizes by decades the frequency of complications of arteriosclerotic heart disease or myocardial infarction in both our studies and the Framingham survey. Despite our rigid selection of patients, our sample shows an increased prevalence of myocardial infarction in the fourth, fifth and sixth decades for patients with gout even though they had no hypertension, diabetes mellitus or other diseases which might increase risk.

Discussion

In 1963, Mustard et al discovered increased platelet turnover and adhesiveness, with decreased platelet survival times, in patients with primary gout even in those who had a negative family history for vascular disease. In 1958, Kohn and Prozan noted that hyperuricemia occurred as frequently as hypercholesterolemia concomitantly with myocardial infarction.

Hyperuricemia has been frequently associated with cerebrovascular occlusive disease and peripheral vascular occlusive disease. Smythe et al found that gout patients had increased platelet turnover, accelerated platelet adhesiveness and plasma thromboplastin activity; these changes were reversible with the use of the uricosuric agent, sulfinpyrazone.

Electron microscopy reveals circulating platelets to be either round or with one or several short, blunt pseudopodia. When activation of platelets occurs, they assume a spread form and aggregate. In 1968, Bradshaw reported from our laboratory a marked increase in spread platelet forms as well as platelet aggregates in some gout patients following a study of platelet differential counts from 25 patients with primary gout. This increase correlated best with a hyperuricemia greater than 6 mg per 100 ml. Our subsequent findings continue to suggest that platelets are activated abnormally in about 50% of patients with gout. Platelet surface activation as denoted by spread platelet forms and/or increased adhesiveness as denoted by platelet aggregation is increased.

The mechanism of increased arterial thrombosis may relate to the accelerated surface activation of the circulating platelet population in response to hyperuricemia or the response to vascular damage induced by deposition of urate. Together with the fact that sulfinpyrazone, a uricosuric agent, has been shown to diminish platelet turnover, this makes a ver...
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... attractive premise that lowering of serum uric acid may benefit vascular integrity. When activation of platelets is initiated, they morphologically assume a spread form and platelet aggregation occurs. In the initial phase of the arterial thrombosis, platelets adhere to the endothelium and release intrinsic platelet factors which potentiate plasma coagulation. Our population data suggests an increased risk of developing coronary artery disease in the presence of primary gout with arthritis. Population surveys published previously were concerned with the relationship of hyperuricemia to coronary artery disease but were not based solely on individuals with gouty arthritis. Because of the variations which are seen in serum uric acid levels in relation to sex, race and drugs, we selected only those patients with clinical gout who were non-diabetic and not receiving hypotensive drugs. Due to the wide differences in numbers between the population we studied and those reported by the Framingham survey, valid statistical correlations cannot be made. However, we believe that the data presented for myocardial infarction is of sufficient significance to stimulate further prospective studies regarding the relationship of hyperuricemia and arterial thrombosis.

References

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