



COMMENTARY

Does vitamin D deficiency contribute to post-burn bone loss?

[v1; ref status: indexed, <http://f1000r.es/QLDkCs>]

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v1 **First Published:** 28 Nov 2012, 1:57 (doi: 10.12688/f1000research.1-57.v1)
Latest Published: 28 Nov 2012, 1:57 (doi: 10.12688/f1000research.1-57.v1)

Abstract

Burn injury results in the acute loss of bone as well as the development of progressive vitamin D deficiency. Bone loss occurs acutely due to resorption, which is then followed by apoptosis of osteoblasts preventing repair of the bone loss. The acute resorption is due to a combination of the inflammatory response and the stress response to the burn injury. The resultant production of inflammatory cytokines and endogenous glucocorticoids initially stimulate the osteoblasts to produce RANK ligand, which stimulates marrow stem cell differentiation into osteoclasts. As the stress response persists for approximately one year post-burn the glucocorticoids produced by the body will cause osteoblast apoptosis and adynamic bone, impairing the ability of bone to recover its resorptive losses. The vitamin D deficiency is due to the failure to supplement the diet of burn patients with vitamin D on discharge from hospital and to failure of the skin to make normal quantities of vitamin D on sunlight exposure. Because the bone resorption can be prevented by the acute administration of bisphosphonates it is unlikely that vitamin D deficiency is responsible for the early-onset bone loss following burns. However, because a deficit in trabecular bone remains for at least two years post-burn, it is possible that vitamin D deficiency prevents the recovery of trabecular bone density over the long term.

Article Status Summary

Referee Responses

Referees	1	2	3
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1	Dominique Garrel , Hotel Dieu de CHUM Hospital Canada		
2	Daniel Bikle , University of California/VAMC USA		
3	Jon Tobias , Bristol Royal Infirmary UK		

Latest Comments

No Comments Yet

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How to cite this article: Klein GL (2012) Does vitamin D deficiency contribute to post-burn bone loss? [v1; ref status: indexed, <http://f1000r.es/QLDkCs>] *F1000Research* 2012, 1:57 (doi: 10.12688/f1000research.1-57.v1)

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Grant information: This work was supported in part by grants from the Shriners Hospitals for Children and by the National Institutes of Health 1P50 GM60338.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The author has served on the Bone Toxicity Advisory Board for Novartis Pharmaceuticals, August 2012.

First Published: 28 Nov 2012, 1:57 (doi: 10.12688/f1000research.1-57.v1)

First Indexed: 30 Nov 2012, 1:57 (doi: 10.12688/f1000research.1-57.v1)

Commentary

Children who have been severely burned develop a progressive vitamin D deficiency¹ as characterized by low circulating levels of 25-hydroxyvitamin D (25(OH)D) between 14² and 24 months post-burn with normal circulating levels of 1,25-dihydroxyvitamin D (1,25(OH)₂D). Unlike rickets there is no compensatory rise in 1,25(OH)₂D and this may be due to persistent low serum parathyroid hormone (PTH) concentrations^{2,3}. The hypoparathyroidism is likely due to a persistent post-burn up-regulation of the parathyroid calcium sensing receptor^{3,4}. By 7 years post-burn, there is a continued reduction in serum levels of 25(OH)D in all patients but now there is also a reduction in circulating concentrations of 1,25(OH)₂D¹.

There are at least two reasons for this progressive deficiency. The first explanation is that burn patients are not routinely given vitamin D supplements following hospital discharge¹ and even if they are given a standard amount of vitamin D supplementation, i.e. 400 international units per day, for six months post-burn, serum levels of 25(OH)D are found to be in the “insufficient” range, approximately 20 ng/ml⁵. Therefore, the proper dose of vitamin D to administer to these children is unknown. The second explanation is that following burn injury, not only the burn scar tissue but also the adjacent normal-appearing skin cannot convert normal quantities of the precursor 7-dehydrocholesterol (7DHC) to vitamin D₃ when subjected to UVB irradiation². Moreover, the epidermal cells both in burn scar tissue and in adjacent normal-appearing skin contain subnormal quantities of 7DHC suggesting abnormalities in cholesterol biosynthesis in skin following burn injury².

Bone loss following burn injury can be attributed to least two non-specific adaptive responses: the inflammatory response and the stress response. Both occur as a result of the destruction of skin, which is an important barrier to infection. The inflammatory response involves significant elevations of circulating cytokines, especially interleukin (IL)-1 β and IL-6⁶. The stress response is characterized by a 3–8-fold rise in endogenous glucocorticoid production as measured by urine free cortisol excretion^{6,7}. Acutely, both processes stimulate osteoblast production of the ligand of the receptor activator of NF κ B (RANKL), which then stimulates marrow stem cell differentiation into osteoclasts and results in increased bone resorption. The success of acute intravenous administration of bisphosphonates either as a single or once-repeated dose in preventing the bone loss⁸ is evidence that this is the case. Because the stress response is sustained for as long as one year post-burn, persistence of the elevated endogenous production of glucocorticoids leads to osteoblast and likely osteocyte apoptosis and reduction of marrow

stromal cell differentiation into osteoblasts⁷. Thus the now adynamic bone cannot recover the deficit caused by the acute resorption. It is only after the stress response has dissipated after about one year post-burn, that remodeling resumes⁹.

Because the intravenous administration of bisphosphonates prevents the acute bone loss entirely⁸ for up to two years⁹, it is highly unlikely that the documented vitamin D deficiency plays a role in the immediate post-burn bone loss. Moreover, we have also shown that, at least acutely, there are low circulating levels of both vitamin D binding protein and albumin¹⁰, with albumin recovering by 6 months post-burn⁵. Therefore, whether there is true vitamin D deficiency during the first six months post-burn is difficult to determine. Nevertheless, what we do see in these burn patients is that by two years post-burn, cortical bone deficits, as measured by total body bone mineral content, in those not receiving acute bisphosphonate therapy recover to the level of those who did receive bisphosphonates⁹ while the deficit in trabecular bone, as measured by lumbar spine bone density, persisted^{9,11}.

A recent report by Zhou *et al.*¹² has shown that in adult human marrow stromal cell culture, the clinical conditions under which the bone biopsies were obtained influenced the ability of the stromal cells to differentiate into osteoblasts in response to 1,25(OH)₂D. In particular it was noted that vitamin D deficiency impaired this differentiation. This finding raises the possibility that progressive vitamin D deficiency as experienced by children post-burn may explain the persistence of their trabecular bone deficit, although why vitamin D deficiency would uniquely affect trabecular bone is not at all clear. Perhaps future studies looking at the differential effects of vitamin D on cortical and trabecular bone might determine whether this hypothesis is viable.

Competing interests

The author has served on the Bone Toxicity Advisory Board for Novartis Pharmaceuticals, August 2012.

Grant information

This work was supported in part by grants from the Shriners Hospitals for Children and by the National Institutes of Health 1P50 GM60338.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Current Referee Status:



Referee Responses for Version 1



Jon Tobias, Musculoskeletal Research Unit, Bristol Royal Infirmary, Bristol, UK

Approved with reservations: 22 January 2013

Ref Report: 22 January 2013

My reservations are as follows:

1. Since children are not routinely supplemented with vitamin D, the lack of vitamin D supplementation in burn victims is not in itself an explanation for their low vitamin D levels.
2. The assertion that elevated endogenous glucocorticoids contribute to bone loss in this context, through inhibition of osteoblast survival and generation, is somewhat over-stated. Although adverse effects of glucocorticoids on osteoblast function are well described, the literature mainly applies to pharmacological doses of glucocorticoid. The evidence cited here, concerning possible adverse effects of endogenous glucocorticoids, relates to a small observational study which provides weak circumstantial evidence at best.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Competing Interests: No competing interests were disclosed.

1 Comment

Author Response

Gordon Klein, Department of Orthopaedic Surgery and Rehabilitation and Shriners Burns Hospital, University of Texas, Medical Branch, USA

Posted: 30 Nov 2012

The comments from Dr Tobias are greatly appreciated. If I did not make it clear in the commentary I listed two contributory factors to post-burn vitamin D deficiency. The failure to supplement is not of itself a causative factor, I agree, but the fact that the skin cannot make vitamin D normally on exposure to UVB radiation coupled with the lack of routine supplementation means that the burn victims have no way to compensate for the skin's failure to normally synthesize vitamin D3 from its precursor.

With regard to the comment on endogenous glucocorticoids clearly Dr Tobias is correct in stating that the literature on glucocorticoid-induced osteoporosis relates to the exogenous administration of glucocorticoids. The studies that I have cited, albeit they are my own, demonstrate that the body produces large quantities of endogenous glucocorticoids in response to stress, coupled with lack of surface osteoblasts and a reduction in markers of osteoblast differentiation in marrow stromal

cells taken from the burn victims as compared to unburned controls. The point to be emphasized, I believe, is that currently there is no way to equate the quantity of endogenous glucocorticoids produced in response to stress with the dosage of glucocorticoids given as therapy. In the absence of work corroborating our observations I raise the issue of similar effects of endogenous and exogenous glucocorticoids in order to increase awareness that in the case of burns at least the classic manifestations of glucocorticoid induced osteoporosis also exist in children who did not receive exogenous glucocorticoids, I would certainly agree that more studies in this area and in different conditions in which a patient is subject to stress would help clarify the situation, but I would not dismiss the argument for lack of evidence.

Competing Interests: No competing interests were disclosed.



Daniel Bikle, Department of Medicine and Dermatology, University of California/VAMC, San Francisco, CA, USA

Approved: 30 November 2012

Ref Report: 30 November 2012

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.



Dominique Garrel, Endocrinology Department, Hotel Dieu de CHUM Hospital, Montreal, Canada

Approved: 28 November 2012

Ref Report: 28 November 2012

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Competing Interests: No competing interests were disclosed.
