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A pediatric critical care perspective on vitamin D

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The mechanisms of action of vitamin D are the subject of intense investigation. Evidence now suggests vitamin D affects immune function and cell proliferation, prompting interest in its role in critical illness and cardiac disease. Multiple studies demonstrate strong associations between vitamin D deficiency and severity of illness including need for higher inotrope support, more fluid resuscitation, and longer intensive care unit stay. The pediatric cardiac population may be at even more risk and nearly twice as likely to be deficient compared to the noncardiac population. Low vitamin D levels have been found in postoperative cardiac patients, where investigators speculate cardiopulmonary bypass alters levels directly or indirectly. Patients with congestive heart failure who are deficient also seem to benefit from vitamin D supplementation. This review summarizes recent studies in children that investigate the relation between vitamin D status and clinical outcomes in the critically ill including those with cardiac disease.

Vitamin D, its receptor, and its properties have recently become the subject of intense investigation. It is estimated that about one billion people around the world are vitamin D deficient or insufficient. There is no universal definition of vitamin D deficiency; however, the 2011 Institute of Medicine report considered 25 hydroxycholecalciferol 25(OH)D levels of 50 nmol/l to be sufficient in 97.5% of the population (1,2). Levels less than 50 nmol/l are considered inadequate and reflect a state of deficiency. It has been long known that vitamin D deficiency causes rickets in children and osteomalacia in adults (2). Among healthy children and adolescents in the United States, the prevalence of deficiency is 9–18% (3–5).

It is less clear what impact deficiency has on the critically ill. Among critically ill adults, prevalence rates are reported between 17 and 80% (6,7) whereas among critically ill children rates are 35–70% (8–10). There is increasing evidence that deficiency in critically ill populations is associated with increased mortality risk, longer stay in intensive care units and increased risk of infections (6,7,11). While it is possible that vitamin D is itself a marker of illness, the presence of vitamin D receptors on tissues such as cardiomyocytes and immune cells that respond to the active form of vitamin D suggests it is more likely directly involved in the pathophysiology of illness and inflammation (12). This review focuses on what is currently known about vitamin D status in critically ill children including those with cardiac disease.

VITAMIN D KINETICS

The concentration of 25(OH)D in plasma is 1,000-fold higher than that of $1\alpha25(OH)_2D$, which is the metabolically active hormone (13). Because 25(OH)D has a much longer half-life (15 d) than $1\alpha25(OH)_2D$ (15 h), it is widely accepted that measurement of 25(OH)D provides the best reflection of vitamin D nutritional status (13–15).

Eighty-five to 90% of 25(OH)D in serum is bound to vitamin D binding protein (VDBP), while 10–15% is bound to albumin and less than 1% is free in plasma (16). Genetic polymorphisms in the VDBP genes have been described (17). These polymorphisms result in VDBP variants that have different affinities to 25(OH)D and vary with race (18–20). Powe *et al.* even suggest that the bioavailable 25(OH)D (not bound to VDBP) may represent a better indicator of deficiency. However, their methodologies of measuring vitamin D and VDBP are not standardized (21).

VITAMIN D RECEPTOR

VDR has been isolated in as many as 30 tissues and cell types in humans including B and T lymphocytes, adipose tissues, muscle, and bone marrow (22). In mice, the VDR has even been isolated in t-tubules of cardiomyocytes (23). In their work, Tishkoff *et al.* showed that the acute rapid (5 min) effect of $1\alpha25(OH)_2D$ on cardiomyocytes is to accelerate relaxation, which has implications in diastolic dysfunction (23). In addition, they demonstrated that VDR knock-out myocytes exhibited increased rates of contraction and relaxation which disturbed contractile kinetics. This suggests that vitamin D affects contractility directly through a mechanism that is independent of serum calcium though perhaps related to intracellular sarcoplasmic reticular calcium. Literature also suggests that vitamin D has anti-inflammatory properties, which may improve overall cardiovascular function (24,25). The role of vitamin D in immune function and pediatric infections was previously reviewed by Walker and Modlin (26).

VITAMIN D AND CRITICAL ILLNESS

In 2009, Lee *et al.* were among the first to report a high prevalence of vitamin D deficiency among critically ill adults and

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furthermore demonstrated worse outcomes in those patients (27). Since then a number of adult studies have reported associations between vitamin D deficiency and worse outcomes, including mortality (7,27–31). Braun *et al.* demonstrated that critically ill patients who were vitamin D deficient had a 1.9-fold increased risk of 30-d mortality (95% confidence interval (CI) = 1.15–2.98; $P = 0.01$) compared to vitamin D sufficient patients. The authors also reported that deficiency was an independent predictor of mortality (7). Similar findings were reported by Amrein *et al.* in a single center review where critically ill patients with deficient 25(OH)D levels had a significantly higher risk of adjusted hospital mortality (hazard ratio of 2.05, 95% CI = 1.331–3.22) compared to sufficient patients. Currently, interventional studies are underway in adult critically ill deficient patients, including a large randomized controlled trial (28,32,33). The results of which are eagerly awaited.

Within pediatric critical care vitamin D status is less studied. In our literature review, we searched PubMed, Ovid MEDLINE and ISI Web of Science for articles published within the last 10 y containing the terms "vitamin D and intensive care or critical care or critical illness." We limited the articles to "all child (0–18 years old)" and "English." We then reviewed the abstracts and full texts of all relevant articles. We obtained 62 articles from PubMed, 26 articles from Ovid MEDLINE and 16 articles from ISI Web of Science. Fifty-eight articles were excluded due to duplication or were irrelevant. Upon further review, there were only four studies that included data on epidemiology and outcomes of vitamin D adequacy in critically ill pediatric patients, which are reviewed here (**Table 1**) (8–10,34). Currently, there is one interventional phase II trial underway investigating vitamin D replacement in preoperative congenital heart disease patients (www.clinicaltrials.gov; NCT01838447). This review will highlight the recent studies among pediatric critically ill children.

Madden *et al.*, conducted a prospective cohort study at Boston Children's Hospital pediatric intensive care unit (PICU) looking at vitamin D levels around the time of admission, though cardiac surgery patients were excluded (8). The authors found a significant association between 25(OH)D deficiency and worse clinical outcomes. Deficient patients had higher severity of illness scores and more likely to require vasopressor support. There was no association found between 25(OH)D levels and duration of mechanical ventilation. Interestingly, almost all patients had normal ionized serum calcium levels (8). The authors concluded that these findings are probably secondary to vitamin D's role in immune modulation, inflammation, and calcium homeostasis rather than hemodilution and fluid shifts.

Table 1 Summary of vitamin D studies in critically ill children

Reference	Study design[a]	Type	*N*	Results
8	Prospective cohort	Medical/ surgical[b]	511	Prevalence 40%
	2009–2010			Median 56 nmol/l (IQR = 41–78)
	Single center (United States)			Lower levels associated with higher admission day illness severity (OR = 1.19 for 1 quartile increase in pediatric risk of mortality III score; 12 nmol/l decrease 95% CI = 1.10–1.28; $P < 0.0001$)
				Increasing vasopressor use correlated with decreasing 25(OH)D levels ($r = -0.19$, $P < 0.0001$)
10	Prospective cohort	Medical/ surgical	316	Prevalence 34.5%
	2010–2011			Median 56 nmol/l (IQR = 44–70), median 66 nmol/l (IQR = 52–84 nmol/l) PICU vs. 52 nmol/l (IQR = 41–64) cardiac; $P < 0.05$
	Single center (Australia)			Deficiency more common in cardiac 40.5 vs. 22.6% medical patients; $P = 0.002$
				Higher inotrope score in cardiac patients who are deficient; $P = 0.006$
				No difference in ICU stay or mortality in patients with deficiency
9	Prospective cohort	Medical/ surgical	326	Prevalence 69% (95% CI = 26–30), within cardiac population 40% deficient
	2005–2008			Mean 43 nmol/l
	Multicenter (Canada)			Deficiency independently associated with longer PICU stay (+1.92 d, 95% CI = 0.2–3.7; $P = 0.03$) and increase severity of illness scores (1 point increases the likelihood of being deficient by 8%)
34	Prospective observational comparing PICU vs. healthy controls	Medical/ surgical[c]	156 PICU	Prevalence 29.5% (95% CI = 22.0–37.0) PICU vs. 15.6 % (95% CI = 12.2–20.0) healthy controls ($P = 0.01$; OR = 2.26 (CI = 1.41–3.61))
	Single center (Spain)		289 Healthy controls	Median of 65 nmol/l (IQR = 48–89) PICU vs. 76 nmol/l (IQR = 58–96) healthy controls; $P = 0.007$
				Deficiency not associated with higher mortality risk, length of stay, inotropic or respiratory support
				First to compare to healthy controls

CI, confidence interval; IQR, interquartile range; *N*, number; OR, odds ratio; PICU, pediatric intensive care unit.
[a]All studies collected vitamin D samples within at least 24 h of admission to pediatric intensive care unit, defined deficiency as <50 nmol/l, and used immunoassay techniques, except reference (9), which used mass spectrometry. [b]Excluded cardiac surgery patients. [c]Did not report whether cardiac patients were included in postoperative population.

McNally *et al.* also showed worse outcomes in their multicentered study of critically ill children across Canada (9). Interestingly the mean 25(OH)D levels (43 nmol/l) were considerably lower than the mean level of 67–75 nmol/l reported among healthy Canadian and US children (5,35). Lower 25(OH)D levels were found in patients who required catecholamine infusions, were hypocalcemic, received more than 40 ml/kg of fluid resuscitation and needed mechanical ventilation. Deficiency was also independently associated with an increase of ~2 d stay in the PICU (9). The authors speculate that acute drops in vitamin D may be more physiologically significant than chronic deficiency because during critical illness compensatory mechanisms are affected by inflammation and multiorgan dysfunction. This same group is currently working on a phase II trial investigating vitamin D supplementation prior to cardiac surgery.

Somewhat different findings were observed by Rippel *et al.* in their study of critically ill children of which two thirds were postoperative cardiac patients (10). Contrary to other studies, no association was found between 25(OH)D deficiency and need for mechanical ventilation, vasoactive support, ICU or hospital length of stay, severity of illness scores or mortality. Of note, cardiac patients were nearly twice as likely to be deficient when compared to noncardiac patients (10).

Rey *et al.* is the most recent to investigate vitamin D deficiency within the PICU (34). In this study, vitamin D levels of critically ill children were compared with levels of healthy children within the same area of Spain. Despite the PICU patients having nearly twice the rate of deficiency compared to healthy controls, no difference in risk of mortality scores was found for deficient patients (34).

A limitation of the pediatric studies is that no preillness vitamin D levels were measured; therefore, it's uncertain whether lower levels are a result of illness, acute therapies, or represent a preillness chronic deficiency state. The discrepant results among these studies demonstrate the continued need for research to truly understand the role of vitamin D during critical illness. Interestingly, children who are postoperative from cardiac surgery seem to be an especially vulnerable population and further investigation into this specific population will need to be evaluated.

VITAMIN D IN CARDIOPULMONARY BYPASS

One hypothesis regarding why postoperative cardiac surgery patients had higher risk of vitamin D deficiency was the effects of cardiopulmonary bypass (CPB). In adults, CPB significantly lowered serum 25(OH)D levels in patients undergoing elective cardiac surgery (36,37). This was thought to be a dilution effect secondary to volume expansion. However, in the pediatric population, there are conflicting reports. In neonates, undergoing cardiac surgery, CPB did not have any effect on 25(OH)D although 84% were deficient prior to surgery (38). More recently, McNally *et al.* showed a marked decline in 25(OH)D levels postoperatively in their single center prospective cohort study of children less than 18 y old undergoing cardiac surgery (39). Blood was collected at three time points: preoperatively, intraoperatively and postoperatively in a total of 54 patients who underwent CPB. The mean 25(OH)D level before surgery was 60 nmol/l and 42% of patients were deficient. CPB resulted in a decrease of the mean to 35 nmol/l with 84% of patients deficient. Low postoperative 25(OH)D levels were also associated with increased catecholamine levels, fluid requirements, and longer duration of mechanical ventilation. Interestingly, there were low levels of 25(OH)D in the modified ultra-filtrate of the bypass circuit suggesting that a mechanism other than a simple dilution effect may be taking place (39). Future studies should also focus on VDBP fluctuations during CPB to gain better understanding of 25(OH)D status.

VITAMIN D AND CONGESTIVE HEART FAILURE

Beyond the acute setting, vitamin D's anti-inflammatory effects were reproduced *in vivo* in adults with congestive heart failure (40). In a randomized controlled trial among congestive heart failure patients, supplementation with vitamin D over 9 mo increased the anti-inflammatory cytokine interleukin 10 (IL-10) and prevented the rise of the proinflammatory marker tumor necrosis factor α (TNF-α) (40). Although, vitamin D supplementation in adults with congestive heart failure did not improve physical performance as measured by peak oxygen consumption (41). In children, vitamin D supplementation was beneficial in treatment of congestive heart failure, as demonstrated by a recent double-blind placebo controlled study (42). Here, infants with congestive heart failure secondary to dilated cardiomyopathy or congenital heart disease with systemic left ventricular systolic dysfunction were randomized into vitamin D and placebo treatment groups (42). Both groups received anti-congestive heart failure therapy with digoxin, captopril, and spironolactone. Forty-two patients received 1,000 IU of Cholecalciferol oral drops (vitamin D group). Thirty-eight patients received placebo oral drops (placebo group). After 12 wk, there was a statistically significant increase in the anti-inflammatory cytokine IL-10 and decrease in the proinflammatory cytokines IL-6 and TNF-α in the vitamin D group ($P < 0.001$). These changes were coupled with echocardiographic improvements in left ventricular dimensions and systolic function indices. Comparatively, there was some improvement in systolic function indices in the placebo group, but no improvement in IL-6, IL-10, or TNF-α (42). Should these findings become reproducible, vitamin D supplementation may become an adjunct in treatment of pediatric congestive heart failure.

FUTURE DIRECTIONS

In summary, it is unclear if vitamin D deficiency plays a role in pediatric critical illness and cardiac disease. While pediatric studies report lower vitamin D levels in critical illness, results are contrary if deficiency is associated with severity of illness or other clinical outcome measures. The cardiac population is especially vulnerable and twice as likely to be deficient. This has prompted investigation into the potential effects of cardiopulmonary bypass on vitamin D status as well as supplementation in those with heart failure. Studies thus far have been small and

warrant further investigation. The next step should be interventional studies that target critically ill-25(OH)D deficient children with vitamin D supplementation to address whether there are improvements in clinical outcomes such as severity of disease, need for organ support or duration of stay. Potential studies should also focus on how best to supplement vitamin D during critical illness as this has yet to be determined.

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