Nutrition and the Upper Respiratory Tract

14

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Keywords
Zinc • Omega-3 • Vitamin A • Vitamin D • Probiotics • Milk • Immunity • Allergy • Infection • Upper respiratory

Core Messages

- Nutrient deficiencies are common among children and the elderly.
- Probiotics may have a role in the prevention of upper respiratory infections
- Zinc taken daily reduces the incidence of the common cold and reduces both the duration and severity of symptoms once one has developed a cold.
- Vitamin D deficiency is common in the developed world.
- Increasing evidence indicates that vitamin D supplementation has a potential role in the prevention of upper respiratory disease; however, optimal vitamin D levels and dosage regimens remain to be determined.

14.1 Introduction

While many basic scientific studies indicate that nutritional deficiencies can lead to illness and disease, in clinical practice diagnosing and treating potential deficiencies can be difficult. Nutrient deficiencies vary between developing and developed countries. In developing countries multiple nutritional deficiencies may be present, whereas in developed countries obesity and vitamin D deficiency are important nutritional issues (Taylor and Camargo 2011). Nutrient deficiencies are common in children (Black et al. 2008) and in the elderly particularly those in long-term residential care (Cowan et al. 2004). Increasing evidence indicates that zinc and vitamin D supplementation may have a potential role in the prevention of upper respiratory disease (Bartley 2010; Singh and Das 2011; Taylor and Camargo 2011).

14.2 Probiotics

Probiotics are live organisms that, when consumed in adequate quantities, provide health benefits to the host (Reid et al. 2003). Probiotics may have a role in the treatment of both upper

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respiratory infection and allergic rhinitis. Animal studies indicate that probiotics could be beneficial in the treatment of upper respiratory infection (Yasui et al. 2004; Racedo et al. 2006). Probiotics appear useful in reducing acute upper respiratory infection frequency and reducing antibiotic use, but they do not reduce the infective episode length (Hao et al. 2011).

In vitro*,* certain human upper respiratory flora strains, mainly streptococcal species, appear able to prevent pathogenic colonization and infection of the upper respiratory tract (Fujimori et al. 1996; Brook and Gober 1999; Bernstein et al. 2006). *Corynebacterium* spp., a common bacterium of healthy nasal flora, has prevented *Staphylococcus aureus* colonization of nasal cavities in 71 % of volunteers (Uehara et al. 2000). In vivo Esp-secreting *Staphylococcus epidermidis* eliminates *Staphylococcus aureus* from the anterior nose (Iwase et al. 2010). The possibility also exists that the local application of "healthy bacteria" could prevent upper respiratory disease.

> The possibility exists that the local application of "healthy bacteria" could prevent upper respiratory disease, but this has yet to be translated into clinical practice.

When compared to allergic children, *Bifidobacteria* and *Lactobacilli* are found more commonly in the intestinal flora of healthy children (Kalliomaki et al. 2001; Özdemir 2010). Probiotic bacteria in the intestinal microbiota appear to protect against atopy. When probiotics have been given, clinical improvement in allergic rhinitis symptoms has been reported (Peng and Hsu 2005; Giovannini et al. 2007; Ivory et al. 2008; Kawase et al. 2009; Kopp and Salfeld 2009). However, the selection of which probiotic strain/strains, supplement timing, as well as the dosage and method of administration continues to be debated (Kopp and Salfeld 2009; Özdemir 2010).

14.3 Iron

Bacteria need iron for the respiration, DNA synthesis, and free radical-scavenging mechanisms (Doherty 2007). In nasal mucus, the iron-binding proteins transferrin and lactoferrin maintain low iron levels, which protects against microbial infection (Johnson and Wessling-Resnick 2012). In the host, iron deficiency impairs cell proliferation and immune function (Gera and Sachdev 2002). However, iron deficiency is not associated with an increased risk of acute lower respiratory tract infection (Gera and Sachdev 2002), which indicates that it is probably not an upper respiratory infection risk factor. Low iron levels can be associated with other micronutrient deficiencies, particularly zinc deficiency (Bhandari et al. 2007; Grant et al. 2011).

14.4 Vitamin A

Vitamin A is required for epithelial integrity, the production of red blood cells, as well as humoral and cellular immunity. Vitamin A deficiency increases the susceptibility to a number of illnesses including diarrhea (Fischer Walker and Black 2007), measles (Hussey and Klein 1990), and lower respiratory infections (Mayo-Wilson et al. 2011), but not susceptibility to upper respiratory infections (Brown and Roberts 2004). Cod liver oil, as well as children's multivitamin/mineral supplement with selenium and other trace metals, reduces pediatric visits for upper respiratory illness during the winter and early spring by 36–58 % (Linday 2010). Cod liver oil contains vitamin A, but it also contains vitamin D and omega-3 fatty acids, which makes it difficult to totally attribute these results to vitamin A.

14.5 Omega 3

Omega 3 and omega 6 oils are essential fatty acids oils that are eicosanoid precursors, which play important roles in the inflammatory response (Thien et al. 2002; Bath-Hextall et al. 2005). High levels of omega-3 fatty acids in the diet are associated with a decreased risk of allergic rhinitis (Hibbeln et al. 2007). Regular fish consumption before the age of 12 months is also associated with a reduced risk of allergic sensitization to inhalant allergens during the first 4 years of life (Nafstad et al. 2003; Kull et al. 2006). However, omega-3 fatty acid supplementation alone does not improve allergic rhinitis symptoms (Thien et al. 1993). In those patients with Samter's triad (salicylate intolerance, asthma, and nasal polyps), high-dose omega-3 supplementation can be useful clinically (Healy et al. 2008).

High-dose supplementation with omega 3 may be useful in patients with Samter's triad (salicylate intolerance, asthma, and nasal polyps).

14.6 Zinc

Zinc is important in innate immunity. Zinc is involved in T and B lymphocyte function, as well as Th1 cytokine production. The macrophage, in particular, is adversely affected by zinc deficiency (Shankar and Prasad 1998; Haase and Rink 2009). The role of zinc supplementation in the prevention of lower respiratory infection (Brooks et al. 2005; Aggarwal et al. 2007) does not appear to have been translated into the possible prevention of upper respiratory bacterial infection. Zinc taken daily reduces the incidence of the common cold in young children (Singh and Das 2011). Zinc also reduces both the duration and severity of symptoms once one has developed a cold (Singh and Das 2011), although the interpretation of this meta-analysis has been debated (Science et al. 2012). In clinical practice, the assessment of zinc deficiency can be difficult (Gibson et al. 2008).

14.7 Milk

Excessive milk consumption has a long association with increased respiratory tract mucus production and asthma (Bartley and McGlashan 2010). Such an association cannot be explained using a conventional allergic paradigm. In the human colon, ß-casomorphin-7 (ß-CM-7), an exorphin derived from the breakdown of A1 milk, stimulates mucus production from gut MUC5AC glands (Zoghbi et al. 2006). In the presence of inflammation similar mucus overproduction from respiratory tract MUC5AC glands characterizes many respiratory tract diseases (Kirkham et al. 2002; Ding and Zheng 2007). ß-CM-7 from the blood stream could stimulate the production and secretion of mucus production from these respiratory glands. One would have to have a slightly leaky gut and coexisting respiratory inflammation.

A number of studies suggest that the exclusion of milk products from the diet may improve asthma symptoms. In the 1950s, Rowe and Rowe suggested that a variety of foods could contribute to asthma and found symptoms often improved in asthma patients on an exclusion diet (Rowe and Rowe 1956). In an unblinded study, when milk was excluded from the diet, the symptoms of cough and nasal congestion improved particularly at night. Recording bias was used to explain the effect (Pinnock et al. 1989). More recently, in a single-blind prospective study, 22 children with asthma (13 in the experimental and 9 in the control group) received an egg- and milk-free diet for 8 weeks. The children of the experimental group exhibited distinctly decreased IgG antibody concentrations toward ovalbumin and beta lactoglobulin. In 5 children in the experimental group, the peak expiratory flow rate was increased markedly when compared to children in the control group (Yusoff et al. 2004). These studies support the clinical observation that in some situations a cow's milk exclusion diet benefits some patients.

Vitamin D has an important role in innate immunity through the production of the two antimicrobial peptides: cathelicidin and defensin ß2.

14.8 Vitamin D

Vitamin D (25(OH)D) deficiency is common around the world (Holick 2007). Vitamin D is made largely by sun exposure (Holick 2007). Vitamin D appears to have important roles in both innate and adaptive immunity (Bartley 2010). Vitamin D has an important role in innate immunity through the production of the two antimicrobial peptides (AMPs): cathelicidin and defensin ß2. AMPs are synthesized and released largely by epithelial cells and neutrophils. AMPs kill bacteria by inserting themselves into the bacterial cell membrane bilayers to form pores by "barrel-stave," "carpet," or "toroidal-pore" mechanisms. Recent evidence also suggests that AMPs inhibit cell-wall synthesis, nucleic-acid synthesis, protein synthesis, enzymatic activity as well as disrupt mitochondrial membranes (Brogden 2005).

In American adults, serum 25(OH)D levels >75 nmol/L were associated with a reduced incidence of upper respiratory tract infection (Ginde et al. 2009). Rickets is associated with an increased risk of acute respiratory tract infection, particularly pneumonia (Mariam and Sterky 1973; El-Radhi et al. 1982; Banajeh et al. 1997; Muhe et al. 1997; Najada et al. 2004; Banajeh 2009). Pinto and colleagues found low 25(OH)D levels in urban African American, but not white subjects, with chronic rhinosinusitis (Pinto et al. 2008).

Historically, supplementation with cod liver oil (containing vitamin D) was shown to reduce upper respiratory tract infection frequency. The beneficial effect was attributed to vitamin A (Holmes et al. 1932, 1936). In one interventional cohort study where 60,000 IU of vitamin D was given weekly for 6 weeks to children with recurrent respiratory tract infection the incidence of recurrent respiratory tract infection in the children receiving supplementation reduced to that of the control group (Rehman 1994). In some studies where 25(OH)D was given for skeletal health, a reduction in infection risk has also been noted (Aloia and Li-Ng 2007; Avenell et al. 2007).

In recent years a number of randomized controlled trials (Table 14.1) looking at the role of vitamin D supplementation in the prevention of upper respiratory tract infection have been published (Li-Ng et al. 2009; Laaksi et al. 2010; Urashima et al. 2010; Camargo et al. 2012). Li-Ng and colleagues randomized 162 adults to receive 2,000 IU vitamin D_3 daily or matching placebo for 12 weeks. No difference in the duration or severity of URI symptoms was found (Li-Ng et al. 2009). The authors attributed this to a number of reasons. Firstly, the subjects started vitamin D supplementation during winter, rather than at the beginning. Since the half-life of 25(OH)D is at least 2–3 weeks, it is generally accepted that it takes 2–3 months for blood 25(OH)D levels to plateau with vitamin D supplementation if a loading dose is not given (Bacon et al. 2008). This meant that the subjects were reaching optimum 25(OH)D levels at the end of winter and the end of the trial. Secondly, the vitamin D dosage may have been inadequate and thirdly, the baseline 25(OH)D levels were higher than in previous studies meaning that vitamin D supplementation may have been less effective.

Urashima and colleagues gave 334 Japanese school children vitamin D_3 1,200 IU daily or placebo (Urashima et al. 2010). There was a 50 % reduction in children who were diagnosed with influenza A (primary outcome). However, if one combines the number of cases of influenza A and influenza B, there was no reduction in total influenza infections between the vitamin D treated and the control group. Laaksi and colleagues supplemented 164 young Finnish men with only 400 IU/day of vitamin D_3. Absence from duty due to respiratory tract infection and number of days absent was lower in the treated group. The proportion of subjects without any days absent was slightly higher in the vitamin D supplementation group (Laaksi et al. 2010). Martineau and colleagues used high-dose vitamin D_3 in the treatment of pulmonary TB (Martineau et al. 2011). The number of people who had upper respiratory tract infection symptoms was recorded. One of seventy-one patients receiving at least one dose of vitamin D_3 as compared to 6 of 70 receiving at least one dose of placebo reported symptoms. This secondary outcome was of borderline statistical significance ($p = 0.06$). In a recent RCT of 247 Mongolian children with vitamin D deficiency in winter, vitamin D supplementation halved the risk of upper respiratory infections (Camargo et al. 2012).

In the randomized controlled trial (RCT) where Japanese children were given 1,200 IU daily or placebo, children with a previous diagnosis of asthma, there was also a significant reduction in number of asthma attacks (Urashima et al. 2010); only 2 asthmatic children taking vitamin D and 12 taking placebo had "asthma

Table 14.1 Randomized controlled trials (RCTs) on the effect of vitamin D supplementation on respiratory infection

Study authors and n	Type of study, vitamin D dosage, and duration of intervention	Results	Comment
Aloia and Li-Ng (2007), $n=204$	3-year RCT using 2,000 IU/day of vitamin D_3 in African American women	Number of flu or cold episodes in the treated group were 1/3 of the placebo group (8 vs 26, respectively)	Significant reduction of reported flu; small sample
Avenell et al. (2007), $n=1,700$	RCT using 800 IU D_3/day for 24–62 months	No difference in infection or antibiotic usage in previous week	Small dose
Li-Ng et al. (2009), $n=162$	RCT using 2,000 IU vitamin D_3/day for 12 weeks	No significant difference in incidence of flu or cold symptoms	With this dose regimen, it may take more than 3 months to achieve adequate vitamin D levels
Urashima et al. (2010), $n=334$	RCT using 1,200 IU vitamin D_3/day in school children for 4 months	RR of 0.58 compared with control group ($p=0.04$). Asthma attacks significantly reduced in treatment group ($p=0.006$)	Significant reduction of influenza A but not influenza B
Laaksi et al. (2010), $n=164$	RCT using 400 IU vitamin D_3/day for 6 months	No statistically significant difference in days off ($p=0.06$); supplemented group reported as healthier	Low vitamin D supplement and supplemented group almost showed a significant result
Martineau et al. (2011), $n=126$	RCT – 100,000 IU vitamin D_3 at baseline, 12, 28, and 42 days	No significant difference in time to sputum culture conversion ($p=0.14$). Reduction in upper respiratory infection ($p=0.06$)	Sputum culture conversion hastened in *tt* genotype of the *Taql* VDR polymorphism ($p=0.02$)
Majak et al. (2011), $n=48$	RCT of a single dose of 500 IU D_3/day	A significant reduction in acute infective asthma exacerbations due to an upper respiratory infection ($p=0.029$)	Children with a decreased 25(OH)D level eight times more likely to have an asthma exacerbation
Camargo et al. (2012), $n=247$	RCT of 300 IU D_3/day in vitamin D-deficient Mongolian children	Incidence of upper respiratory tract infections halved	

attacks." Recently, Majak and colleagues reported in an RCT on the role of vitamin D supplementation (vitamin D_3 500 IU daily) vs placebo for 6 months in Polish children with newly diagnosed asthma (Majak et al. 2011); the investigators observed a significant reduction in asthma exacerbations due to acute upper respiratory tract infections ($p=0.029$).

Vitamin D deficiency has been linked to an increased incidence of atopy including allergic rhinitis (Ehlayel et al. 2011). However, Hyppönen and colleagues have reported that regular vitamin D supplementation (≥2,000 IU/day) of Finnish infants increases the risk of developing allergic rhinitis and asthma at the age of 31 (Hyppönen et al. 2004). In a separate study in the UK, they also linked deficient (<25 nmol/L) and excessively high (>135 nmol/L) serum 25(OH)D levels with elevated serum IgE levels (Hyppönen et al. 2009). The relationships of vitamin D with allergy appear complex, but a possible "U" shape relationship exists with both low and high 25(OH)D levels predisposing to atopy (Bartley 2010).

A number of RCTs are currently underway worldwide investigating the role of vitamin D supplementation in upper respiratory infection and allergic disease (Bartley 2010). While preliminary data appears promising, optimal 25(OH)D levels and vitamin D treatment regimens for the prevention and/or management of respiratory infections remain to be determined.

Conclusions

Increasing evidence indicates that probiotics, zinc, and vitamin D supplementation could be important clinically. The diagnosis of zinc deficiency in clinical practice can be difficult (Gibson et al. 2008). A number of trials investigating the role of vitamin D supplementation in the prevention of upper respiratory disease are currently underway. Increasing evidence indicates that in vitamin D-deficient patients, vitamin D supplementation can be beneficial in the prevention of upper respiratory tract infection particularly in asthmatic children.

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