- 2 Chalmers A, Scheifele D, Patterson C, *et al.* Immunization of patients with rheumatoid arthritis against influenza: a study of vaccine safety and immunogenicity. *J Rheumatol* 1994;**21**:1203–6.
- 3 Edwards JC, Szczepanski L, Szechinski J, *et al.* Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. *N Engl J Med* 2004;**350**:2572–81.
- 4 Leandro MJ, Cambridge G, Ehrenstein MR, Edwards JC. Reconstitution of peripheral blood B cells after depletion with rituximab in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;**54**:613–20.
- 5 Horwitz SM, Negrin RS, Blume KG, *et al.* Rituximab as adjuvant to high-dose therapy and autologous hematopoietic cell transplantation for aggressive non-Hodgkin lymphoma. *Blood* 2004;**103**:777–83.
- 6 van der Kolk LE, Baars JW, Prins MH, van Oers MH. Rituximab treatment results in impaired secondary humoral immune responsiveness. *Blood* 2002;**100**:2257–9.
- 7 Palmer DF, Dowdle WR, Coleman MT, Schild GC. *Haemagglutination-inhibition test, Advanced laboratory techniques for influenza diagnosis*. Procedural guide. Atlanta, GA: US Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, 1975:25–62.
- 8 Masurel N, Ophof P, de Jong P. Antibody response to immunization with influenza A/USSR/77 (H1N1) virus in young individuals primed or unprimed for A/New Jersey/76 (H1N1) virus. *J Hyg (Lond)* 1981;**87**:201–9.
- 9 Oren C, Mendelbaum M, Paran D, *et al.* Vaccination against influenza in rheumatoid arthritis patients: the effect of rituximab on the humoral response. *ACR 2006 abstract no. 1234*.

Changes in serum levels of glucosamine and sulphate after ingestion of glucosamine sulphate with and without simultaneous ingestion of glucose

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Glucosamine as its chloride or sulphate salt is now in widespread over-the-counter use for the treatment of osteoarthritis, ostensibly by stimulating or stabilizing cartilage chondroitin sulphate. Clinical trials have, however, provided equivocal results concerning its effectiveness,^{1–3} and measurements of serum⁴ and plasma⁵ glucosamine levels after ingestion indicate that circulating glucosamine levels are probably too low to have any direct effect on cartilage.

Suggestions have been made that the sulphate of glucosamine sulphate might have a positive clinical effect on cartilage as a result of an increase in circulating levels after its ingestion.^{6–7} This may be particularly pertinent because we previously described⁸ a 9.3% mean decrease of sulphate levels after three hours of fasting by 14 experimental subjects, with a doubling of this mean decrease to 18.9% by the concomitant ingestion of 75 g glucose. In addition, we have described an effect of glucosamine sulphate ingestion by these subjects on glucose and insulin levels when 75 g glucose was ingested.⁹ Results were in contrast to other investigations¹⁰ that have indicated little or no effect when glucose was ingested the day after the ingestion of glucosamine rather than ingestion at the same time.

We have now examined the reciprocal effects of glucose ingestion on serum sulphate and glucosamine levels during a three hour period after an overnight fast. Methods, materials, subjects, study protocol, serum collection and analyses are detailed in previous publications.^{4–8,9}

Sulphate levels during three hours after overnight fasting with no additional ingestion, with 0 time ingestion of 75 g glucose, 0 time ingestion of 1500 g glucosamine sulphate, and 0 time ingestion of 75 g glucose plus 1500 g glucosamine sulphate are shown in fig 1A. The ingestion of glucosamine sulphate without glucose restored mean sulphate levels to slightly above baseline at each time interval, in contrast to the decreases with fasting when no glucosamine sulphate was ingested as previously reported.⁸ The simultaneous ingestion of glucose and glucosamine sulphate compared with glucose alone resulted in restoration to somewhat less than baseline for the first two hours and to slightly higher afterwards. The total amount of sulphate ingested (325 mg equal to 3.25 mmol) is consistent with the incremental amounts that were found in serum.

Mean glucosamine levels (fig 1B) demonstrated a delay in appearance and were higher and still climbing when glucose

was ingested along with glucosamine sulphate, probably reaching still higher levels if serum had been taken at later times. Two subjects had later samples obtained, however, showing a drop towards baseline at five hours and baseline at eight hours. The delay in the increase in glucosamine levels when ingested with glucose rather than without glucose is

Figure 1 Effects of ingested glucose on serum sulphate and glucosamine levels. (A) Mean serum sulphate levels at timed intervals after ingestion of glucosamine sulphate with glucose (●—●), without glucose (▲—▲), and for comparison, without glucosamine sulphate with glucose (○—○), without glucose (△—△). (B) Mean serum glucosamine levels at timed intervals after ingestion of glucosamine sulphate with glucose (●—●), without glucose (▲—▲).

consistent with the competitive inhibition of glucosamine by glucose for transport from the gastrointestinal tract. Furthermore, higher serum levels might be expected because glucose would competitively inhibit the uptake of glucosamine into the liver, thus allowing a higher concentration of glucosamine to enter the peripheral circulation. We do not believe that the minimal raising or extending glucosamine levels would be of significant therapeutic benefit.

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Support was provided by the Medical Research Service of the Department of Veterans Affairs, a grant to J.E.S. by the Arthritis Foundation, and by the Tufts University General Clinical Research Center, funded by the Division of Research Resources of the National Institutes of Health (NIH) under grant no. MO1-RR00054, US Department of Health and Human Services, NIH and Agency for Healthcare Research and Quality, Ruth L. Kirschstein National Research Service Award (T-32).

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Accepted 27 March 2007

REFERENCES

- 1 Richy F, Bruyere O, Ethgen O, *et al*. Structural and symptomatic efficacy of glucosamine and chondroitin in knee osteoarthritis: a comprehensive meta-analysis. *Arch Intern Med* 2003;**163**:1514–22.
- 2 Hughes R, Carr A. A randomized, double-blind, placebo-controlled trial of glucosamine sulphate as an analgesic in osteoarthritis of the knee. *Rheumatology (Oxford)* 2002;**41**:279–84.
- 3 Clegg DO, Reda DJ, Harris CL, *et al*. Glucosamine, chondroitin sulfate, and the two in combination for painful knee osteoarthritis. *N Engl J Med* 2006;**354**:795–808.
- 4 Biggee BA, Blinn CM, McAlindon TE, *et al*. Low levels of human serum glucosamine after ingestion of glucosamine sulphate relative to capability for peripheral effectiveness. *Ann Rheum Dis* 2006;**65**:222–6.
- 5 Persiani S, Roda E, Rovati LC, *et al*. Glucosamine oral bioavailability and plasma pharmacokinetics after increasing doses of crystalline glucosamine sulfate in man. *Osteoarthritis Cartilage* 2005;**13**:1041–9.
- 6 Hoffer LJ, Kaplan LN, Hamadeh MJ, *et al*. Sulfate could mediate the therapeutic effect of glucosamine sulfate. *Metabolism* 2001;**50**:767–70.
- 7 Cordoba F, Nimni ME. Chondroitin sulfate and other sulfate containing chondroprotective agents may exhibit their effects by overcoming a deficiency of sulfur amino acids. *Osteoarthritis Cartilage* 2003;**10**:228–30.
- 8 Blinn CM, Biggee BA, McAlindon TE, *et al*. Sulphate and osteoarthritis: decrease of serum sulphate levels by an additional 3-h fast and a 3-h glucose tolerance test after an overnight fast. *Ann Rheum Dis* 2006;**65**:1223–5.
- 9 Biggee BA, Blinn CM, Nuite M, *et al*. Effects of oral glucosamine sulphate on serum glucose and insulin during an oral glucose tolerance test of subjects with osteoarthritis. *Ann Rheum Dis* 2007;**66**:260–2.
- 10 Tannis A, Barban J, Conquier M. Effect of glucosamine supplementation on fasting and non-fasting plasma glucose and serum insulin concentrations in healthy individuals. *Osteoarthritis Cartilage* 2004;**12**:506–11.

High association of mycobacterial infections with polymyositis in a non-endemic country for tuberculosis

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Ann Rheum Dis 2007;**66**:1404–1405. doi: 10.1136/ard.2007.070177

The susceptibility to mycobacterial infections of immunosuppressed subjects, for example, those treated actively for rheumatic diseases, is widely recognized.^{1,2} However, the co-existence of mycobacterial infection (caused either by *Mycobacterium tuberculosis* or other mycobacterial infections) and polymyositis (PM) has been reported only in small series of patients^{2–5} predominantly from countries where tuberculosis (TB) is endemic^{2,3} or in immigrants in a Western country.^{4,5}

We assessed the frequency of mycobacterial infections in patients with PM and dermatomyositis (DM) in Finland, a non-endemic country for TB that has kept detailed registry for TB. All patients with an ICD-8 code for PM (716.00) and DM (716.10) who had been discharged from any Finnish hospital during the years 1969 to 1985 were identified by using the information from the National Discharge Registry. During this period, diagnostic studies for PM and DM were usually performed on inpatients. Therefore, the present series of patients represents the vast majority of PM and DM cases in Finland during this period.

We found 176 patients with PM and 72 with DM who fulfilled the diagnostic criteria of Bohan and Peter.^{6,7} We followed their progress by studying the records until they died or until the end of August 1995. At the time of the diagnosis of myositis, 26 (10%; 19 with PM and 7 with DM) of the whole series of 248 patients had a history of TB. In addition, 13 out of 176 patients (7.4%) with PM and 2 out of 72 patients (2.8%)

with DM were documented to have a mycobacterial infection after a median time (range) of 20 (3–111) months from the diagnosis of myositis. Only one of them (who had PM) was in the group with a history of TB (57 years earlier).

Cumulative probability of mycobacterial infections among patients with PM was 4.8% (95% CI 2.4 to 9.4%) in 5 years and 9.3% (95% CI 5.4 to 15.6%) in 10 years (fig 1). On the basis of acid fast stain and mycobacterial culture, we determined that 11 out of the 15 mycobacterial infections were caused by *M. tuberculosis* (nine of them in PM patients) and four by other mycobacteria (*M. avium intracellulare* or mycobacteria group IV). At the time of the diagnosis of the mycobacterial infection, all the patients used corticosteroids, and seven PM patients also used or had used azathioprine. The risk factors for developing mycobacterial infections did not differ between patients with and without the infection.

Altogether, in 40 out of 248 (16%) patients with myositis — in 31 out of 176 (18%) with PM and 9 out of 72 (13%) with DM — there was a former or diagnosed mycobacterial infection noticed during the follow up. To the best of our knowledge, the present study is the first one reporting a high frequency of mycobacterial infections in a large, systematically collected population of subjects with PM and DM in a Western non-endemic area for TB.

It may be supposed that, at least in part, the high incidence of mycobacterial infections during the treatment of myositis is caused by the reactivation of a former infection. The association