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Bone Metabolism in Pediatric Burned Patients: A Review

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Abstract

Burn injuries in pediatric patients can lead to growth delays, bone loss, and wasting of lean body mass and muscle with subsequent long-term effects such as osteoporosis. The following review examines eleven randomized, placebo-controlled prospective clinical trials in pediatric burns between 1995 and 2017. These studies included approximately 250 burned pediatric subjects in total, and they were conducted in order to evaluate the impact of burn injury on markers of bone formation and bone metabolism. Some trials also analyzed current therapy regimens such as pamidronate and vitamin D. The clinical utility of these outlined biomarkers is uncertain with respect to acute burn care as the current literature remains unclear. This review thus serves to address the impact of burn injury on markers of bone formation and bone metabolism in pediatric patients, but will not focus on the clinical utility of the markers. It is the goal of this review to summarize the findings of the trials to guide the future care of burned patients in order to maximize their bone recovery.

Keywords

bone metabolism; vitamin D; burns; osteocalcin; calcium; aluminum; type I collagen; bone morphogenic protein-2; urine-free cortisol; parathyroid hormone; vitamin D; sclerostin

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Conflicts of Interest

No conflicts of interest declared.

INTRODUCTION

Severe burn injuries in pediatric patients can cause growth delays, bone loss, and wasting of lean body mass and muscle [1–3]. The risk of fractures is increased post burn, particularly because of the reduced bone mass and possibly secondary to slowed growth velocity [4, 5]. This effect can be attributed to the significant increase of endogenous glucocorticoid secretion as well as the increase in pro-inflammatory cytokine production [6]. Additionally, the bone mass decrease may also be attributed to hypoparathyroidism and calcium wasting, as well as a consistent vitamin D deficiency [4, 7–12].

Within six weeks of burn injury, lumbar spine bone density in trabecular bone is reduced by 7% of admission bone mass with no improvement seen during 2–5 year follow up [5, 13]. Additionally, a 3% loss of total body bone mineral content, which is primarily cortical bone, appears to recover between 18–24 months post-burn [13]. With no apparent improvement in trabecular bone mass, severely burned patients face increased risk for reduced peak bone mass and therefore are possibly at greater risk for osteoporosis in adulthood. Annual extrapolated fracture incidence for those patients followed for 5 years post-burn is twice that of age-matched unburned males and 50% higher than in age-matched unburned females [5].

The following review outlines the key biomarkers in bone metabolism and remodeling after burn injury in pediatric patients. Specifically, it will describe the results obtained from eleven clinical trials in burns that measured inflammatory markers, glucocorticoids, urine-free cortisol, osteoblast and osteoclast activity, osteocalcin, aluminum, bone morphogenic protein-2, calcium, copper and zinc, magnesium, parathyroid hormone, sclerostin, type I collagen, and 25-hydroxy Vitamin D as markers of bone formation. The uncertain clinical utility of these outlined biomarkers during acute burn care has been questioned as the current literature remains unclear [14]. This review serves to address the impact of burn injury on markers of bone formation and bone metabolism in pediatric patients, but will not focus on the clinical utility of the markers.

METHODS

Our review examines eleven randomized, placebo-controlled prospective clinical trials in pediatric burns between 1995 and 2017. To obtain these eleven studies, a PubMed search was conducted using the terms “vitamin D”, “burns”, “pediatric”, “children”, and “bone” in various combinations. We limited the selections for our review to studies that were prospective placebo controlled trials conducted between 1995–2017. We were interested in the effect of vitamin D supplementation on key biomarkers in bone metabolism and remodeling after burn injury; specifically: inflammatory markers, glucocorticoids, urine-free cortisol, osteoblast and osteoclast activity, osteocalcin, aluminum, bone morphogenic protein-2, calcium, copper and zinc, magnesium, parathyroid hormone, sclerostin, type I collagen, and 25-hydroxy Vitamin D. While each of these biomarkers has received its own section in this review and we attempted to isolate information regarding these biomarkers to their respective sections, this proved difficult as they interact and are often correlated with one another. As a result, an attempt was made to include the information in the most suitable section without unnecessarily repeating information. We attempted to control for

bias by only including studies that disclosed their bias risk and the impact on results. We independently reviewed the results of each study to extract and organize their results. Once extracted, results from each study were organized into the Table 1 which is included in this review for comparison.

RESULTS

Inflammatory Markers

IL-1, IL-6, and acute phase reactants are all considered markers of inflammation. These markers, particularly IL-6, are significantly elevated in burned patients [4]. It has previously been shown that the residual bone resorption that occurs after burn is likely to result from the high circulating levels of resorptive cytokines (IL-1, IL-6), which may further stimulate production of endogenous corticosteroids [4].

Glucocorticoids

In 2004, a study was performed to assess if increased production of endogenous glucocorticoids contributes to the bone loss in pediatric patients (n=17, TBSA ≥40%) by bone histomorpometry evaluation [7]. Subjects were also assessed for features of bone loss secondary to corticosteroid use, such as reduced number of osteoblasts and down-regulation of the bone receptor for glucocorticoids. Additionally, subjects were evaluated for markers of osteoblastic differentiation, which are known to decrease as a result of glucocorticoid toxicity. At approximately 3 weeks post-burn, bone biopsies from each of the subjects were taken for study. The evaluation of type-I collagen mRNA in the burned subjects did yield a statistically significant reduction ($p<0.01$) compared to unburned subjects.

Urine Free Cortisol

As cortisol is widely recognized as a stress response hormone, urinary free cortisol is often measured as a marker of stress in the burned patients. An eightfold elevation in urinary free cortisol excretion beyond the upper limits of normal was found. An inverse relation between mean urinary free cortisol and osteoid area ($r = -0.57$, $p<0.05$) was reported, but no correlation was found with biochemical markers of bone formation [4].

Osteoblast and Osteoclast Activity

The homeostasis of bone relies on the intricate relationship between the resorption of bone secondary to osteoclasts, and the formation of bone by osteoblasts [24]. Additionally, the maturation process of osteoclasts is dependent on the stimulation of RANK by the RANK ligand expressed on osteoblasts [24]. Measuring the activity of these two cell lines can be utilized to evaluate the formation of bone. A 1995 study found 60% of the severely burned patients with age-related BMD z scores less than −1, and 27% of severely burned patients with BMD age-related z scores of less than −2 [5]. Thirty one percent of the patients labeled as moderately burned, presented with z scores less than −1, but only 6% had z scores less than −2. Biochemical studies demonstrated an initial decline in the rate of bone formation with an elevation in the rate of resorption, and persistenly low formation when observed long-term.

Burned patients have been shown to have a decreased bone formation and mineral apposition rate, reduced osteoblast differentiation, along with lowered osteoclast surfaces, osteoid area, surface, and width. Additionally, Klein *et al* found no detectable osteoblasts at the osteoid seam with bone formation, along with low levels of the resorptive markers urinary pyrinoline and deoxypyridinoline [4]. Bone area and eroded surface did not vary from unburned subjects [7, 17]. Following burn injury, it takes approximately one year for remodeling to resume [17]. Additionally, severely burned pediatric patients are growth impaired for up to three years following the burn injury, indicating that it make take several years for cortical and trabecular bone to fully recover. [17].

Osteocalcin

Osteocalcin is often measured in serum when evaluating bone formation. As an osteoblast specific protein, osteocalcin is thought to play a role in the mineralization of bone and calcium ion homeostasis [25]. Thus, when osteocalcin levels are low, the rate of bone formation is subsequently low as well. Four independent studies that measured osteocalcin reported significantly reduced serum concentrations in burned patients compared to matched, unburned patients [4, 5, 10, 17]. One of these studies also reported that in a 7-year follow-up of burned patients, osteocalcin was significantly low in nine out of twelve patients [10]. The reduction in osteocalcin is indicative of decreased bone formation.

In 1995, Klein et al reported bone mass deficit continued following burn injury, and in moderately (total body surface area [TBSA] 15–36%) to severely (TBSA >40%) burned children and adolescents the corresponding decline in bone mass was correlated with increase in fracture frequency (n=68) [5] Bone biopsies from their study revealed both a reduction in unmineralized osteid area as well as reduced bone formation [5]. Patients were surveyed for fractures post injury and following their release from the hospital. Fracture location and circumstances under which the fractures occurred were noted. Although not statistically significant, evidence of increased fracture incidence following discharge was reported. Levels of osteocalcin were also found to be low in the burned patients. Prior to this study, bone turnover in young adult burn patients had not been reported.

Also in 1995, a study characterized the acute histologic response of bone following burn injury in pediatric subjects (n=24, 6–18 years, mean TBSA 63%). Additionally biochemical markers of bone formation and bone resorption were compared with histologic changes to the bone [4]. Each week, samples of urine and serum were obtained from the first two to three weeks post admission until an intraoperative biopsy sample of iliac crest bone was collected an average of 26 days post-burn. Serum osteocalcin levels were also found to be significantly reduced.

Parathyroid Hormone (PTH)

PTH is a hormone secreted by the parathyroid gland that is essential to bone metabolism and remodeling. PTH establishes both mineral and skeletal homeostasis by influencing calcitropic activities in the kidneys, gastrointestinal system, and bone [31]. Bone resorption follows elevations in PTH as osteoclasts are indirectly activated. Several studies analyzed the levels of PTH in burned patients, with conflicting results. The inflammatory response

resulting from burn injury leads to up-regulation of the parathyroid CaSR [31]. This upregulation ultimately results in a state of hypocalcemic hypoparathyroidism [31].

In 1993, it was reported that in burned patients, intact PTH levels were elevated; however, levels of PTH did not correlate with urinary calcium [17]. In 1993 it was reported that PTH levels were normal and stable in burned patients [5]. Two years later Klein and Herndon found that PTH levels were significantly reduced in pediatric burned patients [21]. It was thought that depleted magnesium may prevent cyclic AMP generation in parathyroid cells, ultimately leading to insufficient PTH secretion and hypocalcemia. This study also demonstrated renal resistance to exogenous PTH [21].

Serum intact PTH levels were normal by 6 months post-burn in 2009 [22]. Mean serum PTH levels increased from 15 ± 11 pg/ml at admission to a level of to 21 ± 11 pg/ml. An inverse correlation between serum levels of 25(OH)D and iPTH was approached, however this trend did not reach a significant value (p=0.20).

In a 2017 study, Kagan et al. studied pediatric burn patients (n= 50, TBSA of 55.7% ± 2.6%) and their response to either vitamin D2 or vitamin D3 supplementation. All 50 patients received a standardized multivitamin and either 100 IU/kg D2, D3, or placebo. Serum levels of parathyroid hormone were measured at baseline, midpoint, discharge, and finally one year after the initial burn injury. PTH levels as well as clinically relevant outcomes were not found to be significantly different between the various groups [26].

Aluminum (Al)

It is believed that aluminum administration may hinder bone formation [15, 16]. As aluminum levels rise, the risk of diseased bone also rises. Currently, it is believed that aluminum inhibits bone formation and induces bone impairment by inhibiting the Wnt/β-catenin signaling pathway [16]. In 1993, a study (n=12, 18–41 years, TBSA >50%) was designed to determine the magnitude of bone disease attributable to exposure to aluminum. Aluminum intake via the use of antacids and albumin, partial immobilization, and increased production of endogenous glucocorticoids were evaluated [17]. The study was designed to determine how both the formation of bone and the homeostasis of calcium are affected following burn injury given the Al exposure resulting from burn therapy. Each week, samples of the subject's serum and urine were collected and evaluated for biomarkers until five weeks post-burn. Overall, serum levels of osteocalcin were low (p-value not given)[17]. An inverse correlation was found between urine Al and serum osteocalcin (p< 0.05)[17]. In 60% of patients, bone Al was measurable in significant quantities by stain or quantitation (p<0.05).

Bone Morphogenic Protein-2 (BMP-2)

Bone morphogenic protein-2 is recognized as a stimulant of bone production and can thus be used to evaluate the process of bone formation [18]. It has been shown that the expression of BMP-2, even briefly, is sufficient to induce bone formation [19]. Klein *et al* tracked BMP-2 and found a statistically significant decrease of 18% in bone morphogenetic protein-2 of the burn patients at days 3 and 7 compared to the matched control patients (p<0.05) [7].

Calcium

Half the studies in our review analyzed blood calcium concentration in patients post-burn [5, 17, 20–22]. As a component of hydroxyapatite and thus deposited into the organic matrix of the skeleton, calcium is critical for the structure and strength of the skeleton [23]. Additionally, calcium is utilized as a marker of bone formation because the process itself involves the incorporation of calcium into the bony matrix [23]. Extracellular calcium has also been shown to stimulate the acute signaling responses of osteoblasts and osteoclasts [31]. Extracellular calcium also increases the migration, proliferation, survival, expression of terminal differentiation markers, and mineralizing functions of these cell types by triggering the CaSR [31]. Results regarding calcium levels were less consistent than the results from other markers such as osteocalcin.

In 1992, total serum concentration of calcium in pediatric burned children and adolescents were noted to be low on admission, but by 6 months post-burn, serum calcium levels were found to be in the normal range (n=68) [5]. One year later, calcium in both serum and in urine in burned adult patients (n=12, 18–41 years, <50% TBSA burned) was evaluated [17]. Most patients had mild hypercalcemia (mean: 1.15 ± 0.06 mM) but only a third had hypercalciuria (mean: 137.5 ± 404.5 μmol/dl glomerular filtrate). In 2009 a study followed patients for 6 months to determine if supplementation with 400IU of vitamin D2 supplied by daily standard multivitamin would raise serum levels of 25-hydroxyvitamin D [25(OH)D] to normal [22]. Burned children (n=8, ages 5–18 years; TBSA >40%) were compared to age-matched burned children previously studied without the supplement (n=7). After 6 months, serum levels of 25(OH) D,1,25-dihydroxyvitamin D [1,25(OH)2D], intact parathyroid hormone (iPTH), calcium, phosphorus, albumin, total protein and bone mass via dual energy X-ray absorptiometry were measured. In this study, blood ionized calcium levels were normal at 6 months post-burn[22].

Copper (Cu) and Zinc (Zn)

In 2005, Voruganti *et al* reported the status and administration of zinc (Zn) and copper (Cu) plasma concentration in children after a burn, during hospitalization, and following nutritional care, specifically calcium repletion (n=6, ≥40% TBSA)[20]. Upon admission, samples of patient's blood, wound exudates, 24-h urine and anthropometric measurements were collected. Twenty-four hour diet and supplement records established subject's nutrient intakes during the hospital stay. Nutritional care for the subjects was determined based on calculations using the Galveston Formula and the DRI for calcium, copper, and zinc.

In five of the six children, calculated required energy and protein intakes were not met. In five of six children, daily recommended intake(DRI) of calcium was surpassed. Subsequently, positive correlations between calcium intake and urinary zinc (r2=0.92, p=0.009) and urinary copper (r2=0.94, p=0.006) at time of discharge were found. This indicated that as calcium intake increased, urinary zinc and copper both increased and plasma levels fell. Low plasma levels of zinc and copper following burn injury may lead to inadequate bone mineralization as collagen cross-linking is dependent on both these minerals. Additionally, as the mineral composition of bone, including zinc and copper, is decreased following a significant burn injury, construction and resorption are also reduced

[20]. This study demonstrated that a diet satisfying the DRI for mineral intakes for normal children may be insufficient to restore plasma levels in children with burn injuries.

Magnesium

Often, severely burned children and adults develop hypomagnesemia, hypocalcemia, hypoparathyroidism, as well as renal resistance to exogenous PTH. In 1998, Klein and Herndon evaluated magnesium regulation post-burn in pediatric burned subjects (n=10, ≥30% TBSA) and found 70–80% with decreased levels of ionized serum calcium and magnesium [21]. Two patients were found to have elevated preservation of a standard magnesium infusion. This suggested that there is continued magnesium depletion despite normal levels of serum magnesium. Thus, it was proposed that the excessive losses of magnesium were through the burn wound or by hypermagnesuria secondary to up-regulation of the CaSR.

The elevated metabolic rate found in burned patients is also suggested to contribute to the subsequent hypomagnesaemia. The increased metabolic rate may stimulate intracellular magnesium uptake to supplement the elevated required energy in these patients. Cyclic AMP, which is essential in cellular energy production, depends on magnesium as a cofactor. Thus, depleted magnesium may prevent cyclic AMP generation in parathyroid cells, ultimately leading to insufficient PTH secretion and hypocalcemia.

Sclerostin

Sclerostin is produced by osteocytes and has anti-anabolic effects on bone formation. Only one of the studies reported levels of sclerostin in burned patients. In 2015, a follow-up study of a previously reported randomized double-blind, controlled trial utilizing bisphosphonate pamidronate was performed by Klein *et al* [27]. Pamidronate administration significantly prevented resorptive bone loss in pediatric burn subjects within the first 10 days post-injury. Serum samples from subjects (n=21, ages 5–18 years; TBSA >40%) were analyzed for fibroblast growth factor (FGF)-23 and sclerostin. In almost all obtained specimens, FGF-23 was not detected, irrespective of pamidronate administration. A significant difference in the slope of sclerostin over time by treatment group was found (p=0.016) with a positive slope was seen in the patients who received the bisphosphonate supplementation. This may demonstrate the conservation of osteocyte utility, an explanation reinforced by the reports of Bellido and Plotkin[28]. Klein, however, speculated that the increase in sclerostin may be independent of pamidronate and instead due to a currently unidentified source of sclerostin.

Type I Collagen

Type I collagen, often utilized as a biochemical marker of bone formation, was utilized in various forms by three different studies. Type I collagen makes up nearly 95% of the collagen substance of bone and approximately 80% of the total proteins found in bone. It is believed that type 1 collagen thus influences the mineralization of bone and ultimately the strength of bone [29]. Klein et al followed type I collagen telopeptide [4, 5] in pediatric burned patients[4,] Hospitalized burned patients had a significantly elevated level of type I collagen telopeptide and thus bone resorption; however, this level normalized by the time of discharge.

Vitamin D

Vitamin D is a fat-soluble micronutrient that preserves sufficient serum calcium and phosphate concentrations to allow for normal bone mineralization. Notable risk factors for decreased vitamin D concentrations include decreased skin production, use of sunscreen, its decreased bioavailability and production, liver or kidney dysfunction, malabsorption disorders, the use of cholesterol-lowering agents, and increased glucocorticoids [30]. It has been previously reported that a direct correlation amongst serum concentrations of 25-hydroxyvitamin D (25[OH]D) and lumbar spine bone mineral density (BMD) Z-scores exists [10].

Klein *et al* initially evaluated vitamin D in pediatric burned patients (n=24, ≥40% TBSA burned). The hypothesis was based on previous studies demonstrating that children with burn injuries surpassing 40% TBSA burned are at risk of irregularities in the metabolism of bone and calcium. These irregularities include acute as well as chronic loss of bone, and thus have an elevated risk for the development of adult-onset osteoporosis. These children often receive counseling to avoid sunlight post-burn to preclude the development of hyperpigmentation of their burn scar. As a result, these children may enter a Vitamin D depleted state. Serum 25(OH)D was below normal in 10 of the 11 patients and that 1,25(OH)2D was below normal in 5 of the 11 patients at 7 years post-burn [10]. Osteocalcin was low in 9 of the 11 patients 7 years post-burn, while iPTH concentrations were in the lowest quartile in 5 of the 12 patients. In the 7 years post-burn group, Serum 25(OH)D levels were found to be associated with bone mineral density z-scores ($r=0.53$, $p<0.05$) and related inversely to iPTH levels ($r=0.66$, $p<0.05$).

In 2004, a study demonstrated if burn scar or bordering unburned skin is able to produce vitamin D3 from 7-dehydrocholesterol in pediatric burn patients (n=12, mean TBSA burned: 52%) [11]. During routine reconstructive surgery, biopsied skin samples were obtained from burned scar and unburned skin bordering to the scar, and foreskins after circumcision as well as two intraoperatively obtained wound site skin from healthy adults were used as controls. Initially the study showed that there was no identifiable difference between the infant and the adult controls in the precursors of vitamin D. In the burn scar, levels of skin 7-dehydrocholesterol were found to be significantly lower when matched to unburned controls ($p=0.016$). Pre-vitamin D3, however, was significantly decreased when compared to controls in both the burn scar surface ($p=0.004$) and the unburned skin surface bordering the scar ($p=0.004$). Additionally, modification of 7-dehydrocholesterol to pre-vitamin D3 was reduced significantly when compared to unburned controls in both burn scar and bordering unburned skin ($p=0.004$). Lastly, 8 of the burned subjects had diminished concentrations of serum 25-dihydroxyvitamin D, while serum 1,25-dihydroxyvitamin D levels were within normal limits in all cases. It was concluded that the area of skin incapable of synthesizing vitamin D routinely goes beyond the TBSA included in the burn; scar tissue has increased amounts of ultraviolet B-absorbing constituents comparable to melanin and sunscreens.

In a 2009 study, no significant difference was found in the levels of serum 25(OH)D in children receiving supplementation with vitamin D (400 IU daily for six months) compared with the unsupplemented children [22]. Six months following the burn injury, levels of serum 25(OH)D in supplemented children were found to be 21 ± 11 ng/mL (range: 9–46

ng/mL). Seven out of the eight values fell below the anticipated target of 30 ng/mL. The unsupplemented children had serum levels of 16 ± 7 ng/ml (range: 5–23 ng/mL).

In their 2017 study previously discussed, Kagan et al. also evaluated the serum levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 25-hydroxyvitamin D2, and 25-hydroxyvitamin D3 in their 50 pediatric burn patients. Serum levels of vitamin D did not vary significantly between groups. However, at discharge >10% of patients were found to have a 25-hydroxyvitamin D deficiency (Kagan-1). By the one year follow up, worsening of the deficiency was observed in the placebo (75%), D2 (56%), and D3 (25%) groups [26].

These studies demonstrate significant depletion of Vitamin D following burn injury in pediatric patients. This can lead to clinically relevant concerns such as lifelong osteoporosis.

CONCLUSIONS

Burned pediatric patients may not entirely recuperate following an acute insult and may subsequently acquire lifelong osteoporosis [5]. An understanding of the key biomarkers of bone metabolism and their relationship to one another is essential for both acute and long-term management of pediatric burn patients.

Table 1 summarizes the data gathered from our literature review. The current literature on this topic is incomplete and uncertain. The following four factors are recommended for further evaluation: aluminum loading, partial immobilization, increased endogenous corticosteroid production, and increased production of cytokine specifically tumor necrosis factor alpha [17]. In addition to understanding these markers on a chemical level, the clinical utility of these biomarkers and how they can be controlled must be further explored.

It is further recommended that all children, following hospital discharge after receiving treatment for severe burn injury, should receive, at a minimum, a daily multivitamin that contains 400 IU/day of vitamin D. These children should receive routine and clinically monitored supplementation, as the absence of this follow-up may lead to depletion of vitamin D [10].

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Highlights:

- This review examines eleven randomized, placebo-controlled prospective clinical trials in pediatric burns between 1995 and 2017, including approximately 250 burned pediatric subjects in total.
- These studies were conducted in order to evaluate the impact of burn injury on markers of bone formation and bone metabolism and some trials analyzed current therapy regimens such as pamidronate and vitamin D.
- It is recommended that all children, following hospital discharge after receiving treatment for severe burn injury, should receive, at a minimum, a daily multivitamin that contains 400 IU/day of vitamin D.

TABLE 1-

Summary of biomarker trends following burn injury

Article	Osteocalcin	Calcium	Aluminum	Type 1 collagen mRNA	BMP 2	Urine free cortisol	Inflammatory markers	PTH	Vit D	Sclerostin	Magnesium
Klein, 1995 [4]	↓			↓		↑	↑				
Klein, 1995 [5]	↓	↓ on admit, rose to normal		↑				Remained stable			
Klein, 2004 [7]				↓	↓	↑ with ↓ total bone GRα					
Klein, 2002 [10]								↓	↓		
Klein, 2004 [11]									↓ 25-D. 1,25-D WNL		
Klein, 1993 [17]	↓	↑	↑					↑			WNL
Voruganti, 2005 [20]		↑ with ↑ urinary Zn and Cu									
Klein, 1998 [21]		↓						↓			↓
Klein, 2009 [22]		Normal at 6 months postburn						Normal at 6 months post-burn	No difference between groups		
Gottschlich, 2017 [26]								No difference between groups	No difference between groups.		
Klein, 2015 [27]										↑	