Journal of Medical Sciences

ISSN 1682-4474

science alert

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Research Paper

J. Med. Sci., 5 (1): 47-51
January-March, 2005

Clotting Factors in Patients with Acute and Chronic Gout

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Since clotting factor abnormalities could contribute to the raised cardiovascular risk profile of patients with gout, this project was to assess possible changes in Factor VII and VIII. Levels of fibrinogen and of clotting Factor VII and VIII were measured in patients with clinical gout, both acute and chronic (intercritical) and were compared with those in healthy controls, closely matched for age and sex. Median levels of fibrinogen were significantly higher in patients with acute gout than in patients with intercritical gout ($p = 0.02$) or controls ($p = 0.005$). In view of the already raised thrombotic risk profile in gout patients as a group, it is reassuring that hyperfibrinogenaemia only seems to be present during acute attacks of gout, presumably as an acute phase response. It is unlikely, therefore, that the hyperfibrinogenaemia noted during acute attacks of gout contributes significantly to the chronically raised cardiovascular risk profile of long-term gout patients.

Key words: Gout, clotting factors, Factor VII, Factor VIII, fibrinogen

JMS (ISSN 1682-4474) is an International, peer-reviewed scientific journal that publishes original article in experimental & clinical medicine and related disciplines such as molecular biology, biochemistry, genetics, biophysics, bio-and medical technology. JMS is issued four times per year on paper and in electronic format.

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INTRODUCTION

Gout is associated with a number of risk factors for cardiovascular disease including hypertension[1], obesity[2], a high alcohol intake[3], hyperlipidaemia[4] hyperpre-betalipoproteinaemia[5,6]. We have therefore examined several key elements of the coagulation cascade to determine whether these may contribute to this risk, focussing on Factor I (fibrinogen), VII and VIII.

Fibrinogen concentration correlates positively with many cardiovascular risk factors; age, hypertension, hyperprebetalipoproteinaemia, smoking, diabetes mellitus, obesity, stress and lack of physical activity[7]. Fibrinogen concentration is also an independent risk factor for cardiovascular disease and an increased fibrinogen concentration may be a single mechanism by which several major risk factors promote coronary heart disease[8]. Elevated levels of Factor VII and VIII have been associated with increased thromboembolic risk in several different disease states[9-14].

It is of interest, therefore, to know whether fibrinogen and Factor VII and VIII are elevated in acute and/or chronic (intercritical) gout. It is also important to establish whether any abnormal concentrations of fibrinogen and/or Factor VII and VIII in gout patients during acute attacks remain abnormal between attacks, since such clotting factor abnormalities could increase gout patients' already abnormal vascular risk profiles.

MATERIALS AND METHODS

Patients: This study was approved by the Epsom Health Care District Medical Ethics Committee. Consecutive out-patients with gout attending Epsom General Hospital and from two local Primary Care Groups were investigated and fibrinogen, Factor VII and Factor VIII levels were measured over two years. Controls were either healthy subjects (e.g. medical personnel, ambulance men, visitors, relatives etc), or patients attending the hospital with conditions without systemic implications e.g. from the hearing aid clinic. Since Factor VII and fibrinogen both increase with age and obesity[15], patients and controls were matched for sex and ±10 years of age. Half lives of fibrinogen, Factor VII and VIII are 90 h[16], 5 h[17] and 10 h[17], respectively. Since levels are affected by stress, surgical[18], or otherwise[19] subjects known to have undergone significant stress in the previous week were excluded.

Cigarette smoking raises fibrinogen[15,20], while moderate alcohol consumption lowers fibrinogen], so smoking status alcohol status were recorded. Various drugs affect fibrinogen and/or Factor VII and VIII levels including testosterone, anabolic steroids, combined oral contraceptive[21], hormone replacement therapy[22] and antidiabetic drugs. Subjects taking any drugs known to affect fibrinogen or Factor VII or VIII were excluded.

Since fibrinogen is a major acute phase protein it increases by hepatic synthesis in conditions associated with inflammation or tissue necrosis and in pregnancy. In this study, the Erythrocyte Sedimentation Rate (ESR) was easured in patients and controls to exclude such inflammatory conditions.

Acute gout was defined as the presence of an existing painful inflammatory episode of gouty arthritis associated with elevated ESR and usually with increased plasma urate. When possible, synovial fluid was removed

Table 1: Paired comparisons between all gout patients and matched controls

	Fibrinogen (g L^{-1})		Factor VII (i.u.dL^{-1})		Factor VIII (i.u. dL^{-1})		Uric acid (mmols L^{-1})	
Statistic	Gout	Control	Gout	Control	Gout	Control	Gout	Control
Median	3.4	3.1	145	147	165	150	0.41	0.35
95% CI for median	(3.1, 3.7)	(3.0, 3.2)	(130, 160)	(140, 150)	(143.3, 181.4)	(145.0, 162.3)	(0.36,0.46)	(0.31,0.37)
Number of pairs	89		87		87		68	
Wilcoxon signed rank test								
Median deference	0.3		0		2		0.06	
95% CI for median difference	(0.01, 0.60)		(-17.4, 10.6)		(-10.3, 40.4)		(0.01,0.11)	
p-value	0.005		0.74		0.12		0.001	

Table 2: Group comparisons between acute and chronic gout patients

	Fibrinogen (g L^{-1})		Factor VII (i.u.dL^{-1})		Factor VIII (i.u. dL^{-1})		Uric acid (mmols L^{-1})	
Statistic	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Median	3.99	3.20	140.00	150.00	190.00	160.00	0.44	0.37
95% CI for median	(3.2, 4.3)	(3.0, 3.5)	(111.5, 160.0)	(130.4, 165.0)	(136.1, 257.4)	(130.0, 180.0)	(0.30,0.50)	(0.36,0.44)
sample size	25	59	23	59	23	59	25	55
p-value from Wilcoxon 2-sample test	0.02		0.26		0.17		0.23	

and examined under polarised light for the presence of negatively birefringent urate crystals. Chronic or (intercritical) gout patients were defined as those with a proven history of repeated episodes of acute gout extending over more than 1 year, but who were not suffering from an acute attack during the present investigation.

Measurements: Fibrinogen was measured by the method of modified Clauss[23] Factor VII by a standard assay based on 1 stage prothrombin time[24] and Factor VIII by a standard assay based on activated partial thromboplastin time[24].

Uric acid levels were measured by the method of uricase on Olympus AU 640 and platelet counts were measured by a Beckman Coulter STKS[25].

Analysis: Since not all the variables of interest were Normally distributed, data were summarised as medians, with 95% confidence intervals. For statistical analysis we used a Wilcoxon signed rank test to compare gout patients and their matched controls and the Wilcoxon 2-sample test to compare median values in chronic and acute gout patients. A significant difference was assumed when $p<0.025$, a value less than the conventional $p<0.05$, to adjust for multiple testing.

RESULTS AND DISCUSSION

The mean ages (95% CI) in years of the acute gout, chronic gout and control patients were 60.1 (54.6 to 65.5), 64.1 (60.6 to 67.6) and 63.1 (60.4 to 65.9). There were 76, 85 and 82% of males in the acute gout, chronic gout and control patient groups, respectively.

On comparing all gout patients, acute and chronic, with matched controls, fibrinogen levels and uric acid levels were significantly higher on average in the gout patients than in controls (Table 1). Levels of Factor VII and VIII were not significantly different between all gout patients and controls (Table 1).

Median fibrinogen levels were significantly higher in acute than in chronic gout patients. (Table 2). Median levels for Factor VII and VIII and uric acid levels were not significantly different between acute and chronic gout patients (Table 2).

There were no significant differences between chronic gout patients and controls in fibrinogen, Factor VII and VIII and uric acid levels ($p = 0.15$, $p = 0.75$, $p = 0.73$ and $p = 0.05$, respectively).

While the clotting factors measured here are not the only ones which may be relevant to the increased thromboembolic risk in gout, they each have been associated similar risk in other conditions. Raised fibrinogen levels have long been recognised as a significant risk factor for thrombosis[26-28]. Factor VII is also associated with thrombosis[9] and correlates well with body mass index, raising the possibility that it may one of the factors which contributes to the increased cardiovascular risk with obesity[29]. The beneficial effects of omega-3 fatty acids has been ascribed to an inhibitory action on Factor VII[30] Factor VIII has also been associated with increased thromboembolic risk[12] including that following recurrent pregnancy[31] and with increased risk of ischaemic stroke[13], ischaemic heart disease[14] and the increased coagulability rebound after treatment for haemophilia[32]. Inhibition of Factor VIII appears to be a viable approach to anti-thrombotic therapy[33].

There has been little interest to date in levels of fibrinogen and clotting factors in gout patients and in differentiating between levels in acute and chronic (intercritical) phases of the disease. Raised ESR and fibrinogen levels have previously been reported in gout patients during acute attacks (Werynska-Przybulska *et al.* Personal Communication) with a prompt return to normal after attacks, but clotting factor assessments have not previously been made in a controlled study. Werynska-Przybulska *et al.* (Personal Communication) investigated 227 gouty men over a period of one to seventeen years (average 7.2 years). Forty-three percent of patients had abnormal fibrinogen levels and 12.7% of patients had ischaemic heart disease.

Fibrinogen may encourage thrombus formation on atheromatous plaques by romotion of a hypercoagulable state[34] and it has an important role in determining blood rheology[8]. Increasing fibrinogen concentration causally increases platelet aggregability[22] and together with its metabolites, it causes endothelial damage, disorganisation and dysfunction[35]. As a result, hyperfibrinogenaemia is associated with increased blood viscosity and red cell aggregation, reduced blood flow and oxygen diffusion. Plasma fibrinogen concentration is a significant risk factor for stroke, myocardial infarction[36] and ischaemic heart disease[37].

That fibrinogen is elevated after stroke[38] and myocardial infarction[39] has been known for many years but, it has also been shown to be raised before such events, as in transient ischaemic attacks[40], peripheral[41] and diabetic vascular disease, idiopathic Raynaud's syndrome[42], scleroderma and with deficient fibrinolytic activity, in thrombophlebitis and venous liposclerosis[43]. Results from the Northwick Park Heart Study (NPHS) showed that men who died from cardiovascular disease had significantly higher levels of Factor VII, VIII and fibrinogen on entering the study than those who survived[44]. Men with peripheral vascular disease showed a significant increase in Factor VIII and fibrinogen compared with controls.

The significantly raised fibrinogen levels in gout patients could give rise to concern in view of the already abnormal thrombotic risk profile of gout patients as a group. However, if, as in this study, only fibrinogen level raised significantly during attacks of acute gout, it is presumably acting as an acute phase response in the acute attack. Since the fibrinogen level is not significantly raised in patients with chronic gout, when compared with controls, the thrombotic cardiovascular risk from hyperfibrinogenaemia is unlikely to be great, since acute attacks are relatively short-lived and relatively infrequent in most gout patients.

ACKNOWLEDGMENTS

The authors gratefully acknowledge the help of Dr. G. Gardner, Dr. S.R. Cotton, Dr. J.J. De Corter, Dr. K.S. McIntyre, Dr. J. Ruzicka, Dr. R.P. Sarsam and Dr. E.A. Warburton for their assistance with sample collection and of Mrs Glenda Primarolo and Mrs. Alison Smith for their clerical support.

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