Bone pathology in experimental osteoporosis: A review

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Abstract: New implants for the internal fixation of porotic bone should first be evaluated in experimental animals before they can be used in humans. If relevant results are to be generated, it is imperative that there is an adequate animal model for these studies. A literature survey of procedures used to develop osteoporosis in experimental animals indicated that none of the models described satisfactorily fulfilled the requirements for an optimal model for the study of porotic bone fracture fixation. The rat model exhibits major pathological differences compared to humans (different pattern of bone remodeling, little or no secondary Haversian remodeling in cortical bone, stable skeletal mass for a life span, small body size, short life span, low blood volume, and high basal metabolic rate). Large animals, such as dogs and primates, require a much longer time to reach a steady-state bone loss and none of them suffer from bone fragility. In the optimal animal model for the study of porotic bone fracture fixation, the histopathological pattern of osteoporosis should be similar to that of humans, and bone loss should be well controlled, appear early, not reverse spontaneously, and be associated with bone fragility.

Key words: osteoporosis, animal model, fracture fixation

Introduction

New implants are usually evaluated in experimental animals before they are used in human patients. Whereas a number of animals can be used for testing implant biocompatibility, the selection of an adequate animal model to test the fixation of porotic bone fractures is difficult, as large animals rarely develop osteoporosis.

The term “osteoporosis” designates a group of diseases of different etiologies, all characterized by the disappearance of the normal bony structure as the main symptom. A consensus conference defined osteoporosis as: “a disease characterized by low bone mass and microarchitectural deterioration of bony tissue, leading to an enhancement of bone fragility and a consequent increase in fracture risk”.1

Osteoporosis can be classified as primary or secondary. Primary is the most frequent, and includes idiopathic osteoporosis in childhood and involutional osteoporosis in adults and the elderly. The main forms of involutional osteoporosis are postmenopausal and senile osteoporosis, also called type 1 and type 2. Postmenopausal osteoporosis is by far the commonest form of age-related bone loss.2 Secondary osteoporosis is usually associated with a recognizable disease or medical therapy and accounts for 10% of osteoporotic patients.

Osteoporosis is a disease of immense socioeconomic significance.34-57 In the United States and Northern Europe, the lifetime risk of hip fracture in women at the age of 50 years is between 11% and 18% and is similar in magnitude to the risk of other major osteoporotic fractures (Table 1).34,11

The treatment of osteoporotic fractures is a complex challenge in orthopedic surgery; none of the available implants offers a totally satisfactory fixation and implant failures are common.9,23,38,82 This calls for the development of new implants to fix porotic bone fractures and their testing in an adequate experimental animal. Defining such a model will play an important role in understanding the etiology, pathophysiology, and diagnosis of osteoporosis, as well as in understanding preventive and therapeutic techniques.

Many different experimental approaches to induce osteoporosis in animals have been suggested. Based on
the definition of an animal model for the study of various diseases, an osteoporotic animal can be defined as one in which the characteristics of bone loss and its consequences resemble those found in osteoporotic patients. While such an animal model may not satisfactorily reflect the human situation, it would still be useful for the study of certain aspects of bone loss.

At least three aspects should be taken into account when selecting an animal model for the study of a particular problem. These are: convenience, relevance, and appropriateness. Convenience refers to ease, and for a long time it was the main criterion in choosing an animal model. Relevance refers to the comparability of the phenomenon being studied in an animal with that in the human. Appropriateness refers to the complex of other factors that make a given species the best for studying particular phenomenon.

The purpose of this review was to explore whether the animal models described in the literature meet Wessler’s requirements, i.e., convenience, relevance, and appropriateness, when the fixation of fractures of porotic bones is studied.

### Procedures for creating experimental osteoporosis

**Disuse osteoporosis model**

Various methods have been used to induce non-usage of limbs; e.g., excision of the calcaneal tendon, immobilization in plaster of Paris, fracture together with plaster of Paris, resection of the peritendinous tissue of the calcaneal tendon, and resection and excision of 1 cm of sciatic nerve. Most of the studies indicate that the initial rapid bone loss subsequent to immobilization tends to slow down with time. An acceleration of osteoclastic activity and a retardation of the ossification process due to impaired osteoblastic function or to recruitment are responsible for the observed changes. Not all bones or bone structures show the same pattern of loss. Some investigators deny the potential for recruitment and immobilization, timing of observation after remobilization, and the analytical method used for the evaluation of bone mineral content.

A study of the effect of animal age on immobilization showed that, in mature rats, immobilization caused a decrease in bone mass, and an increase in vascularization, particularly in the femoral head. Increased activity led to an increase in bone mass without any other specific changes. In growing rats, the changes were much more pronounced. Immobilization caused a decrease in overall body weight and a decrease in the vascularization of the femoral head, a decrease in the size and weight of the long bones, and a distortion in bone shape, particularly of the femoral head and the proximal tibia.

In a study of the effects of the thyroid and parathyroid glands on disuse osteoporosis it was found that disuse osteoporosis occurred in rats in the virtual absence of these glands, although the bone loss in the immobilized femur and tibia was less pronounced in thyroparathyroidectomized rats compared to intact animals. It should be mentioned, however, that the effect of these glands on disuse osteoporosis is controversial.

**Diet**

Calcium deficiency leads to osteoporotic changes in the skeleton of both juvenile and adult rats provided that vitamin D is supplied in the diet. A low-calcium diet produces osteoporosis by a secondary hyperparathyroid-dependent mechanism. Rats have a well-developed calcium absorptive mechanism. They can absorb large quantities of calcium in the absence of vitamin D, provided the dietary level of calcium is high. The bone loss caused by calcium deficiency is first observed in the jaw bones, especially the alveolar bone, and then in decreasing order, in skull, ribs, vertebrae, and finally the long bones, and is dependent on the species and on the age of the animals. In another study, rats that were nonpregnant, pregnant without lactation, or pregnant with lactation were kept on a calcium-deficient diet with the addition of oxalate. This resulted in a significant reduction of long bone growth, although the growth was not halted completely. The ash content in the metaphyseal area was reduced. Animals in the control group and the group subjected to the calcium-depriving regimen showed the same ash content in cortical bone. The different bones seemed to be affected equally.

Some experimental osteoporotic models are based on unbalanced diets of vitamins A and D. The administration of a large amount of vitamin D to the animals caused a thinning of the cortex accompanied by accelerated bone production in the medullary cavities of the long bones, with large quantities of osteoids around the original trabeculae and calcification in the soft tissues. Toxic amounts of vitamin D decreased the ash content.

<table>
<thead>
<tr>
<th>Fracture site</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Proximal femur</td>
<td>17.5 (16.8–18.2)</td>
<td>6.0 (5.6–6.5)</td>
</tr>
<tr>
<td>Vertebral</td>
<td>15.6 (14.8–16.3)</td>
<td>5.0 (4.6–5.4)</td>
</tr>
<tr>
<td>Distal forearm</td>
<td>16.0 (15.7–16.7)</td>
<td>2.5 (2.2–3.1)</td>
</tr>
<tr>
<td>Any of the above</td>
<td>39.7 (38.7–40.6)</td>
<td>13.1 (12.4–13.7)</td>
</tr>
</tbody>
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