three months and further fractures two months later.

They suggest that MTX osteopathy may be more common than expected in patients treated with low dose methotrexate, yet all the evidence suggests the opposite. MTX is now the most commonly prescribed disease modifying antirheumatic drug for rheumatoid arthritis in America and parts of Europe.[2 3] We conservatively estimate that 120 000 patients receive low dose MTX in the UK alone, with historically a greater proportion of patients in America receiving the drug. Yet cases of proposed MTX osteopathy with low dose treatment are vanishingly rare (six reported cases in adults). Moreover, recent data suggest that low dose MTX has no effect on bone turnover at all.

In this case only a low dose of MTX was used and is the suggested cause of the fractures. Data from paediatric cases suggest that extremely high doses of MTX (20 g/m^2, 80 g/m^2, and 135 g/m^2) are associated with MTX osteopathy.[4] Smaller cumulative doses have been implicated in adults, but in the only other published case with short duration (nine months) the patient received almost fivefold more MTX.[5] It is surprising that the authors do not comment on the role of the high doses of prednisolone treatment (estimated cumulative dose of 92 g) or the presence of inflammatory disease over 27 years, both important risk factors for insufficiency fractures.

There is a growing body of evidence to refute the fact that MTX has any clinically significant effect on bone mineral density (BMD) or a significant impact on the osteoblast lineage. Patel *et al* carried out a prospective study of patients with psoriasis and low dose MTX treatment, and reported no significant change in markers of bone turnover or BMD after 21 months' follow up.[5] Minaur *et al* found that the proliferation and maturation of cells of the osteoblast lineage were not affected by MTX.[6] In a study of 116 patients, no direct association of MTX with BMD loss or bone turnover markers was found, and in a small subset, no impact on bone formation was shown by biopsy.[7]

There appears to be sufficient evidence to doubt the pathogenic role of MTX in this case. Further information about the treatment of the patient in the study of Rudler *et al*, her BMD, parathyroid hormone levels, and long term outcome are necessary. Did she receive any treatment at all after her initial fractures? In the last paragraph the authors refer to stress fractures. Are they implying that undue stress or activity contributed to the clinical picture? We believe they should be described as insufficiency fractures. The former are fractures occurring in otherwise normal bones by an abnormally applied mechanical load and the latter are due to abnormal bone.

Currently, it is thought that the possibility of a detrimental impact of MTX on the skeleton, even with concomitant corticosteroids, is low. It is important to emphasise that MTX has had a major impact in improving the health and bones (through corticosteroid sparing) of patients with inflammatory arthritis as well as other inflammatory conditions, which greatly outweighs any possible detrimental effects.

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Authors' reply to Rozin and Quinn *et al*

We read with interest the comments by Rozin and by Quinn and colleagues about our recent publication on low dose methotrexate (MTX) osteopathy in a patient with polyarticular juvenile idiopathic arthritis. Our report was not intended to suggest that MTX osteopathy may be more common than expected, and we agree that reported cases of low dose MTX osteopathy are exceedingly rare compared with the number of patients treated with MTX. Certainly, at a first glance it might not be very surprising that this patient developed serial insufficiency bone fractures after 25 years of prednisone treatment. However, the temporal association with the introduction of MTX and the multiplicity of fractures was striking.

We acknowledge that we did not provide further information about other possible factors that might have influenced the risk fracture in this patient. This 35 year old woman was not menopausal, did not smoke, and had a normal diet, and her physical activity was markedly restricted as her polyarticular joint involvement was severe. Unfortunately, family history of osteoporosis and bone mineral density were not assessed.

We disagree with Rozin about his interpretation of the technetium-99m diphosphonate bone survey. The multiple areas of increased uptake are asymmetric, which would be unlikely for a flare of polyarticular juvenile idiopathic arthritis. Moreover, the enhanced uptake which was localised to the femoral condyles and right calcaneum is not compatible with joint involvement. The increased uptake is certainly too marked and too diffuse to be related to multiple enthesopathies, which would also be very unusual clinical features in this type of inflammatory rheumatism. In a scintigraphic study of the cruciate deficiency model of knee arthritis in dog, the uptake ratio (unstable knee/contralateral knee) did not exceed 2.0 (controls value: 1.0 to 0.10).[1] Conversely, in a semiquantitative ("scintimetric") ^{99m}Tc diphosphonate scintigraphic follow up study of patients with peripheral fractures, the uptake ratio (fracture/normal reference site) was much higher (5.0 to 8.0).[2] In our patient the uptake ratio was 5.5 and 3.7 for the left knee/right knee and right calcaneum/left calcaneum, respectively, which is further evidence for the diagnosis of multiple fractures.

Data for the in vitro effect of MTX on osteoblasts are conflicting, but we agree with Rozin and Quinn and colleagues that the in vivo effect assessed on bone mineral density is reassuring in most studies.[3–6] Moreover, better control of the inflammatory arthritis should allow an increase of physical activity, which in turn may improve osteoporosis. The hypothesis of bone hypersensitivity or idiosyncrasy to MTX that is discussed by Rozin is only speculative, but appealing. Finally, we obviously concur with both comments and agree that such an exceptional observation of MTX osteopathy should certainly not deter from the use of MTX in idiopathic juvenile arthritis or other inflammatory arthritides when it is indicated.

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Clinical comparisons of RA between different populations: are they feasible?

Rheumatoid arthritis (RA) is the most common chronic inflammatory disease,

affecting about 1% of the white population, particularly female patients, and has considerable physical, psychological, and social repercussions.[1]

In a paper published previously in the *Annals*, Dadoniene *et al* described and compared two cohorts of patients with RA from Vilnius (Lithuania) and Oslo (Norway).[2] There were no significant differences in sex, age, extra-articular manifestations, education, or family history of RA between the groups. None the less, there were important differences in disease activity, disability, pain, emotional, mental and general health, with patients in the Vilnius group having the worst scores. The number of patients who had never used a disease modifying antirheumatic drug (DMARD) was similar in both groups. Vilnius patients had more commonly used azathioprine, sulfasalazine, and antimalarial drugs, whereas Oslo patients had used methotrexate, gold salts, cyclosporin, and D-penicillamine. Surgery was more common in the Oslo patients. That study was developed to compare the evolution and outcomes of two different populations with RA and was the first to include health related quality of life. The authors attributed the differences between these groups to differences in economic status, medical care, drugs used and, to a lesser extent, genetic differences.

During the past years the HLA system has been gaining an increasingly important role in the pathogenesis of autoimmune diseases. HLA polymorphism has multiple effects on the immune system.[3]

HLA-DRB1 alleles have been associated with RA in a number of populations. In the third hypervariable region of their DRβ1 chain, they share a sequence of amino acids named ''the shared epitope'' (SE).[4]

In a mestizo Colombian population we found that the SE ^{70}QKRRA^{74} in DRB1*04 alleles had the strongest association with RA.[5] However, we did not find any significant association between HLA and RA in African Colombians, emphasising the importance of genetic differences even among populations living within the same country.[6]

There have been different findings from one area to another. In Latin America, the differences are important. In Chilean patients the most common HLA-DRB1 alleles were DRB1*0404 and *0408 and the SE influenced the radiographic evolution of hands erosions.[7 8] In the Argentinian population the DRB1*0404 was also important but only DRB1*1001 was related to RA severity.[9] In the Peruvian population an association between RA and the SE was not found.[10] There was a lack of uniformity in the development of these trials, but they all showed a lack of association between DRB1*0401 and RA in the Latin American population.

These findings suggest that SE inheritance and genetic influence may vary depending on the genetic background of the studied population even in apparently closely located countries. The previous study comparing the Norwegian and Lithuanian populations without inclusion of genetic typing may be misleading. Furthermore, not only may the HLA system play a part in the disease outcome and disease progression of these patients but pharmacogenetics may also be at least as important. The efficacy of methotrexate, sulfasalazine, and other DMARDs in reducing the radiological progression of RA erosions has been proved; however, their efficacy and tolerability may be influenced by mutations in their metabolic pathways or in their cellular targets.[11 12]

Epidemiology of autoimmune diseases is becoming more complex as our knowledge of HLA and genetics becomes more complete. The time is coming when diseases will be defined not only by their symptomatology but also by the genetic background of their hosts.

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Authors' reply

We thank Drs Cadena and Anaya for their important and interesting comments on our paper reporting differences in disease activity and health status between matched patients in Norway and Lithuania.[1]

Cadena and Anaya focus on the difference in the genetics of the HLA system or pharmacogenetic differences as a potential explanation for our findings. They refer to several studies, mainly from their own region of the world, where genetic markers have been associated with disease severity and progression. We agree that rheumatoid arthritis is associated with genes, mainly in the region encoding the major histocompatibility complex genes.[2] However, the relative importance of genes is controversial also because low disease concordance has been found in studies of monozygotic twins. Some of the genetic studies indicate only a limited influence of genetic factors on disease susceptibility and progression, and this may suggest a relatively stronger importance of environmental factors.[3]

However, we completely agree with the comments of the authors that genetic factors, ideally, should have been examined in both populations. However, blood samples were not available for such analyses, but our results would have been stronger if data on the genetic background of the populations had also been available.

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