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Review article

The effect of glucocorticoids on bone and muscle

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Abstract

This article examines the current knowledge of the effects of both exogenous and endogenous glucocorticoids on bone and muscle. It demonstrates the similarity of effects of supraphysiologic loads of glucocorticoids regardless of whether they enter the body in the form of medication or are manufactured by the body in response to stimuli such as inflammation. The effects of endogenous glucocorticoids and the systemic inflammatory response resulting from pediatric burn injury are compared and the difficulty in sorting out which of the two factors is responsible for the ultimate effects on bone and muscle is pointed out. The focus then switches to the body's response to the influence of both glucocorticoids and inflammatory cytokines and evidence supporting a common pathway of response to oxidative damage caused by both is discussed. Current recommended medical management of glucocorticoid-induced bone and muscle loss is discussed and the failure to reconcile current management with known mechanisms is highlighted.

Keywords: Glucocorticoids; Bone; Muscle; Oxidative stress; Forkhead box O

1. Introduction

Much has been learned since 1932 when Harvey Cushing described the set of symptoms that denoted hypersecretion of ACTH most often due to a pituitary adenoma. A set of symptoms prominently featured include truncal obesity, a rounded face, increased fat around the neck, and peripheral muscle wasting, weakened bones, leading to vertebral compression fractures, striae on the abdomen and buttocks, hirsutism, fatigue, muscle weakness, fluid retention, hypertension, and hyperglycemia [1].

The original publication by Cushing [2], as it turns out, was the first description of the effects of *endogenous* glucocorticoids on bone and muscle, a description that became identified with the effects of *exogenous* glucocorticoids, or steroid medication for a variety of chronic inflammatory and neoplastic diseases. Thus for the longest time the deleterious effects of glucocorticoids on bone and muscle were identified exclusively with steroid-based medications.

This review will touch on the clinical side-effects of glucocorticoid medications and then will proceed to the more complex subject of the effects of endogenous glucocorticoids on bone and muscle and the interactions of glucocorticoids with the systemic inflammatory response. Following this the discussion will move on to focus on the identification of a common mechanism of glucocorticoid effect on both bone and muscle and will conclude by examining unanswered questions regarding the interactions of bone and muscle under the influence of glucocorticoids. A discussion of current management of these glucocorticoid side effects will provide a perspective as to how far we have yet to go in order to match mechanism with clinical management. It is hoped that this review will shed light on both the depth and the complexity of glucocorticoid effects on bone and muscle.

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2. The epidemiology and clinical effects of steroid medications on bone and muscle

The clinical side-effects of steroid medications on bone and muscle have been the subject of numerous reviews and textbook descriptions. Glucocorticoid-based medications have potent anti-inflammatory effects and are widely used to treat chronic inflammatory conditions such as inflammatory bowel disease, systemic lupus, rheumatoid arthritis, neuromuscular diseases such as Duchenne muscular dystrophy, reactive airway diseases such as asthma, and immunosuppression in organ transplantation, among other situations. As concisely stated in a review by Ziegler and Kasperk [3], glucocorticoids can cause both muscle wasting and decreased bone formation. There is a question as to whether they truly cause calcium malabsorption with resultant secondary hyperparathyroidism and resorptive bone loss, but this has recently been reported in mice with the mechanism attributed to glucocorticoid-associated decreased expression of intestinal calcium channel TRPV6 [4]. It is unclear, however, as to the significance of this mechanism in humans. Nonetheless, the effects of exogenous glucocorticoids on bone formation and peripheral muscle wasting are well described. The likelihood of muscle wasting and steroid-induced osteoporosis increases if the duration of treatment exceeds 3 months or consists of 3–4 courses of treatment per year with an oral dose of at least 5 mg prednisone per day [5]. To minimize the chances of systemic steroid side effects the dose of oral steroids should be less than 7.5 mg daily, should last less than 3 months, and should be given less than 3–4 times per year [6].

Glucocorticoid-induced osteoporosis is a condition that causes fractures in 30–50% of adults on long-term treatment and approximately 1.5% of post-menopausal women in the United Kingdom receive long-term treatment with glucocorticoids [7]. In 2000 approximately 1% of the population of the United Kingdom was treated with steroids at any one time with 22% of the total treated for more than six months [7]. From data obtained in Iceland approximately 26% of the population treated with long-term glucocorticoids developed osteoporosis [7]. While fracture rates increase with age, long-term steroid intake of prednisolone 5 mg/day or greater increases the fracture rate by an additional 20%, a figure that increases to an additional 60% if the amount of prednisolone taken reaches 20 mg/day [7].

3. The effects of endogenous glucocorticoids on bone and muscle

While steroid side effects can be produced by supra-physiologic doses of steroid medications, it is well-known from Cushing's initial description that endogenous glucocorticoids are capable of producing identical effects, whether it be from a pituitary tumor, as first described [2], or from another condition. It is important for the physician to be aware of which conditions have been documented to produce excessive endogenous glucocorticoids. Representative conditions can be found in Table 1.

Table 1
Pathologic conditions stimulating endogenous glucocorticoid production.

Inflammation [8]
Hypothalamic–pituitary–adrenal axis tumor or multiple endocrine neoplasia [2]
Burn injury [9]
Other catabolic conditions:
Diabetes [10]
Sepsis [10]
Angiotensin II infusion [10]
Metabolic acidosis [10]
Starvation [10]

The mechanism of action by which angiotensin II infusion stimulates endogenous glucocorticoid production is not identified to date but urinary production of glucocorticoids is elevated in mice and rats [11].

A good illustration of the pathophysiologic elevation of endogenous glucocorticoids is the scenario that occurs following a severe burn injury. Burns can be considered to be an appropriate case study to examine mechanisms of glucocorticoid effects on bone and muscle because in clinical situations, with the exception of glucocorticoid-producing tumors, elevation of glucocorticoids does not occur in isolation. Although it can be argued that burn injury causes tissue damage and necrosis, which may result in activation of pathways other than what is observed with exogenous glucocorticoid injury, the injury itself results in at least two major adaptive responses that occur immediately following a burn injury. The first is the systemic inflammatory response, during which a variety of pro-inflammatory cytokines are released, notably interleukin (IL)-1β and IL-6, the former being three-fold elevated and the latter one hundred-fold elevated [9]. At approximately the same time, urinary free cortisol excretion is 3–8-fold elevated [9]. It is not certain whether the trauma of the burn injury activates both responses independently of each other or whether the release of pro-inflammatory cytokines precedes the rise in endogenous glucocorticoid production [6]. The timing of this sequence has not yet been studied. Nonetheless both responses are vigorous and both occur acutely following burns and to argue that necrosis may trigger different mechanisms is speculative.

The initial effect on bone, as illustrated in a sheep model of burn injury [12], is an acute increase in urinary excretion of the C-telopeptide of type I collagen, or CTx, a biomarker of bone resorption, on day one post-burn. By day 5 post-burn there is histologic evidence of increased bone resorption, as shown by the presence of scalloping on scanning electron microscopy [12]. The significance of this finding is that in those first five days at least, despite the elevation of urinary free cortisol excretion, there is no significant steroid-mediated apoptosis of osteoblasts or osteocytes. The reason for the persistence of resorption despite the presence of large quantities of glucocorticoids that can cause osteoblast and osteocyte apoptosis is not understood.

The dictum that glucocorticoids can stimulate bone cells to transiently increase production of the ligand of the receptor