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Concept Paper

The Products of Bone Resorption and Their Roles in Metabolism: Lessons from the Study of Burns

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Abstract: Surprisingly little is known about the factors released from bone during resorption and the metabolic roles they play. This paper describes what we have learned about factors released from bone, mainly through the study of burn injuries, and what roles they play in post-burn metabolism. From these studies, we know that calcium, phosphorus, and magnesium, along with transforming growth factor (TGF)-β, are released from bone following resorption. Additionally, studies in mice from Karsenty's laboratory have indicated that undercarboxylated osteocalcin is also released from bone during resorption. Questions arising from these observations are discussed as well as a variety of potential conditions in which release of these factors could play a significant role in the pathophysiology of the conditions. Therapeutic implications of understanding the metabolic roles of these and as yet other unidentified factors are also raised. While much remains unknown, that which has been observed provides a glimpse of the potential importance of this area of study.

Keywords: bone resorption; calcium; phosphorus; TGF-β; undercarboxylated osteocalcin

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1. Introduction

In recent years we have learned much about the mechanisms of bone formation and resorption, the cells involved, and many of the factors that affect and link the two processes. What we have not learned is the breadth of factors released by bone on resorption, the relationship of these factors to each other, what controls their release, and how they are utilized by the body's metabolism under a wide variety of conditions. The study of certain conditions, such as burn injury, provides clues to what is released by bone and how they may operate. However, the large number of conditions, such as hyperparathyroidism, Paget's disease, renal osteodystrophy, inflammation, and immobilization potentially affected by bone factor release are variable. Therefore, it is important to understand how the release system works in one condition at a time so as not to become overwhelmed by the complexity of the task facing us. The importance of understanding the mechanisms involved in bone factor release and utilization lies in the potential to regulate these releases for therapeutic purposes depending on the underlying pathologic condition.

The organization of this paper will describe what we know about factor release from resorbing bone and the actions of these factors on specific metabolic needs within the context of burn injury and will end with some speculation about other conditions such as secondary hyperparathyroidism, but where the bulk of the experimental work still needs to be performed. While parts of this argument have previously appeared in print, specifically in relation to muscle, this paper is the first attempt to provide a comprehensive framework for the argument and to propose to expand what we have learned from burn injury to the study of a wide variety of other resorptive conditions.

2. Burn Injury: An Overview

The most recent review of the contribution of the musculoskeletal system to post-burn hypermetabolism was published in 2019 [1] and details the considerations to be raised here.

Acute burn injury generates two major immediate responses by the body: the systemic inflammatory response and the stress (fight or flight) response. The former involves the production of large quantities of pro-inflammatory cytokines, predominantly interleukin (IL)-1β and IL-6, both of which are elevated systemically (2). The latter involves markedly elevated endogenous production of glucocorticoids, resulting in a 3–8-fold elevation of urinary cortisol excretion [2,3]. In addition, absolute or relative immobilization due to recurrent skin grafting needs is associated with sympathetic overdrive and increased resorption of bone, which is normally independent of parathyroid hormone (PTH) production. Since the β-adrenergic receptors located on the osteoblasts mediate the osteoclastogenesis, apoptosis of osteoblasts by about three weeks post-burn in theory should end the sympathetic drive to bone resorption. Usually at about this time, bone formation and bone resorption are suppressed [2] and bone becomes adynamic, at least in burned children. Therefore, it is likely that the immobilization-associated sympathetic overdrive and resorption becomes less relevant over time while the inflammatory and stress responses linger for months or longer post-burn.

3. What Factors Are Released by Resorbing Bone?

Given that we are still discovering elements and factors that are released by resorbing bone, it is reasonable to assume that there are many factors still awaiting discovery. However, we can only work with those which we currently know and are beginning to understand. Those which we currently know of are the following: calcium, phosphorus, magnesium, transforming growth factor-β and osteocalcin. What we have learned from the study of burns is that resorbing bone releases calcium, phosphorus, magnesium and transforming growth factor (TGF)-β while we do not know how much undercarboxylated osteocalcin is released and under what circumstances. While each of the first four listed factors is released in burn-induced bone resorption, the serum concentration of these does not necessarily reflect their metabolic fate inasmuch as some may have paracrine effects that serve to reduce circulating concentrations of these factors. We will explore each within the context of burn injury.

3.1. Calcium

Inasmuch as 99% of the body's calcium is stored in bone [4], the release of calcium is the most immediate factor to examine. Bone is resorbed due to the robust systemic inflammatory response that develops due to the destruction of the skin barrier to entry of microorganisms into the body as well as possibly the effects of systemic glucocorticoids produced by the stress response. Calcium handling by burned children and adults appears to be different and this has been dealt with in two earlier publications [5,6]. In children [7], as in sheep [8], the inflammatory response leads to an upregulation of the parathyroid calcium-sensing receptor (CaSR), the G-protein coupled calcium-sensing receptor located on the membrane of the parathyroid chief cells [8–11]. This action lowers the amount of circulating calcium needed to suppress PTH secretion, in essence a lowering of the calcium threshold for suppression of PTH secretion. The result is a hypocalcemic hypoparathyroidism. Studies in adults with burn injury report that ionized calcium is normal to be slightly elevated while PTH concentration in serum is also normal to be slightly elevated [12,13]. Is this a significant finding? A study by Rossol et al. [14] showed that extracellular calcium can upregulate the nod-like receptor (NLR) P3 inflammasome, which will stimulate the monocytes and macrophages of the innate immune system to produce IL-1. Another study by Klein et al. [15] reported that cultures of peripheral blood mononuclear cells of adult volunteers resulted in chemokine production or suppression in direct or inverse relationship to the calcium content of the culture medium. Taken together, these studies provide evidence supporting intensification and/or prolongation of the inflammatory response. It has been shown by Finnerty et al. [16] that adults suffering the same extent of burn injury as children have greater burn morbidity. Thus, the higher circulating calcium in burned adults may prolong or intensify the inflammatory response

while the ability of the hypoparathyroid pediatric burn patients to excrete excess calcium by means of the upregulated CaSR may have the effect of diminishing the inflammatory response in those patients. The mechanism for initiating failure to upregulate the CaSR in response to burns is at this point not identified.

3.2. Phosphorus and Magnesium

The first evidence obtained that bone phosphorus and magnesium are important in burn metabolism came to light when Borsheim et al. [17] reported results of stable isotope studies of muscle protein balance in burned children who had participated in a double-blind randomized controlled trial of a bisphosphonate to prevent bone resorption following burn injury. While the outcome of the anti-resorptive study showed success in prevention of bone resorption [18,19] when examining the muscle protein kinetics it was found that while muscle protein breakdown was reduced in the bisphosphonate group, muscle protein synthesis was also reduced [17]. Inasmuch as the ATP requirements for muscle function go up significantly following burns, it is likely that bone resorption provided the phosphorus and magnesium necessary to promote synthesis of the ATP to be used in muscle protein synthesis.

Moreover, the upregulation of the CaSR by the inflammatory response lowered PTH and FGF23 [20] thus helping to preserve phosphate for use in generating more ATP. Paradoxically, CaSR upregulation also leads to more urinary magnesium excretion thus perhaps putting a greater strain on bone to release more magnesium in the face of CaSR upregulation [21]. This issue has not been addressed.

3.3. Transforming Growth Factor (TGF)-β

Bone matrix is rich in TGF-β. The molecule is synthesized in osteoblasts, stored in the matrix, and released from the matrix by the action of osteoclastic proteolysis of the latent TGF-β binding protein-1 mediated by matrix metalloproteinases (MMP)-2 and -9 [22]. Waning et al. [23] identified TGF-β release from bone as the cause of the paracrine effect on muscle wasting in patients with bone metastases from either breast or lung cancer. The mechanism explaining this was the oxidation of the ryanodine receptor with consequent calcium wasting resulting in weakness and wasting of the muscle. In burn injury, the results reported by Borsheim et al. [17] were explained by Pin et al. [24]. They reported that in vitro studies of murine myoblasts cultured with serum from burn patients who received treatment either with a bisphosphonate to prevent bone resorption or a saline placebo demonstrated that burn injury resulted in a reduction in myotube size, an increase in the catabolic pathway as represented by ubiquitin concentration and a reduction in phosphorylation of the anabolic AKT/mTOR pathway. Myoblasts cultured with serum from patients treated with bisphosphonates, in contrast, demonstrated partial rescue of myotube size, a significant reduction in ubiquitin concentration in the medium and an increase in phosphorylation of the AKT/mTOR pathway. More importantly, when the myoblast culture experiments were repeated with the addition of anti-TGF-β antibody to the cultures, rescue of myotube size in the placebo group reached the magnitude initially seen in those cultures with serum from the bisphosphonate-treated patients while in the cultures of myoblasts with serum from bisphosphonate-treated patients, there were negligible changes in myotube size from the original experiments without the anti-TGF-β antibody. These data support TGF-β release from bone as a significant factor in muscle wasting in two discrete groups of patients, mature women with breast cancer metastases to bone and pediatric burn patients.

3.4. Osteocalcin

Work from the laboratory of Karsenty et al. [25,26] and others has shown that the undercarboxylated form of osteocalcin, also synthesized by osteoblasts, is an important factor in muscle fiber uptake of glucose and nutrients, thus constituting an anabolic factor. It is released from the bone matrix by IL-6 generated by muscle in response to osteocalcin.

IL-6 will then stimulate osteoblast synthesis of the ligand of the receptor activator of nuclear transcription factor κB (RANK ligand or RANKL), which will stimulate osteoclastogenesis, increase bone resorption and release more undercarboxylated osteocalcin for anabolic action on muscle. Additionally, undercarboxylated osteocalcin stimulates pancreatic β cells to secrete insulin and renders muscle more sensitive to insulin action. It should be pointed out that undercarboxylated osteocalcin has not been specifically studied in burn patients. Only total serum osteocalcin has been examined and those results have all been low [27], not surprisingly since bone is being lost due to resorption. However, undercarboxylated osteocalcin is mentioned here inasmuch as it exerts anabolic action as opposed to the catabolic action of TGF-β, therefore serving as a potential counterbalance to TGF-β and raising the question, to be posed in the next section, of how does the bone decide, if it indeed does decide, to release catabolic as opposed to anabolic factors for metabolic use.

4. Discussion and Questions

We see that bone resorption results in release of several factors from the resorbing bone. These include the elements calcium, phosphorus and magnesium as well as the proteins TGF-β, a catabolic agent for muscle, and undercarboxylated osteocalcin, an anabolic agent for muscle. Four of the five factors released were discovered during the study of burn injury. However, the release of these factors raises many basic questions regarding what happens during bone resorption. We will ask these questions now.

4.1. Questions about Products of Bone Resorption

It is now clear that products of bone resorption have diverse and conflicting effects on metabolism. Thus, it would be appropriate to ask how release of these factors from bone is controlled. What signals determine which factors are released from bone and in what quantity and rate? What terminates the release of these factors?

Are release of factors from bone matrix always in the same proportion or are they variable depending on age and specific resorptive condition? If they are in the same proportion what determines how they are utilized by the body's metabolism? Are differences in rates of utilization of resorption-released factors a determinant of the rate and quantity of factor liberation from resorbing bone?

To what extent do different pathologic conditions resulting in resorption alter the pattern of use of released factors? To what extent do they influence the quantity and rate of factor release and what is the mechanism behind it?

Can knowledge of underlying mechanisms controlling bone factor release provide therapeutic targets for some or all of the pathological conditions giving rise to bone resorption?

4.2. Pathological Conditions That Generate Bone Resorption and Subsequent Factor Release

4.2.1. Inflammation

Inflammation stimulates the production of cytokines, notably interleukins (IL)-1 and -6 as well as tumor necrosis factor (TNF)-α, that stimulate osteoblasts and osteocytes to produce the receptor activator of NFκB ligand (RANKL), which stimulates marrow stem cell osteoclastogenesis, causing bone resorption. What is unknown is whether there is a threshold effect of inflammation. In other words, what might be the differences in factor release between acute and chronic inflammation or between high-grade and low-grade inflammation? What role would anti-inflammatory medications play in affecting bone factor release during resorption? We know from burn injury studies that calcium release can intensify or prolong an inflammatory response, and phosphate and magnesium release can provide ATP to fuel muscle protein synthesis while TGF-β release can promote muscle protein degradation.

4.2.2. Immobilization

It is clear that immobilization can act to immediately cause significant bone resorption in bed rest studies performed in preparation for space flight [28]. One way in which

immobilization produces resorption is to stimulate beta adrenergic drive. Osteoblasts have β2 receptors that would be stimulated by immobilization, as in pediatric burn injury [29]. Thus the increased sympathetic tone could play a role in resorptive bone loss as well. The role of mechanosensors may be important as well. Suzuki et al. [30] have identified that deficiency of transient receptor potential vanillin (TRPV)4 may inhibit bone unloading. Other mechanosensors within the osteocyte, such as connexin 43 and primary cilium, have been identified as possible contributors to the transduction of fluid flow, along with calcium channels and G protein-coupled receptors [31]. Rate of bone loss has not been studied and whether changes in rate alter the release of metabolic factors from bone is still unclear.

4.2.3. Glucocorticoids

It is well known that glucocorticoid administration is associated with osteoporotic bone loss. What is not clearly established is the mechanism by which this occurs. How much is due to suppression of bone formation and how much is due to stimulation of acute bone resorption? According to a recent review by Compston [32], glucocorticoid-induced bone resorption is acute but transient, allowing for a potential role of glucocorticoids in bone factor release following resorption. The role of stress in the stimulation of increased endogenous glucocorticoid production is also unclear. In pediatric burn injury, urinary glucocorticoid excretion ranges from 3–8-fold to normal [2]. To what extent stress-induced production of endogenous glucocorticoids produces resorptive bone loss is another question.

4.2.4. Hyperparathyroidism

It is well known that hyperparathyroidism, either primary or secondary, leads to resorptive bone loss. It is clearly understood that the release of calcium into the blood is intended to restore low circulating calcium concentrations to normal. It is also clear that the phosphate released from bone is excreted in the urine while the kidney tubules reabsorb filtered calcium. However, what is the cost of these actions of parathyroid hormone? Is excess TGF-β released to cause muscle wasting? What about undercarboxylated osteocalcin? Is that released in the same quantities as TGF-β? Are other factors released that have not yet been identified? Muscle wasting has been a classic presentation of hyperparathyroidism.

4.2.5. Renal Osteodystrophy

The inability of the kidneys to excrete phosphate, due in part to progressive loss of the renal cofactor for fibroblast growth factor (FGF)-23, klotho, in response to phosphate intake in patients with chronic kidney disease, is associated with the robust secondary hyperparathyroidism observed in this condition. Yet the marked secondary hyperparathyroidism should cause significant bone resorption resulting in the release of more phosphate into circulation. How much of the phosphate release from bone is added to the dietary phosphate intake to exacerbate the secondary hyperparathyroidism? Should anti-resorptive use attempt to address this question? Furthermore, TGF-β release from bone has been observed in renal osteodystrophy [33] and while it is mentioned in conjunction with the effects of PTH on bone resorption, it is also possible that it is contributing to muscle wasting associated with the overall condition.

4.2.6. Paget's Disease

Paget's disease, a genetic condition of uncertain etiology, manifests itself primarily as excessive bone resorption. While we know that Pagetic marrow stromal cells release RANK ligand [34], thus stimulating continued osteoclastic resorption, it is unknown what factors are released from bone in this setting that influence metabolism in these patients.

4.2.7. Rare Diseases Which Reduce Bone Resorption

On the other hand, there are certain rare conditions in which bone resorption is lower than normal and the metabolic effect of failure to release bone factors, especially anabolic

ones, such as undercarboxylated osteocalcin, or minerals such as calcium, phosphate or magnesium, may affect the course of the disease. These conditions include osteopetrosis and pycnodysostosis with cathepsin K deficiency [35].

4.3. Therapeutic Implications

Understanding what factors are released from bone and what roles they play in the metabolic changes particular to the conditions in which they occur at the very least will provide a complete metabolic picture of the metabolic consequences of these hyper or hyporesorptive conditions. What we currently know is that metastatic bone disease, especially from breast and lung cancers, and pediatric burn injury can both produce muscle wasting secondary to the release of TGF-β from bone matrix during resorption. We know that the use of an anti-resorptive agent, such as a bisphosphonate can prevent the release of TGF-β in both conditions [24,25] and preserve muscle mass and strength [17,24]. We need to understand how to use pharmaceutical agents in other conditions involving excessive or insufficient bone resorption in order to understand whether bone agents would be useful in those pathologic conditions as well.

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