

## Prevention and treatment of nutritional rickets

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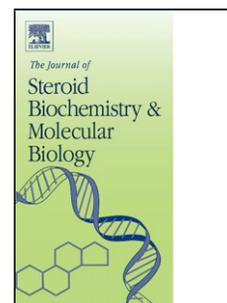
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## Prevention and treatment of nutritional rickets

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**Highlights**

- Nutritional rickets is due to a variable combination of vitamin D deficiency and dietary calcium deficiency in growing children
- There is evidence of an increasing incidence of nutritional rickets in several developed countries
- Prevention of nutritional rickets can be achieved by ensuring that pregnant women and infants receive regular supplements of vitamin D
- Treatment of nutritional rickets requires a combination of oral vitamin D and adequate dietary calcium intake
- Vitamin D supplementation of infants should be regarded as having a similar level of importance as immunisation.

**Abstract**

Nutritional rickets continues to be a significant health problem for children worldwide with recent evidence of increasing incidence in many developed countries. It is due to vitamin D deficiency and/or inadequate dietary calcium intake with variation in the relative contributions of each of these dependant on environmental factors such a dietary intake and sunlight exposure. Key to the prevention of rickets is ensuring that pregnant women and their infants receive vitamin D supplementation with good evidence from randomised controlled trials that infants who receive 400iu daily can achieve levels of 25 hydroxyvitamin D of > 50 nmol/l. However public health implementation of daily supplementation is more challenging with a need to revisit food fortification strategies to ensure optimal vitamin D status of the population. Treatment of nutritional rickets has traditionally been with Vitamin D2 or D3, often given as a daily oral dose for several weeks until biochemical and radiological evidence of healing. However other treatment regimes with single or intermittent high doses have also proved to be effective. It is now recognised that oral calcium either as dietary intake or supplements should be routinely used in conjunction with vitamin D for treatment.

Keywords: Nutritional rickets, Vitamin D, dietary calcium deficiency

## **Incidence**

Despite the fact that nutritional rickets is a readily preventable condition it continues to be prevalent around the world with evidence of increasing incidence in several developed countries. There was a recognised resurgence of children presenting with rickets in the United Kingdom at the end of the twentieth century[1]. A survey of paediatricians in the West Midlands region in 2001 identified an overall incidence of 7.5 per 100,000 children under 5 years but with striking ethnic differences of 38 per 100,000 South Asian and 95 per 100,000 African-Caribbean children respectively[2]. A survey in Southern Denmark between 1995 to 2005 in children up to age 15 years showed an incidence of 2.9 per 100,000 with again much higher incidence in those of African or Middle Eastern ethnic origin[3]. A survey of X-ray confirmed cases in Minnesota children less than 3 years over the twenty year period 1980-2000 showed a tenfold rise from 2.2 to 24.1 per 100,000[4]. A survey of hospital discharge episodes of cases of rickets in England between 1968 to 2011 showed low rates in the 1960's and 1970's which declined further in the 1980's and 1990's but started to increase in the 2000's with an annual incidence between 2007 to 2011 of 4.78 per 100,000 children less than 15 years[5]. In an attempt to obtain accurate contemporary data on the incidence of rickets in UK children the British Paediatric Surveillance Unit is conducting a prospective survey of all reported cases of rickets due to Vitamin D deficiency.

## **Aetiological Factors**

Although traditionally nutritional rickets is felt to be due to Vitamin D deficiency it is increasingly clear that dietary calcium deficiency is an important factor. The relative contributions of vitamin D deficiency and inadequate dietary calcium intake vary in different parts of the world. A recent case control study of infants with rickets presenting to a tertiary centre in Northern India showed that despite similar concentrations of 25-hydroxyvitamin D the cases had a much lower dietary calcium intake of 204 mg daily in contrast to the controls with 453 mg daily[6]. The proportion of dietary calcium obtained from dairy sources was only 85mg daily in the cases with 401 mg in the controls.

Vitamin D deficiency is due to a variety of factors that may affect the synthesis, dietary intake or metabolism of Vitamin D ( see Table 1). Reflecting the fact that cutaneous synthesis from sunlight exposure on the skin is the main source of Vitamin D those factors that compromise sunlight exposure are often the most important. However in an individual child there are often several interacting factors eg a dark skinned infant born to a severely deficient mother in a climate with inadequate ultraviolet radiation for many months of the year.

### **Prevention**

The prevention of nutritional rickets is potentially achievable by three mechanisms these being sunlight exposure, food fortification and vitamin D supplementation. Although many guidelines on prevention of Vitamin D deficiency recommend “safe sunlight exposure” it is often not clearly defined. Studies undertaken in healthy adults using ultraviolet radiation chambers to simulate UK summer sunlight exposure has shown that white subjects can achieve a 25-hydroxyvitamin D level of  $> 50$  nmol/l if they spend thirty minutes three times per week in the sun[7]. However none of the South Asian subjects were able to achieve such a level and they would require a fourfold longer duration ie two hours three times per week. It is clear that reliance on sunlight exposure would not be adequate for many ethnic groups. Food fortification has been shown to be an effective strategy for improving Vitamin D status. A study undertaken in Indian schoolchildren who were randomised to consume 200mls of milk daily for 12 weeks that was either unfortified or contained 600 or 1000iu of Vitamin D showed that those receiving fortified milk could achieve 25-hydroxyvitamin D levels of  $> 50$  nmol/l[8]. However food fortification of staple foods with Vitamin D varies throughout the world with this being limited to margarine, breakfast cereals and some yoghourts in the UK whilst in Canada and the USA most cows milk is fortified. Therefore many countries rely on Vitamin D supplementation of vulnerable groups to prevent rickets. Several lines of evidence have shown that to prevent rickets in infants they need to have a 25-hydroxyvitamin D concentration of  $> 30$  nmol/l. An RCT undertaken in healthy breastfed infants in Montreal who were randomised to one of four daily Vitamin D doses showed that those receiving 400iu daily could achieve a satisfactory 25OHD concentration at 3, 6 and 12

months[9]. This dose was shown to be effective when provided free of charge to all Turkish infants up to age 12 months with the prevalence of rickets in the Erzurum region falling from 6% to 0.1%[10]. A similar strategy employed in Birmingham, UK was shown to reduce the incidence of symptomatic vitamin D deficiency in young children by 59%[11]. However it is recognised that uptake of daily vitamin D supplements can be difficult with a study from Quebec showing that despite free vitamin D supplements for all breastfed infants the annual prevalence of vitamin D exposure was only 17.9% with 50% of mothers only obtaining one bottle of the supplements[12]. Vitamin D supplementation also needs to be provided to pregnant and lactating women. Although there is considerable debate as to the amount of vitamin D required it is felt that 600iu daily is adequate to prevent maternal vitamin D deficiency.

## **Treatment**

The treatment of nutritional rickets has usually been with ergocalciferol ( Vitamin D<sub>2</sub>) or cholecalciferol ( Vitamin D<sub>3</sub>) given on a daily basis for several weeks. Many of the existing guidelines recommend daily doses of between 1000 to 10,000iu depending on the age of the child for between 8 to 12 weeks. However there is little good evidence to support these dose regimes with a lack of randomised controlled comparison trials to demonstrate safety and efficacy. An alternative strategy is the use of high doses of vitamin D given as a single dose or split doses over several weeks which is referred to as stoss therapy. A non randomised study undertaken in Turkish children with 25OHD concentrations < 20 ng/ml (50 nmol/l ) compared 2,000iu of Vitamin D<sub>3</sub> given daily for 6 weeks with a single dose of 150,000iu orally. Higher concentrations of 25OHD were seen at 6 weeks in those who received a single dose (50.4 ng/ml, 126 nmol/l ) than those who received daily dosing (25.4 ng/ml, 63.5 nmol/l) with no episodes of hypercalcaemia or hypercalciuria[13]. Indian children with rickets were randomised to receive either 300,000 or 600,000iu vitamin D<sub>3</sub> as a single dose. Although all subjects had radiological evidence of healing at 12 weeks hypercalcaemia was seen in 5 children, two who received the lower dose and three with the higher dose[14]. Several studies have examined the combination of oral calcium supplements in conjunction with vitamin D. A study undertaken in Northern Nigeria of

children with calcium deficiency rickets showed that those who were treated with daily calcium (1000mg) either alone or in conjunction with vitamin D had a better healing response than those who only received vitamin D[15]. A similar result was seen in a study of Indian children with rickets randomised to receive a single intramuscular dose of 600,000iu of vitamin D3, oral calcium of 75mg/kg daily for twelve weeks or a combination of the two. A higher proportion of those receiving the combination (50%) achieved a normal alkaline phosphatase and radiological healing at 12 weeks than those receiving calcium alone (11.7%) or vitamin D alone (15.7%)[16]. An international consensus meeting on Nutritional Rickets held in May 2014 has recommended that a minimum vitamin D2 or D3 dose of 2,000iu daily for a period of 12 weeks and that oral calcium 500mg daily either as dietary intake or supplements is routinely used in conjunction with vitamin D for treatment[17] (Table 2).

Unfortunately nutritional rickets continues to be the commonest form of bone disease in children worldwide. Current patterns of migration ensure that many high risk groups are present in many countries. Adequacy of vitamin D and dietary calcium intake are essential in its prevention. Vitamin D supplementation should be regarded with a similar level of importance as immunisation and health care systems need to develop mechanisms to ensure a high level of uptake.

## References

1. Pal BR, Shaw NJ. Rickets resurgence in the United Kingdom: improving antenatal management in Asians. *J Pediatr*. 2001 Aug;139(2):337-8
2. Callaghan AL, Moy RJ, Booth IW, DeBelle G, Shaw NJ. Incidence of symptomatic vitamin D deficiency. *Arch Dis Child* 2006;91(7):606-7.
3. Beck-Nielsen SS, Brock-Jacobsen B, Gram J, Brixen K, Jensen TK. Incidence and prevalence of nutritional and hereditary rickets in southern Denmark. *Eur J Endocrinol*. 2009 Mar;160(3):491-7.
4. Thacher TD, Fischer PR, Tebben PJ, Singh RJ, Cha SS, Maxson JA, Yawn BP. Increasing incidence of nutritional rickets: a population-based study in Olmsted County, Minnesota. *Mayo Clin Proc*. 2013 Feb;88(2):176-83
5. Goldacre M, Hall N, Yeates DG. Hospitalisation for children with rickets in England: a historical perspective. *Lancet*. 2014 Feb 15;383(9917):597-8
6. Aggarwal V, Seth A, Aneja S, Sharma B, Sonkar P, Singh S, Marwaha RK. Role of calcium deficiency in development of nutritional rickets in Indian children: a case control study. *J Clin Endocrinol Metab*. 2012 Oct;97(10):3461-6.
7. Farrar MD, Webb AR, Kift R, Durkin MT, Allan D, Herbert A, Berry JL, Rhodes LE. Efficacy of a dose range of simulated sunlight exposures in raising vitamin D status in South Asian adults: implications for targeted guidance on sun exposure. *Am J Clin Nutr*. 2013 Jun;97(6):1210-6.

8. Khadgawat R, Marwaha RK, Garg MK, Ramot R, Oberoi AK, Sreenivas V, Gahlot M, Mehan N, Mathur P, Gupta N. Impact of vitamin D fortified milk supplementation on vitamin D status of healthy school children aged 10-14 years. *Osteoporos Int*. 2013 Aug;24(8):2335-43.
9. Gallo S, Comeau K, Vanstone C, Agellon S, Sharma A, Jones G, L'Abbé M, Khamessian A, Rodd C, Weiler H. Effect of different dosages of oral vitamin D supplementation on vitamin D status in healthy, breastfed infants: a randomized trial. *JAMA*. 2013 May 1;309(17):1785-92.
10. Hatun Ş, Ozkan B, Bereket A. Vitamin D deficiency and prevention: Turkish experience. *Acta Paediatr*. 2011 Sep;100(9):1195-9.
11. Moy RJ, McGee E, Debelle GD, Mather I, Shaw NJ. Successful public health action to reduce the incidence of symptomatic vitamin D deficiency. *Arch Dis Child*. 2012 Nov;97(11):952-4.
12. Millette M, Sharma A, Weiler H, Sheehy O, Bérard A, Rodd C. Programme to provide Quebec infants with free vitamin D supplements failed to encourage participation or adherence. *Acta Paediatr*. 2014 Oct;103:e444-9.
13. Emel T, Doğan DA, Erdem G, Faruk O. Therapy strategies in vitamin D deficiency with or without rickets: efficiency of low-dose stoss therapy. *J Pediatr Endocrinol Metab*. 2012;25(1-2):107-10.
14. Mittal H, Rai S, Shah D, Madhu SV, Mehrotra G, Malhotra RK, Gupta P. 300,000 IU or 600,000 IU of oral vitamin D3 for treatment of nutritional rickets: a randomized controlled trial. *Indian Pediatr*. 2014 Apr;51(4):265-72.

15. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Isichei CO, Reading JC, Chan GM. A comparison of calcium, vitamin D, or both for nutritional rickets in Nigerian children. *N Engl J Med*. 1999 Aug 19;341(8):563-8.
16. Aggarwal V, Seth A, Marwaha RK, Sharma B, Sonkar P, Singh S, Aneja S. Management of nutritional rickets in Indian children: a randomized controlled trial. *J Trop Pediatr*. 2013 Apr;59(2):127-33.
17. Munns CF, Shaw N, Kiely M, Specker BL, Thacher TD, Ozono K, Michigami T, Tiosano D, Mughal MZ, Mäkitie O, Ramos-Abad L, Ward L, DiMeglio LA, Atapattu N, Cassinelli H, Braegger C, Pettifor JM, Seth A, Idris HW, Bhatia V, Fu J, Goldberg G, Säwendahl L, Khadgawat R, Pludowski P, Maddock J, Hyppönen E, Oduwole A, Frew E, Aguiar M, Tulchinsky T, Butler G, Högl W. Global Consensus Recommendations on Prevention and Management of Nutritional Rickets – *J Clin Endocrinol Metab* 2015 –In press.

**Table 1: Vitamin D Deficiency – Aetiological Factors**

|                                    |
|------------------------------------|
| • Vitamin D synthesis:             |
| Latitude                           |
| Atmospheric pollution              |
| Clothing                           |
| Melanin pigmentation               |
| Sunlight exposure                  |
| • Vitamin D intake:                |
| Prolonged exclusive breast feeding |
| Maternal Vitamin D deficiency      |
| Unusual diets                      |
| • Vitamin D metabolism:            |
| Low calcium intake                 |
| Intestinal calcium absorption      |
| Genetic variation                  |

**Table 2: Treatment Doses for Nutritional Rickets**

| Age                   | Daily dose for 12 weeks | Single Dose | Maintenance daily dose |
|-----------------------|-------------------------|-------------|------------------------|
| < 3 months            | 2000 iu                 | N/A         | 400 iu                 |
| 3 – 12 months         | 2000 iu                 | 50,000iu    | 400 iu                 |
| 12 months to 12 years | 3000-6000 iu            | 150,000 iu  | 600 iu                 |
| ➤ 12 years            | 6000 iu                 | 300,000 iu  | 600 iu                 |

Ensure a daily calcium intake of 500mg. Reassess response to treatment after 12 weeks as further treatment may be required.