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## Global consensus on nutritional rickets: Implications for Australia

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## **Introduction**

In 2016, an international group of specialists from various disciplines was supported by their respective professional societies to develop a global consensus for prevention, diagnosis and management of nutritional rickets. Given that nutritional rickets is a preventable disorder with potentially life-long or fatal sequelae, the group advocated for the “eradication of nutritional rickets and osteomalacia”, through vitamin D supplementation of all infants, pregnant women, and individuals from high-risk groups and the implementation of international food fortification programs to ensure nutritional sufficiency of vitamin D and calcium for the whole population<sup>1</sup>. The current Australian and New Zealand (ANZ) position statement for pregnant women, infants, children and adolescents (2013)<sup>2</sup> accompanies a position statement for adults (2012)<sup>3</sup>. Both statements were commissioned by the Australian and New Zealand Bone and Mineral Society (ANZBMS) to be prepared by multidisciplinary teams of experts in areas including adult and paediatric endocrinology, nutrition, exercise, measurement, obstetrics and sun exposure. With support of the council of the Australasian Paediatric Endocrine Group (APEG), members of the APEG Bone and Mineral Working Group have reviewed the global consensus document and summarised key areas highlighting differences focusing on the ANZ paediatric statement to provide a guide for interpretation and clinical practice.

## **Assessment of strength of recommendations and level of evidence**

Recommendations of the global consensus statement were evaluated using the Grading of Recommendations, Assessment, Development and Evaluation

system (GRADE)<sup>4</sup> addressing areas of definition, diagnosis, treatment and prevention of nutritional rickets (NR)<sup>1</sup>. The National Health and Medical Research Council (NHMRC) recommends the GRADE system for the development of guidelines<sup>5</sup>. This system uses a combination of numbers to assess the recommendation and symbols for the level of evidence (table 1)<sup>4</sup>. We have added the evaluation of the consensus group in the text.

The 2012 and 2013 Australian and New Zealand (ANZ) position papers<sup>2,3</sup> were based on literature searches for articles regarding vitamin D dosing in paediatric age groups, during pregnancy/ lactation and in adults. The level of evidence was described following the NHMRC grading (table 1)<sup>5</sup>. Initial evidence-based statements were circulated amongst senior colleagues and members of respective professional societies that included the Australian and New Zealand Bone Mineral Society (ANZBMS), Endocrine Society of Australia (ESA) and APEG. Revisions were incorporated with consensus from the authoring working group.

### **Definition and diagnosis of Nutritional Rickets**

Nutritional rickets (NR) is a childhood condition characterized by impaired mineralisation of the growth plate and osteoid mainly affecting infants and toddlers<sup>1</sup>. The global consensus puts emphasis on both calcium and vitamin D deficiency as factors contributing to the pathophysiology of NR. NR is usually seen in children who have both 25-hydroxy vitamin D (25OHD) and nutritional calcium deficiency. Severe deficiency in either vitamin D or dietary calcium alone can also result in nutritional rickets<sup>6</sup>. Insufficiency of either vitamin D or calcium and combinations of normal 25OHD and deficient calcium levels and vice versa are clinically asymptomatic<sup>6</sup>.

Nutritional rickets should be diagnosed on the basis of history, physical examination, biochemical testing and confirmed by radiographs (1+++ , A)<sup>1</sup>. Individuals with nutritional rickets may have a history of poor calcium and/or vitamin D intake. Maternal vitamin D deficiency can be a contributing factor in

infants<sup>1,2</sup>. Osseous clinical signs include widened epiphyses of wrists and ankles, leg deformities, craniotabes, rachitic rosary, frontal bossing, delayed closing of the fontanelle as well as delayed tooth eruption. Bone and muscle pain has been described<sup>1,2</sup>. Non osseous features include delayed gross motor development, poor linear growth and less frequently raised intracranial pressure and cardiomyopathy<sup>2</sup>. Once compensatory mechanisms have been exhausted, biochemically NR presents with decreased 25OHD, serum calcium, serum phosphate and urinary calcium; alkaline phosphatase (ALP), parathyroid hormone (PTH) and urinary phosphate are elevated. Typical radiographic findings are splaying and cupping of the metaphyses with coarse trabecular features and signs of osteopenia<sup>2</sup>.

Clarity was also provided on a clinically relevant issue, with the global consensus highlighting that only children with radiographically confirmed rickets have an increased risk of fracture, not children with isolated biochemical 25OHD deficiency (1++O, B)<sup>1,7</sup>. The APEG bone and mineral working group recommends following the definition of the global consensus statement.

### **Interpretation of Vitamin D status**

25OHD levels reflect an individual's vitamin D status. There are a variety of assays in use. For the interpretation of results significant intra- and inter-assay variability needs to be considered<sup>8</sup>.

Cutoffs for the interpretation of 25OHD results are described in table 2. The APEG working groups agrees with both statements in that more data are required to determine whether higher levels of 25OHD (i.e.: a cut-off 75 nmol/L) are needed to cover potential non-skeletal functions of vitamin D.

The global consensus does not recommend routine 25OHD screening in healthy children (1+++ , A), but rather universal supplementation of all infants <12 months of age and supplementation of children at risk of vitamin D deficiency<sup>1</sup>. Targeted screening and supplementation are currently recommended in Australia if risk factors for vitamin D deficiency are present<sup>2,3</sup>.

These risk factors include lack of sun exposure (UVB), highly pigmented skin, veiling, hospitalisation, obesity, chronic illness such as liver and renal disease, fat malabsorption (in cystic fibrosis, coeliac or inflammatory bowel disease). Risk factors specific to infants are maternal vitamin D deficiency and exclusive breastfeeding<sup>2</sup>. In Australia migrants are at increased risk of vitamin D deficiency<sup>9</sup>. There are no specific recommendations for indigenous Australians. A study from Western Australia revealed higher vitamin D levels for those living in rural areas compared to those living in Metropolitan settings<sup>10</sup>.

The APEG Bone and Mineral Working Group supports the position of the global consensus and recommends to introduce universal supplementation of all infants <12 months of age and supplementation of children at risk of vitamin D deficiency in Australia and New Zealand. Screening for vitamin D deficiency should be restricted to populations at risk. There remains no indication for the universal screening of adolescents<sup>11</sup>.

### **Interpretation of Calcium intake**

It is highlighted that both serum 25OHD level and dietary calcium intake contribute to bone mineralisation. The optimal source of calcium for infants is human milk<sup>12</sup>, cow's milk and dairy products are preferred sources outside of early childhood. Breast milk contains 250mg of calcium/litre<sup>13</sup>. The bio-availability of calcium from breast milk is higher than from formula and cow's milk. Hence the calcium concentration in infant formulas has been increased. There are no specific recommendations for routine calcium supplementation of breast milk- or formula fed infants<sup>12</sup>, and alterations in maternal calcium intake do not affect the calcium concentration in breast milk<sup>13</sup>. Recommendations vary between guidelines looking at groups 0-6 months and >1 year of age (table 3)<sup>2,14</sup>. The APEG working group supports the higher recommendations for each respective group.

### **Risk factors for vitamin D deficiency**

Guidelines agree that high-risk groups for vitamin D deficiency include children and adolescents with fat malabsorption, liver disease and renal insufficiency. Special attention is directed to maternal vitamin D deficiency (1+++ , A)<sup>15</sup>. Vitamin D deficiency is more prevalent in infants born to a mother with low vitamin D and exclusive breast-feeding combined with at least one other risk factor<sup>1,2</sup>. Strong evidence is provided for the important role of UVB (1+++ , A). Maternal and infant/ childhood risk factors include full body clothing cover, dark skin pigmentation or restricted sun (UVB) exposure (1+++ , A)<sup>16,17</sup>. It is pointed out in the global statement that no safe threshold of UV exposure allows for sufficient vitamin D synthesis across the population without increasing skin cancer risk and that there is no firm evidence to provide a recommendation for a specific period of time for “safe” sun exposure (2++O, C).

The APEG bone and mineral working group follows the criteria describing groups at risk of vitamin D deficiency. For guidance regarding safe sun exposure we refer to the recommendation of the Australian Cancer Council.

### **Pregnancy and lactation**

According to the global consensus the relationship between vitamin D during pregnancy, infant growth and bone mass, is graded as weak, with moderate evidence<sup>18-20</sup>. There is however an undeniable association between maternal vitamin D at delivery and that of the newborn. It is concluded therefore, that all pregnant women should be given supplementation with vitamin D at 600 IU/d, without having evidence from RCTs (2++O, C)<sup>21</sup>. Lactating women should meet the dietary recommendations for vitamin D of 600 IU/d (1+++ , A)<sup>22-25</sup> without taking extra vitamin D to supplement their infant (2++O, C). The approach from the ANZ statement suggests dosing vitamin D supplementation during pregnancy and lactation based on 25OHD levels<sup>2</sup>. Recent local data has posed some concerns with this approach and the APEG bone and mineral working group supports universal supplementation of pregnant women<sup>26</sup>.

The global consensus document<sup>1</sup> states that pregnant women do not need

calcium intakes above recommended non-pregnant intakes (1+++, A)<sup>27-29</sup> and that maternal calcium intake during pregnancy or lactation is not associated with breast milk calcium concentrations (1+++, A)<sup>30</sup>. The ANZ statement recommends a calcium intake of 1300 mg/day for 14-18 year old and 1000 mg/day for 19-50 year old pregnant and lactating women<sup>2</sup>.

The APEG Bone and Mineral Working Group supports that all pregnant women should be given supplementation with vitamin D at 600 IU/d and is of the opinion that this area needs further study and discussion amongst specialist societies in Australia to reach consensus on the issue of universal supplementation (global consensus document) and targeted supplementation (ANZ position paper).

### **Supplementation with vitamin D**

Recommendations are for use of oral vitamin D2 or D3 as daily and intermittent vitamin D3 high-dose therapy (also called “stoss therapy”). Stoss therapy has not been recommended for infants <3 months of age (1+++, A)<sup>31,32</sup> (table 4). Clinically groups that can benefit from stoss therapy are those older than 3 months at risk of non-adherence. Intramuscular treatment is a therapeutic option for patients with malabsorption. Oral calcium supplementation (500 mg/day) should be routinely used in conjunction with vitamin D regardless of age or weight for the treatment of NR (1+++, A)<sup>33,34</sup>.

Current Australian recommendations are specified according to 25OHD levels and not predicated on the treatment of NR (table 4). The ANZ statement for infants, children and adolescents<sup>2</sup> provides specific dosing schedules for groups with vitamin D insufficiency (25OHD 30-49 nmol/L) that are at risk of vitamin D deficiency (table 4). Any treatment of nutritional rickets needs to be followed by maintenance supplementation with vitamin D.

The APEG Bone and Mineral Working Group endorses the dosing schedule for nutritional rickets as suggested by the global consensus guidelines. However, we point out that further studies are needed to clarify dosing for preterm infants.

Use in combination with ANZ guidelines is recommended to provide guidance for the treatment of vitamin D insufficiency.

Based on clinical events in Australia we raise concerns and a warning against self-medication with high doses of vitamin D obtained through the internet. These medications can cause vitamin D intoxication if not administered under medical supervision<sup>35,36</sup>.

### **Public Health strategies**

Within the general paediatric population there are data suggesting an increase in the incidence of vitamin D deficiency<sup>26,37,38</sup>. For adults the Australian Health Survey<sup>39</sup> showed vitamin D deficiency in 31% of 18-34 year olds, 15% of 65-74 year olds and 20% in those aged 75 years and older. Fifteen percent of 12-17 year olds were deficient with similar rates for males and females. There were no data for younger age groups. A study of the Australian Paediatric Surveillance Unit (APSU) revealed an incidence for vitamin D deficiency rickets of 4.9/100,000 in children with a median age of 6.3 years (range 0.2-15 years). Most children had dark or intermediate skin colour and were from Africa with a refugee background<sup>9</sup>. In New Zealand the incidence of rickets in children aged <15 years was 2.2/100,000 (95%CI 1.4-3.5); in those <3 years 10.5/100,000 (95%CI 6.7 - 16.6)<sup>40</sup>. Internationally, nutritional rickets is a significant health problem in Asia, Africa and the Middle East<sup>37</sup>.

Establishing public health strategies to “eradicate rickets” is a very strong component of the global guidelines. Nutritional rickets, osteomalacia, and vitamin D and calcium deficiencies are characterized as preventable global public health problems in infants, children, and adolescents (1+++ , A). Recommendations are made against population-based screening with serum 25OHD, serum alkaline phosphatase, or radiographs (1+++ , A)<sup>41,42</sup>. Instead, screening for nutritional rickets should be based on clinical features, followed by radiographic confirmation of suspected cases (1+++ , A)<sup>41,42</sup>.

Suggested public health strategies for rickets prevention include universal supplementation (1+++ , A)<sup>43</sup> with vitamin D supplements being incorporated into childhood primary health care programs and antenatal care programs.

A study from Turkey demonstrated that the incidence of rickets could be reduced through universal vitamin D supplementation and public health initiatives as advocated in most European countries<sup>37,44</sup>. Doses recommended by the global consensus for universal vitamin D supplementation are 400 IU/day (10 mcg/day) for all infants from birth to 12 months of age (1+++ , A)<sup>21</sup>. Only individuals with risk factors should receive 600 IU/d (15 mcg/day) thereafter, independent of the mode of feeding(1+++ , A)<sup>21</sup>. Rickets prevention programs should be implemented in populations with a high prevalence of vitamin D deficiency or limited vitamin D and/or calcium intakes and in groups of infants and children at risk of rickets (1+++ , A)<sup>43</sup>. This is different to the paediatric ANZ position statement that recommended prevention with 200 IU/day for preterm infants and 400 IU/day for age groups from <3 month old term infants to 18 years only in populations with risk factors.

Furthermore it is suggested by the global consensus to fortify staple foods with vitamin D and calcium, as appropriate, based on dietary patterns, because food fortification has been shown to increase 25OHD levels and dietary calcium intake sufficiently to prevent rickets in infants, children and adolescents (1+++ , A)<sup>45,46</sup>. In Australia and New Zealand there is experience with food fortification from the addition of iodine and folic acid to bread (Food Standards Australia New Zealand, [www.foodstandards.gov.au](http://www.foodstandards.gov.au)).

There is a need for health economic models to analyse the cost-effectiveness of supplementation strategies and food fortification programs for vitamin D to be initiated in Australia. To our knowledge a campaign for universal vitamin D supplementation has not been started in Australia or New Zealand. North American and European countries have extensive experience with programs for universal vitamin D supplementation. A public health strategy combining

universal vitamin D supplementation and health education in an ethnic minority at risk of vitamin D deficiency was described in Birmingham, United Kingdom<sup>47</sup>. An example of and analysis of a prevention program looking at older adults has been provided by Lee et al. (2013)<sup>48</sup>. Factors for analysis include medication cost, quality of life and health benefit<sup>48</sup>. An internet search (Search question: “vitamin D suspension Australia”) revealed that over the counter vitamin D supplements cost approximately AU\$ 0.22 for 400 IU/day. Data on the impact on quality of life and health benefit were not available.

In principal the APEG Bone and Mineral Working Group supports the goal of promoting efforts to address the public health impact of nutritional rickets as both a clinical and a public health issue.

We conclude that updated global recommendations for therapy of nutritional rickets complement previously published position statements for Australia and New Zealand. Screening, universal vitamin D supplementation, management and the implementation of public health strategies need to be further explored for Australia.

#### **Competing interests statement**

Competing interests: No relevant disclosures.

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**Tables**

- Table 1: Grading of Recommendations, Assessment, Development and Evaluation system (GRADE) and National Health and Medical Research Council (NHMRC) levels of evidence
- Table 2: Classification of 25OHD status comparing the global consensus guidelines and the ANZ position paper
- Table 3: Classification of calcium intake comparing the global consensus guidelines and the ANZ position paper
- Table 4: Overview of vitamin D dosage regimens comparing the global consensus guidelines and the ANZ position paper

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Table 1

## GRADE System

Recommendation	Level of evidence	
<b>1: Strong</b> Applies to most patients, benefits outweigh the risk  <b>2: Weak</b> Expert consensus, recommendation should be considered, benefits depend on patient situation; benefits and risk are closely balanced or uncertain	<b>+++</b> High quality	Prospective cohort studies or randomised controlled trials, RCT, low risk of bias
	<b>++O</b> Moderate quality	Observational studies, trials with methodological issues, inconsistent or indirect evidence
	<b>+OO</b> Low quality	Case series or nonsystematic clinical observations

## NHMRC levels of evidence

Grade of recommendation	Description
<b>A</b>	Body of evidence can be trusted to guide practice
<b>B</b>	Body of evidence can be trusted to guide practice in most situations
<b>C</b>	Body of evidence provides support for recommendation(s) but care should be taken in its application
<b>D</b>	Body of evidence is weak and recommendation must be applied with caution

Table 2: Classification of 25OHD status

25OHD (nmol/L)	ANZ: Children and adolescents position paper (2013) <sup>2</sup>	Global guidelines (2016) <sup>1</sup>	APEG Working group comment (2020)
<12.5	Severe deficiency	Deficiency	Consistent definitions. The global guidelines combine moderate and severe deficiency. The working group recommends the global definitions.
12.5-29	Moderate deficiency		
30-49	Mild deficiency	Insufficiency	
50	≥50: Sufficient	>50: Sufficiency	
>250	Elevated	Toxicity	

Table 3: Classification of calcium intake

Age group	ANZ: Children and adolescents position paper (2013) <sup>2</sup>	Global guidelines (2016) <sup>1</sup>	APEG Working group comment (2020)
0-6 months	AI 200 mg/d	AI <sup>†</sup> 200 mg/d	The APEG working group follows these recommendations that are identical in both publications
6-12 months	AI 200 mg/d	AI 260 mg/d	The APEG working group follows the global guidelines recommending higher intake of 260mg/d between 6-12 months of age
>1 yr	RDA <sup>‡</sup>  1-3 yr: 700 mg/d 3-8 yr: 1000 mg/d 9-18 yr: 1300 mg/d	Deficiency <300 mg/d  Insufficiency 300-500 mg/d  Sufficiency >500 mg/d	There is no specific calcium intake recommended in the global guidelines, instead a guide is provided of what is classified as sufficient or not.  The APEG working group follows the ANZ guidelines
Pregnant/lactating women	14-18 yr: 1000 mg/d >18 yr: 1300 mg/d	N/A	The APEG working group follows the ANZ guidelines

†: Adequate intake, ‡: Recommended daily allowance

Table 4: Overview of vitamin D dosage regimens

	ANZ: Children and adolescents position paper (2013) <sup>2</sup>	Global guidelines (2016) <sup>1</sup>	APEG Working group comment (2020)
<b>Vitamin D Supplementation</b>			
<b>Age group</b>	<b>25OHD 30-49 nmol/L</b>	<i>Only for the prevention of nutritional rickets</i>	Recommendations of the global consensus are based on the presence of nutritional rickets. There are no specific doses for supplementation based on 25OHD levels like in ANZ guidelines. The ANZ paediatric statement provides specific dosages for vitamin D insufficiency. The APEG working group recommends following the global guidelines for <b>treatment and prevention of nutritional rickets</b> . For patients with 25OHD levels between <b>30-49 nmol/L, specifically preterm babies</b> we recommend following the ANZ paediatric guidelines
Preterm	200 IU/d, max 400 IU/d	No specific recommendation	
<3 months	<400 IU/d for 3 mo	400 IU/d	
3-12 months	400 IU/d for 3 mo		
1-18 years	1000-2000 IU/d for 3 mo or 150,000 IU stat	600 IU/d	
	<b>25OHD &lt;30 nmol/L</b>	<i>If nutritional rickets present – spectrum of vitamin D and/or calcium deficiency</i>	
Preterm	800 IU/d, review after 1 mo	No specific recommendation	
<3 months	1000 IU/d for 3 mo	2000 IU/d for 90 d, single dose not recommended	
3-12 months	1000 IU/d for 3 mo or 50,000 IU stat, review after 1 mo and consider repeat	2000 IU/d for 90 d single dose 50,000 IU	
1-18 years	1000-2000 IU/d for 6 mo, 3000-4000 IU/d for 3 mo or single dose 150,000 IU and repeat after 6 weeks	+1 to 12 yr: 3000-6000 IU for 90d single dose 150,000 IU >12 yr: 6000 IU/d x 90d, single dose 300,000 IU	
<b>Maintenance</b>			
preterm	Preterm: 200 IU/kg/d, max 400 IU/d	No preterm recommendations	The APEG working group recommends following the ANZ paediatric guidelines for preterm infants and the global guidelines for other age groups
<3-12 months	400 IU/d	400 IU/d	
1-18 years	400 IU/d or 150,000 IU stat at beginning of autumn	600 IU/d	