MATTERS ARISING

Effect of intensive exercise on patients with active RA

The effect of intensive exercise on disease activity in rheumatoid arthritis (RA) is an interesting one.¹ Although we would not dispute that such exercise does indeed have a beneficial effect on parameters of disease activity, we wish to propose an alternative hypothesis as to its mechanism. In particular, we would argue that the effect of raised intra-articular pressure on synovial blood flow during exercise is not as the authors suggest.

The intra-articular pressure in chronically inflamed joints undoubtedly rises during exercise, and exceeds capillary perfusion pressure within the synovium.^{2–3} This pressure rise occurs in joints with and without effusions. It is clearly difficult to measure intra-articular pressure during dynamic exercise, but we would speculate that the pressure rises which occur during dynamic exercise are similar to those occurring during static exercise. The study that is quoted by the authors suggests that synovial blood flow increases during dynamic exercise such as walking and cycling and was only measured in joints with effusions.⁴ We would argue that raised intra-articular pressure during any form of exercise not only *compromises* synovial blood flow, resulting in synovial hypoxia, but is the initiating step in reperfusion injury.⁵ Hypoxia-reperfusion injury is one of the mechanisms by which reactive oxygen species (ROS) are produced, including the highly toxic hydroxyl radical.⁶ Damage by such ROS to biomolecules and tissues within the rheumatoid joint is well documented.^{7,8} Oxidative damage to fine nociceptor nerve endings within the synovium renders the joint relatively anaesthetic⁹ and perhaps allows the patient to exercise the joint more vigorously. We propose therefore that intensive exercise brings about an “auto-synovectomy”, effectively reducing the amount of inflammation within the joint and thereby reducing the disease activity score.

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Authors’ reply

In our study we observed a statistically non-significant decrease in all measured parameters of disease activity in patients with active rheumatoid arthritis who participated in an intensive exercise programme. In all exercise forms only the larger joints, in particular, the knee joints, were involved. None of the exercises focused on the hand joints. We assessed the 28 swollen joint count as proposed by Fuchs and Pincus.¹ If intensive exercise brings about an “auto-synovectomy” as suggested by Edmonds and colleagues one would expect a decrease in the number of swollen knees and a stable number of swollen joints in the hand. To test this hypothesis we compared in our data the number of swollen knee and hand joints (proximal interphalangeal joints and metacarpophalangeal joints) at baseline and at 24 weeks of follow up in patients who completed the study.

Table 1 shows that within the group undergoing intensive exercise both the number of swollen knees and the number of swollen hand joints decreased significantly. Differences between groups were not statistically significant. In our opinion hypoxia-reperfusion injury may induce “auto-synovectomy”, but this hypothesis does not fully explain the decrease in inflammation after vigorous exercise in other than exercised joints.

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Table 1 Changes in numbers of swollen knee and hand joints in patients randomly assigned to an intensive or conservative exercise programme during a stay in hospital

	Intensive exercise (n=28)	Conservative exercise (n=20)	Mean difference
Knee joints (max = 2)			
Baseline, mean (SD)	1.3 (0.8)	1.4 (0.8)	
Change at 24 weeks (95% CI)	−0.7 (−1.1 to −0.3)	−0.5 (−0.9 to 0.0)	0.3 (−0.3 to 0.9)
Hand joints (max = 20)			
Baseline, mean (SD)	12.1 (4.5)	11.9 (3.9)	
Change at 24 weeks (95% CI)	−4.0 (−6.2 to −1.8)	−2.3 (−5.0 to 0.4)	1.7 (−5.1 to 1.6)

Pulmonary function in patients with primary Sjögren’s syndrome

I read with interest the recent paper entitled “Ten year follow up of pulmonary function in patients with primary Sjögren’s syndrome” by Davidson *et al.*¹

This is an excellent 10 year follow up review of patients with primary Sjögren’s syndrome and the development of pulmonary manifestations. Pulmonary disease was found to occur predominantly in anti-Ro antibody positive patients and presents early in the course of the disease.

These findings confirm the relatively benign pulmonary disease in patients with primary Sjögren’s syndrome and the good long term prognosis.² This information is consistent with previous reports. In addition, the incidence of intestinal lung disease of about 25% is comparable with the incidence found in previous studies.^{3–5}

These findings are important and amplify the information previously published about pulmonary disease in Sjögren’s syndrome.

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LETTERS TO THE EDITOR

RS3PE and ovarian cancer

A variety of rheumatological diseases are associated with malignancies; among these polymyositis-dermatomyositis, carcinomatous polyarthritis, and palmar fasciitis are the most common.^{1,2} Other associated diseases include reflex algoneurodystrophy—that is, shoulder-hand syndrome or Sudeck’s atrophy. In 1985 a syndrome characterised by tenosynovitis of the sheaths of the tendons of hands, symmetrical distal synovitis, pitting oedema over the hand dorsum and the feet

(less commonly over the pretibial region), and rheumatoid factor seronegativity was described.³ This syndrome, with generally benign prognosis, was reported during the 1990s, but only in 1994 were clinical criteria for diagnosis proposed.⁴ In a few cases this syndrome was associated with malignancies: one with endometrial adenocarcinoma, two with gastric carcinoma, four with prostatic carcinoma, and one with colic carcinoma.⁵⁻⁷ We report the case of a woman affected by remitting seronegative symmetrical synovitis with pitting oedema (RS3PE) and concurrent ovarian carcinoma.

CASE REPORT

In January 1995 a 69 year old woman was admitted to our institute with severe pain and stiffness of the shoulders, hips, and ankles lasting up to two months, which did not respond to cortisone (prednisone 15 mg/day). Laboratory findings showed inflammation was increased and tumour markers were all negative. Table 1 reports the laboratory data. Erythrocyte sedimentation rate, C reactive protein, gammaglobulins, alanine aminotransferase were increased, whereas other parameters were normal. Rheumatoid factor was repeatedly absent.

Serum autoantibodies (antinuclear, anti-mitochondrial, anti-smooth muscle, anti-neutrophil cytoplasmic, extractable nuclear antigen antibodies) were evaluated owing to the rheumatological findings, but were negative, as were the tumour markers assessed (CA 19.9, carcinoembryonic antigen, α fetoprotein, and mammalian carcinoma antigen). Radiological findings of the hands, wrists, hips, ankles, and feet disclosed an increase in the space between the cutaneous surface and the bones, showing a soft tissue swelling. The patient was discharged in February 1995 with a diagnosis of benign oedematous polysynovitis and, after treatment with prednisone 15 mg/day her symptoms improved rapidly for about six months. In September 1995 the patient was readmitted to our division with the same symptoms as described above but, additionally, with ovarian swelling. Leucopenia and anaemia were present, and values

of lactic dehydrogenase, alanine aminotransferase, creatinine, and blood urea nitrogen (or azotaemia) had increased (table 1).

Because of the suspected ovarian tumour the patient was admitted to the institute of obstetrics and gynaecology of our hospital. Examination showed diffuse articular pain and myalgia and limited motion of ankles, hips, wrists, and shoulders. A tenosynovitis of muscle tendons of the hands as well as a pitting oedema of hands, feet, ankles, and knees were also present bilaterally.

We performed a pelvic ultrasonography and showed that the uterus had a normal density, but the ultrasound findings of the right ovary were compatible with a tumour. Computed tomography of the abdomen and pelvis confirmed the presence of an irregular pelvic mass in the right adnexal site with maximum diameter of 5 cm associated with a retroperitoneal adenopathy affecting the lumboaortic lymph nodes with a moderate ascites in the Douglas pouch. The serum Ca 125 level was much higher than normal and the interleukin 6 serum concentration was increased (table 1).

Surgical intervention allowed debulking and the biopsy specimen showed the presence of a serous cystoadenocarcinoma, moderately differentiated (FIGO stage IIb, grading G2). The pitting oedema, the absence of muscular pain, laboratory findings, and the muscle biopsy ruled out a diagnosis of polymyositis-dermatomyositis. In addition, the absence of eosinophilia and involvement of the palmar fascia excluded other characteristic diseases associated with neoplasms. After debulking, the patient underwent cytoreductive chemotherapy (CisPlatinum 75 mg/m², Adriblastin 30 mg/m², and cyclophosphamide 750 mg/m² (PAC schedule), for four cycles of 28 days). Subsequently, owing to a positive response, the patient had a total hysterectomy. In October 1995 the patient was discharged with treatment with prednisone 20 mg/day, which was tapered to 10 mg/day after the first month. From November 1995 the rheumatological symptoms were absent, and in January 1996 the patient suspended the prednisone treatment and underwent six cycles of

adjuvant PAC based chemotherapy. To date, the patient is alive and none of the previously reported symptoms have reappeared.

DISCUSSION

Several cases of RS3PE have been reported.⁸⁻¹² This syndrome has been recognised since 1985, and an association with a malignancy was found in only two cases. It is probably related to HLA-B7 (relative risk 9.5)^{3,13,14} and to HLA-A2 haplotypes¹⁵ and affects more men than women (sex ratio M:F=2:1) and the elderly. Our patient showed all the symptoms and signs of RS3PE: she was elderly, had a symmetrical polysynovitis, pitting oedema over the major joints, seronegativity for rheumatoid factor, symmetrical involvement of the sheath of the flexor muscle tendons of the hands, morning stiffness, spreading pain, and partial ankylosis of the shoulder. Some authors have reported a rapid response to low doses of steroids, with a progressive and complete recovery. In our patient, the signs indicating that this was not a simple RS3PE were the coexisting neoplasm, the poor response to the steroids given, and the disappearance of symptoms after total hysterectomy and lymphadenectomy. The clinical findings of RS3PE before the discovery of the neoplasm and its disappearance after the hysterectomy suggest a definite association between oncological and rheumatological diseases, even though a linkage has not yet been demonstrated. In fact, the remission of RS3PE with chemotherapy against the tumour might be due to the efficacy of this treatment on immunological and inflammatory diseases. However, findings leading to a diagnosis of RS3PE, which is not responsive to steroids, may predict the presence of a neoplasm at an early stage before its clinical manifestation. If this were the case RS3PE would behave as other “sentry” syndromes found in rheumatology—for example, neurological findings before a clear diagnosis of systemic lupus erythematosus, or respiratory disease before the renal involvement in Wegener’s disease. We found that the serum interleukin 6 concentration was higher than normal, as previously reported in the association with prostatic adenocarcinoma.⁷

Our experience suggests that a diagnosis of RS3PE, not responsive to low doses of steroids, may indicate an association with a neoplasm before the clinical manifestation of the latter, allowing a fundamental advance in the diagnosis and treatment of the malignancy.

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Table 1 Haematological parameters of our patient

Parameter*	Reported case	8 months earlier	Normal values
RBC ($\times 10^{12}/l$)	2.9	3.15	4–6
WBC ($\times 10^9/l$)	4.6	8.1	5–8
BUN (mmol/l of urea)	30.0	11.4	3.6–17.9
Creatinine ($\mu\text{mol/l}$)	140	90	40–110
Blood glucose (mmol/l)	6.3	4.9	3.6–5.8
ALT (U/l)	68	51	0–35
LDH (U/l)	784	512	0–450
ESR (mm/1st h)	120	42	0–10
CRP (mg/l)	108	65	5–10
RF	Negative	Negative	Negative
Gammaglobulins (%)	24	20	12–19
Mucoproteins (mg/l)	70	50	20–50
ANA	<1/40	<1/40	<1/40
ASMA	<1/20	<1/20	<1/20
ANCA	<1/20	<1/20	<1/20
ENA	<25	<25	<25
AMA	<1/20	<1/20	<1/20
CA 19.9 (U/l)	13	10	<15
CEA (U/l)	10	5	<5
α Fetoprotein (mg/l)	40	40	<50
MCA (U/l)	11	8	<15
Ca 125 (U/l)	680	Not evaluated	<37
IL6 ($\mu\text{g/l}$)	12.8	8.8	1–4

*RBC = red blood cells; WBC = white blood cells; BUN = blood urea nitrogen; ALT = alanine aminotransferase; LDH = lactic dehydrogenase; ESR = erythrocyte sedimentation rate; CRP = C reactive protein; RF = rheumatoid factor; ANA = antinuclear antibodies; ASMA = anti-smooth muscle antibodies; ANCA = antineutrophil cytoplasmic antibodies; ENA = extractable nuclear antigen antibodies; AMA = antimitochondrial antibodies; CEA = carcinoembryonic antigen; MCA = mammalian carcinoma antigen; IL6 = interleukin 6.

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Differential expression of cytokines and nitric oxide synthase isoforms in human rotator cuff bursae

Subacromial “bursitis” is a significant source of shoulder pain in patients with rotator cuff tear. The nature of the inflammatory pro-cesses in the subacromial bursal tissue is con-troversial and incompletely investigated. Macroscopically, subacromial bursa of pa-tients with rotator cuff dysfunction have thickened walls, tears, and are erythematous.

Histological studies, however, showed pre-dominantly fibrovascular tissue with an in-consistent degree of synovial hyperplasia, fibrosis, and, usually, minimal “inflammatory cell infiltrate”.¹ To characterise the nature of the processes in the subacromial bursa of painful shoulders we aimed at determining which cytokines and which isoforms of nitric oxide synthases (NOSs) are expressed in patients with rotator cuff tear.

Cytokines have key roles in the induction and effector phases of all immune and inflammatory responses.² Cytokines are also key molecules in soft tissue response to injury and wound healing.^{3–5} Nitric oxide, a free radical produced by NOSs, is another potent stimulator and mediator of biological pro-cesses, including immune and inflammatory responses, as well as wound healing⁶ and ten-don healing.^{7–8}

Seventeen patients with shoulder symp-toms due to rotator cuff tear were included in the study (table 1). Subacromial bursal sam-ples were collected at open surgery and total RNA was extracted from the tissue samples. The mRNA expression of interleukin 1β (IL1β), IL6, IL8, tumour necrosis factor (TNFα), and granulocyte macrophage colony stimulating factor (GM-CSF), as well

Table 1 Patient details

No	Age (yrs)	Duration of symptoms (months)	History of trauma	History of steroid injection	Shoulder pain		Clinical signs		Cytokines†‡				
					Pain intensity score‡	Pain frequency score§	Subacromial impingement	Supraspinatus weakness	IL6	GM-CSF	IL8	TNFα	IL1
1	42	60	No	No	7	12	Yes	No	17.0	7.7	7.3	0	0
2	76	2	Yes	Yes	7	9	Yes	Yes	9.3	16.8	5.4	0	0
3	80	96	No	Yes	11	10	Yes	Yes	20.8	11.0	8.0	0	0
4	68	8	No	No	7	9	Yes	Yes	61.8	13.3	28.7	0	0
5	65	3	Yes	No	9	9	Yes	No	51.1	26.2	4.5	0	0
6	50	12	No	Yes	6	6	Yes	No	44.6	35.9	2.3	0	0
7	66	2	Yes	No	6	9	Yes	Yes	77.2	26.8	11.2	25.0	0
8	77	3	Yes	No	7	8	Yes	No	57.5	19.0	2.1	0	0
9	46	16	No	Yes	9	12	Yes	No	50.7	10.5	1.9	0	0
10	55	2	Yes	No	7	11	Yes	Yes	28.1	17.7	1.9	0	0
11*	68	9	No	Yes	9	12	Yes	Yes	65.5	45.8	31.2	0	0
12	61	36	No	No	7	9	Yes	Yes	42.1	2.4	11.4	0	0
13	57	1	Yes	No	12	12	Yes	Yes	72.5	29.8	11.7	0	0
14	69	9	Yes	Yes	6	12	Yes	No	60.8	35.2	9.7	0	0
15†	71	8	Yes	Yes	6	12	Yes	Yes	15.3	0	3.7	0	0
16	64	4	Yes	No	6	10	Yes	Yes	21.0	0	10.4	0	0
17	40	20	Yes	Yes	11	12	Yes	No	69.9	36.9	18.3	0	0

*Patient with rheumatoid arthritis managed with non-steroidal anti-inflammatory drug.

†Patient with polymyalgia rheumatica managed with oral steroid.

‡Pain intensity at night, at rest, and with activities were scored as: 0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain, and 4 = very severe pain, and the three scores combined (maximum 12).

§The frequency of severe pain, pain at night, and pain with activities were scored as: 0 = never, 1 = monthly, 2 = weekly, 3 = daily, and 4 = constantly, and the three scores combined (maximum 12).

¶Relative expression given as the percentage of the positive control (concanavalin A induced peripheral blood mononuclear cells). IL = interleukin; GM-CSF = granulocyte macrophage colony stimulating factor; TNFα = tumour necrosis factor α.

Figure 1 mRNA expression of nitric oxide synthase (NOS) isoforms in human rotator cuff bursae by reverse transcriptase-polymerase chain reaction (RT-PCR). Lane MM = DNA molecular markers; lane PC = positive control PCR products for NOS isoforms (inducible NOS (iNOS) = interleukin 1β induced human chondrocytes at 500 bp, endothelial NOS (eNOS) = cultured human umbilical endothelial cells at 471 bp, neuronal NOS (nNOS) = human muscle at 486 bp); lanes 1–17 = PCR products of subacromial bursal samples for NOS isoforms and β-actin (643 bp); lanes A–C = PCR products for β-actin of the positive control samples.

as inducible, endothelial, and neuronal isoforms of nitric oxide synthase (iNOS, eNOS, and nNOS) were examined by semiquantitative reverse transcriptase-polymerase chain reaction. Densitometry readings were standardised against the housekeeping gene β -actin. Data were compared using Spearman rank order correlation test.

There was a consistent pattern of cytokine mRNA expression in the subacromial bursal samples. All 17 samples expressed IL6, IL8, and 15 out of 17 expressed GM-CSF as well, but there was no detectable mRNA expression for IL1 β , and only in one sample for TNF α . Positive, significant correlations were found between IL6 and GM-CSF ($r_s=0.7$, $p<0.05$), and IL6 and IL8 ($r_s=0.5$, $p<0.05$), demonstrating a concomitant expression of these cytokines.

iNOS and eNOS mRNA expression was detected in all samples, while nNOS was found in five out of 17 samples (fig 1). Significant correlation was found between the mRNA expression of eNOS and IL8 ($r_s=0.7$, $p<0.05$). This study was unable to detect correlations between the expression levels of cytokines or NOS isoforms and patient age, duration of symptoms, and shoulder pain scores.

In systemic immune response, proinflammatory cytokines tend to increase together. A temporal sequential expression of cytokines has been reported during wound healing. IL1 and TNF are expressed mainly in the early (inflammatory and proliferative) phase of wound healing,⁵ whereas IL6 levels are highest at a later (revascularisation) stage.⁴ Increase in IL6 and decrease in IL1 levels have been reported in cultured human tendon fibroblasts subjected to repetitive motion.³ It may be, therefore, that the pattern of cytokine expression, which we observed in the subacromial bursa, may reflect a dominance of reparative processes, or a response to altered mechanical stimuli rather than inflammatory or destructive processes.

In joint cartilage, production of NO has generally been implicated as a pathogenetic factor. However, increased local NO production seems to be essential for normal tissue healing.⁶ The expression of NOS isoforms in the subacromial bursa is a new finding and generates interesting questions.

The molecular events involved in the subacromial space are likely to be complex. Whether induction or inhibition of certain cytokines and NOS isoforms impairs or enhances the overall healing processes remains to be answered.

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Is parenteral methotrexate worth trying?

Methotrexate is widely accepted as a useful disease modifying drug for the management of rheumatic diseases, against which new treatments are often compared.^{1–3} However, apart from those who are intolerant of oral methotrexate despite folate supplementation, some patients simply do not respond. This may relate to compliance, but may also reflect pharmacokinetic variables, which influence the absorption of oral methotrexate.^{4–5} To overcome compliance and pharmacokinetic problems, some units have begun using parenteral methotrexate, either intramuscular or subcutaneous, the latter providing the potential for self treatment.⁶ However, although some authors have shown that parenteral methotrexate works,⁷ and many have examined the theoretical aspects of such treatment,^{4–5} hardly any have examined the clinical utility of switching patients from oral to parenteral methotrexate.

In this small cross sectional study we examined the case notes of all 24 patients (17 female) who had started treatment with intramuscular methotrexate at this rheumatology department. The indication for methotrexate treatment was mostly rheumatoid arthritis (RA), except for one patient with

polymyositis and one with juvenile arthritis. Mean (range) age was 56 (9–70) years. Median (range) dose of oral methotrexate was 17.5 (5–25) mg a week before the initiation of intramuscular methotrexate. At the time that the case notes were reviewed, 20 patients had improved, one patient was worse, and three were unchanged—an assessment reached by reviewing their clinicians' most recently recorded observations. Median (range) duration of parenteral treatment was 5 (1–55) months and dose of parenteral methotrexate at the time of this review was 15 (7.5–25) mg a week. Mean (range) C reactive protein fell from 53 (5–122) measured at the time parenteral methotrexate was started to 34 (7–111) mg/l when the case notes were reviewed.

It seems inevitable that the role of parenteral methotrexate will expand as institutions resolve the issues related to delivery of treatment and disposal of the cytotoxic waste it engenders. It also seems highly unlikely that a substantial clinical trial comparing continued oral treatment with initiation of parenteral methotrexate in patients unresponsive to oral methotrexate will ever be performed. At least this small study suggests that not only is it a development that ought to work but also it actually seems to improve disease control for these patients.

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