Editorial

Vitamin D and child health: some emerging issues

The recent series in *The Lancet* highlights the global burden of maternal and child undernutrition and underscores that nearly 11% of all under five deaths are related to four micronutrient deficiencies (vitamin A, zinc, iron and iodine) (Black *et al.* 2008). However, little is known about the global magnitude of vitamin D deficiency and related interventions that might potentially make a difference to health and nutrition outcomes (Bhutta *et al.* 2008). While severe vitamin D deficiency is widely recognized as a cause of acquired rickets in countries with cold climate and poor exposure to sunlight (Wharton & Bishop 2003), the problem is regarded as multi-factorial. Vitamin D deficiency has now been recognized in many instances as a combination of dietary inadequacy and poor exposure to sunlight (Holick 2006). In several regions such as Africa (Pettifor 2004) and the Middle East (Dawodu *et al.* 2001) the contribution of dietary calcium and vitamin D deficiency to rickets has been underscored. Subclinical vitamin D deficiency has thus been described from many developing countries, even in those with reasonable exposure to sunlight (Salimpour 1975; Garabedian & Ben-Mekhbi 1991; Ghai & Koul 1991; Zhao 1991). In other instances subclinical vitamin D deficiency in mothers has been associated with hypocalcaemia and seizures in young infants (Ahmed *et al.* 1995), indicating that the problem may also be associated with subclinical intrauterine deficiencies.

Our understanding of the metabolism and regulation of vitamin D has greatly improved over the last few years (Holick 2007). Solar ultraviolet B radiation (wavelength, 290–315 nm) penetrates the skin and converts 7-dehydrocholesterol to previtamin D3, which is rapidly converted to vitamin D3. Dietary intake of preformed vitamin D (either as D2 or D3) becomes important in circumstances with poor exposure to sunlight. Both forms of vitamin D are 25-hydroxylated to an intermediate metabolite, 25-hydroxyvitamin D (25OHD) which is further altered to 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], the major active form of vitamin D, in the kidneys and some extra renal tissues. Serum phosphorus, calcium, fibroblast growth factor 23, and other factors can influence the renal production of $1,25(OH)_2D$. $1,25(OH)_2D$ enhances renal calcium and intestinal calcium and phosphorus absorption and also induces the expression of the enzyme 25OHD-24-hydroxylase which catabolizes both 25OHD and $1,25(OH)_2D$ into biologically inactive, water-soluble calcitroic acid. While renal production of $1,25(OH)_2D$ by 1α-hydroxylase activity is tightly-regulated by parathyroid hormone, the extra-renal synthesis of $1,25(OH)_2D$ is thought to be preferentially regulated by autocrine/paracrine factors (e.g. cytokines such as interferon-γ) (Vidal *et al.* 2002). The expression of the machinery required to synthesize $1,25(OH)_2D$ in normal human tissues seems to be much more widespread than originally thought and may indicate a greater role for vitamin D in health and disease than skeletal and calcium metabolism.

1,25-dihydroxyvitamin D directly or indirectly controls more than 200 genes, including genes responsible for the regulation of cellular proliferation, differentiation, apoptosis and angiogenesis (Nagpal *et al.* 2005; Holick 2006; Holick & Garabedian 2006). $1,25(OH)_2D$ is also recognized as a potent immunomodulator when produced in monocytes or macrophages, is released to act locally on activated T lymphocytes which regulate cytokine synthesis, and activated B lymphocytes which regulate immunoglobulin synthesis (Nagpal *et al.* 2005). Wang *et al.* (2004) have also shown that $1,25(OH)_2D$ directly induces antimicrobial gene expression (camp and deficin B2 expression). Monocytes and macrophages exposed to a lipopolysaccharide or to *Mycobacterium tuberculosis* up-regulate the vitamin D receptor gene and the 25OHD-1α-hydroxylase gene. Increased production of $1,25(OH)_2D$ result in synthesis of cathelicidin, a peptide capable of destroying *M. tuberculosis* as well as other infectious agents. In an elegant experiment (Liu *et al.* 2007) the human monocytic cell line THP-1 was infected with *M. tuberculosis* H37Ra and then activated with the active $1,25(OH)_2D$ resulting in expression of cathelicidin mRNA and protein. This $1,25(OH)_2D$-induced antimicrobial activity was

completely inhibited in the presence of siRNA against cathelicidin, instead leading to enhanced intracellular growth of mycobacteria. In another landmark study it was demonstrated that Toll-like receptors (TLRs) activation of human macrophages up-regulated expression of the vitamin D receptor and the vitamin D-1-hydroxylase genes, leading to induction of the cathelicidin and killing of intracellular *M tuberculosis* (Liu *et al.* 2006). It was also observed that sera from African-American individuals, known to have increased susceptibility to tuberculosis, had low 25OHD and were inefficient in supporting cathelicidin messenger RNA induction. These experimental data support a link between TLRs and vitamin D-mediated innate immunity and suggest that differences in the ability of human populations to produce vitamin D may contribute to susceptibility to microbial infection.

These laboratory data are supported by epidemiological observations indicating the link between vitamin D deficiency and increased susceptibility to tuberculosis. In a recent systematic review (Nnoaham & Clarke 2008) of seven observational studies published between 1980 and July 2006, it has been shown that low serum vitamin D levels are associated with higher risk of active tuberculosis [the pooled effect size representing the mean reduction in vitamin D levels in patients was 0.68 with 95% confidence intervals (CI) 0.43–0.93, random effects]. These findings suggested that low body vitamin D levels increase the risk of active tuberculosis in susceptible populations.

Despite the epidemiological information on widespread vitamin D deficiency among children in developing countries, corresponding data on associated risk of infections are lacking. A large proportion of children with respiratory infections have been shown to have rickets (Zhuravskaia 1962; Salimpour 1975; Rehman 1994) and there is indirect evidence to suggest that vitamin D deficiency may substantially increase the risk of severe pneumonia among children aged less than 5 years. In a study from Ethiopia (Muhe *et al.* 1997), in contrast to 4% among controls, 42% of children hospitalized with pneumonia had rickets (adjusted odds ratio 13.4, 95% CI 8.1–24.2). In India (Wayse *et al.* 2004), 80% of children with pneumonia had subclinical vitamin D deficiency compared with 31% of healthy children. However, there are no published intervention studies exploring the potential benefit of supplementing with vitamin D on acute respiratory infections or pneumonia in children.

What are the next steps? We certainly need better and more representative information on the epidemiology, risk factors and distribution of vitamin D deficiency among children globally. Although dietary calcium deficiency has been suggested as a major risk factor for rickets in tropical climates (Pettifor 2004), there are convincing reports that lack of exposure to sunlight plays a significant role in the development of rickets as well (Lulseged & Fitwi 1999). It is likely that development of rickets in children may be a consequence of several risk factors, including low calcium intake, vitamin D deficiency, dietary constituents (e.g. phytates), and genetic polymorphisms affecting vitamin D metabolism (Pettifor 2004; Kaneko *et al.* 2007). Given the possibility that both vitamin D and calcium deficiency may be associated with rickets and stunting in developing countries, there is an urgent need to obtain greater representative clinical information on the global and regional prevalence of this disorder. With the emerging evidence that vitamin D status is related to immune function and propensity to develop infections, it is important to obtain information on the potential contribution, if any, of this deficiency to the burden of respiratory illness and mortality in children. If subclinical vitamin D deficiency contributes to the global burden of respiratory and other childhood infections, there can be exciting potentials to ameliorate the burden through appropriate nutrition interventions.

Zulfiqar A. Bhutta
Husein Lalji Dewraj Professor and Chairman
Department of Paediatrics and Child Health
The Aga Khan University
Karachi
E-mail: zulfiqar.bhutta@aku.edu

References

Ahmed I., Atiq M., Iqbal J., Khurshid M. & Whittaker P. (1995) Vitamin D deficiency rickets in breast-fed infants presenting with hypocalcaemic seizures. *Acta Paediatrica* **84**, 941–942.

Bhutta Z.A., Ahmed T., Black R.E., Cousens S., Dewey K., Giugliani E. *et al*. (2008) What works? Interventions for maternal and child undernutrition and survival. *Lancet* **371**, 417–440.

Black R.E., Allen L.H., Bhutta Z.A., Caulfield L.E., de Onis M., Ezzati M. *et al*. (2008) Maternal and child undernutrition: global and regional exposures and health consequences. *Lancet* **371**, 243–260.

Dawodu A., Dawson K.P., Amirlak I., Kochiyil J., Agarwal M. & Badrinath P. (2001) Diet, clothing, sunshine exposure and micronutrient status of Arab infants and young children. *Annals of Tropical Paediatrics* **21**, 39–44.

Garabedian M. & Ben-Mekhbi H. (1991) Is vitamin D deficiency rickets a public health problem in France and Algeria? In: *Rickets* (ed. F.H. Glorieux), pp. 247–252. Raven: New York.

Ghai O.P. & Koul P.B. (1991) Rickets in India. In: *Rickets* (ed. F.H. Glorieux), pp. 247–252. Raven: New York.

Holick M.F. (2006) Resurrection of vitamin D deficiency and rickets. *The Journal of Clinical Investigation* **116**, 2062–2072.

Holick M.F. (2007) Vitamin D deficiency. *The New England Journal of Medicine* **357**, 266–281.

Holick M.F. & Garabedian M. (2006) Vitamin D: photobiology, metabolism, mechanism of action, and clinical applications. In: *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism* (ed. M.J. Favus), pp. 129–137. American Society for Bone and Mineral Research: Washington, DC.

Kaneko A., Urnaa V., Nakamura K., Kizuki M., Seino K., Inose T. *et al*. (2007) Vitamin D receptor polymorphism among rickets children in Mongolia. *Journal of Epidemiology and Community Health* **17**, 25–29.

Liu P.T., Stenger S., Li H., Wenzel L., Tan B.H., Krutzik S.R. *et al*. (2006) Toll-like receptor triggering of a vitamin D-mediated human antimicrobial response. *Science* **311**, 1770–1773.

Liu P.T., Stenger S., Tang D.H. & Modlin R.L. (2007) Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. *The Journal of Immunology* **179**, 2060–2063.

Lulseged S. & Fitwi G. (1999) Vitamin D deficiency rickets: socio-demographic and clinical risk factors in children seen at a referral hospital in Addis Ababa. *East African Medical Journal* **76**, 457–461.

Muhe L., Lulseged S., Mason K.E. & Simoes E.A. (1997) Case-control study of the role of nutritional rickets in the risk of developing pneumonia in Ethiopian children. *Lancet* **349**, 1801–1804.

Nagpal S., Na S. & Rathnachalam R. (2005) Noncalcemic actions of vitamin D receptor ligands. *Endocrine Reviews* **26**, 662–687.

Nnoaham K.E. & Clarke A. (2008) Low serum vitamin D levels and tuberculosis: a systematic review and meta-analysis. *International Journal of Epidemiology* **37**, 113–119.

Pettifor J.M. (2004) Nutritional rickets: deficiency of vitamin D, calcium, or both? *American Journal of Clinical Nutrition* **80** (Suppl. 6), S1725–S1729

Rehman P.K. (1994) Sub-clinical rickets and recurrent infection. *Journal of Tropical Pediatrics* **40**, 58.

Salimpour R. (1975) Rickets in Tehran. Study of 200 cases. *Archives of Disease in Childhood* **50**, 63–66.

Vidal M., Ramana C.V. & Dusso A.S. (2002) Stat1-vitamin D receptor interactions antagonize 1,25-dihydroxyvitamin D transcriptional activity and enhance stat1-mediated transcription. *Molecular and Cellular Biology* **22**, 2777–2787.

Wang T.T., Nestel F.P., Bourdeau V., Nagai Y., Wang Q., Liao J. *et al*. (2004) Cutting edge: 1,25-dihydroxyvitamin D_3 is a direct inducer of antimicrobial peptide gene expression. *The Journal of Immunology* **173**, 2909–2912.

Wayse V., Yousafzai A., Mogale K. & Filteau S. (2004) Association of subclinical vitamin D deficiency with severe acute lower respiratory infection in Indian children under 5 years. *European Journal of Clinical Nutrition* **58**, 563–567.

Wharton B. & Bishop N. (2003) *Rickets.* Lancet **362**, 1389–1400.

Zhao X.H. (1991) Rickets in China. In: *Rickets* (ed. F.H. Glorieux), pp. 253–261. Raven: New York.

Zhuravskaia E.L. (1962) Effect of rickets prevention on bronchopneumonia morbidity and mortality in children during the 1st vear of life in rural areas. *Pediatriia Akusherstvo i Ginekologiia* **5**, 32–33.