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Estrogen levels in elderly men are not only related to bone mineral density, but also the risk of hip fracture

# Estrogen levels and hip fracture in men

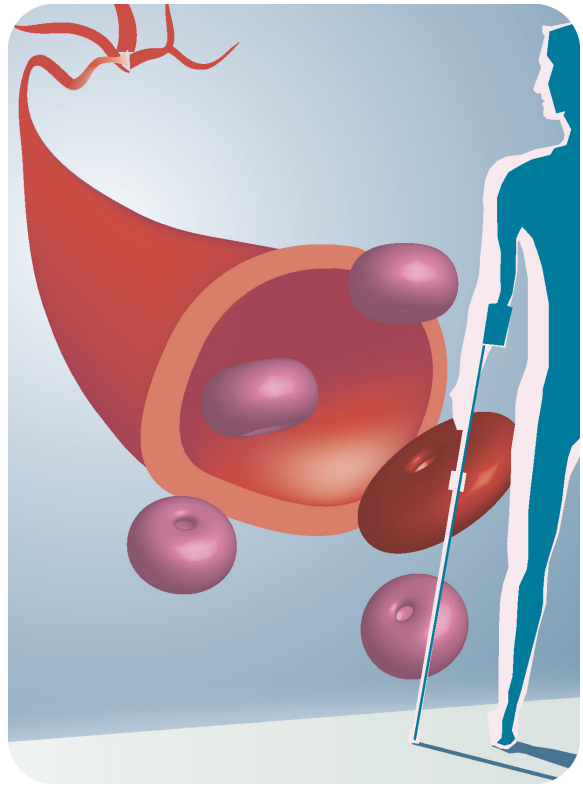
A study published recently in the *American Journal of Medicine* is the first to show that men with low levels of estrogen are at an increased risk of hip fracture. This risk is increased further in men with both low estrogen and testosterone levels.

Many women are aware of the detrimental effects of low estrogen levels on bone and may take steps to prevent bone loss; however, in general men are less likely to be concerned with the health of their bones or take supplements such as calcium and vitamin D. Lifestyle habits such as smoking, lack of exercise and excessive alcohol intake are connected with low bone mineral density and associated conditions, such as osteoporosis, in men.

'...those with low levels of both estrogen and testosterone were found to be at the highest relative risk of hip fracture...'

Low estrogen levels are known to be associated with low bone mineral density, a fact that is particularly apparent in postmenopausal women. While bone mineral density and estrogen levels in elderly men are also known to be connected, the link to hip fracture was previously unexplored. Hip fracture is an important concern, since approximately half of all men who experience such a fracture need institutionalized care. Many fractures may require major surgery and possibly result in prolonged or permanent disability. In addition, hip fractures are associated with increased mortality; up to 37% of men die within 1 year of a fracture. By identifying the risk factors involved in hip fractures it is hoped that rheumatologists will be in a better position to prevent them.

The study, conducted by Shreyasee Amin (Mayo Clinic, MN, USA) and colleagues, followed 793 men between 1981 and 1999. The participants had a mean age of 71 years and were involved in the Framingham heart study (www.framingham.com/heart). Total estradial and testosterone levels were measured between 1981 and 1983, and medical records up to 1999 were reviewed for incidences of hip fracture (those not associated with high trauma). The men were placed in one of three groups based on their estrogen levels (high [≥34.3 pg/ml] midrange and low [≤18 pg/ml]) and a Cox-proportional hazards model was run to assess the risk of fracture. The model was adjusted for age, body mass index, height and smoking status. Similar analyses were run for groups based on testosterone and both estrogen and testosterone levels.



Prior to the study, none of the men had a history of hip fracture. Over the period studied, a total of 39 men sustained a low-trauma hip fracture. The adjusted hazard ratio for men with low levels of estrogen found that this group had a 3.1-times higher risk of fracture than the high-level group (95% confidence interval [CI]: 1.4–6.9). The risk relative to that of the mid-level group was also increased (0.9-times higher; 95% CI: 0.4–2.0). The analyses showed no significantly increased risk to be associated with low testosterone levels. However, when both testosterone and estrogen were taken into account, those with low levels of both were found to be at the highest relative risk of hip fracture, by a factor of 6.5 times (95% CI: 2.9–14.3).

'...up to 37% of men die within 1 year of a hip fracture.'

In current practice, estrogen levels in men are not routinely measured. Identifying those patients at increased risk (i.e., those with low estrogen and particularly those with both low testosterone and estrogen levels) would allow strategies, such as dietary and lifestyle adjustments or dietary supplements, to improve their bone mineral density and lower their risk of hip fracture.

## Priority Paper Alerts

**A TNF receptor loop peptide mimic blocks RANK ligand-induced signaling, bone resorption, and bone loss.**
Aoki K, Saito H, Itzstein C *et al.*: *J. Clin. Invest.* doi: 10.1172/JCI22513.
A contact site of the tumor necrosis factor receptor (TNFR) involved in osteoclast differentiation is partly conserved in the receptor activator of nuclear factor-κB (RANK). The peptide WP9QY mimics this TNFR contact site and *in vivo* prevented increased bone loss and osteoclastogenesis induced in wild-type and $TNFR^{-/-}$ mice by ovariectomy or low dietary calcium. This suggests that peptides mimicking TNFR contact sites may block bone resorption by interfering with the recruitment and activation of osteoclasts by the RANK ligand and TNF.

**Alefacept in combination with methotrexate for the treatment of psoriatic arthritis: results of a randomized, double-blind, placebo-controlled study.**
Mease PJ, Gladman DD, Keystone EC: Alefacept in Psoriatic Arthritis Study Group: *Arthritis Rheum.* 54(5), 1638–1645 (2006).
This study evaluated the safety and efficacy of alefacept in combination with methotrexate (MTX) for the treatment of psoriatic arthritis. A total of 185 patients were assigned to receive either alefacept plus MTX or placebo plus MTX. The primary end point was the proportion of patients with an American College of Rheumatology (ACR) improvement of 20% in disease activity (ACR-20). When assessed at week 24, 54% of patients in the alefacept plus MTX group achieved an ACR-20 response, compared with 23% of the placebo plus MTX group. There was a low incidence of adverse events and most were of mild-to-moderate severity. The combination of MTX and alefacept may be a safe and effective treatment for psoriatic arthritis.

**The world of biologics.**
Symmons DP, Silman AJ: *Lupus* 15(3), 122–126 (2006).
UK guidelines for the use of anti-TNF therapy for the treatment of rheumatoid arthritis recommend all patients treated with these agents be listed on a national register, to study the long-term safety effects of biologic drugs. Data analyses show that rates of serious infection were not increased in anti-TNF-treated patients compared with those receiving traditional disease-modifying antirheumatic drugs. Rates of malignancy and mortality were also not increased, but rates of skin and soft tissue infection and intracellular infection were. Further follow-up of patients treated with anti-TNF drugs is needed to fully determine their long-term safety.

# Herbal remedies for back pain

Devil's claw, white willow bark and Cayenne pepper are effective in the management of low-back pain

A systematic review has found that herbal preparations may be as effective as conventional pain medication in controlling low-back pain. However, the lack of knowledge regarding the possible interactions of these herbal remedies with other drugs is a potential risk and further studies into their effects are recommended.

*'Harpagophytum procumbens* and *Salix alba* were found to be as effective as 12.5 mg rofecoxib.'

The review aimed to determine the efficacy of herbal medicine, defined as 'plants that are used for medicinal purposes', in the treatment of low-back pain. This is a common complaint that poses a significant economic burden on industrialized societies. Many patients suffering from low-back pain look to complementary and alternative medicines for pain relief. Various sources were searched for relevant articles, including the Cochrane database and personal contact with authors and known experts in the field. The studies included in the review were randomized, controlled trials involving adults with nonspecific low-back pain, with the primary outcome measures of pain and function. The methodology and clinical relevance of the studies were assessed by the review authors.

A total of ten trials involving approximately 1600 patients were included in the review. Strong evidence for the efficacy of *Harpagophytum procumbens* (devil's claw; 50 or 100 mg harpagoside) in short-term improvement over placebo was found in two high-quality trials. A third trial found *Harpagophytum procumbens* to be comparable to rofecoxib 12.5 mg/day in effectiveness. The effects of *Salix alba* (white willow bark) were investigated in two high-quality trials, which observed a greater improvement in short-term pain relief over placebo. Again, a third additional trial found *Salix alba* to be equivalent to rofecoxib 12.5 mg/day. The benefits of various topical preparations of *Capsicum frutescens* (Cayenne pepper) over placebo were also found, although these trials were of low quality.

Given the current debate surrounding the class of selective cyclo-oxygenase (Cox) inhibitors and the withdrawal of some from the market, patients suffering from joint and muscle pain may be more inclined than previously to look to herbal medications for pain relief. However, some medical practitioners advise caution, as little is known regarding the possible side effects of these remedies. There can be a great deal of variability in the preparations of these treatments and potential adverse effects are not well known, although they can include prolonged bleeding time and interaction with anesthetic agents.

While these remedies do appear to offer greater benefit than placebo for pain relief, they should not be seen as a replacement for conventional pain killers. Additional, high-quality trials comparing these herbal medicines with standard therapies would be useful to fully determine their safety and efficacy.

## Bone marrow lesions are predictors of cartilage loss

Bone marrow lesions (BMLs), known to be predictors of joint space loss, have also been shown to be predictive of cartilage loss in knee osteoarthritis (OA).

A recent study investigated BMLs using longitudinal magnetic resonance imaging (MRI) to study the natural history of these lesions and their relationship to cartilage loss and other structural changes in OA. A strong association was found between BMLs that get larger with time and cartilage loss in knee OA, which is mediated by malaligned limbs. Therefore, authors suggest that correcting alignment may protect against the structural progression of knee OA.

Knee MRI scans were performed on 122 men and 95 women with primary knee OA at months 0, 15 and 30. Each scan was assessed for subchondral bone marrow abnormalities, and cartilage morphological features in the medial and lateral tibiofemoral joints were scored using a semiquantitive scale. In order to assess mechanical alignment, long limb filaments were also collected at 15 months.

At baseline, 57% of knees had BMLs. Of these, 99% either remained the same or grew in size over the course of the study. Knee compartments with a higher baseline BML score showed greater cartilage loss. New or growing BMLs were seen mostly in malaligned limbs on the side of the malalignment and were found to be associated with further cartilage loss.

The authors concluded that BMLs are unlikely to resolve; an increase in their size is common and more strongly linked to increased cartilage loss. Changes in BMLs are linked to malalignment, suggesting that further evaluation of strategies to improve alignment would be beneficial with regards to long-term structural changes in knee OA.

## MRI as good as arthroscopy

Cartilage tears in the shoulder can be detected with similar accuracy by MRI or arthroscopy

Researchers from the Neuroskeletal Imaging Institute (FL, USA) have found that higher strength MRI (3.0 Tesla) is comparable to arthroscopy for detecting shoulder cartilage tears, reducing the need for surgery.

Shoulder MRI scans of 100 consecutive patients were reviewed, 67 of whom also underwent arthroscopy to detect whether they had torn cartilage in the shoulder. Of these patients, 46 were diagnosed with cartilage tears. Using 3.0 Tesla MRI scans, the researchers were able to detect tears in 42 of these patients, showing a good correlation between MRI and arthroscopy results.

The high agreement between results from MRI scans and arthroscopy means that fewer patients will have to undergo surgery for diagnosis of cartilage tears.

## Drug combination more effective in reducing dyspepsia

Researchers have found that a combination of nonsteroidal anti-inflammatory drugs (NSAIDs) and a proton pump inhibitor (PPI) is more effective in protecting patients who are taking pain-relief medication from dyspepsia than selective Cox-2 inhibitors (Coxibs).

Dyspepsia is a common side effect that affects many people on NSAIDs and is, therefore, a condition that affects many chronic arthritis sufferers. Dyspepsia is a gastrointestinal problem with syptoms such as nausea, bloating and gas, which are more common than the more serious side effects of NSAIDs, such as ulcers and bleeding.

Meta-analyses comparing rates of dyspepsia between patients receiving a nonselective NSAID alone with those receiving a Coxib, or a NSAID in combination with a PPI, were undertaken by researchers from the University of California and Veterans Affairs (LA, USA). One meta-analysis of 26 studies involving over 41,000 people compared the incidences of dyspepsia with Coxib versus NSAID monotherapy. A 12% reduced relative risk of dyspepsia was found with the selective Coxibs over nonselective NSAIDs. In a second meta-analysis of four studies comparing the use of a combination of a NSAID plus a PPI with NSAIDs alone, results showed a 66% reduced risk for patients receiving the combination therapy. These analyses revealed that the combination of NSAIDs and PPI may be more beneficial than selective Coxibs in the treatment of chronic arthritis, with regards to reduced rates of dyspepsia.

These results may help to guide treatment decisions for arthritis patients receiving pain medication who are susceptible to adverse gastrointestinal events, with the choice of the combination of a NSAID and PPI being preferred over a Coxib.

**About the Bulletin Board**

The Bulletin Board highlights some of the most significant events and launches in rheumatology and research on systemic diseases. The editorial team welcomes suggestions for timely, relevant items. If you have newsworthy information, please contact:

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