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Blood Coagulation and Platelet Economy in Subjects with Primary Gout

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ABSTRACT

Previous studies have suggested that there is an increased incidence of degenerative vascular disease in patients with gout and an increased rate of turnover of blood platelets in patients and animals with atherosclerosis. A disturbed uric acid metabolism and "secondary" gout have long been known to occur with bone marrow diseases. A study of platelet economy and blood clotting factors in subjects with primary gout was therefore undertaken.

Twenty-two male subjects with gout but with no clinical evidence of vascular disease were studied. Half of these had a negative family history for vascular disease and half had less fortunate ancestors. The most striking differences were found when gouty patients with a negative family history for vascular disease were compared with similar control subjects. The mean platelet half-life was 2.85 days in the gouty subjects and 3.74 days in the controls. The mean platelet turnover (number/c.mm./day) was 58,750 in gouty subjects, 42,370 in controls. Platelet adhesiveness and plasma thromboplastic activity were correspondingly increased in the gouty subjects. Control subjects with a positive family history all showed relatively active clotting system and platelet turnover, similar to the values found in atherosclerotic subjects. The data indicated that there is increased platelet destruction and production in some patients with primary gout. The relation between this anomaly and the vascular disease, and disturbed urate metabolism in gouty subjects, remains to be investigated.

THE occurrence of secondary gout in patients with myeloproliferative disorders is generally attributed to an overproduction of urate. This in turn is attributed to an augmented degradation of nucleic acids and a consequent liberation of excess intermediary purines, including the end product uric acid.[1-4] A significant proportion of patients with so-called primary gout also show evidence of overproduction of urate as indicated by an excessive urinary excretion of uric acid when they are on a purine-restricted diet.[1-3] As a result of isotopic studies the inference has been made that at least in some gouty patients excessive quantities of urate are synthesized from the precursors without intermediary incorporation into nucleic acids.[5-9] Incorporation of labelled glycine into uric acid recovered from these patients occurs at a more rapid rate, reaching a peak within two days; this has to be contrasted with normal subjects, and with gouty patients not excreting excessive amounts of urate in whom the peak is not reached until the third or fourth day. In the few patients with gout secondary to polycythemia who have been studied, the rate of incorporation, but not necessarily the quantity, has been considerably slower, the peak being reached in 10 to 14 days,[10] reflecting the slower turnover of nucleic acids associated with increased erythropoiesis characterizing the polycythemic state. The excessive and more rapid rate of incorporation of precursors into uric acid in a proportion of patients with primary gout, together with a lack of evidence of an accelerated breakdown of endogenous nucleic acids, has led to the

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TABLE I.—FAMILY HISTORY POSITIVE

Subject	Age	WBCT (min.)	PTT (sec.)	OSPT (sec.)	PAI	PCT (sec.)	PC (no./c.mm.)	Platelet half-life (days)	Platelet turnover (exponential) (thousands per c.mm./day)
Cl	35	15.4	9.9	14.5	1.09	394	224.0	2.010	77.300
Co	51	8.7	11.8	14.9	1.42	203	246.7	2.766	61.820
Di	62	10.3	11.2	15.1	1.39	296	254.0	2.194	80.250
Hu	37	9.8	11.4	14.0	1.18	292	180.0	2.234	55.850
Hu	33	14.6	12.7	13.9	1.17	246	212.0	2.048	71.750
Ma	47	9.2	10.2	13.6	0.98	239	135.0	2.980	31.400
Wi	51	12.5	11.4	13.1	1.39	344	211.4	2.368	61.880
Wr	58	14.9	12.1	15.1	1.18	331	200.0	5.093	27.220
Yo	52	14.9	11.4	15.2	1.41	365	300.0	2.892	71.900
Fi	40	12.4	9.6	13.9	1.18	303	230.0	2.243	71.900
Cl	42	12.4	9.5	14.9	1.52	315	202.0	3.036	46.123

FAMILY HISTORY NEGATIVE

Subject	Age	WBCT (min.)	PTT (sec.)	OSPT (sec.)	PAI	PCT (sec.)	PC (no./c.mm.)	Platelet half-life (days)	Platelet turnover (exponential) (thousands per c.mm./day)
Bi	43	13.8	10.4	14.9	1.14	243	145.0	1.697	59.230
Co	31	10.7	11.5	14.9	1.04	412	310.0	3.659	58.720
Dr	55	10.2	11.0	13.9	1.02	388	243.0	3.285	51.280
El	52	13.0	12.7	14.2	1.20	409	155.0	3.321	32.350
Hu	51	9.7	12.1	14.6	1.21	457	460.0	3.532	90.260
Ma	50	10.0	11.9	14.9	1.08	428	186.0	3.018	42.720
Mi	67	9.5	11.6	14.0	1.19	307	298.3	2.415	85.620
Ra	60	12.8	10.3	13.9	1.20	319	180.0	2.053	60.770
Sh	65	11.6	11.4	15.7	1.07	277	168.0	2.780	41.960
St	48	11.7	11.4	15.6	1.36	248	227.5	3.011	52.370
Sm	52	12.4	10.4	15.2	1.47	270	260.0	2.539	70.990

view that there is a "shunt mechanism" for urate synthesis from precursors (such as dietary glycine) without intervention of nucleic acids and purines.[5-9] At least one observer has voiced opposition to such a concept.[11]

Since patients with myeloproliferative disorders frequently exhibit hyperuricemia which may be associated with the clinical manifestations of gouty arthritis, our attention has been directed to study of the rapidly multiplying elements of the bone marrow in primary gout. In addition to other marrow components it has been suggested that megakaryocytes may be a factor in the overproduction of uric acid in the myeloproliferative disorders.[12] While the packed cell volume of the platelets (about 0.5%) is small[13] compared with that of the red cells (40-45%), their mean survival is shorter (about three to five days[14] compared with 120 days for the red blood cells). Thus the turnover of platelets and of red blood cells is of comparable magnitude. In consequence, megakaryocytes and platelets also may be relatively important components in nucleoprotein metabolism.

The importance of the blood platelet in patients with gout has been suggested by an additional observation. There is some indication that patients with gout are more prone to develop degenerative vascular disease and thrombotic complications,[15-18] while patients with complications of atherosclerosis exhibit a relatively high incidence of hyperuricemia.[19-21] One product of the bone marrow which has been incriminated in the pathogenesis of vascular disease and its complications is the platelet. Studies already published have shown that subjects with vascular complications of atherosclerosis exhibit an increased activity of blood clotting, a shortened platelet survival and an increased platelet turnover.[14]

For these reasons we have examined blood coagulation and platelet survival and turnover in a group of subjects with primary gout. The results have been compared with those obtained in studies on a group of atherosclerotic and a group of control subjects previously reported.[14]

MATERIALS AND METHODS

Tests of Blood Coagulation

Whole blood clotting time (WBCT), one-stage prothrombin time (OSPT), platelet count (PC), platelet adhesive index (PAI), platelet clumping time (PCT) and plasma activity in the thromboplastin generation test (PTT) were carried out by techniques which have been previously described.[22]

Platelet Survival and Turnover

These studies were done by the method of Leeksma and Cohen.[23] The technique, which uses di-isopropyl fluorophosphate as P^{32} (DFP^{32}), has been modified as previously described.[14, 24] Platelet survival has been computed under the assumption of random destruction which we have good reason to believe is more appropriate than the Gaussian treatment.

Statistical Considerations

We have previously discussed the distribution of the values in the clotting tests and platelet survival and turnover.[14, 24] All were normal except for the WBCT and PCT, which were lognormal, and PTT, which was harmonic-normally distributed. Appropriate transformations have been made before any statistical calculations were done, but mean values have been transformed back to the original units of measurement before being inserted in the tables. Although there is some difference in mean ages between the groups being compared, there is a large overlap in the distributions, and the age effect (which is in any case slight) has been fully corrected by covariance analysis.

Subjects

Twenty-two white male Canadian veterans with a history of gout were studied. All had a serum uric acid level greater than 6.5 mg. per 100 ml. by the Archibald[25] modification of the method of Kern and Stransky. None had evidence of such clinical complications of atherosclerosis as myocardial infarction, angina pectoris, heart failure, cerebrovascular accident or intermittent claudication. The atherosclerotic and control groups with whom they have been compared have been previously reported.[14] None of the subjects was suffering from an acute attack of gout during the period of study, nor was any receiving specific uricosuric agents. However, one subject (W.R.) was maintained on colchicine therapy. There were no restrictions of diet or smoking.

RESULTS

In a previous study it was found that subjects tend to have more active clotting if they have a positive family history for complications of atherosclerosis.[14] For purposes of comparison, it was therefore necessary to classify subjects accordingly. This practice has been continued in the present study. The 22 gouty subjects were divided into 11 with a positive family history and 11 with no family history of complications of atherosclerosis (Table I). Differences between the two gouty groups were unimpressive (Table II) but followed the trends found in earlier comparisons of this kind.[14]

Comparison Between Gouty and Control Subjects

Mean platelet survival was found to be shorter and platelet turnover correspondingly greater in the gouty than in the control subjects (Table III). The differences, however, were significant only in those with a negative family history. Corresponding differences were found between the mean values for the plasma thromboplastin time and platelet adhesive index. Tests of the later stages of coagulation[14] failed to show significant differences.

TABLE II.—COMPARISON BETWEEN GOUTY SUBJECTS WITH AND WITHOUT A POSITIVE FAMILY HISTORY FOR ATHEROSCLEROSIS

	Mean values			
	Family history positive	*Family history negative*	*Age-adjusted t value*	*p*
Number	11	11		
Mean age	46.2 ± 2.9	52.2 ± 3.0		
Age range	33 - 62	31 - 67		
In vitro tests				
Adhesive index	1.265	1.180	1.583	<0.2
PCT (seconds)	297.0	334.0	1.321	<0.3
PTT (seconds)	10.92	11.30	0.678	<0.6
OSPT (seconds)	14.4	14.7	0.914	<0.4
WBCT (minutes)	12.05	11.33	0.549	<0.6
Platelet count (thousand/mm.³)	217.7	239.4	0.654	<0.6
In vivo tests				
Exponential treatment				
Half-life (days)	2.71	2.85	0.185	<0.9
Turnover (No./mm.³/day)	59,690	58,750	0.067	<1.0

Comparison Between Gouty and Atherosclerotic Subjects

There were no significant differences between the mean values for any of the tests (Table IV).

DISCUSSION

The *in vitro* tests of blood coagulation showed that subjects with gout have increased activity of the early stages of blood clotting as indicated by the platelet adhesive index and the plasma thromboplastin time. The whole blood clotting time, the one-stage prothrombin time, and platelet clumping time, which depend primarily upon changes in the later stages of clotting, are little affected. This evidence is strengthened by the shortened platelet survival and increased platelet turnover, which can be regarded in part as a measure of endogenous coagulation. The relationship between platelet survival, coagulation and *in vitro* tests of coagulation is discussed elsewhere.[14, 24]

The major manifestations of primary gout are an explosive, episodic arthritis, a possible anomaly in the handling of urate by the renal tubules, an inconstant but sometimes marked overproduction of uric acid, and an increased susceptibility to complications of vascular disease. Only the attacks of acute arthritis are specific for gout. Hyperuricemia with increased tubular reabsorption of urate, uric acid overproduction, and hypertensive and degenerative cardiovascular disease may be found singly or in combination in subjects who have not had gouty arthritis.

The relation of the blood coagulation and platelet survival findings to gout is not immediately apparent, but several points may be considered. It is possible that the shortened platelet survival and increased platelet turnover seen in gouty subjects are due to extensive atherosclerosis. However, the gouty subjects in the present study were carefully screened to exclude manifest vascular disease and in this sense seem more comparable to our "control" group. Moreover, among our patients with frank vascular disease, there was a clear difference between those with a negative and those with a positive family history, just as there was in the "control" group; but this difference is not evident

TABLE III.—COMPARISON BETWEEN *In Vitro* AND *In Vivo* CLOTTING TESTS IN CONTROL AND GOUTY SUBJECTS

	Mean values					
	Control		*Gout*			
	Family history positive	*Family history negative*	*Family history positive*	*Family history negative*	*Age-adjusted t value*	*p*
Number	16	28	11	11		
Mean age	41.1 ± 2.6	49.5 ± 2.8	46.2 ± 2.9	52.3 ± 3.0		
Age range	21 - 61	24 - 74	33 - 62	31 - 67		
Adhesive index	1.174		1.265		1.568	<0.2
		1.037		1.180	3.410	<0.005
PCT (seconds)	299		297		0.064	<1.0
		318		334	0.693	<0.5
PTT (seconds)	12.18		10.92		2.890	<0.01
		12.66		11.30	3.937	<0.001
PT (seconds)	13.9		14.4		2.053	<0.1
		14.4		14.7	1.374	<0.2
WBCT (minutes)	11.87		12.05		0.000	<1.0
		12.47		11.33	1.575	<0.2
Platelet count (1000/mm.³)	225.9		217.7		0.449	<0.7
		207.8		239.4	1.525	<0.2
Platelet survival						
Exponential treatment						
Half-life (days)	2.88		2.71		0.482	<0.7
		3.74		2.85	2.303	<0.05
Turnover (No./mm.³/day)	59,360		59,690		0.024	<1.0
		42,370		58,750	2.883	<0.01

in the gouty subjects. This suggests perhaps that increased platelet turnover in gout is attributable to some factor other than vascular disease, and that indeed it may be a primary mechanism.[26] An increased tendency to vascular disease in subjects with gout may possibly be a consequence of increased platelet turnover.

There is no evidence available bearing on the turnover of the other bone marrow elements. However, it is known that in myeloproliferative disorders in which any or all of the cellular elements of the marrow are produced in excess, gout is a not uncommon complication.[1-4]

It has been demonstrated that gouty subjects who excrete excessive amounts of uric acid incorporate labelled precursors into uric acid at an unusually rapid rate.[27, 28] This observation has been interpreted as favouring the theory that an anomalous pathway of uric acid synthesis may exist.[27, 28] It is possible, however, to explain this, at least in part, by increased myeloproliferative activity.

Diets rich in fat, in particular dairy fats and eggs,

TABLE IV.—COMPARISON BETWEEN *In Vitro* AND *In Vivo* CLOTTING TESTS IN ATHEROSCLEROTIC AND GOUTY SUBJECTS

	Mean values					
	Atherosclerosis		*Gout*			
	Family history positive	*Family history negative*	*Family history positive*	*Family history negative*	*Age-adjusted t value*	*p*
Number	16	15	11	11		
Mean age	54.5 ± 2.8	56.1±2.9	46.2 ± 2.9	52.3 ± 3.0		
Age range	39 - 75	37 - 70	33 - 62	31 - 67		
Adhesive index	1.291		1.265		0.037	<1.0
		1.207		1.180	0.354	<0.8
PCT (seconds)	304		297		0.143	<0.9
		313		334	0.790	<0.5
PTT (seconds)	11.45		10.92		0.619	<0.6
		11.78		11.30	1.216	<0.3
PT (seconds)	14.1		14.4		1.864	<0.1
		14.1		14.7	1.961	<0.1
WBCT (minutes)	12.66		12.05		0.538	<0.6
		12.65		11.33	2.034	<0.1
Platelet count (1000/mm.³)	225.7		217.7		0.097	<1.0
		219.0		239.4	0.719	<0.5
Platelet survival						
Exponential treatment						
Half-life (days)	2.58		2.71		1.292	<0.3
		3.15		2.85	1.436	<0.2
Turnover (No./mm.³/day)	64,700		59,600		0.804	<0.5
		51,320		58,750	1.403	<0.2

produce a shorter platelet survival and greater platelet turnover than low-fat diets.[24] It is possible that the dietary habits of gouty subjects, who often are overweight, may be a factor in the increased clotting activity and platelet turnover. This would provide an alternative explanation to supposing a primary myeloproliferative disturbance.

SUMMARY

In male subjects with primary gout, platelet survival was shortened and platelet turnover correspondingly increased. *In vitro* tests which measure the early stages of coagulation showed heightened activity. This increased turnover may explain at least in part the enhanced turnover of uric acid in some subjects with primary gout; and in view of the importance of the platelet in atherogenesis and thrombus formation, it may bear on the frequency with which vascular disease complicates this disorder.

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