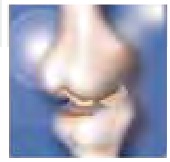
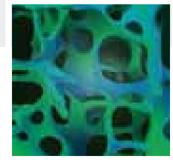


Bulletin Board

Long-term use of bisphosphonates associated with increased risk of atypical fractures

A population-based, nested case–control study involving 205,466 women has demonstrated an increased risk of atypical (subtrochanteric or femoral shaft) fractures in older women taking bisphosphonates for 5 years or more.

The study analyzed a cohort of women 68 years of age or older from Ontario, Canada, who started oral bisphosphonate treatment between 1 April 2002 and 31 March 2008. Case patients, defined as women hospitalized with an atypical fracture, were matched to up to five control participants without such fractures and follow-up of participants continued until 31 March 2009.

The main analysis evaluated the association between hospitalization for an atypical fracture and duration of bisphosphonate therapy. The association between bisphosphonate use and fractures of the femoral neck or intertrochanteric region was also assessed, as these are characteristic of osteoporotic fractures. This secondary analysis enabled the investigators to assess the specificity of findings from the primary analysis.

A total of 716 women had an atypical fracture after starting bisphosphonate therapy, and 9723 women had a typical osteoporotic fracture of the intertrochanteric region or femoral neck.

The primary analysis showed that the use of bisphosphonates for 5 years or longer was associated with a 2.7-times higher odds of hospitalization for atypical fracture compared with transient use of less than 100 days in total. The secondary analysis, which examined the risk of typical osteoporotic fractures, included 9723 women with fractures of the femoral neck or intertrochanteric region (typical osteoporotic fractures) during bisphosphonate use. Bisphosphonate use for greater than 5 years was associated with a 24% reduced risk of fracture compared with transient use. Intermediate bisphosphonate use (3–5 years) demonstrated a similarly low risk, while a shorter duration of bisphosphonate use (100 days to 3 years) was associated with a nonsignificant reduction in the risk of osteoporotic fractures. The secondary analysis therefore demonstrated the positive effects of long-term bisphosphonate use in osteoporotic fracture prevention.

Among the women taking bisphosphonates for more than 5 years, additional analysis suggested that more than half of atypical fractures were attributable to extended bisphosphonate use, and that approximately 10% of atypical fracture cases in the population might be preventable if no patient received more than 5 years of bisphosphonate therapy.

"Our findings provide strong evidence that prolonged bisphosphonate therapy is associated with an increased risk of subtrochanteric or femoral shaft fracture, although the absolute risk of these fractures is low. It may be appropriate to consider a drug holiday for selected patients, particularly as the cumulative duration of bisphosphonate therapy surpasses 5 years. Additional research is needed to better understand the prognosis of subtrochanteric or femoral shaft fractures among frail older adults, identify the specific subgroups of long-term users at the highest risk for these adverse effects, and explore whether interruptions in therapy reduce the risk of subtrochanteric or femoral shaft fractures over the long term", commented the investigators.

However, the researchers were keen to reassure clinicians and patients of the established benefits of bisphosphonates and that they should not be deterred by their results. They noted that the absolute risk for atypical fractures is low, with the benefits of bisphosphonate therapy still appearing to outweigh the risks. "Our study confirms the known benefits of bisphosphonate treatment

in the news...

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for typical osteoporotic fracture, and evidence suggests that bisphosphonate therapies are underused in individuals at high risk of fracture despite their established efficacy", they concluded.

Source: Park-Wyllie LY, Mamdani MM, Juurlink DN *et al.*: Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 305(8), 783–789 (2011).

Nitroglycerin helps reduce bone loss in postmenopausal women

A recent study published in the *Journal of the American Medical Association* has demonstrated that an ointment containing nitroglycerin modestly reduced bone loss and increased bone formation in postmenopausal women.

The double-blind, placebo-controlled study involved 243 women and found that application of the ointment resulted in substantial improvements in bone mineral density of the lumbar spine, total hip and femoral neck, as well as improving bone structure and some measures of bone strength.

The researchers analyzed the efficacy of 15-mg/day nitroglycerin ointment after 2 years and found that the percentage increases in bone mineral density were 6.7, 6.2 and 7.0% at the lumbar spine, total hip and femoral neck, respectively, with all being significant at $p < 0.001$. A 34.8% increase was also observed in bone-specific alkaline phosphatase (a marker of bone formation) and a 54% decrease in urine *N*-telopeptide (a marker of bone breakdown), with both changes significant compared with placebo ($p < 0.001$).

However, the adverse events associated with nitroglycerin use, particularly headaches, often hindered patients continuing with the study. The study initially involved a 1-week run-in phase in 400 postmenopausal women, who applied the nitroglycerin ointment at bedtime. A total of 157 women dropped out due to adverse events, with 93 due to headaches. The study also excluded women with osteoporosis and so the researchers caution that "it is possible that the effects might differ somewhat in those women with lower bone mineral density".

Sundeep Khosla, Mayo Clinic, MN, USA, author of an accompanying editorial to the study, commented, "If such a study demonstrates

in brief...

Methotrexate in juvenile localized scleroderma: a randomised, double-blind, placebo-controlled trial. Zulian F, Martini G, Vallongo C *et al. Arthritis Rheum.* (2011) (Epub ahead of print).

The safety and efficacy of methotrexate (MTX) was assessed in patients with active juvenile localized scleroderma (JLS). Patients with active JLS were randomized (2:1) to double-blinded oral MTX, 15 mg/m² (to a maximum of 20 mg) or placebo, once a week, for 12 months or until treatment failure. Both groups also received oral prednisone (1 mg/kg/day, to a maximum of 50 mg) for the first 3 months. A total of 70 patients were randomized, with 46 receiving MTX and 24 receiving placebo. After an initial response in all patients, disease relapsed in 15 MTX patients (32.6%) and 17 on placebo (70.8%) ($p < 0.005$). New lesions appeared in three MTX patients (6.5%), compared with four on placebo (16.7%). Mean skin score rate decreased from 1 to 0.79 with MTX compared with 1.1 on placebo and mean target lesion temperature decreased 44.4% in the MTX group compared with 12.1% on placebo. In total, 26 patients (56.5%) of the MTX group and 11 patients (45.8%) of the placebo group experienced mild treatment-related side effects, but none were severe enough to halt treatment. Therefore, MTX is an effective and well-tolerated treatment for patients with JLS.

Modified-release sildenafil reduces Raynaud's phenomenon attack frequency in limited cutaneous systemic sclerosis. Herrick AL, van den Hoogen F, Gabrielli A *et al. Arthritis Rheum.* 63, 775–782 (2011).

The effect of sildenafil in patients with Raynaud's phenomenon (RP) secondary to limited cutaneous systemic sclerosis was examined in a double-blind, placebo-controlled study. A total of 57 patients with the condition were randomized to receive modified-release sildenafil 100 mg once daily for 3 days followed by modified-release sildenafil 200 mg once daily for 25 days, or placebo. The mean reduction from baseline to day 28 in RP attacks was -44% in the sildenafil group, compared with -18% for placebo ($p = 0.034$). The mean number of attacks per week also improved in both groups, with the sildenafil reducing from 30.5 to 18.7 and the placebo group reducing from 25.0 to 19.3. Secondary end points, such as Raynaud's Condition Score and duration of attacks, were not significantly different between the groups. The majority of adverse events were mild or moderate and the most commonly reported were headache and dyspepsia. The authors conclude that modified-release sildenafil reduced attack frequency in patients with RP secondary to limited cutaneous systemic sclerosis and was well tolerated, providing a potential treatment option in this patient population.

efficacy for reducing fractures, clinicians would have a novel and inexpensive therapy for osteoporosis", but went on to say that further research into other nitrate compound is necessary, to find suitable alternatives with greater efficacy and lower adverse events.

The results suggest that nitroglycerin, which is inexpensive and available in many generic formulations, may provide a new option in helping reduce bone loss, opening up the possibility of a future role in osteoporosis prevention.

Sources: Jamal SA, Hamilton CJ, Eastell R, Cummings SR: Effect of nitroglycerin ointment on bone density and strength in postmenopausal women: a randomized trial. *JAMA* 305(8), 800–807 (2011); Khosla S: Is nitroglycerin a novel and inexpensive treatment for osteoporosis? *JAMA* 305(8), 826–827 (2011).

Double knee replacement may be better than single in patients with low cardiovascular risk

A study presented at the Annual Meeting of the American Academy of Orthopedic Surgeons, involving over 35,000 patients undergoing replacement surgery of both knees, has demonstrated that replacing both knees in one surgical procedure is associated with significantly fewer prosthetic joint infections, as well as further operations on the knee within 1 year postsurgery, compared with total knee replacements carried out in two separate procedures.

The study included 11,445 patients undergoing simultaneous bilateral knee replacement surgery and 23,715 patients who had both knees replaced in two separate procedures several months apart. The results showed that the risk of developing a serious joint infection, requiring additional knee revision surgery, was significantly higher in the staged procedure patients compared with simultaneous bilateral knee replacement patients. In addition, revision surgery on the knees for problems unrelated to infection was also higher in the staged procedure patients.

"Our study found that the risk of developing a serious joint infection that required an additional knee revision surgery was two-times higher in patients who had staged knee replacements compared with the patients who had both knees replaced at the same time (2.2% after staged knee replacements and 1.2% after bilateral knee replacements)", commented John Meehan, orthopedic surgeon from the University of California, Davis (CA, USA) and study author.

However, the simultaneous replacement of both knee joints in one procedure was associated with a moderately higher risk of cardiovascular outcomes within 30 days after surgery, with a higher risk of heart attack and pulmonary embolism observed in this group.

Meehan suggests that further research is needed to determine which patients should be considered for bilateral simultaneous surgery, but the results are nonetheless encouraging for patients with low cardiovascular risk. "These findings indicate that performing simultaneous knee replacements would significantly reduce the incidence of major orthopedic complications, and at the same time reduce the number of hospitalizations and the number of operating room sessions", Meehan concluded.

Source: American Academy of Orthopaedic Surgeons: www6.aaos.org/news/pemr/releases/release.cfm?releasenum=965

About the Bulletin Board

The Bulletin Board highlights some of the most important events and research in the field of rheumatology. If you have newsworthy information, please contact:

Chris Facey, Commissioning Editor, International Journal of Clinical Rheumatology, Future Medicine Ltd,
Unitec House, 2 Albert Place, London N3 1QB, UK
Tel.: +44 (0)20 8371 6090;
c.facey@futuremedicine.com

Hamstring grafts proven more effective in anterior cruciate ligament knee reconstruction

Researchers have demonstrated that patients who received anterior cruciate ligament (ACL) knee reconstruction with hamstring tendon grafts were less likely to suffer from pain and mobility issues 15 years postsurgery, than those who received patellar tendon grafts.

Leo Pinczewski, North Sydney Orthopaedic and Sports Medicine Center, Wollstonecraft, Australia and lead researcher of the study has previously studied the overall success of ACL knee reconstruction in athletes after 15 years, but the new study directly compares the effectiveness of different tendon grafts in treating the condition.

"While we have seen excellent results in terms of knee symptoms and function with both graft types, comparing the two definitely showed differences. Patients with a hamstring graft reported less knee pain and discomfort and demonstrated a higher activity level", reported Pinczewski.

The study followed a total of 180 knee reconstruction patients, with 90 receiving a patellar tendon graft and 90 receiving a hamstring tendon graft. After 15 years, 80% of the patellar tendon group and 73% of the hamstring tendon group were assessed on pain, swelling and knee mobility. Significantly higher activity levels were demonstrated in the hamstring tendon group, with 77% of assessed patients performing at least strenuous activities, compared with 62% in the patellar tendon group. When evaluating pain when kneeling, the researchers found that 42% in the patellar tendon group reported moderate or greater pain, compared with 26% of patients reporting pain in the hamstring tendon group. In addition, the patellar tendon group also showed worse outcomes in tests for motion loss and osteoarthritis.

Pinczewski believes the results provide valuable information that may help doctors determine the best approach in treating ACL reconstruction. "We know that these surgeries work, but this information helps us determine which approaches can be most effective. Getting athletes back on the field is certainly important, but long-term success rates are crucial as well".

Source: American Orthopaedic Society for Sports Medicine: www.sportsmed.org/tabs/newsroom/AOSSMPressReleaseDetails.aspx?DID=760

Pulmonary embolism following knee arthroscopy quantified

A study of over 400,000 knee arthoscopy cases has been undertaken to try to quantify the risk to the patient of pulmonary embolism during the procedure.

Pulmonary embolism involves a clot in the main artery of the lung that formed in another part of the body, for example from a deep vein thrombosis in the legs. It is a serious condition and can cause low blood oxygen, chest pain and difficulty breathing, and in severe cases, lung collapse and death.

Iftach Hetsroni, an orthopedic surgeon from Meir General Hospital in Israel, led a study of records from 374,033 patients who underwent 418,323 arthoscopies at the Hospital for Special Surgery, New York (NY, USA) between 1997 and 2006. The authors investigated the incidence of pulmonary embolism and possible risk factors associated with that incidence.

"We anticipated the incidence of pulmonary embolism after knee arthroscopies would be low but we wanted to uncover exactly what risk patients were undergoing and who might be at increased risk", said Hetsroni.

The number of recorded pulmonary embolisms was 117 in the study population, an incidence of 0.028%. Pulmonary embolism was defined as admission to hospital with symptomatic pulmonary embolism within 90 days of the arthroscopic procedure. One death was noted among the pulmonary embolism cases.

The study also highlighted several risk factors (such as patients over 30 years of age are six-times more at risk than patients younger than 20 years, longer operations were associated with a higher risk than shorter operating times, females are 1.5-times more at risk than males and history of cancer is associated with three-times more risk). Some factors that had previously been thought to be risk factors (such as anesthesia type or operation complexity) were shown not to correlate with pulmonary embolism incidence.

"While knee arthroscopy performed as an outpatient seems like an innocent procedure, patients with one or more of these risk factors should talk with their doctors about any precautions before or after surgery", said Dr Hetsroni. "For example, our study may encourage some surgeons to consider thromboprophylaxis, or blood-thinning techniques, for patients who have multiple risk factors".

This study should encourage surgeons to remain vigilant for breathing difficulties or low blood oxygen as an important part of knee arthroscopy aftercare, especially with regards to patients with one or more risk factor. It is hoped that this will also be brought up in presurgical liason to obtain informed consent.

Source: Hetsroni I, Lyman S, Do H, Mann G, Marx RG: Symptomatic pulmonary embolism after outpatient arthroscopic procedures of the knee: the incidence and risk factors in 418,323 arthroscopies. *J. Bone Joint Surg. Br.* 93(1), 47–51 (2011).