Steroids cause osteoporosis

We read with great interest the article by Gudbjornsson and colleagues and concur with the accompanying leader by Dr Paget on the issue of corticosteroid associated osteoporosis. Osteoporosis is a major public health problem, associated with significant morbidity and mortality, and is estimated to cost £614 million annually in England and Wales alone. Despite well published guidelines on the prevention and treatment of corticosteroid associated osteoporosis, as a profession, we are failing to meet the targets set by these guidelines.

In the light of the American College of Rheumatology guidelines in 2001, we performed an audit of our current practice relating to the issue of steroid prescription, calcium supplementation, measurement of bone density, and the prescription of anti-resorptive treatment to see if we had been adhering to the recommendations of the National Osteoporosis Society. Our rheumatology department has a continually updated database on all current and past patients who have attended our unit. This contains information on patient demographics, primary rheumatological diagnosis, comorbid conditions, current drug treatment, past disease modifying treatment (including corticosteroids), and records all patient generated events, including outpatient and inpatient episodes. From our database of over 10 000 patients, we identified 258 patients who were currently receiving prednisolone and had been taking the drug for a minimum of three months.

Forty patients (29 female) were randomly selected. The median patient age was 63 years (range 33–85). The patients were taking a mean daily dose of 6.7 mg prednisolone (range 1–45) and had been prescribed prednisolone for a median of 6 years (range 3 months–20 years). The most common reason for the prescription of prednisolone was for polymyalgia rheumatica for 14 (35%) of those selected, followed by systemic lupus erythematosus (SLE) in nine (23%), rheumatoid arthritis or associated complications for four (10%), and mixed connective tissue disease for three (8%). There were also isolated prescriptions for juvenile idiopathic arthritis, dermatomyositis, polymyositis, psoriatic arthritis, Wegener's granulomatosis, iritis, and unspecified systemic vasculitis.

Encouragingly, 34 (85%) of our cohort were receiving some form of bone protective treatment: 22 (55%) were taking an oral bisphosphonate and one patient received intravenous pamidronate. Four of the postmenopausal women were taking hormone replacement therapy and two patients were receiving calcitriol. Twenty (50%) were prescribed calcium and vitamin D supplements, and this was the only treatment in eight (20%) of the cohort. However, of the six patients not receiving any form of bone therapy, five were over the age of 65 years and the one patient under the age of 65 years had been treated with prednisolone continuously for 20 years for SLE, up to a maximum dose of 80 mg/day.

Twenty four (60%) of the 40 patients had bone density measured by dual x-ray absorptiometry (DXA) scan. Of these, seven (29%) were normal, eight (33%) showed osteopenia, and nine (38%) demonstrated osteoporosis at the lumbar spine or the neck of the femur, or both. All patients who had either osteopenia or osteoporosis had been treated with prednisolone for a median of 6 years (range 3 months–20 years), and 15% were neither receiving long term treatment with corticosteroids, nor calcium or vitamin D supplementation.

We interviewed 24 patients by telephone. Eighteen (75%) recalled being informed of steroid side effects. Seven had received written information on steroids, but only three had received written information on osteoporosis.

Although our results are encouraging, a significant number of patients are not being treated to prevent osteoporosis and reduce future fracture risk. The fact that all patients with an abnormal bone density scan are treated is reassuring, but we cannot be sure what proportion of patients who have not been scanned require treatment. In 1996, Walsh and colleagues found that only 14% of patients receiving long term prednisolone were receiving some form of preventative treatment against osteoporosis. Although matters have improved to a degree, a substantial proportion of patients treated with steroids is still undertreated and considerable progress has to be made nationally and internationally to prevent further bone associated morbidity among patients treated with corticosteroids.

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We appreciate the comment by Dr Gordon and her coworkers on our article on the prevalence of decision making against steroid-induced osteoporosis, which was recently published in the Annals and which included a leader from Dr Paget. In their letter, they further highlight the importance of prevention against corticosteroid-induced osteoporosis. They also reported their experience at their rheumatological clinic with more than 10 000 patients. Surprisingly, only 2.6% of their patients with various rheumatological disorders were receiving long term treatment with corticosteroids, in comparison with 0.7% of our unselected population based cohort. More than half of their patients were receiving bisphosphonate, but unfortunately they did not report whether this was primary or secondary prevention or treatment against manifest osteoporosis, nor did they report the prevalence of fragility fractures in their patient group. Although this is a much higher proportion than ours and others have previously reported, still 20% of their patients were not treated with any antiresorptive agent and 15% were neither receiving specific bone protective treatment nor calcium or vitamin D supplementation.

These figures show that even in a specialist clinic with attention to osteoporosis, further work needs to be done in primary prevention against steroid-induced osteoporosis. Since we performed our study in northeast Iceland an Osteoporosis Clinic with DXA has been established in the study area, and the Department of Public Health in Iceland has published clinical guidelines concerning this issue. Thus, it will be of interest to re-perform our study in the near future for evaluation of the actual improvement in preventing bone morbidity in patients in need of long term treatment with corticosteroids.

References

Authors’ response

We appreciate the comment by Dr Gordon and her coworkers on our article on the prevalence of decision making against steroid-induced osteoporosis, which was recently published in the Annals and which included a leader from Dr Paget. In their letter, they further highlight the importance of prevention against corticosteroid-induced osteoporosis. They also reported their experience at their rheumatological clinic with more than 10 000 patients. Surprisingly, only 2.6% of their patients with various rheumatological disorders were receiving long term treatment with corticosteroids, in comparison with 0.7% of our unselected population based cohort. More than half of their patients were receiving bisphosphonate, but unfortunately they did not report whether this was primary or secondary prevention or treatment against manifest osteoporosis, nor did they report the prevalence of fragility fractures in their patient group. Although this is a much higher proportion than ours and others have previously reported, still 20% of their patients were not treated with any antiresorptive agent and 15% were neither receiving specific bone protective treatment nor calcium or vitamin D supplementation.

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Sjögren’s syndrome criteria

In the June issue of the Annals Manthorpe comments on the recently proposed US-European classification criteria for Sjögren’s syndrome (SS).1 We would like to deal with some of the issues he raises, and add some comments.

Now that the classification criteria have evolved from rather subjectively biased ones to more objective assessments, it is surprising that the two most disease-specific objective parameters currently available for SS are subject to a non-critical attitude of course. Of course, when serological and histological items are emphasised in the new SS classification criteria, their individual disease sensitivity and specificity should always be kept in mind.

In fact, all six items that are included in the classification criteria may be subject to discussion. For example, the Schirmer-I test, and unstimulated whole saliva flow test have been criticised in a number of papers,2 but these items are recommended in Manthorpe’s paper.

Manthorpe expresses his concerns about the accuracy of sublabial salivary gland biopsies (SLGBs), referring to one paper in which a change of diagnosis of 25 % is reported after a second examination of the SLGBs. However, the authors themselves report that not using the focus scoring system was probably the most important reason for the change of diagnosis on the second examination. They did not conclude that the focus score itself—which is mandatory to fulfil item VI—changed dramatically upon re-examination of the specimens!

Other ways of bypassing interobserver variability are also available—for example, measuring two parameters instead of one (for example IgA% and focus score) provides a system that is much more objective for the accuracy of diagnosis;4 and, moreover, computer aided scoring methods may provide non-observer dependent data. For measuring the IgA% reliably and reproducibly objective data from the biopsies are obtained by combining microscope, computer, and calibrated software. These biopsies show what is going on in the target organs of this disease and may provide early diagnostic markers; one should not put them aside too easily.

Manthorpe also criticises the SS classification criteria for the interdependent relation between anti-Ro/anti-La antibodies (item IV) and the focus score (item V). They are certainly associated with each other, but why is that a problem? The worldwide accepted American Rheumatism Association criteria for rheumatoid arthritis also contain interdependent items—for example, positive rheumatoid factor serology is generally considered as strongly associated with radiological joint damage. Interdependency can also be found in the American College of Rheumatology classification criteria for systemic lupus erythematosus (presence of antinuclear antibodies is a distinct item from presence of anti-dsDNA or anti-Sm, items 11 and 10 respectively). Furthermore, it appears inconsistent that Manthorpe recommends including the pathohistological signs in the SS classification criteria. This would also introduce an interdependent item.

The dependency does not equal a one-on-one relation—that is, seronegative patients may have a positive focus score and vice versa. In particular, because numerous reports have shown that the focus score alone can be false positive or false negative,5,6 the presence of anti-Ro/anti-La antibodies which are still the most disease-specific objective parameters available, has additional value for the accuracy of diagnosis. Finally, it has yet to be proved that the suggested new antibodies (anti-fodrin, anti-muscarin) are more sensitive and disease-specific than the existing classic anti-Ro and anti-La antibodies. Therefore it is too early to include such items in classification criteria.

While our knowledge of Sjögren’s syndrome increases, classification criteria may develop in a way that enhances early diagnosis of possibly reversible target organ damage. Therefore not the end stage symptoms and signs (items I–III and V) but rather the early target organ histological signs and serological signs are likely to retain their place in the classification criteria. Therefore, in our view the US-European consensus group is right to emphasise items IV and VI, which should not be neglected but better alternatives have been introduced.

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References

Author’s reply
Zandbelt and van den Hoogen raise and discuss some important issues. It is a pity that forward in the June Leader of the Annals concerning Sjögren’s syndrome (SS) criteria published by a consensus group consisting of European and North American SS experts.

The title reads: “American-European (US-Eur) and Japanese Groups’ criteria compared and contrasted.” Zandbelt’s and van den Hoogen’s points are well taken, although the issues put forward are not new. I agree with them that final diagnostic criteria must evolve on the day when we know the aetiopathogenesis. Until that happens we trust (and are stuck with) classification criteria that are primarily set up as research tools, but nevertheless find their way into daily clinical practice. I am of the opinion that it is best to have as few preliminary classification criteria as possible. When coming up with new proposals these should include changes that are up to date in all aspects, otherwise other proposals will arise too soon. It is here, among other things, that I am disappointed by the consensus group’s latest proposal.

Most SS specialists agree that it is difficult to diagnose SS without close collaboration between clinical specialists within ophthalmology, oral medicine/oral surgery, and rheumatology. The US-Eur proposal is written by 3 authors but not a single person is an ophthalmologist! We have known for some years that patients with genuine SS do not complain of dry eyes because the cornea—although heavily innervated—lacks nerves that register dryness. This makes item I in the proposed criteria set invalid and should have been changed.

As far as smoking is concerned, it seems of great importance that clinicians know such details just as they know the medical history. When did smoking start and stop? What was the weekly consumption of cigarettes? Patients, who are present or past smokers, and who have at least two abnormal objective test results from both the main affected exocrine organs, lachrymal and salivary glands, very often lack circulating anti-SSA/B autoantibodies. Until heavy smoking is avoided such criteria are not valid. As the greatest percentage of the world population is present or past smokers with a consumption of >21 cigarettes/week some will have eye and oral symptoms similar to patients with SS (item I updated plus item III), and I find it difficult to accept that such
patients would not be diagnosed as having SS if the US-Eur criteria were followed. Given that the patient in question is a present or past smoker should lead to the consequence that a focus score ≤1 and/or absence of anti-SSA/B autoantibodies (item IV and VI) cannot be trusted and consequently should be disregarded. Besides, peronal family consequences it might have great social effects in some countries. In Sweden, for example, patients might get their dental repair bill subsidised by the State if they have SS diagnosed according to the Copen- teria (also termed Japanese III), which look different from the US-Eur consensus criteria, the SS criteria, might be considered very disturbing rather different from the US-Eur consensus criteria. In Japan was very much applauded. I hope that this international group will not look like the American (item VI) cannot be described polyarticular chondrocalcinosis. We regret that this paper failed to mention the famous spas of the Czech Republic, Slova- kia, Hungary, and Romania. From their conception, Czech and Slovak spas became gathering places not only for aristocrats but also for kings and emperors. Hungary, one of the richest countries of thermal waters in the world, has a bath culture dating back to the pre-Roman Celtic times. Budapest is a capital unique for its thermal waters. It is renowned for Lake Hévíz, the second biggest hot lake in the world, second to Rotorua, New Zealand. We are proud to have published in English the first double blind controlled trials with thermal water. Hungary is the only country where medical use of thermal waters is practised based on its efficacy proved in controlled trials. We profoundly disagree with the authors, that “taking the water, balneotherapy, spa therapy, hydrotherapy are more or less inter- changeable.” We are certain that they are not. Even in their paper, they quote Priesnitz and Kneipp, who distinguished between thermal water (balneotherapy) and hydrotherapy.1) Hydrotherapy uses only the physical qualities of water (buoyancy of water, resistance, sometimes its temperature (cold or warm), whereas thermal waters are not only naturally warm (>20°C) but their mineral content is also significant. In Hungary a recognised min- eral water should have minerals ≥1 g/l or more, but no nitrates, nitrate, or bacterial growth. It is not known whether the minerals of mineral water penetrate the body surface, but they are known to cause a so-called spa or mineral water reaction. The mineral water reaction includes tiredness and fatigue especially after 5–8 baths with an associated rise in the leu- cocyte count and erythrocyte sedimentation rate even within the normal range. The mineral water reaction passes away after 5–10 baths, and the optimal “taking the waters” is a total of 15–22 baths taken daily. There is no question about thermal mineral waters and spa therapy either. As we pointed out in a debate in the columns of the Journal of Rheumatology2) the effect of thermal mineral waters and the effect of complex spa therapy should be distinguished. We performed our double blind trials on inhabitants of ordinary Hungarian towns and villages with no spa facilities to exclude the placebo effect of a change in environment, physio- therapy, and being in a holiday atmosphere. In spa surroundings no double blind trials can be done. The results of follow up of these subjects suggest that non-spa treatment can be used as a control for future studies. Furthermore, the effect of spa water and heated tap water can be used for local residents to exclude the pla- cebo effect of spa atmosphere, associated physiotherapy, and they want to have evidence based proof for thermal mineral water or spa treatment, or both, we should keep strictly to these rules. We agree that spa resorts are excellent places for the rehabilitation of patients with rheumatic diseases, especially ankylosing spondylitis. In addition, rehabilitation treat- ments are available for patients with fibro- myalgia, a group who are frequent users of spa facilities. Most of the German, Czech, Slo- vak, Hungarian, and Russian spas also func- tion as rehabilitation centres. In Hungary, thermal mineral water and spa treatment is a recognised treatment for rheumatic patients, although hard data are lacking. The Hun- garian government has launched a new spa programme for the development of Hungarian spas. In addition, the Hungarian National Activity Network of the Bone and Joint Decade was given the task by the minister of health to start evidence-based research on the effect of mineral water and spa treatment. Hungary organises the 34th World Congress of the International Society of Medical Hydrology and Climatology at Budapest and Hévíz in October this year. Attendance by rheumatolo- gists and rehabilitation experts is expected. We feel it is time to create European co-operation in rheumatology spa and mineral water research. We are convinced that multicentre trials would be valuable in studying differences in mineral concentration, tem- peratures, cultures and beliefs. Underdevelop- ment of evidence-based physiotherapy is partly due to lack of funding for necessary trials. The situation is similar in therapy and spa treatment trials. This problem may be overcome by conducting multicentre trials in many countries. Such trials may result in an evidence-based approach to therapeutic or recreational bathing.

Authors’ reply

We thank the Drs Bender, Balint, and Balint for their comments on our study and their additional remarks. We did not intentionally exclude the spas in countries such as the Czech Republic, Slovakia, Hungary, and Ro- mania. In our paper we provided some exam- ples of spas in European countries which we had found mentioned in published reports. We are, however, well aware of the central role of spas elsewhere in the world both in the past and the present and their major influences on the development of rheumatology as a medi- cal profession.1,2 We fully agree that because spa therapy has an important role in rheumatology in many countries more research should be done and
also support the idea of multicentre studies. We regret, and we have experienced this, that those who finance research projects are extremely reluctant to fund trials in this field. We hope that, as has been suggested, with the creation of European cooperation in rheumatology spa and mineral water research we will be able to provide strong scientific evidence for the effectiveness of spa therapy in the near future.

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References

BOOK REVIEW

Pathological basis of orthopaedic and rheumatic disease


The author provides an overview of the pathology of orthopaedic and rheumatic diseases which could help pathologists in finding the correct diagnosis and also support clinicians and rheumatic disease oriented researchers in obtaining information about a broad range of distinct pathological disorders. There are eight chapters starting with skeletal structure development and progressing to injuries, infections, disorders of the skeletal development, and metabolic and other generalised diseases of the skeleton. Final chapters deal with diseases of articular tissues, including osteoarthritis and rheumatoid arthritis, and also describe tumours and tumour-like lesions of bone and soft tissue. The last two chapters covering tumour pathology comprise 40% of the content.

FORTHCOMING EVENTS

7th International Conference on Eicosanoids and Other Bioactive Lipids in Cancer, Inflammation and Related Diseases
14–17 Oct 2002; Nashville, Tennessee, USA
Contact: Lawrence J Marnett, Biochemistry Department, Vanderbilt University, School of Medicine, Nashville TN 37232-0146, USA
Tel: (615) 343 7329
Fax: (615) 343 7334
Website: www.eicosanoids.science.eaynu.edu

3rd International Conference on Sex Hormones, Pregnancy, and the Rheumatic Diseases
21–24 Oct 2002; New Orleans, LA, USA
Contact: Anne Parke
Tel: 860 679 8190
Fax: 860 679 1287
Email: parke@nso.uchc.edu

66th American College of Rheumatology AGM
25–29 Oct 2002; New Orleans, USA
Contact: ACR, Ronald F Olejko, Director of Conferences and Meetings, 1800 Century Place, Suite 250, Atlanta, Georgia 30045-4300, USA
Tel: +1 404 633 3777
Fax: +1 404 633 1870
Email: acr@rheumatology.org
Website: www.rheumatology.org

Third International Meeting on Social and Economic Aspects of Osteoporosis and Osteoarthritis
7–9 November 2002; Barcelona, Spain
Contact: Yolande Piette Communication, Boulevard Klever 108, 4000 Liege, Belgium
Tel: 32 4 254 12 25
Fax: 32 4 254 12 90
Email: ypccompuservce.com

Certifying Examination in Pediatric Rheumatology
18 Nov 2002
Contact: American Board of Pediatrics, 111 Silver Cedar Court, Chapel Hill, NC 27514-1513, USA
Tel: 919 929 0461
Fax: 919 918 7114 or 919 929 9255
Website: www.abp.org

10th APLAR Congress of Rheumatology
1–6 Dec 2002; Bangkok, Thailand
Contact: APLAR 2002 Secretariat
Fax: 66 2 716 6525
Email: secretariat@aplar2002.com
Website: www.aplar2002.com

Eleventh Intensive Applied Epidemiology Course for Rheumatologists
24–28 Feb 2003; ARC Epidemiology Unit, Manchester
No previous experience in epidemiology is required. The course is residential and limited to 25 places
Contact: Ms Lisa McClaire, ARC Epidemiology Unit, Manchester, Oxford Road, Manchester M13 9PF, UK
Tel: 44 0161 275 5953
Fax: 44 0161 275 5043
Email: Lisa@fsl.ter.man.ac.uk

Future EULAR congresses
18–21 June 2003; EULAR 2003 Lisbon, Portugal
9–12 June 2004; EULAR 2004 Berlin, Germany
8–11 June 2005; EULAR 2005 Vienna, Austria
21–24 June 2006; EULAR 2006 Amsterdam, The Netherlands

Each chapter stands by itself and, therefore, it is possible to focus directly on the matter of interest. The structure of description of the particular disease is consistent and logical and helpful to the reader. The normal format is a short introduction to the disease, some clinical features, radiological features, gross pathology, and histopathology. Every chapter ends with a list of references. The author quotes more than 1500 citations. More than 250 figures including histology, gross pathology, radiological pictures, and schematic diagrams and many tables enrich the quality of the volume.

In a future edition, inclusion of colour figures and an indication of the magnification of the histology pictures would be helpful. From our point of view working in the field of rheumatoid arthritis, the subchapter dealing with the disease could be extended, because the incidence of rheumatoid arthritis is 1-3% in Western countries.

What is missing is any reference throughout the text to the molecular and cellular mechanisms of the diseases. However, we suggest that this single volume would be useful for everyone interested in a summary of histological features of numerous orthopaedic and rheumatic diseases as seen in the clinic.

C A Seemayer, R E Gay, S Gay
Steroids cause osteoporosis

M-M Gordon, S Stevenson and J A Hunter

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