

REVIEW ARTICLE

## VITAMIN D DEFICIENCY AMONG CHILDREN: MORE OF A MOUNTAIN THAN A MOLEHILL

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### ABSTRACT

Vitamin D is a fat-soluble vitamin which has both skeletal and extra-skeletal functions in humans. Vitamin D deficiency (VDD) is a common medical problem worldwide. It has been associated with a number of acute and chronic medical conditions. The diagnosis of VDD is straightforward. It however requires identification of risk factors, good history taking and physical examination as well as ordering the appropriate investigations. Health workers looking after children need to be constantly reminded about this common medical condition.

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### Introduction

There has been more interest lately on the role that Vitamin D plays on the health status of children. Vitamin D deficiency (VDD) is thought to be the most undiagnosed medical condition in children and adults.<sup>1</sup> The major consequence of VDD was previously thought to be bone and musculoskeletal problems. However, recent evidence suggests that apart from causing growth retardation and rickets in children, VDD is associated with a number of other clinical conditions in humans. VDD has been associated with increased risk of cardiovascular disease, cancers, autoimmune diseases and depression.<sup>2</sup> It has also been associated with asthma and increased frequency of upper respiratory tract infections, two conditions which account for increased hospital visits and healthcare costs.<sup>3,4,5</sup> This review looks at the effects of vitamin D deficiency on the health status of children.

### Definition of Vitamin D deficiency

The definition of VDD varies across the globe. For instance, the Italian Pediatric Society in a recent consensus paper defined vitamin D levels above 75 nmol/L as normal, levels between 50-75 nmol/L as insufficient, <50 nmol/L as deficient and <25 nmol/L as severe deficiency.<sup>6</sup> The Canadian Paediatric Society defines 25 hydroxyvitamin D levels <25 nmol/L as deficient, 25-75 nmol/L as insufficient, 75-225 nmol/L as optimal and levels >500 nmol/L as potentially toxic.<sup>7</sup> In the United Kingdom, the National Institute for Health and Care Excellence (NICE) considers vitamin D values less than 25 nmol/L as being deficient.<sup>8</sup> The British Paediatric and Adolescent Bone Group defines VDD as plasma concentration of 25 hydroxyvitamin D less

than 25 nmol/L, with insufficiency being 25-50 nmol/L and sufficiency as levels greater than 50 nmol/L.<sup>9</sup> These definitions by the NICE and British group are however based on expert opinion.<sup>8,9</sup>

Kang et al. in their study among Korean children found that the Vitamin D level needed for maximal suppression of parathyroid hormone (PTH) was 18 ng/ml (45 nmol/L) suggesting a cut-off of 45 nmol/L for diagnosing VDD.<sup>10</sup> In their study involving 214 children with Vitamin D and PTH measurements, Atapattu et al. suggested a cut-off level of 34 nmol/L using a best fitting intersection point of PTH and Vitamin D by two-phase linear regression.<sup>11</sup>

Most literature agree that levels above 75 nmol/L are normal. At this level, calcium absorption is maximised, and parathyroid hormone levels are kept within normal limits.<sup>12,13</sup> Values less than 50 nmol/L are generally considered as deficient and values between 50-75 nmol/L are considered by many authors as insufficient.

### Epidemiology

VDD occurs worldwide in all age groups. It is thought to be the most undiagnosed medical condition worldwide.<sup>1</sup> The true prevalence of VDD may be unknown. Prevalence rate varies worldwide depending on the method of measurement used, the population studied, and the cut-off value used to define VDD.

In Iran, up to 93.3% of newborns had VDD using cord blood samples and values less than 35 nmol/L.<sup>14</sup> Among preschool children in Mexico, the prevalence rate was 24%.<sup>15</sup> Among a healthy population of infants and toddlers in Boston, USA 12.1% were found to be deficient.<sup>16</sup> A prevalence rate of 35% was found among children aged 4-18 years in the United Kingdom using a cut-off value of <50 nmol/L.<sup>17</sup> With increasing awareness and testing for VDD, the prevalence could be higher than previously thought. For instance, a 15-fold increase was seen in diagnosis of this condition among children in the United Kingdom between 2008 and 2014 when compared to the period from 2000 to 2007.<sup>18</sup>

### Vitamin D metabolism

Vitamin D is produced mainly in the skin from sun

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exposure. It can also be obtained from diet. Following exposure to sunlight, 7-dehydrocholesterol is converted to previtamin D3.<sup>19</sup> This is then transported to the liver where it is hydrolysed to 25-hydroxy (OH) vitamin D3. It is then transported to the kidneys where it is further hydrolysed to 1,25 dihydroxyvitamin D.<sup>19</sup> 25 (OH) vitamin D is the major circulating form of vitamin D and its level is used as a marker of vitamin D status in the body. 1,25 dihydroxyvitamin D regulates calcium and phosphorus homeostasis. It promotes the absorption of calcium and phosphorus and mediates in bone resorption.

Vitamin D also has extra-skeletal functions. It is now known that many tissues in the body including macrophages, monocytes and dendritic cells contain vitamin D receptors.<sup>20</sup> Vitamin D inhibits the activity of CD4+ Th1 cells resulting in the reduced production of cytokines.<sup>20</sup> It also promotes Th2 cells. These effects of vitamin D are thought to be responsible for its role in autoimmune disorders. Indeed, VDD has been implicated in a number of autoimmune disorders including multiple sclerosis, type 1 diabetes mellitus and systemic lupus erythematosus.<sup>20</sup>

Vitamin D receptors are expressed on activated T and B lymphocytes. Cathelicidin, a protein known to kill infectious agents is produced by macrophages from 1,25 dihydroxyvitamin D. Also 1,25 dihydroxyvitamin D regulates cytokine and immunoglobulin synthesis after its production by monocytes and macrophages.<sup>1</sup> These actions are thought to account for the role Vitamin D plays in preventing some infections.

#### **Risk factors for VDD**

Risk factors for VDD include skin pigmentation, avoiding sun exposure, use of sunscreens, inadequate diet, malabsorption syndromes, obesity, chronic kidney disease and use of medications such as glucocorticoids, anti-epileptic medications, rifampicin and antiretroviral medications. Vitamin D production also varies with latitude, season and time of the day.<sup>1,21</sup> Levels are generally lower in winter.

Dark-skinned individuals are at risk because melanin reduces production of vitamin D.<sup>22</sup> Breastfed children who receive no supplementation are at high risk.<sup>16</sup> Rovner et al. found that about 78% of breastfed babies had VDD during winter.<sup>22</sup> Obese children are at risk of VDD because fat sequesters vitamin D. Cystic fibrosis and inflammatory bowel disease are known risk factors for VDD.<sup>23,24,25</sup>

#### **Role of VDD in acute illnesses**

There is increasing evidence of the role of VDD in acute illnesses. This is not surprising, due to the immune functions associated with vitamin D. In a study comparing vitamin D levels among critically ill children with levels among healthy children, the prevalence of VDD was higher among critically ill children with sepsis.<sup>26</sup> Children with VDD are more prone to acute respiratory infections. Among children admitted for pneumonia in Ethiopia, there was a 13-fold higher incidence in those who had rickets suggesting VDD compared to those without rickets.<sup>27</sup> In Canada, children who were admitted to the intensive care unit with lower respiratory tract infection were more likely to have

low vitamin D levels.<sup>28</sup> In their study among Japanese school children, Urashima et al. found that the incidence of Influenza A in winter was reduced among children who received vitamin D supplementation.<sup>29</sup> They also found a reduced frequency of asthma attacks in asthmatic children on vitamin D supplementation.<sup>29</sup> A systematic review by Martineau et al. concluded that vitamin D supplementation protected against acute respiratory tract infection overall.<sup>5</sup>

Preterm black infants who received at least 400 IU/day of vitamin D through 6 months had reduced risk of recurrent wheeze by 12 months of age.<sup>30</sup> There have been reports of VDD causing benign intracranial hypertension in children.<sup>31,32,33</sup> VDD has also been associated with other acute presentations including seizures and heart failure as well as mortality.<sup>34,35</sup>

These findings are not surprising given the function vitamin D plays within the immune system. It however remains to be proved if this is a consistent finding. More well-conducted studies are however still needed to further examine the role VDD plays in acute illnesses among children.

#### **Role of VDD in chronic illnesses**

Emerging evidence suggests that VDD may contribute to a number of chronic medical conditions. VDD has been implicated in a number of chronic medical conditions including some cancers, autoimmune conditions, neurocognitive dysfunction and heart disease.<sup>1</sup>

The benefits of vitamin D begin in utero. Vitamin D supplementation during pregnancy is associated with improved infant growth without risk of fetal or neonatal mortality or congenital abnormality.<sup>36</sup> VDD is known to cause poor growth and reduced bone mineral density.

VDD may contribute to increased risk of developing type 1 diabetes mellitus. In different studies across the world, children with type 1 diabetes mellitus have been found to have a high prevalence of VDD.<sup>37,38,39,40</sup> In Finland, children who received vitamin D supplements during infancy had less risk of developing Type 1 diabetes mellitus later in life.<sup>41</sup>

VDD has been linked to cardiac problems including cardiomyopathies.<sup>42,43</sup> VDD has been linked with cancers especially among adults. VDD is linked with increased risk of tuberculosis (TB) in children. A multicentre study found increased prevalence of both active and latent TB in children with VDD.<sup>44</sup> Several other studies have found that children with TB, including pulmonary or extra-pulmonary TB are more likely to be vitamin D deficient.<sup>45,46,47</sup>

Among individuals with chronic medical conditions, improvement in their vitamin D levels may lead to an improvement in their conditions. For example, among adolescents with juvenile systemic lupus erythematosus who received vitamin D supplements, there was an improvement in the quality of life, decrease in disease activity and fatigue compared with those who did not.<sup>48</sup>

#### **Evaluation and treatment of the child with VDD**

Good history taking to establish if there are any risk factors for VDD is important. Physical examination may reveal evidence of poor growth and clinical features of rickets. Children may present with non-specific clinical

features so a high index of suspicion is needed in such cases. Indeed, it will not be out of place to check vitamin D levels in the evaluation of children who present with recurrent respiratory infections or recurrent acute exacerbations of asthma.

The diagnosis of VDD is confirmed by checking the level of 25 (OH) vitamin D which is the marker of vitamin D status in the body. PTH levels are not needed to diagnose VDD, however PTH levels are usually elevated in VDD and levels reduce with treatment of VDD.<sup>49,50</sup>

Children who have been diagnosed with VDD should receive appropriate vitamin D treatment. Different treatment options are available and should be guided by local guidelines. One option is to use 1000-10000 IU daily for 2-3 months.<sup>51</sup> Another option is single weekly or monthly high doses, commonly known as stoss therapy.<sup>51,52</sup> When using high doses, caution should be exercised with vitamin D preparations containing propylene glycol as these can be toxic at high doses.<sup>51</sup> It is thought that the stoss therapy may encourage better compliance. However, Tannous et al. found that among Australian children, standard daily therapy achieved higher vitamin D levels and stoss therapy was not associated with better compliance.<sup>52</sup>

Miscible forms of vitamin D3 may be better in achieving higher levels of serum 25 (OH) vitamin D when compared with fat soluble vitamin D3.<sup>53</sup> Whatever treatment option or formulation chosen, it is important to monitor vitamin D levels once treatment is started. Once levels are back to normal, these children need to be continued on long-term prophylaxis.

### Conclusion

It appears that there is still a lot unknown about the role of vitamin D on the health status of children. There is a need for more robust studies are needed in determining the role of vitamin D on health status of children. There is also a need for consensus in defining what the cut-off value of 25 (OH) Vit D should be used in defining VDD, and at what values interventions are needed. Scientific evidence more than just expert opinion is needed for defining these values. Before all these are achieved, it seems appropriate for clinicians taking care of children to pay particular attention to children with risk factors for this condition especially when they present with non-specific symptoms or when they present repeatedly to health care practitioners.

### Compliance with Ethical Standards

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