

Osteoporosis is a serious public health concern that affects almost 28 million people in the United States. Postmenopausal osteoporosis is a chronic, disabling disease of high prevalence in elderly people, particularly women. Its prevalence is becoming very relevant as baby-boomers reach retirement age and as life expectancy increases. Valid animal models are essential to evaluate bone active drugs for the prevention or treatment of osteoporosis. Miniature swine present several attractive features to the osteoporotic scientist. They are polyestrous, omnivorous, small in body size, and have lamellar bone and trabecular and cortical remodeling similar to humans. In addition, the anatomy and physiology of several miniature swine organ systems such as skin, cardiovascular, gastrointestinal, and urogenital systems are very similar to humans. Test compounds can be easily administered to miniature swine through all routes of delivery, including transcutaneous delivery systems (patches).

Previous efforts to standardize the young adult Sinclair miniature swine (SMS) as an animal model of osteopenia were rewarding. Mosekilde (1993) and Boyce (1995) demonstrated that young female SMS fed a mildly restricted calcium diet from 4 mo. of age and ovariectomized (OVX) at 10 mo. had a reduction in spine BMD and biomechanical parameters, and an alteration of the cancellous bone microstructure. The reduction in trabecular bone and the alteration in microstructure appeared primarily due to trabecular perforation. The perforation of trabecular elements occurred in the face of exaggerated resorptive cell function at the level of the remodeling unit. A similar pathogenesis for the microstructural changes occurring in women around menopause has recently been proposed.

The SMS osteopenia model is known to respond favorably and predictably to common bone therapeutic agents, such as estrogen replacement therapy, calcitonin, and biphosphonates. Although the young SMS osteopenia model exhibits significant bone loss and microstructural alterations in compressed time (6 months), Sinclair is evaluating adult miniature swine osteopenia models that will produce a gradual bone loss without growth artifacts. To achieve this purpose, the peak bone mass and calcium requirements of the SMS were determined. Peak bone mass occurs between 2.5 and 3 years of age. Dietary calcium levels above 0.45% were adequate for adult SMS. At 0.37% dietary calcium, serum PTH starts increasing which indicates that this calcium level may be the threshold of deficiency.

Preliminary results of a standardization study of an adult SMS osteopenia model are very encouraging. Ovariectomized adult SMS receiving a moderate calcium diet gradually lost approximately 11.7% versus 6.1% for the Sham normal calcium over 12 months. The difference between both groups is significant ($P < 0.05$). Preliminary results of a limb suspension study using intact adult SMS are also very encouraging. Ten months after gastrocnectomy, a SMS lost 11.6% and 21.1% of bone density in the spine and femur, respectively. Approximately 80% of the bone loss occurred within 2 months after the injury.

The calcium restricted ovariectomized SMS and the new SMS adult osteopenia models appear to be useful models of osteopenia and trabecular plate perforation and promising models for the study of the influence of microstructural changes on bone biomechanics. Recently, two new osteopenia models in miniature swine have shown encouraging results as well, namely, the limb suspension and glucocorticoid induced osteopenia.

As most scientists understand, no one animal model perfectly simulates human osteoporosis or osteopenia in all respects. The Sinclair miniswine model appears to be the most appropriate large animal model for a multitude of reasons.

Mosekilde L. et al. Evaluation of the skeletal effects of combined mild dietary calcium restriction and ovariectomy in Sinclair S-1 minipigs: A pilot study. *JBMR* 8(11):1311-1321, 1993.

Boyce R.W. et al. Microstructural alterations in vertebral cancellous bone in calcium-restricted ovariectomized minipigs: effect of anti-resorptive therapies. *JBMR* 10(Supp 1):T387, 1995.