A new study shows that estrogen metabolism may affect bone mineral density in men

Estrogen levels may be a risk factor for osteoporosis in men as well as in women

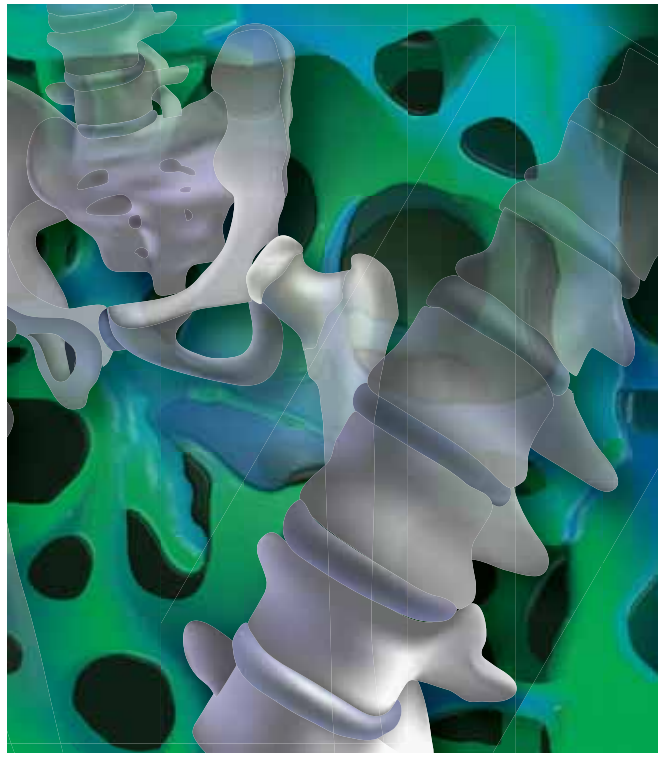
Reduced bone mineral density (BMD) is a risk factor for osteoporosis, which is generally considered to be a condition that predominantly affects women. However, despite this, one in 12 men is afflicted with osteoporosis. Although multiple causes of osteoporosis have been identified, one of the most important factors in postmenopausal women is low estrogen levels. Similarly, in men, estrogen has been shown to be vital in modulating bone homeostasis. However, until recently the role of estrogen metabolism in men had not been investigated.

Estrogen is metabolized in the liver, with one of the major reactions being hydroxylation. Estrogen metabolites may be active (e.g., 16α-hydroxystrone and estriol) or inactive (e.g., 2-hydroxystrone and 2-methoxystrone). Moreover, owing to individual variations in estrogen metabolism, the levels of each metabolite will vary from person to person within a population.

'The authors conclude that estrogen is a critical hormone for bone health in men.'

Researchers at Washington University School of Medicine, MO, USA, have demonstrated that estrogen metabolism in men is important in the pathogenesis of osteoporosis. In particular, low amounts of certain estrogen metabolites increase the risk of developing osteoporosis. Senior author Reina Armamento-Villareal points out that, "…most people don't think about estrogen in men, but men actually have somewhat more estrogen on average than do postmenopausal women". The group designed a study to investigate the correlation between estrogen metabolism and BMD in men, since "…research by other groups had suggested that estrogen may be more important than testosterone for maintaining bone health in men," Armamento-Villareal explains.

A total of 61 healthy Caucasian males aged 50 years and over participated in this study. The researchers measured the levels of estrogen metabolites using enzyme-linked immunoassays and radioimmunoassays, while BMD was determined by dual energy x-ray absorptiometry. A positive correlation was observed between both 16α-hydroxystrone and estriol (i.e., active metabolites of estrogen) and BMD of the proximal femur ($p < 0.05$). Participants with the highest levels of 16α-hydroxystrone also had the highest BMD. By contrast, there was no correlation between BMD and inactive metabolites. Moreover, testosterone levels did not have any affect on BMD. The influence of factors such as smoking, basal mass index (BMI), daily calcium intake and alcohol consumption on BMD were also investigated. Only BMI was found to be related to BMD. The researchers hypothesized that a higher BMI may lead to a higher BMD since these participants also had higher levels of 16α-hydroxystrone and estriol.



'…estrogen metabolism has now been linked to both BMD – and thus osteoporosis – and prostate cancer.'

The authors conclude that estrogen is a critical hormone for bone health in men. Specifically, estrogen modulates bone homeostasis, with metabolism to active metabolites being responsible for maintaining peak BMD. This is in contrast to testosterone, which, although it has a role in producing the larger size and thicker outer layer of male bones, does not influence BMD.

Armamento-Villareal hopes that this research will lead to changes in the healthcare system. "It would be a good idea to measure estrogen levels in older men who present with low BMD or osteoporosis," she says, also pointing out that estrogen metabolism has now been linked to both BMD – and thus osteoporosis – and prostate cancer.

Source: Napoli N, Faccio R, Shrestha V, Bucchieri S, Rini GB, Aramento-Villareal R: Estrogen metabolism modulates bone density in men. *Calcif. Tissue Int.* 80(4), 227–232 (2007).

Priority Paper Alerts

Expression of B-cell activating factor of the tumour necrosis factor family (BAFF) in T cells in active systemic lupus erythematosus: the role of BAFF in T-cell dependent, B-cell pathogenic autoantibody production.

Morimoto S, Nakano S, Watanabe T *et al.*: *Rheumatology (Oxford)*, DOI:10.1093/rheumatology/kem097 (2007) (Epub ahead of print).

This study aimed to identify the role of B-cell activating factor of the tumour necrosis factor family (BAFF) in T-cell dependent, B-cell pathogenic autoantibody production in systemic lupus erythematosus (SLE). The expression of BAFF in $CD4^+$ and $CD8^+$ cells, the expression of the BAFF-receptor (BAFF-R) on $CD20^+$ B cells and the levels of BAFF and BAFF-R mRNA were determined. It was demonstrated that BAFF was expressed in $CD4^+$ and $CD8^+$ T cells from patients with active SLE, but not in those from the control population. Furthermore, BAFF mRNA was only expressed in T cells from SLE patients. By contrast, BAFF-R was expressed on B cells in both SLE patients and controls and there was no significant difference in BAFF-R mRNA expression in SLE and control groups. The study concludes that BAFF may be involved in SLE pathogenesis by stimulating autoantibody production, and BAFF may therefore be a therapeutic target.

Fibromyalgia in women with ankylosing spondylitis.

Aloush V, Ablin JN, Reitblat T, Caspi D, Elkayam O: *Rheumatol. Int.* DOI: 10.1007/s00296-007-0344-3 (2007) (Epub ahead of print).

It is thought that the development of fibromyalgia (FM) may be preceded by other rheumatic diseases. This study aimed to determine the association between FM and ankylosing spondylitis (AS) in women, since FM is more common in women. A total of 18 women with AS were compared with 18 men with AS. Time between age of symptom onset and diagnosis of AS, incidence of FM and the number of tender points and enthsitis sites were recorded. Bath ankylosing spondylitis disease activity index (BASDAI) scores were significantly different between the two groups; 50% of the women with AS also suffered from FM, with FM being associated with higher BASDAI and bath ankylosing spondylitis functional index (BASFI) scores. However, it was not associated with erythrocyte sedimentation rate or physical findings. The study concludes that the reliability of BASDAI and BASFI in assessing AS may be questioned owing to confounding caused by FM.

Switching to etanercept may be of benefit when infliximab fails in rheumatoid arthritis

Paul Emery and colleagues, University of Leeds, UK, have demonstrated that etanercept is effective in treating rheumatoid arthritis (RA) in patients who were unsuccessfully treated with infliximab.

Both etanercept and infliximab are tumor necrosis factor (TNF) antagonists; these agents block the action of TNF-α, an important cytokine in maintaining the inflammatory response. Infliximab is commonly coprescribed with methotrexate as an initial therapy in RA patients. However, infliximab therapy is not always successful in relieving the symptoms of RA. Emery and colleagues have demonstrated that despite failure to respond to infliximab, RA patients may still benefit from treatment with alternative TNF antagonist therapies.

A total of 95 RA patients who failed to respond to infliximab plus methotrexate therapy were enrolled in the 12-week study. Of these, 34 patients had a primary nonresponse, 38 had a secondary nonresponse and 23 showed signs of infliximab toxicity. Twice-weekly doses of etanercept, 23 mg, were administered subcutaneously to these patients, with methotrexate therapy being maintained throughout.

The study demonstrated that following 12 weeks of etanercept therapy, ACR20, -50 and -70 criteria were met by 38, 24 and 15% of patients, respectively. In the primary nonresponder group (i.e., patients who never responded to infliximab), ACR20, -50 and -70 responses were met by 42, 30 and 15% of patients, respectively. By comparison, 34, 21 and 14% of secondary nonresponders (i.e., patients who showed an initial response to infliximab and then relapsed) achieved ACR20, -50 and -70 responses, respectively. Furthermore, no toxicity was experienced in patients who had shown a toxic response to infliximab.

> '…despite failure to respond to infliximab, RA patients may still benefit from treatment with alternative TNF antagonist therapies.'

Moreover, Disease Activity Score was significantly reduced in all patients, regardless of subgroup, and 61% achieved either a moderate or good European League Against Rheumatism Score.

Emery and colleagues conclude that "…this study confirms that etanercept is effective in patients who fail to respond to infliximab and suggests a higher response in patients who have never had a response to infliximab". In addition, clinicians should be aware of the benefits of switching to alternative TNF antagonists since "…it is clear that switching is of clinical importance in the management of TNF-antagonist failures, especially because there is now clear evidence that even in nonresponder patients, structural damage is inhibited".

Source: Buch MH, Bingham SJ, Bejarano V *et al.*: Therapy of patients with rheumatoid arthritis: outcome of infliximab failures switched to etanercept. *Arthritis Rheum.* 57(3), 448–453 (2007).

EGCG compound in green tea may provide therapeutic benefit in rheumatoid arthritis

A potent anti-inflammatory compound derived from green tea, epigallocatechin-3-gallate (EGCG), has been found to inhibit the production of several molecules in the immune system and connective tissue that contribute to the joint damage and inflammation associated with RA.

Lead researcher Salah-Uddin Ahmed said that "our research is a very promising step in the search for therapies for the joint destruction experienced by people who have RA".

Synovial fibroblasts from the joints of patients with RA were cultured in a growth medium and incubated with EGCG before being stimulated with the proinflammatory cytokine interleukin (IL)-1β. This protein is a known causative agent of joint destruction in people with RA. Ahmed and his team investigated whether EGCG could block the activity of two proteins involved in bone erosion in RA, IL-6 and cyclo-oxygenase-2. Preincubation of cells with EGCG was found to prevent the production of these bone-destructive molecules, and it also inhibited the production of prostaglandin E2, a hormone-like substance that causes inflammation in the joints.

From present knowledge of the cell-signaling pathways regulating these molecules the researchers could trace the effects of EGCG and determine that it works by inhibiting these pathways, suggesting that "EGCG, or molecules that could be derived synthetically from the EGCG found in green tea, may be of therapeutic value by inhibiting the joint destruction in RA", commented Ahmed.

Future tests of EGCG in animal models of RA are planned, Ahmed believes that the outcome of these studies will form the basis for future testing of EGCG compounds in humans with RA.

Source: Ahmed S-U, Pakozdi A, Koch AE, Huetwell FGL, Robinson WD: Green tea compound may be a therapy for people with rheumatoid arthritis. Presented at: *Experimental Biology 2007*. Washington DC, USA, 29 April 2007.

Early onset of poor bone mineralization in children with cystic fibrosis

Very early onset defective bone mineralization in the lumbar spine that was not associated with nutritional status or lung disease has been observed in a study of children suffering from cystic fibrosis (CF).

The study, led by Isabelle Serment-Gaudelus of the Service de Pédiatre Générale, Hôpital Necker-Enfants Malades in Paris, included 25 children with CF aged 6 years or younger, 53 children with CF aged 6–10 years and 36 adolescents aged 11–18 years suffering from the disease. They observed that the ideal weight for height, fat-free mass and fat-mass values decreased significantly as the children aged. Lung function tests and staining for *Pseudomonas auruginosa* revealed that pulmonary disease severity increased significantly, mainly in adolescents.

CF is the most prevalent hereditary illness leading to premature death. The disease causes certain glands to produce abnormal secretions that affect the digestive tract and clog the lungs with mucus. Approximately one in every 2500 Caucasian babies is born with CF.

The authors postulate that the reduction in bone mineral density (BMD), seen even in healthy children in early childhood, suggests an initial CF defect in bone, which can be aggravated by additional disease factors, including low fat-free mass, excessive inflammation, poor nutritional status and low vitamin-D levels.

"Deficient BMD is becoming an increasingly important clinical issue in adult patients with CF", said Sermet-Gaudelus. "The pathogenesis of low BMD in individuals with CF remains uncertain and bone histomorphometry studies have, thus far, been limited to adults with usually severe CF disease".

Sermet-Gaudelus noted that "the fact that many of the children with CF in our study were smaller than average for their age might have biased our findings. To compensate for differences in body size, BMD was based on height-adjusted rather than chronological age. Lumbar spine BMD scores were thus calculated with reference to a control population of healthy Parisian children and adolescents matched for statural age, sex and puberty status".

According to the researchers, this is the first study to look at bone status in patients with CF less than 6 years old; "in our study, 60% of the normal-weight patients had a low fat-free mass score, a hidden loss that has been previously reported in adults with CF", said Sermet-Gaudelus.

It is recommended by the researchers that all children with CF undergo assessment of BMD and body composition early in life in order to target those who need preventive treatment.

"Efforts to obtain and maintain normal bone status in these children must begin early in childhood", said Sermet-Gaudelus.

Source: Sermet-Gaudelus I, Souberbielle JC, Ruiz JC *et al.*: Low bone mineral density in young children with cystic fibrosis. *Am. J. Respir. Crit. Care Med.* 175(9), 951–957 (2007).

Many factors, such as age, hypertension, diabetes and smoking, have been implicated in the RA death rate but little is known about the specific influence of genetic factors on mortality

Impact of genetic factors on rheumatoid arthritis mortality rates

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation that takes a progressive toll on the joints and the whole body. RA sufferers face a high risk for early death, often caused by cardiovascular disease. In order to investigate the genetic risk factors associated with RA mortality, UK researchers targeted the human leucocyte antigen (HLA)-DRB1 alleles encoding the shared epitope (SE), a region involved in antigen recognition and already associated with disease susceptibility and severity.

HLA-DRB1 genotyping was carried out on blood samples from 767 patients recruited for the Early RA Study (ERAS), a UK-based, long-term, multicenter study of disease outcomes and predictive features.

"...a higher risk of sudden cardiac death is associated with particular HLA-DRB1 genotypes that are more frequent in patients with RA..."

Cox proportional hazard regression analyses and multivariate stepwise models were used to assess the association of HLA-DRB1 alleles with risk of mortality and the predictive value of HLA-DRB1 genotypes compared with other baseline risk factors, respectively.

Their findings, published in *Arthritis & Rheumatism*, suggest an increased risk of death for RA patients with HLA-DRB1 SE genotypes. In particular, the presence of two SE alleles was strongly linked to a high risk of early death from heart disease or cancer. Of the 767 subjects, 186 (24%; 80 men and 106 women) died. The presence of two SE alleles was associated with a greater risk of mortality; of the patients who died from heart disease or cancer, 29 (32.6%) carried two HLA-DRB1 SE alleles. Analysis of specific SE genotypes (corrected for age and sex) revealed that the *HLA-DRB1*0101/*0401* and *0404/*0404* genotypes were the strongest predictors of mortality from ischemic heart disease. Furthermore, patients who had two SE alleles generally died younger than other patients and, surprisingly, patients with two alleles had no clinical evidence of heart disease up to 1 year before dying of a heart attack.

Lead authors, D Mattey and A Young, comment "our data raise the possibility that a higher risk of sudden cardiac death is associated with particular HLA-DRB1 genotypes that are more frequent in patients with RA ... further studies are needed to determine whether clinically silent ischemic heart disease in RA is associated with certain HLA-DRB1 genotypes".

Furthermore, as Mattey and Young admit, they cannot offer an explanation for the association of these two SE alleles with an increased risk of death in RA patients. They also acknowledge the study's limitations, such as the relatively small and racially homogenous sample, the incomplete information on patients' smoking status and the inability to assess the effects of different therapies on mortality. "The association between specific *DRB1* genotypes and mortality may be modified by more aggressive treatment in patients with genotypes that predispose to more severe disease".

Source: Mattey DL, Thomson W, Ollier WER *et al.*: Association of DRB1 shared epitope genotypes with early mortality in rheumatoid arthritis: results of eighteen years of follow up from the early rheumatoid arthritis study. *Arthritis Rheum.* 56(5), 1408–1416 (2007).

Once-yearly injection offers hope for postmenopausal women with osteoporosis

A study of almost 8000 women, published in *The New England Journal of Medicine*, has shown that a new drug, zoledronic acid (Aclasta®) reduces spinal fractures by 70% and hip fractures by 41% in women with postmenopausal osteoporosis. These findings present hope for millions of women who could be protected against life-threatening hip fractures by a once-a-year treatment. This is the first time that an osteoporosis treatment has reduced the incidence of all types of osteoporotic fractures within a single study.

Osteoporotic fractures, especially hip fractures, are associated with significant morbidity and mortality. According to the National Osteoporosis Society, there are more than 60,000 hip and 120,000 vertebral fractures every year in Britain as a result of the bone-thinning disease osteoporosis; one in five of those who suffer a hip fracture dies within 3 months.

Presently, almost half a million women are prescribed drugs for osteoporosis. This new once-yearly, 15-min infusion, means that women can be protected against developing brittle bones without having to remember to take pills daily or weekly, thus negating the major problem of poor adherence to treatment. Bisphosphonates, to which Aclasta belongs, are effective but do not always achieve their full potential because women stop taking them. "Unfortunately, many patients who are prescribed oral therapies stop treatment or take less than the full dose throughout a full year, which leads to reduced fracture protection," said lead author Dennis Black, University of California, CA, USA.

Aclasta was tested in a trial that included patients throughout the UK administered annual infusions of either Aclasta or a placebo, and followed for 3 years. The 70% reduction in spine fractures seen with Aclasta is greater than rates of 40–50% previously demonstrated with oral bisphosphonates. Additionally, the reduction in spine fractures was sustained over the 3 years (60% in year one, 71% in year 2 and 70% in year 3).

Black and his coauthors concluded that "a regimen of infusions once a year appears to ensure that patients will have a full treatment effect for at least 12 months. By contrast, many patients who receive prescriptions for oral bisphosphonates stop treatment, and most appear to be taking less than 80% of their prescribed pills by 12 months". The National Osteoporosis Society welcomed this "exciting new treatment", saying that "an annual intravenous preparation may prove to be a convenient, cost-effective strategy".

Richard Eastell, University of Sheffield, UK, and a coauthor of the study, said that "the ability to only have the treatment once a year does mean that it simplifies the whole regimen. There is no doubt that Aclasta reduces vertebral fracture, hip fracture and other breaks". David Reid, University of Aberdeen, Scotland, another coauthor, said that the hip fracture data were particularly relevant. "Preventing hip fractures remains the holy grail of treating osteoporosis, as we know that 6 months after a hip fracture, nearly a fifth of patients will be dead. Reducing hip fractures by 41% is therefore highly clinically significant".

Source: Black DM, Delmas PD, Eastell R *et al.*: Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N. Engl. J. Med.* 356, 1809–1822 (2007).

MRI reveals ligament abnormalities in osteoarthritis patients

A collaboration between researchers at Johns Hopkins Hospital, MD, USA, and Thomas Jefferson University Hospital, PA, USA, has found that ligament abnormalities are often observed on magnetic resonance imaging (MRI) in patients with knee osteoarthritis (OA). The ligaments affected are in the lateral collateral ligament complex (LCLC), found on the outside of the knee.

A total of 53 women and 43 men were enrolled in the study. Of these, 51 patients had been previously diagnosed with knee OA. The remaining 45 patients were experiencing knee pain as a result of an injury, but did not have a history of knee OA. The patients underwent MRI to enable the researchers to grade their severity of knee OA and LCLC component abnormalities.

LCLC abnormalities were demonstrated to be more common in OA patients than in patients without OA. Abnormalities in LCLC components were observed in 88% of OA patients, compared with just 12% in the patients without OA. The researchers also found a significant association between lateral compartment OA and fibular collateral ligament abnormalities.

The study shows that LCLC abnormalities cannot always be attributed to an acute traumatic injury and physicians should be cautious when interpreting data from MRI. Furthermore, "…the findings will help to explain some of the common findings we come across in day to day radiology in patients with OA", commented Yung-Hsin Chen, Johns Hopkins Hospital.

Source: Medical News Today: Health News www.medicalnewstoday.com/medicalnews.php?newsid=69980

Economic burden of arthritis

A recent study, published in *Arthritis & Rheumatism*, reports that the economic burden of arthritis in the USA is increasing, with both nationwide medical expenditure and loss of earnings escalating. However, this is a result of an increase in the number of sufferers, rather than an increase in mean expenditure and earning losses.

Researchers at the University of California at San Francisco, CA, USA, derived estimates of medical-care expenditure and earning losses for patients with arthritis for 2003. These estimates were derived from the Medical Expenditures Panel Survey and were compared to estimates for 1997, inflated to 2003 terms. Their work was fuelled by the growing concerns over the economic burden of arthritis. Of particular concern were the increasing medical costs, as a result of joint-replacement surgery and biologic agents, and the large aging population.

The study found that between 1997 and 2003 the prevalence of arthritis increased from 18.7 to 21.5% of the population, corresponding to an increase from 36.8 million to 46.1 million adults suffering from arthritis. Over this same period, the mean number of prescriptions per person increased (18.7–25.2%) and the mean cost per prescription increased by US$17. Consequently the expenditure for arthritis medication doubled. However, in 1997, inpatient expenditure was US$508 per person, and this decreased to US$352 per person in 2003. Thus, the average total spent on medical care per patient with arthritis remained relatively stable. A $16 billion increase in total expenditure on medical care for arthritis was attributed to the increase in the number of adults with this condition. The study also found that adults with arthritis earned, on average, US$3613 less than healthy adults in 2003; nationwide earning losses as a result of arthritis totaled US$108 billion, an increase of US$9 billion from 1997.

Charles G Helmick (Centers for Disease Control and Prevention, GA, USA) notes that "…arthritis and other rheumatic conditions exact a large and growing economic toll on the nation as a result of the increase in number of persons affected, rather than an increase in mean expenditures and earning losses". He also warns that by 2030 approximately 67 million people will suffer from arthritis in the USA and thus the economic burden will continue to escalate. There is an urgent need to decrease medical expenses and increase the earning power of arthritis sufferers in order to address this. If such measures are taken, "…population aging need not necessarily result in a proportionate increase in the economic impact of arthritis and other rheumatic conditions," says Helmick.

Source: Yelin E, Murphy L, Cisternas MG, Foreman AJ, Pasta DJ, Helmick CG: Medical care expenditures and earnings losses among persons with arthritis and other rheumatic conditions in 2003, and comparisons with 1997. *Arthritis Rheum.* 56(5), 1397–1407 (2007).

Immune system suppression may lead to new treatments for autoimmune disease

A well-known cell receptor has been shown to send a signal which dampens the immune system. Although the finding does not have an immediate application in treating disease, it raises the possibility that in the future overactive immune systems could be depressed through the targeting of this receptor.

Researchers at The Children's Hospital of Philadelphia, PA, USA, and The University of Pennsylvania, PA, USA, discovered that the cell-surface protein complement receptor (CR)3 inhibits dendritic cells, regarded as the guardians of the immune system, thereby preventing them from triggering the usual full immune response.

"Normally, dendritic cells patrol different tissues and organs and look for danger signals sent by tissues undergoing stress or responding to invading microorganisms," explained Stefania Gallucci, leader of the study team. "We found that when we stimulate CR3 on dendritic cells, CR3 sends a 'nondanger' signal that suppresses the ability of dendritic cells to set off an immune response."

The study used a monoclonal antibody, engineered to bind CR3, to initiate a chain of responses that resulted in decreasing the activation of T cells that would ordinarily be produced.

This research has potential in the fight against inflammatory diseases, such as lupus erythematosus – a chronic autoimmune disease in which the immune system attacks the body's cells and tissue, resulting in inflammation and tissue damage. The study team therefore plan to test the antibody in mouse models of lupus and also rheumatoid arthritis. A possible role for the antibody as an immunosuppressant in transplant patients will also be explored.

Source: Behrens EM, Sriram U, Shivers DK *et al.*: Complement receptor 3 ligation of dendritic cells suppresses their stimulatory capacity. *J. Immunol.* 178(10), 6268–6279 (2007).

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. The editorial team welcomes suggestions for timely, relevant items. If you have newsworthy information, please contact: Sarah Jones, Commissioning Editor, *Future Rheumatology,* s.jones@futuremedicine.com