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Review article

Calcemic response to burns differs between adults and children: A review of the literature

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ABSTRACT

Objectives: The calcemic and parathyroid hormone (PTH) responses to severe burn injury appear to differ between children and adults. In our limited studies children exhibited hypocalcemic hypoparathyroidism consistent with up-regulation of the parathyroid calcium-sensing receptor (CaSR) while adults did not, suggesting a developmental cutoff in cytokine-mediated up-regulation of the CaSR. This difference may be clinically important as published studies indicate that extracellular calcium (Ca) may stimulate the inflammatory response. The aim of this study was to examine the existing literature on burns to see if the differences between pediatric and adult calcemic and PTH responses to burn supported our findings providing stronger evidence to support this developmental difference.

Methods: We reviewed the National Library of Medicine database using the terms burns, PTH and ionized calcium and found 9 articles from 8 different medical centers; one was eliminated due to mixing of adults and children.

Results: There were 245 burn patients reported from the literature, 178 pediatric and 67 adults. The data are mostly consistent with our reported findings. Of the 10 pediatric patients with severe burns that we studied, mean ionized Ca concentration was below the lower limit of normal of 1.10 mM. The 67 adult burn patients reported in the literature had a mean blood ionized Ca concentration that was within the adult normal range or was lower than normal but with secondary hyperparathyroidism. Moreover, serum PTH concentrations were uniformly low in the 178 children in the burn literature but normal or mildly elevated in the 67 adults.

Conclusions: These results support the hypothesis that the difference between pediatric and adult victims is consistent with an age-related CaSR response to cytokine stimulation and may be consistent with a lower level of inflammation in children. Ionized Ca and PTH might serve as possible therapeutic targets to lower the inflammatory response in burn victims.

1. Introduction

Severe burn injury incurs a hypermetabolic response including an acute inflammatory response that causes resorptive bone loss [1] and a stress response that involves increased endogenous glucocorticoid production, which contributes to hypodynamic or adynamic bone at approximately 2 weeks following severe burn injury in children [2,3]. In the study of the metabolic response to burn injury we found that children and adults had a different calcemic response to burn injury (Fig. 1).

From our work, children present with sustained hypocalcemia, hypomagnesemia, and hypoparathyroidism [4] consistent with cytokine-mediated up-regulation of the parathyroid calcium-sensing receptor (CaSR) [5–7] while adults in general present with either normocalcemia or mild hypercalcemia [8]. The reason for this discrepancy is uncertain but one possibility could be that cytokine-mediated up-regulation of the CaSR is age-related.

This difference, if real, may be clinically important, inasmuch as we previously reported that *in vitro* calcium (Ca) affects chemokine production by normal human peripheral blood mononuclear cells

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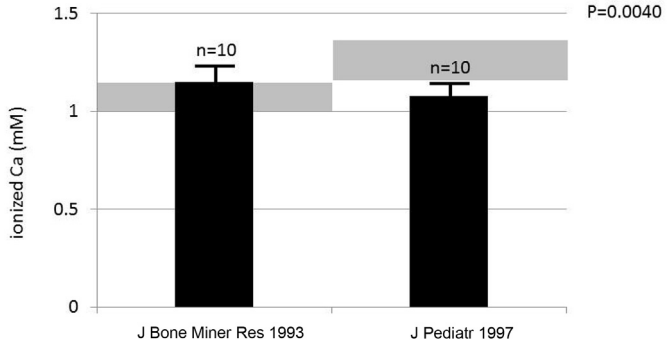

Fig. 1. Mean and standard deviations of pediatric values from publication Klein et al. [4] (J Pediatr 1997) and Klein et al. [8] (J Bone Miner Res 1993) depicting blood ionized Ca 2 weeks following burn injury. The difference between pediatric and adult burn victims is significant (P = 0.0040). The grey areas surrounding each bar represent the normal range.

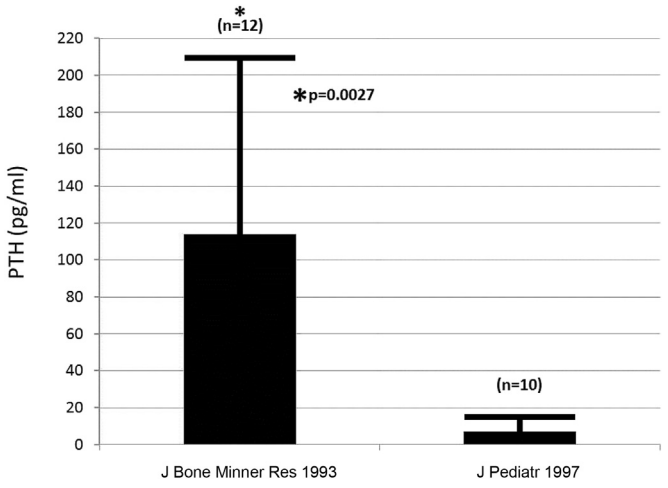

Fig. 2. Mean and standard deviations of pediatric values from publication Klein et al. [4] (J Pediatr 1997) and Klein et al. [8] (J Bone Miner Res 1993) depicting serum parathyroid hormone (PTH) concentrations 2 weeks following burn injury. The difference between pediatric and adult burn victims is significant (*P = 0.0027 compared to pediatric values).

[9]. This finding raises the possibility that cytokine-mediated bone resorption with consequent liberation of calcium into the blood could prolong or intensify the inflammatory response and up-regulation of the CaSR may blunt that effect. Moreover, Rossol et al. [10] had previously reported that extracellular calcium activates the nod-like receptor subtype P3 (NLRP3) inflammasome, eliciting the increased production of interleukin (IL)-1β both *in vitro* and *in vivo*. The NLRP3 is the largest of 4 molecular pattern recognition receptors or inflammasomes, which are caspase containing oligomers that are expressed in myeloid cells and are a component of the innate immune system. They aid in the production of IL-1 and IL-18.

The amount of data we have published is not adequate to answer whether or not there is evidence that cytokine-mediated up-regulation of the CaSR is developmentally regulated. Because other studies in the literature may be able to provide additional evidence to support our observation, the aim of this study was to undertake a literature review to see how much data there might be to support our hypothesis.

2. Methods

We accessed the National Library of Medicine database (PubMed) for all publications in English using the search terms of burns, parathyroid hormone, and ionized calcium levels in the blood of patients who were burned greater than 20% of total body surface area. We tried to avoid using multiple articles from the same medical center in order to diversify the patient population and avoid weighting the data in favor of one center over another. Similarly, we avoided combining data from various institutions given the differences in assays and normal ranges associated with them. The only statistics performed were unpaired *t* tests of ionized Ca (Fig. 1) and PTH (Fig. 2) between children and adults studied at our own institution.

3. Results

Nine papers met the search criteria (Table 1) involving 178 children and 67 adults. Two of them were from the same institution because necessary data were reported separately [11,12]. Inasmuch as the papers were limited to at most two per institution that covered the required data there was minimal opportunity for selection bias. A paper by Sobouti et al. [13] included 118 pediatric subjects but half of the study subjects had burns between 1% and 30% total body surface area. This was the only pediatric paper we encountered that published data on patients with minor burns. In this paper the ionized Ca values were at odds with our own findings although the PTH values were consistent with our report and that by Gottschlich et al. [11]. Moreover, while the ionized Ca data in the Sobouti paper were in the normal range for the assays we use, the normal range of the assay used in that paper was not given or referenced. The one paper eliminated was by Szyfelbein et al. [14], which included subjects ages 6–75 years without stratifying the results obtained in children and adults. That left 4 papers analyzing data from children: that by our group at Shriners Burns Hospital in Galveston, which studied 10 pediatric subjects [4], and those by Gottschlich et al. [11] and Mayes et al. [12] from Shriners Burns Hospital in Cincinnati, which studied 50 subjects, giving a total of 60 subjects in all and the one by Sobouti et al. [13] adding another 118 subjects. For the adults there were 4 studies, that from our institution [8] and that of Rousseau et al. [15] from Belgium and those by Lovén et al. [16] from Sweden and Dolecek et al. [17] from the Czech Republic. The total number of adult subjects from these four studies was 67.

In these subjects, ionized Ca remained in the normal range in the Galveston patients [8] and those of Rousseau et al. [15] but were either low or in the normal range in the subjects studied by Lovén et al. [16] and Dolecek et al. [17]. However, in the paper of Lovén et al. [16] urinary phosphate was elevated and urine calcium excretion was low suggesting that the patients in that study [16] were functionally hyperparathyroid. In the paper of Dolecek et al. [17] PTH was normal in the face of low ionized Ca concentration. Functional hyperparathyroidism is also consistent with data from the study of Rousseau et al. [15] which found blood concentration of fibroblast growth factor (FGF)-23 to be high, while in pediatric burn patients from our institution, FGF-23 was undetectable [18], suggesting functional hypoparathyroidism. When blood PTH concentrations were compared in the Galveston studies of children [4] and adults [8] the PTH in the children was significantly lower (Fig. 2).

Moreover, in the pediatric burn patients we studied [4] as well as in those studied by Gottschlich et al. [11], the mean serum intact PTH concentrations were below the lowest level of the normal range of each assay for age indicating that pediatric burn patients were hypoparathyroid. Surprisingly, even the PTH values in the