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Review

Glucocorticoids, osteocytes, and skeletal fragility: The role of bone vascularity

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ABSTRACT

Glucocorticoid administration is required for many inflammatory and autoimmune diseases, but use of these drugs is associated with skeletal side effects including bone loss, fractures, and osteonecrosis. Fractures often occur without a reduction in bone mineral density, strongly suggesting that glucocorticoid excess adversely affects other aspects of bone strength. Although the primary effects of glucocorticoid excess on the skeleton are directly on bone cells, a vascular connection between these cells and the loss of bone strength appears likely. This review examines this connection and how it may explain the greater decline in bone strength than loss of bone mass that occurs with glucocorticoid excess.

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Introduction

Glucocorticoid administration is the most frequent secondary form of osteoporosis and the most common iatrogenic reason for the disease [1,2]. Often the presenting manifestation is fracture, which occurs in 30 to 50% of patients receiving long-term glucocorticoid therapy. Many fractures are asymptomatic, possibly because of glucocorticoid-induced analgesia, but even asymptomatic fractures are important because they further reduce the vital capacity of patients with chronic lung disease receiving prednisone and increase the risk of subsequent fractures independently of the bone mineral density (BMD) [1,3,4]. In addition to glucocorticoid-induced osteoporosis (GIO), chronic glucocorticoid administration also causes osteonecrosis of the hip; a situation in which deformity and collapse occur in spite of increased radiographic sclerosis signifying a mismatch between the increased skeletal density and decreased bone strength [5]. The primary adverse effects of glucocorticoid excess on the skeleton are directly on bone cells: decreasing the

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production of both osteoblasts and osteoclasts, increasing the prevalence of osteoblast and osteocyte apoptosis, and prolonging the lifespan of osteoclasts (Fig. 1) [6–10].

Determination of the bone impact of glucocorticoid therapy is complicated by the heterogeneity of the diseases that are treated with glucocorticoids and the wide variation in the dose, duration, and route of the administered treatment [1]. In general, bone loss in GIO is biphasic, with an early reduction in BMD of 6–12% within the first year, followed by a later continual loss of about 3% for each additional year of treatment [11]. However, there is more to consider than the reduction in BMD, as bone quality is also an issue [12]. The relative risk of fracture increases rapidly, escalating by as much as 75% within the first 3 months after initiation of glucocorticoid therapy, usually long before much change in BMD is detectable. This increase in fracture risk dissipates shortly after discontinuation of therapy [13]. These features strongly suggest that glucocorticoid-induced fractures are due to more than just decreasing bone mass. Advancing age is another risk factor as shown by the 26-fold greater incidence of symptomatic

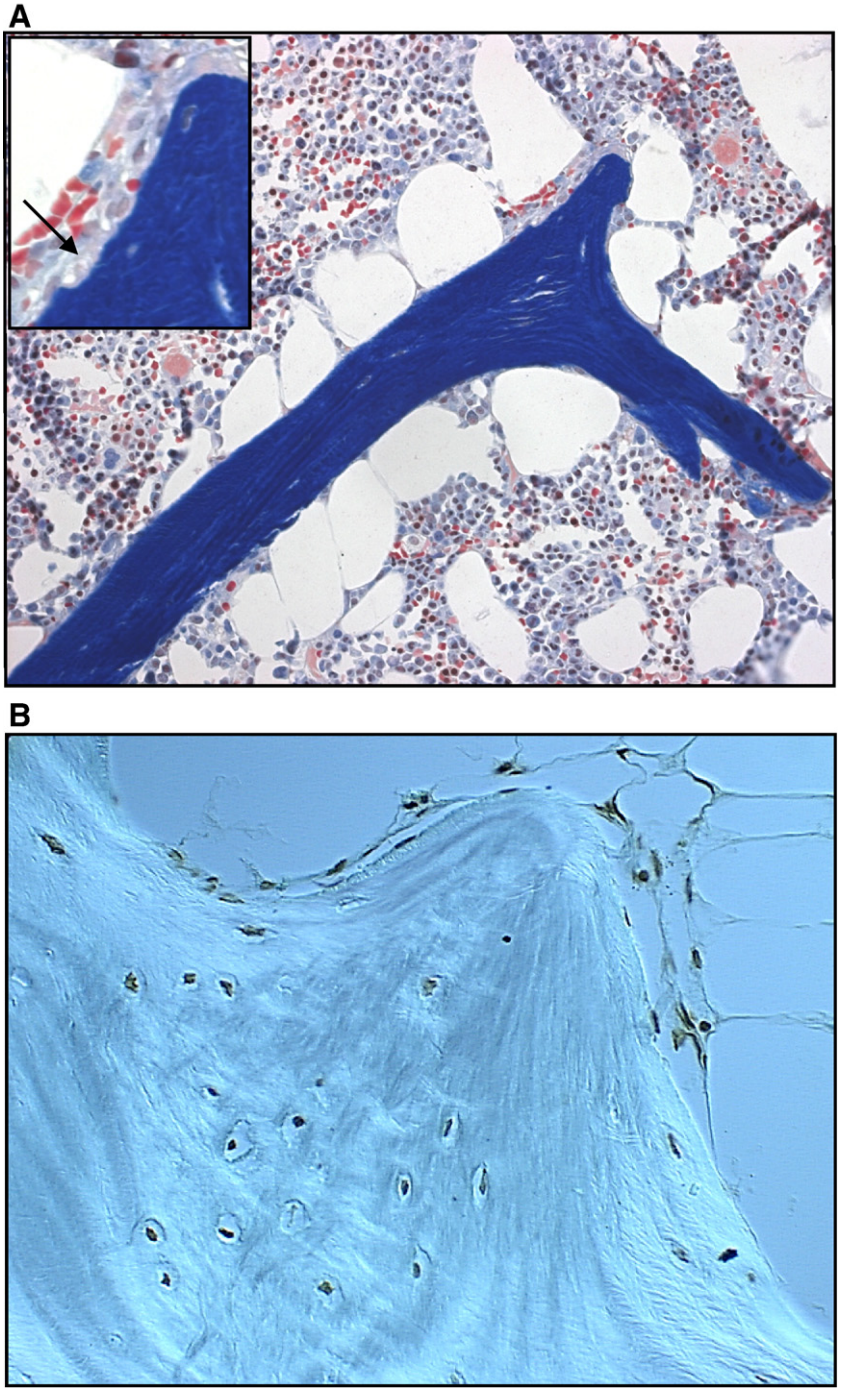

Fig. 1. Glucocorticoid-induced osteoporosis. (A) After long-term prednisone treatment in humans, cancellous bone tissue often shows an excessive number of enlarged adipocytes and atrophic, disconnected trabeculae without osteoblasts. The insert shows the accumulation of erosion cavities devoid of osteoclasts (arrow), measured as the reversal perimeter, which indicate delayed or defective bone formation rather than excessive bone resorption. The red cells in the bone marrow are hematopoietic cells and should not be mistaken for osteoclasts (modified Masson staining, 200× with the insert at 400×). (B) In this specimen obtained from an osteonecrotic hip, virtually all cancellous osteocytes and lining cells are apoptotic as revealed by the dark brown stain (apoptosis staining was done by in-situ end-labeling or ISEL, 630×).