Osteoporosis Associated With Megestrol Acetate

ROBERT A. WERMERS, MD; DANIEL L. HURLEY, MD; AND ANN E. KEARNS, MD

Megestrol acetate is a progestational agent for treatment of metastatic breast cancer and endometrial cancer. Megestrol has also been used as an appetite stimulant for patients with human immunodeficiency virus and malignancy who experience cachexia and wasting; also, megestrol can be beneficial in relieving hot flashes in women and men. Megestrol has been shown to have a glucocorticoidlike effect and has been associated with substantial suppression of plasma estradiol levels. We describe 2 patients who recently presented to our Metabolic Bone Disease Clinic with severe osteoporosis complicated by multiple vertebral fractures experienced while the patients were receiving high-dose megestrol therapy. The patients had evidence of adrenal axis suppression but recovered fully after megestrol was discontinued. We speculate that megestrol was an important factor in the development of osteoporosis and subsequent fractures. Further study is warranted to clarify the relationship between megestrol and its potential for adversely affecting the skeleton.

CASE REPORT

REPORT OF CASES

Case 1

A 68-year-old postmenopausal white woman presented to the Metabolic Bone Disease Clinic for evaluation of severe osteoporosis. Menopause had occurred at age 50 years. The patient had received estrogen-replacement therapy for 15 years; however, therapy was discontinued when she was diagnosed as having esophageal carcinoma at age 66 years.

The patient underwent chemotherapy and radiation therapy before surgical resection of her tumor. Megestrol (400 mg twice daily) was initiated for appetite stimulation and was taken for 2 years, until the patient’s Metabolic Bone Disease Clinic evaluation. Six months previously, the patient had experienced a painful spontaneous vertebral compression fracture of T12. Dual-energy x-ray absorptiometry revealed lumbar spine (L2-4) bone mineral density (BMD) to be 0.665 g/cm² (T score, –3.08; z score, –1.71) and nondominant femoral neck BMD to be 0.532 g/cm² (T score, –4.1; z score, –1.83).

The patient had no history of malabsorption, glucocorticoid exposure, tobacco smoking, or alcohol ingestion and no family history of osteoporosis.

Physical examination revealed a weight of 54.5 kg and a body mass index of 24.2 kg/m². The patient was in a wheelchair because of back pain. Examination of the spine was notable for thoracic kyphosis and tenderness over the thoracic spinous processes. Ecchymoses were present on the patient’s arms, and she had mild facial fullness.

Findings on evaluation for secondary causes of osteoporosis were unremarkable and included the following normal serum studies: complete blood cell count, liver function tests, creatinine, bone alkaline phosphatase, calcium, and albumin. The 25-hydroxyvitamin D level was adequate at 51 ng/mL. The patient’s 24-hour urine calcium excretion was 85 mg, but the specimen was likely undercollected based on a creatinine level of 11 mg/kg per 24 h in the specimen (reference range, 15-25 mg/kg per 24 h). The 24-hour urine type 1 collagen cross-linked amino terminal telopeptide (NTX, a marker for bone resorption) was in the low-normal range at 20 nmol/mmol creatinine (normal premenopausal range, 19-63 nmol/mmol creatinine), but as noted, the collection was likely incomplete. Magnetic resonance imaging of the lumbar spine was notable for multiple vertebral compression fractures including T10, T11, T12, and L1.

The patient’s daughter, a registered pharmacist, had noted her mother’s increased facial fullness and abdominal...
OSTEOPOROSIS ASSOCIATED WITH MEGESTROL ACETATE

distention during megestrol use (Figure 1). Also, the patient had noted that whenever she discontinued megestrol use, she would become ill and experience nausea and vomiting. Cortisol was undetectable in a 24-hour urinary free cortisol test. No exogenous glucocorticoids, other than megestrol, were detected using a synthetic glucocorticoid screening test with tandem mass spectroscopy performed on the same urine specimen. A 1-µg cortrosyn (corticotropin) stimulation test revealed a baseline serum cortisol level of 1.6 µg/dL at 8 AM and maximal cortisol level of 6.0 µg/dL 2 hours later, indicative of adrenal glucocorticoid suppression or adrenal gland insufficiency. The patient’s serum corticotropin level was 4.9 pg/mL (reference range, 10-60 pg/mL) at 8 AM. Megestrol was discontinued, and 5 mg of prednisone was given orally every morning to prevent symptoms of adrenal insufficiency. Two months later, full recovery of the patient’s adrenal gland axis was documented with another 1-µg cortrosyn stimulation test (baseline serum cortisol level of 11 µg/dL at 10 AM and maximal cortisol level of 22 µg/dL 45 minutes later), consistent with adrenal gland suppression during prior megestrol therapy.

Case 2
A 54-year-old postmenopausal white woman was referred to the Metabolic Bone Disease Clinic for evaluation of osteoporosis with multiple vertebral compression fractures. She had undergone surgery for abdominal pain and possible pancreatic carcinoma 13 months previously, but no malignancy had been found. Her postoperative course was complicated by nephritis and a pulmonary embolism, requiring placement of a Greenfield filter and tracheostomy. Megestrol (400 mg twice daily) was initiated for appetite stimulation. Exploratory laparotomy was performed 6 months later for persistent abdominal pain but was unrevealing. Approximately 2 months later, during rehabilitation, the patient experienced compression vertebral fractures of T12 and L4.

Menopause had occurred at age 45 years, and the patient had never received estrogen therapy. She had no history of fractures, osteoporosis, or glucocorticoid use. Medication use included phenytoin and warfarin at the time of her evaluation, both drugs having been initiated during her recent illness. The patient had a history of alcohol abuse but had been abstinent for the past 7½ years. Her family history was unremarkable for osteoporosis. Physical examination was notable for a weight of 55.6 kg and body mass index of 25.4 kg/m², moderate thoracic kyphosis, and tenderness in the lumbosacral region.

The patient’s lumbar spine (L3) BMD, measured by dual-energy x-ray absorptiometry, was 0.75 g/cm² (T score, −3.7; z score, −2.7); her nondominant femoral neck BMD was 0.57 g/cm² (T score, −3.4; z score, −2.4). Magnetic resonance imaging of the thoracic and lumbar spine revealed compression vertebral fractures of T6, T8-T12, L2, and L4. Magnetic resonance imaging of the spine obtained approximately 3 months previously showed only the T6, T12, and L4 compression fractures.

Results of the following serum laboratory studies were normal (reference ranges shown parenthetically): creatinine; serum protein electrophoresis; thyrotropin, 2.7 mIU/L (0.3-5.0 mIU/L); parathyroid hormone, 1.8 pmol/L (1.0-5.2 pmol/L); calcium; phosphorus; and albumin. Other laboratory test results revealed the following: hemoglobin, 11.5 g/dL (12.0-15.5 g/dL); mean corpuscular volume, 101.1 fL (81.6-98.3 fL); 25-hydroxyvitamin D, 23 ng/mL; aspartate aminotransferase, 60 U/L (12-31 U/L); bone alkaline phosphatase, 159 µM/min/L (11-67 µM/min/L); and 24-hour urine calcium, 96 mg, with evidence of an inadequate collection based on creatinine at 6.8 mg/kg per 24 h. A morning serum cortisol level at 10 AM was undetectable. Megestrol was discontinued, and results of a follow-up morning serum cortisol test 3 months later were normal at 11.2 µg/dL.

DISCUSSION
To our knowledge, this is the first report suggesting a possible association between megestrol and osteoporosis. Both of our patients were receiving high doses of megestrol, had evidence of adrenal axis suppression, and recovered fully after discontinuation of the drug. A clear relationship was seen between initiation of megestrol and the timing of vertebral compression fractures. This finding suggests that megestrol, especially at higher doses, may...
negatively affect bone quality and potentially be associated with bone loss and the development of fractures.

The glucocorticoidlike effect of megestrol is 1 mechanism that could lead to the development of osteoporosis. Biologically active progestins, including megestrol, have been shown to have efficient binding to the glucocorticoid receptor and to the progesterone receptor.\textsuperscript{4} In fact, high-dose medroxyprogesterone acetate has been given to patients who have undergone adrenalectomy in the absence of glucocorticoids, with no reported signs of adrenal insufficiency.\textsuperscript{5} Megestrol also has been shown to have considerable affinity for the glucocorticoid receptor of human mononuclear leukocytes and has been associated with immunosuppressive activity in animals.\textsuperscript{6,7} Thus, in vitro data support the concept that certain progestin compounds have an important peripheral glucocorticoidlike effect.

Several cases of Cushing syndrome due to megestrol have been reported.\textsuperscript{1,8,9} These observations are consistent with results of a prospective randomized trial that found that approximately one quarter of patients taking either progestin megestrol or medroxyprogesterone developed a cushingoid appearance after 3 months.\textsuperscript{10} Another prospective evaluation in 12 patients taking 800 mg of megestrol daily revealed that the weight gain associated with megestrol was due to an increase in adipose tissue and not lean tissue mass, again supporting a glucocorticoidlike effect of the drug.\textsuperscript{11} Finally, there have been reports of aseptic necrosis of the hip, presumably due to a glucocorticoidlike effect in HIV-seropositive patients taking megestrol.\textsuperscript{12}

Meglustrol use has been associated with suppression of serum cortisol levels in humans.\textsuperscript{3,13,14} Loprinzi et al\textsuperscript{15} evaluated the effects of megestrol on the adrenal axis in a prospectively followed cohort of 66 patients. Serum cortisol levels were decreased in all patients receiving 800 mg of megestrol daily. Furthermore, serum cortisol levels normalized in 3 patients who discontinued use of megestrol. In 5 patients, corticotropin levels were inappropriately decreased, suggesting suppressed hypothalamic-pituitary function. Hypothalamic-pituitary dysfunction was documented in 2 patients who had no response to metyrapone testing. Clinically, Cushing syndrome was not apparent in any patient in that study. Our patient in case 1 had nausea and emesis when megestrol was discontinued, suggestive of possible adrenal insufficiency. However, this may have simply represented the known benefit of megestrol in improving cancer-related nausea and vomiting.\textsuperscript{16,17}

Corticosteroids have several well-known adverse effects on bone metabolism including direct inhibition of osteoblast function, direct enhancement of bone resorption, inhibition of gastrointestinal calcium absorption, increased urinary calcium loss, and inhibition of gonadal hormones.\textsuperscript{18} Although traditionally the effect of megestrol on peripheral endocrine activity (eg, glucose and bone metabolism) was believed to be minimal, the reported cases of Cushing syndrome associated with megestrol show the potential for a peripheral glucocorticoidlike effect. Furthermore, there is a suggested dose effect of megestrol because Cushing syndrome appears to develop during higher-dose therapy.\textsuperscript{1} The development of multiple spontaneous vertebral compression fractures as seen in our patients would be typical of what often occurs in glucocorticoid-induced osteoporosis. Even more compelling are the reports of adverse skeletal effects from low-dose glucocorticoids that have few clinical features of corticosteroid excess. Clinical examples include reduced BMD in patients using inhaled glucocorticoids\textsuperscript{19} and in patients with Addison disease receiving replacement glucocorticoid therapy.\textsuperscript{20} Also, Van Staa et al\textsuperscript{21} have shown that oral prednisone doses as low as 2.5 to 7.5 mg daily are associated with excess fracture risk.

Another reported effect of megestrol that could lead to osteoporosis is the profound suppression of estradiol production. One group of investigators reported suppression of follicle-stimulating hormone and luteinizing hormone in a group of women with metastatic breast cancer who were taking megestrol.\textsuperscript{1} These changes were associated with a reduction in serum levels of estradiol and sex hormone-binding globulin. A more recent prospective study involving 12 postmenopausal women with advanced breast cancer who took low-dose megestrol (oral doses escalating from 40 to 160 mg daily) for 1 month revealed a reduction in serum levels of testosterone, estradiol, estrone, and estrone sulfate to 18% to 29% of pretreatment values.\textsuperscript{2} The reduction in serum estradiol concentration was similar to that reported with use of the aromatase inhibitor aromatase inhibitor (luteinizing hormone and follicle-stimulating hormone). In that study, the decrease in serum estradiol and testosterone levels was dose dependent, although gonadotropins were suppressed maximally at a dose of 80 mg of megestrol. Low levels of endogenous estrogen in postmenopausal women have been associated with increased bone turnover, reduced bone density, and increased fracture risk.\textsuperscript{22-25} Thus, reduced serum estrogen concentrations associated with megestrol use are not inconsequential and could lead to increased bone loss and skeletal fracture.

Clinical data suggest increased bone turnover and potential bone loss with megestrol use. In a randomized study of postmenopausal women with breast cancer, megestrol was associated with increased biochemical markers of bone resorption compared with placebo.\textsuperscript{26} Likewise, men receiving androgen deprivation therapy (megestrol included) for prostate cancer have been reported to have increased bone loss.\textsuperscript{3} Finally, most prospective studies of
depot medroxyprogesterone in premenopausal women suggest a modest decline in BMD.26

Although our report focuses on the possible adverse skeletal effect of progestational agents, there are data to suggest beneficial skeletal effects. For example, medroxyprogesterone has been shown to have a positive effect on calcium homeostasis when given to premenopausal women receiving gonadotropin-releasing hormone agonist therapy.29 Also, progesterone receptors are present on human osteoblasts, and progesterone may activate bone formation.30,31 Progesterone has been shown to stimulate proliferation and differentiation of osteoprogenitor cells in bone cells derived from adult female rats.32,33 Although progestins have been reported to prevent bone loss in postmenopausal women, other studies have been unable to show this benefit.34-36

The potential association of megestrol and osteoporosis is important to recognize because patients given megestrol likely will have other risk factors associated with the development of osteoporosis (as were present in our patients). Women with breast cancer appear to be at increased risk of osteoporosis because of multiple factors, including premature ovarian failure (a direct effect of chemotherapy) and perhaps breast cancer itself.37 Subjects in the Women’s Health Initiative Observational Study with a history of breast cancer had more than a 28% increased risk of all types of fractures except hip fractures. This fracture risk was present after adjustment for other risk factors during a mean follow-up of 5.1 years.38 Similarly, many patients receiving megestrol are postmenopausal and predisposed to bone loss. Vitamin D deficiency and reduced calcium intake in anorexic or cachectic patients may contribute to secondary hyperparathyroidism and further reduce bone density. Thus, because of the potential adverse skeletal effects of megestrol, its use is of concern and warrants further investigation in a population already predisposed to the development of osteoporosis.

We describe 2 cases that suggest megestrol may have been an important factor in the development of osteoporotic fractures. Clearly, further study is needed to clarify the relationship between megestrol and metastatic breast cancer patients with different dosages of megestrol acetate: dose relations, metabolic and endocrine effects. Eur J Cancer Clin Oncol. 1984;20:33-40.


