

# Fractures, Osteoporosis Common in SLE Patients

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**P**atients with systemic lupus erythematosus who are under the age of 50 have a high rate of fragility fractures, osteoporosis, and poor bone mineral density, according to new research.

And as expected, steroid use was found to be significantly linked to reduced bone mineral density (BMD), reported C-S Yee of the University of Birmingham and col-

leagues (Ann. Rheum. Dis. 2005;64:111-113).

Although bisphosphonates are the only class of drugs that have shown efficacy in the treatment and prevention of corticosteroid-induced osteoporosis, their use in premenopausal women poses serious risks of birth defects in the event of an unplanned pregnancy, noted the authors.

The investigation included 242 participants with systemic lupus erythematosus

(SLE), 231 (95%) of whom were female.

Study participants were asked to complete a questionnaire about risk factors for osteoporosis, including details about previous fractures and family history of fractures. There were also asked about drug use and in particular about the use of glucocorticoids, oral contraceptives, hormone therapy, calcium and vitamin D supplementation, and bisphosphonates.

Bone mineral densitometry screening was also performed.

Among the women, 126 (54%) were premenopausal, 39 (17%) had experienced premature menopause, and 64 (28%) had experienced normal menopause. The menopausal status of two patients was unknown because they did not fully complete the questionnaire.

A total of 123 patients (51%) had reduced BMD (T score less than -1.0), and 25 were in the osteoporotic range (T score less than -2.5).

Ten of the patients with reduced BMD and 3 in the osteoporotic range were taking bisphosphonates at the time of the scan.

There were 22 patients (9%) who had experienced fragility fractures since their

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diagnosis of SLE, all of whom were female. Of these, 2 (9%) had normal BMD, while the other 20 (91%) had reduced BMD, with 7 of these women were in the osteoporotic range.

Most of the patients with fragility fractures (82%) were menopausal, and only 3 were taking bisphosphonates at the time of the scan.

Non-Afro-Caribbean race and exposure to prednisolone (more than 10mg/day) were associated with reduced BMD, while age and menopause were associated with osteoporosis, according to the findings of a regression analysis.

Only low BMD and advanced age predicted fractures. Steroid exposure did not predict fracture rates, noted the authors. However, they noted that “it is likely that the effect of steroids on fractures is mediated predominantly by reduction in bone density in susceptible individuals.”

Despite a high prevalence of fractures in this cohort, the authors noted a low prevalence among the premenopausal women (3%).

Because the teratogenic risks of bisphosphonates are most relevant in premenopausal women, “we recommend bisphosphonates only in those premenopausal SLE patients with osteopenia or osteoporosis who require long-term, high-dose steroids. Bisphosphonates with the least evidence of persistence in the skeleton should be used,” they said.

## Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenic effect of meloxicam was observed in rats given oral doses up to 0.8 mg/kg/day (approximately 0.4-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) for 104 weeks or in mice given oral doses up to 8.0 mg/kg/day (approximately 2.2-fold the human dose, as noted above) for 99 weeks.

Meloxicam was not mutagenic in an Ames assay, or clastogenic in a chromosome aberration assay with human lymphocytes and an *in vivo* micronucleus test in mouse bone marrow.

Meloxicam did not impair male and female fertility in rats at oral doses up to 9 and 5 mg/kg/day, respectively (4.9-fold and 2.5-fold the human dose, as noted above). However, an increased incidence of embryofatality at oral doses  $\geq$  1 mg/kg/day (0.5-fold the human dose, as noted above) was observed in rats when dams were given meloxicam 2 weeks prior to mating and during early embryonic development.

## Pregnancy

### Teratogenic Effects: Pregnancy Category C.

Meloxicam caused an increased incidence of septal defect of the heart, a rare event, at an oral dose of 60 mg/kg/day (64.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and embryofatality at oral doses  $\geq$  5 mg/kg/day (5.4-fold the human dose, as noted above) when rats were given meloxicam during the late gestation and lactation period. In teratogenicity studies up to an oral dose of 4 mg/kg/day (approximately 2.2-fold the human dose, as noted above) throughout organogenesis, an increased incidence of stillbirths was observed when rats were given oral doses  $\geq$  1 mg/kg/day throughout organogenesis. Meloxicam crosses the placental barrier. There are no adequate and well-controlled studies in pregnant women. Meloxicam should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

### Nonteratogenic Effects:

Meloxicam caused a reduction in birth index, live births, and neonatal survival at oral doses  $\geq$  0.125 mg/kg/day (approximately 0.07-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) when rats were treated during the late gestation and lactation period. No studies have been conducted to evaluate the effect of meloxicam on the closure of the ductus arteriosus in humans; use of meloxicam during the third trimester of pregnancy should be avoided.

### Labor and Delivery

Studies in rats with meloxicam, as with other drugs known to inhibit prostaglandin synthesis, showed an increased incidence of stillbirths, increased length of delivery time, and delayed parturition at oral dosages  $\geq$  1 mg/kg/day (approximately 0.5-fold the human dose at 15 mg/day for a 50 kg adult based on body surface area conversion) and decreased pup survival at an oral dose of 4 mg/kg/day (approximately 2.1-fold the human dose, as noted above) throughout organogenesis. Similar findings were observed in rats receiving oral dosages  $\geq$  0.125 mg/kg/day (approximately 0.07-fold the human dose, as noted above) during late gestation and the lactation period.

### Nursing Mothers

Studies of meloxicam excretion in human milk have not been conducted; however, meloxicam was excreted in the milk of lactating rats at concentrations higher than those in plasma. Because of the potential for serious adverse reactions in nursing infants from meloxicam, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

### Pediatric Use

Safety and effectiveness in pediatric patients under 18 years of age have not been established.

### Geriatric Use

Caution should be exercised in treating the elderly (65 years and older).

### ADVERSE REACTIONS

The MOBIC phase 2/3 clinical trial database includes 10,122 OA patients and 1012 RA patients treated with MOBIC 7.5 mg/day, 3505 OA patients and 1351 RA patients treated with MOBIC 15 mg/day. MOBIC at these doses was administered to 661 patients for at least 6 months and to 312 patients for at least one year. Approximately 10,500 of these patients were treated in ten placebo and/or active-controlled osteoarthritis trials and 2963 of these patients were treated in ten placebo and/or active-controlled rheumatoid arthritis trials. Gastrointestinal (GI) adverse events were the most frequently reported adverse events in all treatment groups across MOBIC trials.

A 12-week multicenter, double-blind, randomized trial was conducted in patients with osteoarthritis of the knee or hip to compare the efficacy and safety of MOBIC with placebo and with an active control. Two 12-week multicenter, double-blind, randomized trials were conducted in patients with rheumatoid arthritis to compare the efficacy and safety of MOBIC with placebo. The following adverse events (%) occurred in  $\geq$  2% of MOBIC 7.5 mg daily (n=154) and 15 mg daily (n=156) patients, respectively, in a 12-week osteoarthritis placebo- and active-controlled trial: abdominal pain, 1.9%; 2.6%; diarrhea, 7.8%; 3.2%; dyspepsia, 4.5%; 4.5%; flatulence, 3.2%; 3.2%; nausea, 3.0%; 3.8%; accident household, 4.5%; 3.2%; edema\*, 1.9%; 4.5%; fall, 2.6%; 0.0%; influenza-like symptoms, 4.5%; 5.8%; dizziness, 2.6%; 3.8%; headache, 7.8%; 8.3%; pharyngitis, 0.6%; 3.2%; upper respiratory tract infection, 3.2%; 1.9%; rash†, 2.6%; 0.6%.

The following adverse events (%) occurred with MOBIC 7.5 mg daily in  $\geq$  2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.7%; 4.7%; constipation, 0.8%; 1.8%; diarrhea, 1.9%; 5.9%; dyspepsia, 3.8%; 8.9%; flatulence, 0.5%; 3.0%; nausea, 2.4%; 4.7%; vomiting, 0.6%; 1.8%; edema†, 0.6%; 2.4%; pain, 0.9%; 3.8%; dizziness, 1.1%; 2.4%; headache, 2.4%; 3.6%; anemia, 0.1%; 4.1%; arthralgia, 0.5%; 5.3%; back pain, 0.5%; 3.0%; insomnia, 0.4%; 3.6%; coughing, 0.2%; 2.4%; upper respiratory tract infection, 0.2%; 3.3%; pruritus, 0.4%; 2.4%; rash†, 0.3%; 3.0%; micturition frequency, 0.1%; 2.4%; urinary tract infection, 0.3%; 4.7%.

The following adverse events (%) occurred with MOBIC 15 mg daily in  $\geq$  2% of patients treated, respectively, in short-term (4-6 weeks) and long-term (6 months) active-controlled osteoarthritis trials: abdominal pain, 2.3%; 2.9%; constipation, 1.2%; 2.6%; diarrhea, 2.7%; 2.6%; dyspepsia, 7.4%; 9.5%; flatulence, 0.4%; 2.6%; nausea, 4.7%; 7.2%; vomiting, 0.6%; 2.6%; edema†, 2.0%; 1.6%; pain, 2.0%; 5.2%; dizziness, 1.6%; 2.6%; headache, 2.7%; 2.6%; anemia, 0.0%; 2.9%; arthralgia, 0.0%; 1.3%; back pain, 0.4%; 0.7%; insomnia, 0.1%; 1.6%; coughing, 0.6%; 1.0%; upper respiratory tract infection, 0.0%; 7.5%; pruritus, 1.2%; 0.0%; rash†, 1.2%; 1.3%; micturition frequency, 0.4%; 1.3%; urinary tract infection, 0.4%; 6.9%.

\*WHO preferred terms edema, edema dependent, edema peripheral and edema legs combined. †WHO preferred terms rash, rash erythematous and rash maculo-papular combined.

The following adverse events (%) occurred respectively with MOBIC 7.5 and 15 mg daily in  $\geq$  2% of patients treated in two 12-week rheumatoid arthritis placebo controlled trials: abdominal pain NOS†, 2.9%, 2.3%; diarrhea NOS†, 4.8%, 3.4%; dyspeptic signs and symptoms†, 5.8%, 4.0%; nausea†, 3.3%, 3.8%; influenza like illness†, 2.9%, 2.3%; upper respiratory tract infections-pathogen class unspecified†, 7.0%, 6.5%; joint related signs and symptoms†, 1.5%, 2.3%; musculoskeletal and connective tissue signs and symptoms NEC†, 1.7%, 2.9%; headaches NOS†, 6.4%, 5.5%; dizziness (text vertigo)†, 2.3%, 0.4%; rash NOS†, 1.0%, 2.1%.

†MedDRA high level term (preferred terms): dyspeptic signs and symptoms (dyspepsia, dyspepsia aggravated, eructation, gastrointestinal irritation), upper respiratory tract infections-pathogen unspecified (laryngitis NOS, pharyngitis NOS, sinusitis NOS), joint related signs and symptoms (arthralgia, arthralgia aggravated, joint crepitation, joint effusion, joint swelling), and musculoskeletal and connective tissue signs and symptoms NEC (back pain, back pain aggravated, muscle spasms, musculoskeletal pain).

\*MedDRA preferred term; diarrhea NOS, abdominal pain NOS, influenza like illness, headaches NOS, dizziness (text vertigo), and rash NOS.

Higher doses of MOBIC (22.5 mg and greater) have been associated with an increased risk of serious GI events; therefore the daily dose of MOBIC should not exceed 15 mg.

The following is a list of adverse drug reactions occurring in  $<$ 2% of patients receiving MOBIC in clinical trials involving approximately 16,200 patients. Adverse reactions reported only in worldwide post-marketing experience or the literature are shown in italics and are considered rare ( $<$ 0.1%).

**Body as a Whole:** allergic reaction, anaphylactoid reactions including shock, face edema, fatigue, fever, hot flushes, malaise, syncope, weight decrease, weight increase. **Cardiovascular:** angina pectoris, cardiac failure, hypertension, hypotension, myocardial infarction, vasculitis. **Central and Peripheral Nervous System:** convulsions, paresthesia, tremor, vertigo.

**Gastrointestinal:** colitis, dry mouth, duodenal ulcer, eructation, esophagitis, gastroic ulcer, gastritis, gastroesophageal reflux, gastrointestinal hemorrhage, hematemesis, hemorrhagic duodenal ulcer, hemorrhagic gastric ulcer, intestinal perforation, melena, pancreatitis, perforated duodenal ulcer, perforated gastric ulcer, stomatitis ulcerative. **Heart Rate and Rhythm:** arrhythmia, palpitation, tachycardia. **Hematologic:** agranulocytosis, leukopenia, purpura, thrombocytopenia. **Liver and Biliary System:** ALT increased, AST increased, bilirubinemia, GGT increased, hepatitis, jaundice, liver failure. **Metabolic and Nutritional:** dehydration. **Psychiatric Disorders:** abnormal dreaming, anxiety, appetite increased, confusion, depression, nervousness, somnolence. **Respiratory:** asthma, bronchospasm, dyspnea. **Skin and Appendages:** alopecia, angioedema, bullous eruption, erythema multiforme, photosensitivity reaction, pruritus, Stevens-Johnson syndrome, sweating increased, toxic epidermal necrolysis, urticaria. **Special Senses:** abnormal vision, conjunctivitis, taste perversion, tinnitus. **Urinary System:** albuminuria, BUN increased, creatinine increased, hematuria, interstitial nephritis, renal failure.

**OVERDOSEAGE**

There is limited experience with meloxicam overdose. Four cases have taken 6 to 11 times the highest recommended dose, all recovered. Cholestyramine is known to accelerate the clearance of meloxicam. Symptoms following acute NSAID overdose are usually limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which are generally reversible with supportive care. Gastrointestinal bleeding can occur. Severe poisoning may result in hypertension, acute renal failure, hepatic dysfunction, respiratory depression, coma, convulsions, cardiovascular collapse, and cardiac arrest. Anaphylactoid reactions have been reported with therapeutic ingestion of NSAIDs, and may occur following an overdose. Patients should be managed with symptomatic and supportive care following an NSAID overdose. In cases of acute overdose, gastric lavage followed by activated charcoal is recommended. Gastric lavage performed more than one hour after overdose has little benefit in the treatment of overdose. Administration of activated charcoal is recommended for patients who present 1-2 hours after overdose. For substantial overdose or severely symptomatic patients, activated charcoal may be administered repeatedly. Accelerated removal of meloxicam by 4 gm oral doses of cholestyramine given three times a day was demonstrated in a clinical trial. Administration of cholestyramine may be useful following an overdose. Forced diuresis, alkalization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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