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Review

Histomorphometric analysis of glucocorticoid-induced osteoporosis

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Abstract

Bone histomorphometry or quantitative histology consists of counting or measuring tissue components: cells, extracellular constituents and microarchitecture. Bone histomorphometry is the only method that allows the measurement of mineralization rate and the study of bone formation at three levels: cell, remodeling unit and tissue levels. It is a useful tool to explain the pathogenesis and cellular mechanisms of different metabolic bone diseases such as glucocorticoid-induced osteoporosis (GIO).

Glucocorticoids (GC) affect calcium and bone metabolism at every level, but the main effect is the osteoblastic dysfunction.

Concerning the bone formation, some histomorphometric studies have shown a depressed osteoblastic activity at a cell, bone remodeling unit, and tissue levels. In addition, there is evidence of a shortening of the period in which the osteoblasts work actively forming the bone matrix. This latter effect seems to occur after high cumulative doses of GC. With regard to the resorption, the results are still debated, but histomorphometric parameters seem to be increased in the majority of studies, at least in the first period of the GC treatment. From a structural point of view, GC seem to induce a thinning of the trabeculae without their perforation, which occurs only after high cumulative doses. Antiresorptive treatments, such as bisphosphonates, are able to counteract the negative effects of GC on bone. In particular, along with their active working period, they prolong the lifespan of osteoblasts and osteocytes. In addition, the antiresorptive treatments seem to extend the time for secondary mineralization through a reduction of the Activation Frequency. The latter is an intriguing mechanism of bisphosphonates in GIO that needs further ad hoc investigations.

Keywords: Histomorphometry; Bisphosphonates; Glucocorticoids; Microarchitecture; Osteoporosis

Contents

Abbreviations used BV/TV, Bone Volume; Tb.N, Trabecular Number; Tb.Th, Trabecular Thickness; Tb.Sp, Trabecular Separation; O.Th, Osteoid Thickness; OS/BS, Osteoid Surface/Bone Surface; ES/BS, Eroded Surface/Bone Surface; N.Oc/BS, Osteoclast Number/Bone Surface; W.Th, Wall Thickness; FP, Formation Period; (a+)FP, Active Formation Period; MAR, Mineral Apposition Rate; BFR/BS, Bone Formation Rate/Bone Surface; Aj.AR/BS, Adjusted Apposition Rate/Bone Surface; Ac.f, Activation Frequency; MaSV, marrow star volume; ICI, interconnectivity index; TBPf, trabecular bone pattern factor; D, fractal analysis.

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Table 1
Main histomorphometric parameters

Parameter	Abbreviation	Units
Bone Volume/Tissue Volume	BV/TV	%
Trabecular Number	Tb.N	/mm
Trabecular Thickness	Tb.Th	μm
Trabecular Seperation	Tb.Sp	μm
Osteoid Thickness	O.Th	μm
Osteoid Surface/Bone Surface	OS/BS	%
Eroded Surface/Bone Surface	ES/BS	%
Osteoclast Number/Bone Surface	N.Oc/BS	N/mm
Formation Period	FP	Days
Active Formation Period	(a+)FP	Days
Wall Thickness	W.Th	μm
Mineral Apposition Rate	MAR	μm/day
Bone Formation Rate/Bone Surface	BFR/BS	$\mu m^3/\mu m^2$/day
Adjusted Apposition Rate/Bone Surface	Aj.AR/BS	μm/day
Activation Frequency	Ac.f	N/yr

1. Introduction

Bone histomorphometry or quantitative histology consists of counting or measuring tissue components: cells, extracellular constituents and microarchitecture. It is the only method that allows the measurement of mineralization rate and the study of bone formation at three levels: cell, remodeling unit and tissue levels. The main histomorphometric parameters are shown in Table 1. Histomorphometry is a useful tool in the diagnosis and study of metabolic diseases of the skeleton, especially in the trabecular compartment. Particularly, this approach is important to explain the pathogenesis and cellular mechanisms of different metabolic bone diseases such as glucocorticoid-induced osteoporosis (GIO).

Glucocorticoids (GC) affect calcium and bone metabolism at every level (Fig. 1), but among possible mechanisms of action, the osteoblastic dysfunction is the most important and consistently demonstrated in different models for the genesis of GC-induced bone loss, associated in some studies with an increase in osteoclastic bone resorption. Recently, it has been found out that glucocorticoids act directly on differentiated osteoclasts to extend their lifespan as on osteoblasts to stimulate their apoptosis, leading to an imbalance between the actions of these cells, which are normally coupled (Weinstein et al., 2002).

On the other hand, the decreased calcium absorption and increased urinary excretion, with the consequent hyperparathyroidism are no more considered the main mechanisms in the pathogenesis of GIO, as hypothesized in previous studies (Lukert, 1996; Klein et al., 1977; Suzuki et al., 1983; Adachi, 1997).

These pathways have also been associated to the presence of an hypogonadism in male patients (Fig. 1) (Reid et al., 1988). The relationship between hypogonadism, steroids and decreased skeletal mass was highlighted also in patients with anorexia nervosa (Soyka et al., 2002). In these patients, the elevated plasma cortisol levels and urinary free cortisol excretion seemed to be involved with the suppression of bone turnover along with amenorrhea and estrogen deficiency.

These results fit in well with animal studies on ewes, which showed similar alterations in bone formation than in humans (Chavassieux et al., 1993). Moreover, all the histomorphometric studies of GC-treated patients have confirmed a reduction in bone mass (Lo Cascio et al., 1984, 1995). In particular, Bressot et al. (1979) reported that 63% of 50 women enrolled in their study had a cancellous

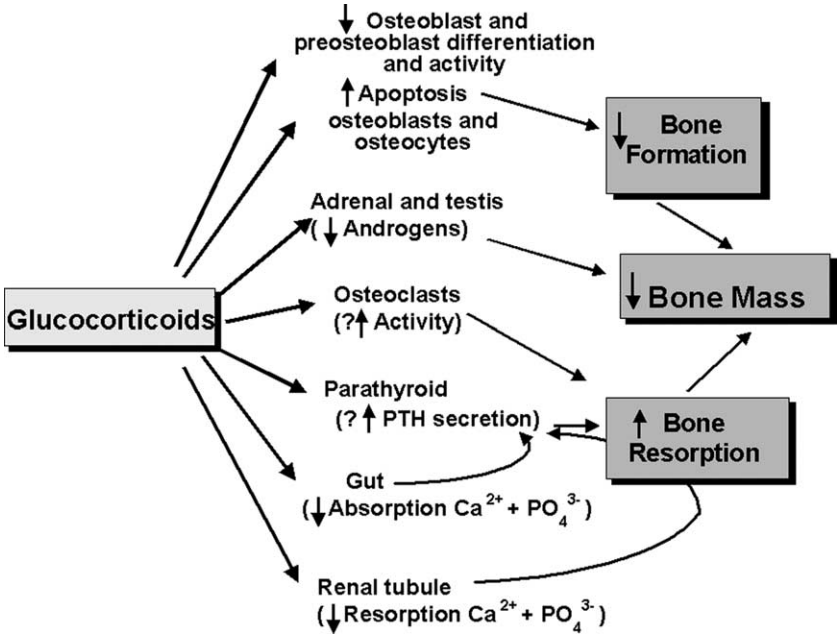

Fig. 1. Effects of glucocorticoids on bone.