LETTERS TO THE EDITOR

Serum skeletal troponin I in inflammatory muscle disease: relation to creatine kinase, CKMB and cardiac troponin I

The measurement of serum creatine kinase (CK), which is used widely in the diagnosis and management of polymyositis and dermatomyositis lacks both sensitivity[1–7] and specificity,[7–9] leading to potential problems if the serum total CK concentration is interpreted as a direct measure of muscle disease activity. Furthermore, in those cases where the total CK is raised reliance on an analysis of the CK isoforms is an unreliable means of determining the presence of myocardial involvement. This is because in chronic inflammatory muscle diseases, regenerating striated muscle contains up to 50% of the CKMB isoform.[6 10 11] This often results in an increase in the CKMB/total CK ratio by more than the 3% threshold commonly used to imply myocardial damage.[6 8 9 11 12]

The need for more sensitive and specific serum markers of striated and myocardial inflammation has led us to a study of the troponins. Skeletal troponin I (sTnI) has been found to correlate with total CK in exercising athletes[13 14] and to be increased in a small series of patients with polymyositis[13] but has not previously been studied in detail in relation to total CK in inflammatory muscle disease. Cardiac troponin I (cTnI) is a highly specific marker of myocardial injury[15] in contrast with CKMB, which is expressed both in myocardial and striated muscle. The behaviour of cTnI has not been reported in the inflammatory muscle diseases.

We report the relation between serum sTnI and total CK in patients with polymyositis and dermatomyositis. In the assessment of myocardial disease the use of serum cTnI has been compared with serum CKMB and the CKMB/total CK ratio.

Serum samples were collected from 43 healthy control subjects (23 female) and 16 patients with polymyositis or dermatomyositis. Patients with inflammatory muscle disease were recruited from the Muscle Clinic at St George's Hospital between 1994 and 1997. Table 1 gives details of the patients. Diagnoses were established according to the criteria of Bohan and Peter[16] from clinical features of proximal muscle weakness with or without rash, serum total CK, EMG, muscle histology and in addition muscle magnetic resonance imaging. Evidence of myocardial involvement was assessed from clinical examination, ECG and echocardiography. Patients were treated with standard immunosuppressants including prednisolone, azathioprine, cyclosporin A and IV immunoglobulin according to clinical and biochemical assessment of disease activity, including serial muscle strength of deltoid and hip abductors using a hand held myometer[17] and serum total CK. In the myositis group between one and six samples were collected per patient

Table 1 Demographic details and CK, CKMB, skeletal and cardiac Troponin I values in patients with polymyositis and dermatoyositis

Case	*Sex*	*Age*	*Race*	*Diagnosis*	*CK (U/l)*	*CKMB (µg/l)*	*sTnI (µg/l)*	*cTnI (µg/l)*
1	F	50	W	PM	89	1.3	<1.6	0.1
2	F	74	W	PM	103		2	
3	M	75	A-J	DM	117	3.5	4.7	1.39
4	M	46	W	PM	123	2.5	1.6	0.03
5	F	56	A	PM	172	2.1	<1.6	0.03
6	F	30	A-C	PM	213	0.8	1.6	0.03
7	F	54	A	PM	227	1.8	<1.6	0.03
8	F	34	W	PM	231	5.1	3.4	0.03
9	F	56	I	DM	333	4.8	3.3	0.03
10	M	24	W	DM	413	17.9	10.4	0.08
11	F	63	A-C	PM	456	12.6	8.2	0.03
12	M	25	W	PM	734		18.5	
13	F	72	W	PM	2089	132	17.5	0.03
14	F	27	I	PM	2165	1183	990	0.03
15	M	40	A-C	DM	8341	294	73.6	<0.01
16	F	45	W	DM		1.7	<1.6	<0.01

sTnI: skeletal Troponin I, cTnI: cardiac Troponin I, M: male, F: female, DM: dermatomyositis, PM: polymyositis, A: African, A-C: Afro-Caribbean, A-J: Anglo-Japanese, W: white, I: Indian. Reference ranges: CK 30–250 U/l (male), 30–180 U/l (female), CKMB <5 µg/l, sTnI <7.5 µg/l, cTnI <0.1 µg/l.

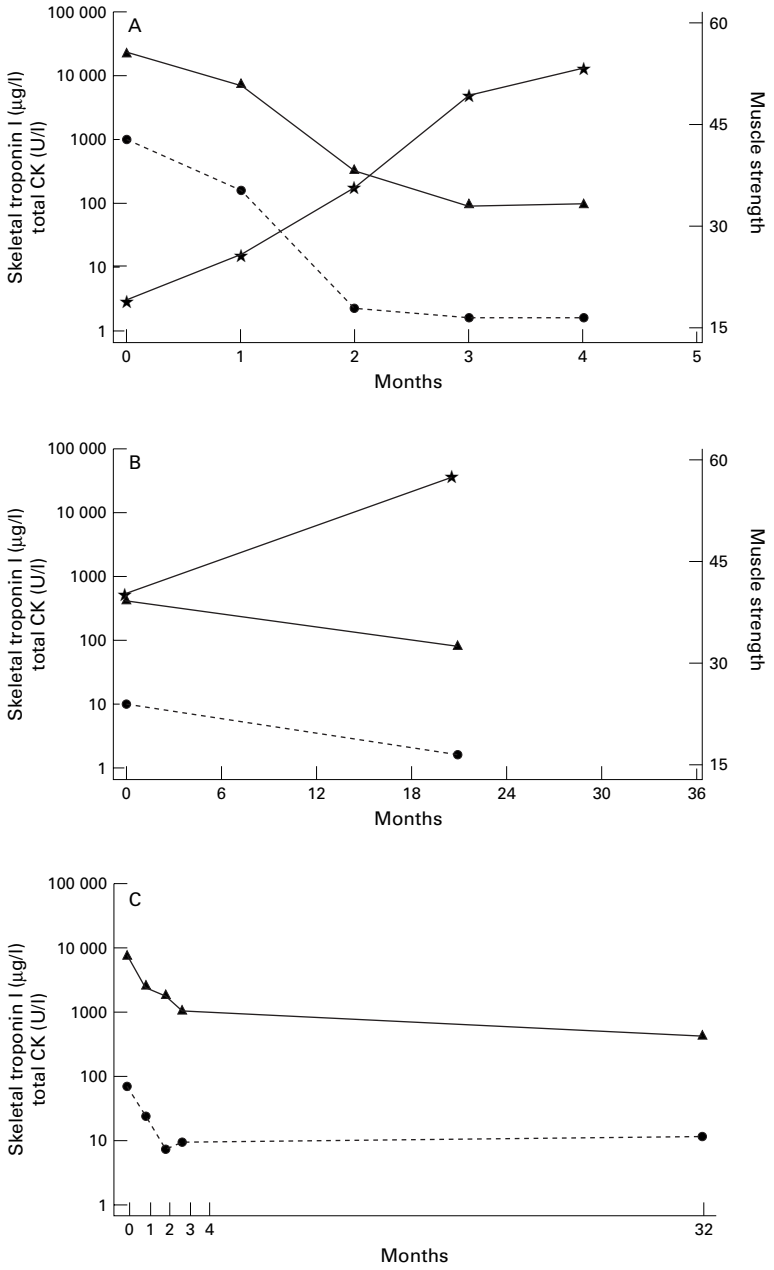

Figure 1 Serial serum skeletal troponin I (filled circles µg/l), total CK (filled triangles U/l) and muscle strength (asterisks, arbitary units) in patients with polymyositis (A) and dermatomyositis (B) and (C).

giving a total of 48 samples in which sTnI results were available.

Fast sTnI was measured by time resolved fluorimmunoassay using a modification of an enzyme immunoassay.[13] Cardiac troponin I and CKMB mass were measured on an automated analyser (Sanofi Access) according to the manufacturer's instructions (Beckman, High Wycombe, UK).

RELATION BETWEEN SERUM STNI AND TOTAL CK

In 43 control subjects the serum sTnI concentration was skewed despite log transformation (range: undetectable 12.7 µg/l, median: undetectable). The reference range, based on 95% of values for sTnI, was estimated to be less than 7.5 µg/l. Total CK values were available on 40 control subjects and correlated well with sTnI values. There were four outliers: three male subjects (CK 277 U/l, sTnI 5.2 µg/l; CK 404 U/l, sTnI 2.9 µg/l; CK 673 U/l, sTnI 5.2 µg/l) and one female subject in whom CK was normal (91 U/l) but the sTnI was increased (12.7 µg/l).

In 15 myositis patients there was a highly significant correlation between sTnI and total CK, Spearman $r = 0.95$ (95% CI 0.86, 0.98, $p < 0.0001$). In four cases the serum total CK was slightly raised in the presence of a normal sTnI. There were no cases of a raised sTnI with a normal total CK (see table 1).

Between two and six serial samples were taken from 14 patients over a three year period. All patients were receiving immunosuppressive treatment. In eight patients the disease was in remission throughout this time and the total CK and sTnI values remained within the normal range in all samples. In the remaining six patients serial samples were taken during the induction of remission and throughout subsequent follow up. In three patients changes in the total CK were mirrored synchronously by similar changes in the sTnI and in two cases were inversely related to the mean muscle strength in deltoid and hip abductors measured by a hand held myometer (see fig 1). In the other three patients there was insufficient variation in either serum marker to draw firm conclusions (not shown).

RELATION BETWEEN TOTAL CK, CKMB AND CTNI

There was a highly significant correlation between the total CK and CKMB (n = 13), Spearman $r = 0.99$, $p < 0.0001$; and also between sTnI and CKMB (n = 14), Spearman $r = 0.98$, $p < 0.0001$. There was no correlation between cTnI and CKMB (n = 14), Spearman $r = -0.11$.

Serum cTnI was increased in one case (1.39 µg/l, see table 1). There was no evidence of myocardial involvement at the time of the sample and the total CK, CKMB and CKMB/total CK ratio were normal. Intriguingly the patient had been treated for malignant hypertension three months earlier and this is the most probable explanation. A repeat cTnI sample two years later was normal.

In 6 of 13 patients (46%) the CKMB/total CK ratio was > 3%. There was no evidence in any of these patients of myocardial involvement and the serum cTnI was < 0.1µg/l in all six cases (see table 2).

Histological evidence of myocarditis has been found in 30% of patients with polymyositis[19] and non-specific evidence of myocardial disease reported in as many as 76%.[19 20] Our series concurs with others who also report a raised CKMB/total CK ratio in patients with inflammatory muscle disease.[8 9 12] However, although a ratio >3% is usually interpreted as indicative of myocardial disease in adults, in inflammatory muscle disease this is more likely to reflect striated muscle damage alone.[6 10 11] In this situation the cTnI is of particular use in distinguishing between a striated and myocardial origin of a raised CKMB/total CK ratio as cTnI is expressed only in cardiac muscle.[15] In our cross sectional study the CKMB correlated with sTnI but not with cTnI, suggesting striated muscle was the source of the CKMB. Furthermore the serum concentration of cTnI was normal in all patients where the CKMB/total CK ratio was >3%, supporting the clinical impression of no myocardial disease. This interpretation concurs with that of others.[12]

Table 2 Cardiac and skeletal troponin I in six patients with a CKMB/CK ratio >3%

Patient	CKMB/ CK %	cTnI (µg/l)	sTnI (µg/l)	CK (U/l)
1	4.2	0.03	<3	110
2	4.8	0.03	4.7	117
3	4.3	0.08	10.4	413
4	6.2	0.03	7.6	1 487
5	8.5	<0.03	26.4	2 813
6	5.5	0.03	990	21 000

In summary the concentrations of sTnI and both total CK and CKMB were significantly correlated in 15 patients with polymyositis or dermatomyositis in a cross sectional analysis and longitudinally during induction of remission of active disease. On grounds of tissue distribution, sTnI should be the preferred marker in skeletal muscle disease but further studies will be required to determine its clinical utility. A CKMB/total CK ratio >3% is more likely to reflect the presence of regenerating striated muscle than myocardial disease. cTnI is a specific tool for distinguishing between striated and myocardial damage in situations where myocardial involvement is suspected or where the CKMB or CKMB/total CK ratio is increased.

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Enlarged spleen detected by abdominal ultrasonography in patients with RA

Rheumatoid arthritis (RA) is a systemic, chronic inflammatory disease of unknown cause. Approximately 5–10% of patients with RA have an enlarged spleen on manual palpation[1] or on isotope scanning.[2]

We measured the size of the spleen in 50 patients with RA (nine men, 41 women; average age 55.8 years (range 25–78)) and 14 healthy control subjects (no men, 14 women; average age 47.8 years (range 25–80)) by abdominal ultrasonography (Aloka, Japan). This examination was done by one skilful examiner (TD) in all cases, and comparisons were made with clinical profile and disease activity. The patients with a diagnosis of Felty's syndrome, categorised as the triad, RA, leucopenia, and splenomegaly, and patients with complications of any viral or bacterial infections were excluded from this study. Mean (SD) disease duration was 6.2 (6.6) years. The disease stage was I (13 patients), II (11), III (nine), IV (17) and the functional class was I (seven patients), II (40), III (three), IV (0), assigned according to Steinbrocker criteria.[3] The following treatment was being used when the sonographic examination was performed: non-steroidal anti-inflammatory drugs (50 patients); gold treatment (12); sulfhydryl compounds (D-

Table 1 Correlation between enlarged spleen and clinical variables in 50 patients with rheumatoid arthritis

Items	Enlarged spleen (−) (n=24)	Enlarged spleen (+) (n=26)	p Value
Age	57.5 (11.0), (24)	54.1 (14.7), (26)	NS*
Sex (M/F)	5/19	4/22	
Disease duration (years)	6.0 (5.8), (24)	6.3 (7.4), (26)	NS
Stage I+II/III+IV	12/12	12/14	
ESR* (mm/1st h)	47.4 (26.2), (23)	46.5 (32.9), (26)	NS
CRP* (mg/l)	27 (24), (24)	31 (34), (25)	NS
RAHA* (titre)	260 (417), (20)	993 (2386), (22)	<0.2
γ Globulin (g/l)	15 (4), (23)	15 (5), (25)	NS
RBC* ($\times 10^{10}$/l)	413 (37), (24)	417 (54), (26)	NS
Haemoglobin (g/l)	120 (15), (24)	118 (18), (26)	NS
WBC* ($\times 10^{6}$/l)	8842 (2538), (24)	7492 (1701), (26)	<0.05
PLT* ($\times 10^{10}$/l)	31.6 (8.4), (24)	30.4 (11.2), (25)	NS

*ESR = erythrocyte sedimentation rate; CRP = C reactive protein; RAHA = rheumatoid arthritis haemagglutination assay; RBC = red blood cell count; WBC = white blood cell count; PLT = platelet cell count; NS = not significant.

penicillamine or bucillamine, 26); sulfasalazine (24); methotrexate (16); cyclophosphamide (one); prednisolone (34: 31 patients <5 mg/d, two patients 7.5 mg/d, one patient 10 mg/d). A splenic index (SI) was calculated as the length of the longitudinal dimension × the transverse dimension in the coronal plane through the splenic hilum. These dimensions were obtained in each test with the subject in the supine position as described by Konus *et al.*[4] The cross sectional area of the spleen (CSAS) in the coronal plane through the splenic hilum was measured by calipers in 13 control subjects and 49 patients with RA. By application of an ultrasonic duplex system, splenic venous blood flow (SVBF) in eight control subjects and 47 patients with RA was calculated from the cross sectional area and the mean blood flow velocity in the splenic vein, according to the method described by Moriyasu *et al.*[5] The SI in 50 patients with RA (mean (SD) 35.4 (8.1)) was significantly greater than that in control subjects (25.4 (5.0), p<0.0001, unpaired Student's *t* test). The CSAS and SVBF in patients with RA (28.0 (6.1) cm^2, n=49; 301.0 (150.2) ml/min, n=47) were also significantly higher (p<0.0001, p<0.01) than in control subjects (20.5 (2.9) cm^2, n=13; 139.1 (43.4) ml/min, n=8). The SI in all cases was significantly correlated with the CSAS (R^2=0.806, p<0.0001, n=62) and with SVBF (R^2=0.297, p<0.0001, n=55). From these results, an enlarged spleen was defined as an SI more than 35.4 (mean + 2SD of control subjects), and was diagnosed in 26/50 (52%) patients with RA. The average age of the patients with RA (55.8 years) differed by about eight years from that of control subjects (47.8 years). However, it is still certain that patients with RA have a larger spleen than control subjects because spleen size decreased with age in healthy subjects aged 18–65 according to a report by Niederau *et al.*[6]

Patients with RA were divided into two groups, those with an enlarged spleen (+) and those without (−), and clinical variables between the two groups were compared (table 1). There was no difference in the spleen size between patients with early or longstanding RA. Values of erythrocyte sedimentation rate and C reactive protein, as indicators of joint inflammation, were the same in both groups. Rheumatoid factor titres obtained by an RA haemagglutination assay in patients with RA with an enlarged spleen tended to be higher than in those without an enlarged spleen (p<0.2). There was no difference between either group of patients with RA in red blood cell counts, haemoglobin concentrations, or platelet cell counts. A significant difference was, however, found in the white blood cell counts (p<0.05). The number of patients receiving steroid treatment did not differ significantly between the two groups (χ^2 test; 17/26 *v* 17/24).

Defective reticuloendothelial system function in patients with RA was shown by determining the clearance of autologous, heat damaged erythrocytes from the circulation.[7] An inverse correlation between splenic function and the level of circulating immune complexes was seen.[7] We found that the number of white blood cells in patients with RA with an enlarged spleen detected by ultrasonography was significantly lower than in those without an enlarged spleen. These results indicated that an enlarged spleen in patients with RA might be caused by a mechanism similar to that in Felty's syndrome,[1] in which white blood cells are sequestered in the spleen to clear the circulating immune complexes—that is, increased removal of granulocytes rather than impaired production of granulocytes. Overall, imaging the spleen in patients with RA with ultrasound is a more sensitive way (52%) to assess the size of the spleen than palpation on physical examination (5–10%). Furthermore, it is possible that 52% of patients with RA with a large spleen might be in the early stage of Felty's syndrome.

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