Vitamin D, Covid-19 and Children

E.J. Molloy¹, N. Murphy⁵,⁶

1. Paediatrics, Trinity College, the University of Dublin.
2. Trinity Translational Medicine Institute (TTMI) & Trinity Research in Childhood Centre (TRICC), Trinity College Dublin.
3. Paediatrics & Neonatology, Children’s Hospital Ireland (CHI) at Tallaght & Crumlin, Dublin.
4. Coombe Women and Infants University Hospital, Dublin.
5. Endocrinology, CHI at Temple St, Dublin.
6. Paediatrics, University College Dublin, Ireland.

The multi-organ and systemic importance of Vitamin D is increasingly recognised. Low vitamin D is associated with morbidity in children and adults. In addition, vitamin D3 appears to decrease mortality in elderly people living independently or in institutional care. Increasing use of sunblock and prevention of melanoma have resulted in lower levels of vitamin D especially on countries of higher latitude in the winter months. This has resulted in public health programmes for vitamin D supplementation in newborns and children.

There has been a well-established link between respiratory illness and vitamin D deficiency from TB to respiratory syncytial virus. Children in interventional studies of vitamin D supplementation had reduced incidence of influenza and other acute respiratory infections. However, Agilpay et al. found no difference in viral respiratory illness in 703 healthy children randomised to either conventional (400 IU/d) or high-dose (2000 IU/d) of vitamin D oral supplementation. In contrast, a systematic review of children with a history of asthma demonstrated that vitamin D supplementation may prevent childhood acute respiratory infections. There is a high prevalence of low Vitamin D levels in preterm infants and an association between vitamin D status and acute respiratory morbidity in preterm infants after birth. In preterm infants vitamin D deficiency was also associated with increased resuscitation requirement at delivery, increased oxygen requirement, increased duration of intermittent positive-pressure ventilation during resuscitation at delivery and greater need for assisted ventilation. Vitamin D insufficiency is common in children and adolescence with key determinants being season, ethnicity, time outdoors and supplementation.

In acute illness vitamin D is frequently low and may be an epiphenomenon secondary to acute inflammation. There is debate about the value of giving mega doses of vitamin D during acute sepsis or critical illness. The VITdAL-ICU trial is the largest published trial to date in adults in ICU regarding vitamin D supplementation and showed no benefits on mortality on primary analysis but improvement suggested in those who were severely deficient (<12 ng/mL) and further information is expected in 2023 from the VITDALIZE Study (NCT03188796). Children in Paediatric intensive care had lower vitamin D levels in suspected sepsis compared to controls and inadequate vitamin D levels were associated with confirmed sepsis and poor outcomes. However vitamin D status may not be accurately assessed by a single sample during critical illness due to several confounders such as albumin levels, binding proteins and haemodilution during resuscitation and free vitamin D metabolites.

High doses of vitamin D are not uniformly immunosuppressive in vitro. In preterm infants, pre but not post treatment with vitamin D before an in vitro endotoxin challenge reversed immune dysfunction. Vitamin D (1,25OHD) may enhance neonatal neutrophil function in the presence of infection thus overcoming endotoxin tolerance which may be beneficial in sepsis. The potential role of vitamin D status in reducing secondary bacterial infections and loss of life.
in pandemic influenza requires further evaluation especially in view of the lack of pharmaceutical interventions\textsuperscript{19}. There are several proposed mechanisms for the anti-inflammatory and immunomodulatory properties of Vitamin D\textsuperscript{20}. Cathelicidin (LL-37 or hCAP-18) is upregulated by Vitamin D which has both antiendotoxin and antimicrobial properties. Cathelicidin levels correlated well with clinical outcomes in children with RSV bronchiolitis (n=82) and may be a relevant biomarker even if vitamin D levels are normal\textsuperscript{21}. Vitamin D also reduces the production of proinflammatory cytokines, which could also explain some of the benefit of vitamin D since Covid-19 infection gives rise to a cytokine storm.

Therefore in agreement with the paper by McCartney\textsuperscript{22} in this journal we suggest that ensuring baseline vitamin D sufficiency is appropriate but acute large doses of vitamin D have not been proven to be beneficial in critical illness.

Funding:
National Children’s Research Centre, Crumlin, Dublin, Ireland and Health Research Board Ireland.

Corresponding Author:
Prof Eleanor Molloy,
Consultant Neonatologist & Paediatrician,
Department of Paediatrics,
Trinity Centre for Health Sciences,
Tallaght University Hospital,
Tallaght,
Dublin 24, Ireland.
Tel: +353 1 896 3763
Email: eleanor.molloy@tcd.ie

References:


14. Clinicaltrials.gov: The VITDALIZE Study: Effect of High-dose Vitamin D₃ on 28-day Mortality in Adult Critically Ill Patients With Severe Vitamin D Deficiency: a Multicenter, Placebo-controlled Double-blind Phase III Randomized Controlled Trial (RCT) NCT03188796


20. D.M. McCartney, D.G. Byrne - Optimisation of Vitamin D status for enhanced immune-protection against Covid-19-Ir Med J; Vol 113; No. 3; P57