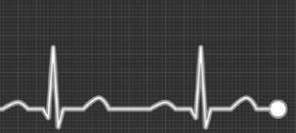

Review Article

Bone Failure in Critical Illness

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Objectives: The origin of systemic inflammatory response syndrome and multiple organ dysfunction syndrome is poorly understood but remains a fundamental concern in the ICU. This paper provides a critical appraisal on whether bone failure may represent an unrecognized component of systemic inflammatory response syndrome/multiple organ dysfunction syndrome.

Data Sources, Data Selection, and Data Extraction: Search of the PubMed database and manual review of selected articles investigating bone pathophysiology in critical illness.

Data Synthesis: Bone hyperresorption is highly prevalent among critically ill patients. Bone breakdown releases numerous systemically active cytokines and bone-sequestered toxins, with the capacity to fuel inflammatory hypercytokinaemia and metabolic toxaemia. Anti-resorptive medication inhibits bone break down and preadmission anti-resorptive use is associated with superior survival among critically ill patients.

Conclusions: We propose that hyperresorptive bone failure is an unrecognised component of systemic inflammatory response syndrome/multiple organ dysfunction syndrome that is causal to critical illness progression. If this hypothesis is valid, bone preservative strategies could reduce the risk of osteoporosis/fractures among ICU survivors, as well as decreasing critical illness mortality. (*Crit Care Med* 2016; 44:2270–2274)

Key Words: bisphosphonate; critically ill; intensive care unit; osteoporosis; vitamin D

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A hallmark of critical illness is the loss of critical organ function, manifesting as multiple organ dysfunction syndrome (MODS) at the most severe end of the spectrum (1). MODS is typically diagnosed when organ-specific parameters deteriorate indicating progressive respiratory, hematologic, hepatic, renal, neurologic and/or cardiovascular failure (1). MODS is also accompanied by hypermetabolism, resulting in a generalised ICU wasting disorder, characterized chiefly by skeletal muscle degradation (2). Although bone constitutes up to 15% of total body weight, loss of bone tissue and/or bone function is not usually considered in the diagnosis of MODS or ICU wasting disorder.

Traditionally, bone has been viewed as inert important only for structural support. Fracture is generally the only recognised manifestation of bone failure. Recent research has however uncovered multiple extra-skeletal functions of bone, mediated via systemic crosstalk through bone-derived factors and bone-responsive paracrine/endocrine axes (3). We herein propose rapid bone loss and bone failure to be unrecognised components of MODS/ICU wasting, with clinically and therapeutically relevant implications.

ELUSIVE ORIGIN OF MULTIPLE ORGAN DYSFUNCTION

The current dogma attributes MODS to be sequential to a primary cause (e.g., sepsis, injury, and hypoperfusion) that triggers an uncontrolled inflammatory response. Various theories have been proposed to explain MODS pathogenesis, including endotoxemia (4), tissue hypoxia (5), dysregulated autophagy (6), as well as endothelial (7) and/or mitochondrial dysfunction (8).

Taken together, these hypotheses present a conundrum—while MODS represents a common endpoint of diverse critical illness, it remains unclear what propagates uncontrolled inflammation, or represses a compensatory anti-inflammatory response (9, 10). Furthermore, while ICU care has improved over time, the rates of systemic inflammatory response syndrome (SIRS)/MODS have actually increased; from 13% to 78% between 1998 and 2009 (11). Increased incidence of SIRS/MODS despite the availability of wide-spectrum antibiotics, renal replacement therapy, comprehensive nutritional treatment, and cardiorespiratory/vascular support regimes suggest the unidentified perpetuator may not be directly attributed to sepsis and/or renal/cardiac/respiratory/vascular failure. Additionally, MODS lasts days to weeks (12), while circulating

proinflammatory cytokines generally fall rapidly over the first week of ICU admission (13), suggesting that a yet-to-be identified continuous perpetuator, uncorrected by current ICU therapeutic measures, must be responsible for the sustained inflammatory response.

Telling clues to the identity of this perpetuator, including its chronicity, the noninclusion within current MODS diagnosis, its escape from modern ICU therapeutic coverage and its strong bidirectional link with immune dysfunction, have led us to hypothesize rapid bone loss to be the perpetuator.

CRITICAL ILLNESS FUELLING BONE HYPERRESORPTION

Bone physiology is seldom investigated in critical care. We searched PubMed for studies investigating bone status during critical illness (keywords: bone and critical illness). Original studies with bone status characterization (i.e., bone turnover markers and/or bone density) in critically ill patients are included. We herein formulate the concept of critical illness bone failure drawing evidence from the 10 original studies that met these criteria (14–23).

The first reports appeared 2 decades ago entailing measurement of bone turnover markers (15, 16), which are collagen breakdown products released from bone remodelling detectable in blood and/or urine. Bone turnover is a constant process during which bone is torn down (resorption) and then rebuilt (formation), two processes that are normally tightly coupled and underpin the ability of bone to respond to stress as well as allowing microfracture repair. A rise in collagen products made when new bone is laid down (e.g., N-terminal propeptide of type 1 procollagen [P1NP]) signifies bone formation, while an increase of those involved in bone degradation (e.g., N-telopeptide of type 1 collagen [NTX]) represents bone resorption. Excursions of formation relative to resorption markers thus provide information on dynamic bone status. For example, a greater rise in resorption relative to formation markers represents a hyperresorptive state, and is predictive of bone loss, as observed among osteoporotic postmenopausal women and vitamin D deficient patients.

From published ICU bone studies (15–21), bone resorption markers were 4–8 times above the reference range, evident within 24 hours of ICU admission, and remained elevated beyond 1 month (**Fig. 1**). The rise in bone resorption was evident as early as the first day of ICU admission, suggesting bone responds rapidly to critical illness insult and hyperresorption could have begun pre-ICU admission. In contrast, bone formation was disproportionally suppressed; with bone formation markers clustering slightly above or within the lower limit of normal reference ranges (Fig. 1). These changes suggest uncoupled bone hyperresorption, found in 85–90% of ventilator-dependent patients (15, 16). Immobilisation, hyperparathyroidism, and hypercytokinemia are proposed contributors to hyperresorptive physiology. The lack of bone anabolic compensation has been attributed to vitamin D deficiency, glucocorticoid therapies, and dampened hypothalamic/pituitary hormone pulsatility (20, 21).

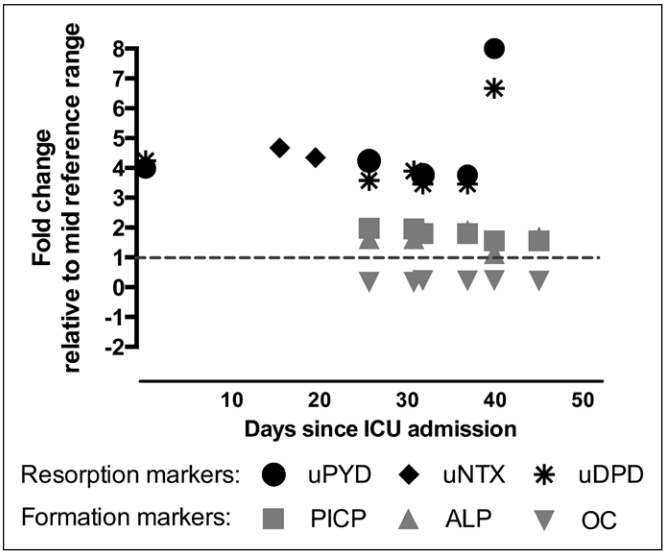

Figure 1. Bone turnover and critical illness. Summary of changes in bone turnover markers during critical illness (days since ICU admission) across published studies (15–21). Measurements were performed on one or more occasions during ICU admission among studies. Each data point represents one measurement reported from one study on a particular day of ICU admission. *Dotted line* represents fold change of 1 (i.e., no change from mid-reference range). ALP = serum bone-specific alkaline phosphatase, OC = serum osteocalcin, PICP = serum carboxyl-terminal extension peptide of type 1 procollagen, uDPD = urinary deoxypyridinoline, uNTX = urinary collagen type 1 cross-linked N-telopeptide, uPYD = urinary pyridinoline.

The most obvious concern arising from bone hyperresorption is bone loss. Not surprisingly, bone mineral density loss heightens in the year after admission to ICU (17). While this highlights health concerns, such as fractures and rehabilitation potential, an intriguing question is whether bone hyperresorption impacts acute critical illness severity and outcome. If we accept bone turnover markers as indices of bone function, then bone loss is highly prevalent among critically ill patients and could fall within the spectrum of MODS. The key question then becomes whether hyperresorptive bone failure is causal to or merely associated with progression and severity of MODS.

HYPERRESORPTIVE BONE FAILURE FUELLING MULTIPLE ORGAN DYSFUNCTION

In addition to its core role in structural support, bone exhibits two less well-recognised functions; namely, bone is also an endocrine organ (24) and "a toxin-sequester" (25). These extraskeletal functions could have multiple organ modulatory effects during acute illness.

First, some of the resorptive products released from bone signal to other tissues thereby restoring systemic homeostasis. For example, osteocalcin, a bone formation product released from osteoblasts, appears to stimulate pancreatic β-cells in mice leading to glucose lowering (26). In contrast, osteopontin secreted by osteoclasts (27) is a potent neutrophil chemotactic agent. Experimental lipopolysaccharides administration in healthy volunteers increased osteopontin levels (28), and osteopontin is capable of up-regulating a full innate immune programme critical in reconfiguring tissue integrity (29). Second,

bone sequesters toxic compounds, including lead, cadmium, and other heavy metals (30). High bone turnover increases the release of lead into the systemic circulation among postmenopausal women (25). Lead and cadmium are known to induce gastrointestinal and pulmonary inflammation in murine models (31, 32). Collectively, it is tempting to speculate hyperresorptive end products, such as osteopontin, and bone-sequestered toxin, such as lead and cadmium, could fuel systemic inflammation and toxemia (33, 34). On the other hand, a state of relative bone formation suppression, manifesting as low osteocalcin levels, may contribute to dysmetabolic states, such as hyperglycemia. Recent studies have indeed reported increased plasma osteopontin and urinary cadmium levels to be predictive of mortality in critically ill patients (35, 36), thus implicating hyperresorption in MODS pathogenesis (**Fig. 2**).

BONE AND ICU-ACQUIRED WEAKNESS

What about bone and ICU-acquired weakness? Recent studies have unveiled crosstalk between bone and nervous system through osteo-innervation (37), as well as bone and muscle via myokines (38). ICU polyneuropathy and myopathy are features of ICU-acquired weakness. These may increase bone resorption because of weakness-associated immobilisation.

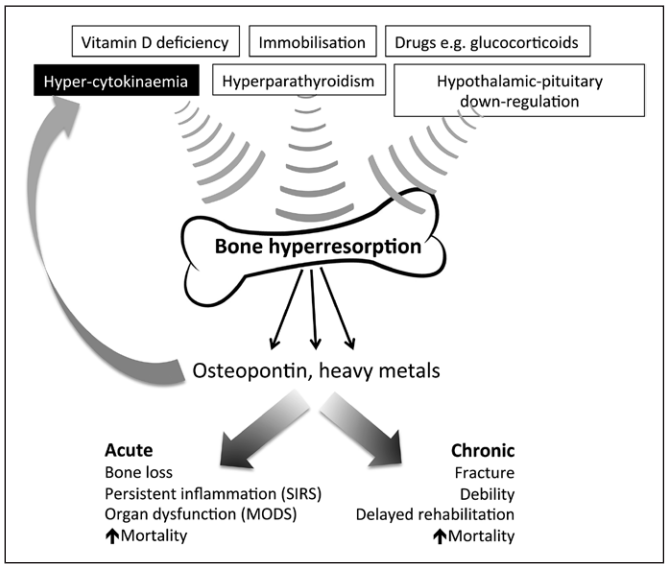

Figure 2. Schematic diagram depicting bone hyperresorption cascade and systemic inflammation interplay. Immobilisation, vitamin D deficiency, hyperparathyroidism, down-regulation of hypothalamic-pituitary pulsatility and medications such as glucocorticoids are causes of bone hyperresorption. Systemic inflammation arising from infection, tissue injury, ischemia, and/or hypoxemia produces hypercytokinemia. Mediators such as tumor necrosis factor-α, interleukin (IL)-1, and IL-6 stimulate osteoclastogenesis while dampening osteoblastogenesis, resulting in uncoupled bone hyperresorption. Uncontrolled bone breakdown releases resorptive bone markers, such as deoxypyridinoline, pyridinoline, and collagen type 1 cross-linked N-telopeptide. Osteoclasts secrete cytokines, such as osteopontin, that has direct chemotactic and immune-activating function, thereby propagating a feed-forward proinflammation-hyperresorption milieu, sustaining hypercytokinemia and fuelling systemic inflammatory response syndrome (SIRS) and multiple organ dysfunction syndrome (MODS). This could be further worsened by escape of bone-sequestered toxin into systemic circulation, such as lead and cadmium, causing toxemia. These result in both acute and chronic deleterious consequences and could potentially increase mortality.

Bone failure may also arise from disruption to bone-neural interaction and/or skeletal secretion of bone-responsive myokines. Alternatively, bone may serve a paracrine modulatory role in muscle preservation as inhibition of bone resorption attenuates muscle loss after burn injury (39).

AN EVOLUTIONARY PERSPECTIVE

So is bone hyperresorption intrinsically harmful, or is it an adaptive response to critical illness? Before the availability of contemporary intensive care in the 1950s, survival of critically ill patients was determined by allostasis, the ability of the patients to restore homeostasis through systemic inflammatory response and immune-neuroendocrine axis modulation (40). Maximal immune up-regulation therefore benefits survival. Accordingly, the release of bone-derived chemotactic and immune-activating factors, such as osteopontin, is evolutionarily life sustaining in the absence of other therapeutic measures. Yet in the modern ICU era, the availability of organ support and antibiotics has relieved the sole reliance on intrinsic allostatic responses for survival. This disengagement of allostasis could contribute to exaggerated inflammation leading to off-target organ damage.

We propose bone hyperresorption to be an intrinsic allostatic regulator of hypercytokinemia through the release of immune-activating osteoid-associated factors. Just as osteopontin exhibits multi-faceted immune-modulatory effects (41), other yet to be discovered "osteo-kines" could influence systemic immune "milieu" thereby impacting clinical outcomes. Indeed a number of circulating factors, such as fibroblast growth factor (FGF) 21 and FGF23, have been implicated in bone loss, energy homeostasis, and critical illness (42–44).

TESTING THE HYPOTHESIS

To validate this hypothesis, inhibition of bone hyperresorption should not only reduce bone loss but also dampen overall systemic inflammation and perhaps even translate into survival benefit. In contrast, uncontrolled bone breakdown would fuel hypercytokinemia and increase mortality. Critical illness encompasses diverse etiologies and a complicated clinical course, so it is unlikely a single dominant factor will be universal across all patients. Rather, the significance of bone failure could be magnified in modern ICU because other organ dysfunction can be partially or completely ameliorated by currently available management strategies and therapeutics.

Tantalising evidence supporting this hypothesis has begun to emerge. Vitamin D deficiency increases bone resorption and a significant proportion of critically ill patients are vitamin D deficient (45, 46). Vitamin D supplementation has been shown to improve survival in the most severely deficient patients (47). Preadmission treatment with bisphosphonates, potent anti-resorptive agents, is associated with improved survival among critically ill patients (14). Neither study included measurement of bone turnover or heavy metals in relation to cytokine profiles. However, as expected, bone loss was attenuated among bisphosphonate-treated patients by over 60%, and

patients who died manifested the greatest degree of bone loss (14). These studies therefore provide a foundation supporting regulatory links between bone resorption and critical illness survival.

A prospective study randomising patients to anti-bone resorptive treatment will shed insight on the importance of bone failure in ICU. However, there are major challenges to such a study. Bone turnover markers depend on baseline bone status. Bone mineral density measurement by dual energy absorptiometry is rarely available and probably unrealistic in unstable ICU patients. Bisphosphonate treatment may precipitate hypocalcaemia especially among vitamin D deficient patients (48). Given the high prevalence of hypovitaminosis D among critically ill patients (49, 50), vitamin D treatment must be incorporated into randomised trial design. These practical, logistic, and safety concerns will necessitate a well-resourced, sufficiently powered, multi-centre trial involving patients who are adequately bone-phenotyped.

CONCLUSION

If this bone failure hypothesis is valid, it will not only advance our current concept of organ dysfunction and systemic inflammation in ICU but will also provide a new therapeutic target in critical illness. It is sobering to realise new drugs entering clinical trials targeting immune system on the surface may be unable to smother the cytokine storm if the fire fuelling the inflammation originates deep within the skeleton.

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