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Gamma glutamyl transpeptidase levels in arthritis: a correlation with clinical and laboratory indices of disease activity

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SUMMARY Gamma glutamyl transpeptidase (GGTP) was measured in 62 patients with rheumatoid arthritis (RA) and 27 with osteoarthrosis (OA). The values for GGTP were significantly higher in the subjects with RA compared with the OA group. The prevalence of elevation of GGTP was higher in the RA subjects (77%) than in the OA patients (33%). Levels of GGTP correlated significantly with a number of objective indices of activity of RA in a separate group of 28 patients. Following treatment with penicillamine, GGTP levels showed a significant drop towards normal levels.

Abnormalities of liver function tests have previously been reported in patients with rheumatoid arthritis (RA) (Kendall *et al.*, 1970; Hilton *et al.*, 1974; Webb *et al.*, 1975). It has generally been assumed that such patients had liver disease in association with RA, eg, primary biliary cirrhosis or coincidental and unrelated primary hepatic pathology. It has been suggested that elevation of hepatic alkaline phosphatase may be an index of activity of RA since raised values are found in patients with severe active arthritis (Kendall *et al.*, 1970). However, the prevalence of this abnormality is relatively low at approximately 22% (Wilding *et al.*, 1975), thereby reducing the application of such an index.

The enzyme gamma glutamyl transpeptidase (GGTP) is widely distributed in body tissues. The highest levels are found in the kidney, pancreas, liver, and prostate. The enzyme is normally present in plasma (or serum) and urine, and high levels are found in bile and seminal fluid (Rosalki, 1975). Estimation of GGTP is currently considered to be the most sensitive method of detection of hepatic damage over the whole spectrum of liver disease (Rosalki, 1975).

The present study was designed to investigate the prevalence of raised GGTP levels in patients with RA and osteoarthrosis (OA), and to evaluate the level of enzyme as an index of activity of RA.

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Patients and methods

The investigation was conducted in two phases.

STUDY 1

In the first study, 89 patients were examined. Of these, 62 had classical or definite RA according to the criteria of the American Rheumatism Association (Ropes *et al.*, 1959). The remaining 27 had OA, the diagnosis being based on clinical findings supported by the appropriate radiological findings and associated with a negative test for rheumatoid factor and a normal value for uric acid. For the purposes of this initial screening study, the patients were unselected for the presence or absence of concomitant disease. The medication usage and alcohol consumption of all subjects were noted. Venous blood was withdrawn for estimation of GGTP, erythrocyte sedimentation rate (ESR), and plasma viscosity. All estimations were carried out within 1 hour of venepuncture.

STUDY 2

A further 28 patients with classical or definite RA were investigated. All had been taking salicylates only for a minimum of 2 weeks before the examination. Disease activity was assessed clinically using the articular index of joint tenderness (Ritchie *et al.*, 1968) and by measuring a series of objective indices. These included platelet count, ESR, plasma viscosity, C-reactive protein, serum sulphydryl,

plasma histidine, haptoglobin, and fibrinogen levels. In addition to determination of disease activity the following estimates of 'liver function' were also noted: bilirubin, alkaline phosphatase, albumin, globulin, and SGOT.

Fifteen of the 28 patients went on to receive penicillamine in increasing doses up to 500 mg daily whilst continuing salicylate therapy. Indices of disease activity and liver function were re-assessed after 3 months' treatment.

Methods used for assessment of disease activity are given in Table 1.

Table 1

Parameter	*Method*	*Study*
GGTP	Colorimetric	Jacobs (1971)
ESR	Sedimentation	Westergren (1924)
Viscosity	Ostwald viscometry	Harkness (1971)
Serum sulphydryl	Spectrophotometric	Gerber *et al.*, (1967)
CRP	Gel diffusion	Crockson (1963)
Histidine	Fluorimetric	Gerber (1970)
Haptoglobins	Column chromatograph	Ratcliff and Hardwicke (1964)
Fibrinogen	Immunodiffusion	Mancini *et al.*, (1965)

CRP = C-reactive protein.

Results

STUDY 1

The mean values for the 3 variables examined are shown in Table 2. All showed significant differences between the 2 patient groups.

The proportion of subjects showing a raised GGTP level in each group was estimated, using the values of 6–28 units/l for males and 4–18 units/l for females as the limits of normality. Forty-eight patients with RA (77·4%) and 9 patients with OA (33·3%) had raised levels of GGTP.

In the patients with RA, significant correlations were demonstrated between the GGTP and ESR values ($r=0·302$, $P<0·05$) and between GGTP and plasma viscosity ($r=0·423$, $P<0·001$). In the patients with OA no significant correlation was demonstrated between GGTP and ESR or GGTP and viscosity. No correlation could be found between the level of GGTP and the alcohol consumption or nature of drug therapy in these patients.

STUDY 2

Table 3 shows the prevalence of abnormal 'liver function' tests in the 28 subjects involved in the second phase of the study. A raised level of GGTP was found in 64·3% of patients, a value comparable with that found in study 1. Alkaline phosphatase levels were elevated in 25% of subjects, this value being similar to that previously reported (Wilding *et al.*, 1975). In the present study, GGTP levels were raised in all the subjects who showed an elevation of alkaline phosphatase and there was highly significant correlation between these 2 variables (Table 4). The values obtained for SGOT were raised in 7 (25%) of the patients studied. In 5 of these patients the GGTP was also increased, and in 3 the alkaline phosphatase was raised. SGOT and GGTP levels did not correlate but there was a significant correlation between SGOT and alkaline phosphatase values ($P<0·05$). All the subjects showed values for albumin levels within the normal range, but 12 had hyperglobulinaemia as defined by the range of normality in the local laboratory. In 9 of these patients there was also an increase in GGTP levels but there was no correlation between GGTP and globulin or albumin levels.

Significant correlations were noted between GGTP and the articular index, ESR, plasma viscosity, serum sulphydryl levels, C-reactive protein, and alkaline phosphatase (Table 4). No correlation was found between GGTP values and levels of platelets, haptoglobins, histidine, or fibrinogen.

Changes in the indices of disease activity in 15 patients followed for 3 months after introduction of penicillamine therapy are shown in Table 5. All the variables studied showed a trend towards normalisation, but statistical significance was not achieved in the changes in plasma viscosity, platelet count, or alkaline phosphatase level. The other variables, including GGTP, showed significant differences after specific drug treatment.

Discussion

Elevation of circulating GGTP levels was found in 73% of all the patients with RA in the study. The prevalence of the abnormality is greater than that of any other test of hepatic integrity, and is significantly

Table 2 *Results (means ± standard error) of 3 variables studied in the first phase*

Cases	*Age (years)*	*ESR (mm/h)*	*Viscosity (cP)*	*GGTP (units/l)*
RA (n = 62)	57·5 ± 1·7	47·0 ± 3·8	1·92 ± 0·02	40·9 ± 4·01
OA (n = 27)	66·1 ± 2·1	21·7 ± 4·3	1·70 ± 0·02	19·7 ± 2·21
		P < 0·001	P < 0·001	P < 0·001

higher in subjects with RA than those with OA. The most obvious explanation is that measurement of the enzyme is a highly sensitive means of detecting liver damage (Rosalki, 1975). Hepatic injury could conceivably occur as the result of intrinsic liver disease or toxic injury as a result of drug therapy. Without histological evidence, it is impossible to confirm or refute the possibility of liver disease, but reactive hepatitis and lymphocytic infiltration have been noted in patients with high GGTP levels (Rau, 1977).

Table 3 *Prevalence of abnormal liver function tests (n = 28)*

	Normal range	*Number abnormal*
GGTP (units/l)		
Females	4–18	18 (64·3%)
Males	6–28	
Alkaline phosphatase (KA units)	4–13	7 (25%)
Bilirubin (mmol/l)	3–15	0
SGOT (IU/l)	8–22	7 (25%)
Albumin (g/l)	37–49	0
Globulin (g/l)	24–37	12 (42·9%)

Conversion: SI to traditional units—Bilirubin 1 mmol/l ≈ 0·0585 mg/100 ml. Albumin and globulin: 1 g/l=0·1 g/100 ml.

In the present study, the pattern of medication usage in the RA and OA groups was broadly similar consisting, in both groups, of anti-inflammatory and analgesic drugs. In 5 patients with RA, specific therapy was used, eg, penicillamine (3 cases) and gold (2 cases). We concluded therefore that the abnormality of GGTP was not related to drug therapy. In addition, there was no correlation with the alcohol usage of the patients.

Raised GGTP levels have been reported in association with the use of enzyme-inducing drugs such as barbiturate and antipyrine (Whitfield *et al.*, 1973). The elevated enzyme levels in such circumstances would be attributable to an overspill of enzyme from metabolically hyperactive cells.

GGTP is involved in protein synthesis (Rosalki, 1975), and in RA there is commonly evidence of increased protein synthesis, manifest chiefly as hyperglobulinaemia. This is reflected in a number of indices of disease activity including ESR and plasma viscosity. In this study, significant correlations have been shown between GGTP levels and several indices of activity of RA, suggesting that GGTP itself may be a useful addition to the battery of acute phase reactants currently used to assess the

Table 4 *Correlation matrix for variables studied in phase 2*

	GGTP	*Articular index*	*ESR*	*Viscosity*	*Sulphydryl level*	*CRP*	*Histidine*	*Platelets*	*Haptoglobins*	*Fibrinogen*	*Alkaline phosphatase*
GGTP		*	*	*	*	†	NS	NS	NS	NS	‡
Articular index			†	*	†	‡	†	*	†	*	NS
ESR				‡	†	‡	*	‡	‡	†	†
Viscosity					*	‡	NS	*	‡	†	*
Sulphydryl						‡	†	*	†	†	†
CRP							‡	†	‡	†	†
Histidine								†	*	NS	NS
Platelets									‡	*	NS
Haptoglobins										†	*
Fibrinogen											*

* P<0·05. † P<0·01. ‡ P<0·001.

Table 5 *Indices of disease activity before and after 3 months' treatment with penicillamine and salicylates in 15 patients with RA*—t *test for paired values*

	Baseline		*3 months*		*t*	*P*
	Mean	*±SE*	*Mean*	*±SE*		
GGTP (units/l)	33·4	6·7	26·7	6·6	2·32	<0·05
Articular index	25·3	3·6	16·3	3·6	2·63	<0·025
ESR (mm/hour)	53·3	8·2	38·0	9·2	2·34	<0·05
Viscosity (cP)	1·96	0·05	1·89	0·07	1·73	NS
Sulphydryl levels (μmol/l)	442·7	14·3	522·7	15·6	4·10	<0·005
CRP (mg/100 ml)	5·43	1·66	2·68	1·20	2·52	<0·025
Histidine (mg/100 ml)	1·28	0·07	1·64	0·10	1·92	NS
Platelets (×109/l)	411·3	40·6	361·3	30·6	1·26	NS
Haptoglobins (g/l)	2·62	0·32	2·11	0·23	3·01	<0·01
Fibrinogen (g/l)	3·24	0·24	2·41	0·26	4·07	<0·005
Alkaline phosphatase (KA units)	13·1	1·3	11·9	1·3	2·09	NS

Conversion: SI to traditional units—Sulphydryl levels: μmol/l ≈ $3 \cdot 3 \times 10^{-3}$ mg/100ml. Platelets: 1×10^9/l = 1×10^3/mm^3. Haptoglobin and fibrinogen: 1g/l=100 mg/ml.

disease. This is also reflected in the change towards normality of GGTP values during the course of treatment with penicillamine. The advantage of GGTP measurement lies in its availability in most routine laboratories, while estimation of the more complex variables such as sulphydryl levels, histidine, and C-reactive protein is available usually in only a few centres. The greater prevalence of abnormal baseline GGTP levels makes measurement of this enzyme more widely applicable than assessment of alkaline phosphatase (Kendall *et al.*, 1970).

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