Review

Cod Liver Oil, Young Children, and Upper Respiratory Tract Infections

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Cod liver oil contains long-chain omega-3 fatty acids, as well as vitamins D and A. It was a traditional source of vitamin D in the United States and was used to prevent and treat rickets. In our clinical research, we used liquid cod liver oil of adequate purity and acceptable taste for infants and young children, as well as a children's multivitamin/mineral supplement with selenium and other trace metals. In a cluster-randomized study of pediatric visits for upper respiratory illness during the winter and early spring, these nutritional supplements decreased mean visits/subject/month by 36%–58%. Cod liver oil is culturally valued and has been used as a folk remedy by many low-income minorities in the United States. Nutritional supplements cannot be purchased with SNAP benefits (formerly called food stamps). Inclusion of cod liver oil in state Medicaid formularies would make it available to low-income children, whose families may not be able to pay for it out-of-pocket.

Key teaching points

- Vitamins A and D and long-chain omega-3 fatty acids have important roles in immunity and inflammation.
- Historical development in the United States of vitamin D deficiency/insufficiency and decreased long-chain omega-3 fatty acid consumption has been documented.
- Economic and regulatory issues limit the availability of cod liver oil for low-income children in the United States.

HISTORY OF COD LIVER OIL

Historically, cod liver oil was used to treat rickets in children and "old pains" in adults. It was used by members of fishing communities before it was recognized as medically valuable by physicians [1]. In the United States, from the 1920s through the 1950s, many children received 1–4 teaspoons of cod liver oil per day, often given in orange juice; this regimen was begun when infants were only a few months old and was recommended by the U.S. Government [2,3]. Cod liver oil was used for tuberculosis and other "wasting" diseases; it was also used to prevent and treat rickets. Historically, it was known that children with rickets had increased susceptibility to colds, bronchitis, and pneumonia [4]. This continues to be a problem in developing countries in our time [5].

Pediatricians in the United States are concerned about lipoid aspiration pneumonia with cod liver oil; this was a problem in the preantibiotic era, when sick young infants were treated with many different oils, which they sometimes aspirated [6]. U.S. pediatricians are also concerned that cod liver oil can cause vitamin A toxicity [7]. However, the highly concentrated formulations of fish liver oils that were associated with vitamin A toxicity have not been marketed in the United States for many years.

When synthetic vitamins became available, vitamin D was added to milk in the United States, and rickets was no longer a major public health problem [8]. Synthetic vitamins did not have the unpleasant taste of many cod liver oil preparations. However, they do not contain long-chain omega-3 fatty acids; an important dietary source of these fatty acids was therefore lost.

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FATTY ACIDS

During human evolution, the ratio of omega-6 to omega-3 fatty acids in the human diet was about 1. However, in the current Western diet, this ratio has increased to 10:1 or even 20:1. Omega-6 fatty acids give rise to inflammatory chemicals in the body, while omega-3 fatty acids give rise to anti-inflammatory substances. Therefore, the current Western diet is an inflammatory diet [9].

Omega fatty acids are named for the position of the first double bond, counting from the methyl end. Therefore, in an omega-3 (ω-3 or n-3) fatty acid, the first double bond starts at the third carbon from the methyl end; in an omega-6 (ω-6 or n-6) fatty acid, the first double bond starts at the sixth carbon from the methyl end; and in an omega-9 fatty acid, the first double bond starts at the ninth carbon from the methyl end of the molecule [10,11].

The human body cannot convert omega-6 fatty acids to omega-3 fatty acids or vice versa. The essential fatty acids (which have 18 carbons) are linoleic acid (omega-6) and alpha-linolenic acid (omega-3). Once these are supplied, the body can elongate the fatty acids and form additional double bonds. However, the body is not particularly efficient at producing the long-chain omega-3 fatty acids that are found in fish oil and cod liver oil [10,11].

A saturated fat has no double bonds and is straight. In a *trans* fat, the hydrogens are on opposite sides of the double bond, which also makes the molecule straight. In a *cis* fat, the hydrogens are on the same side of the double bond, making the molecule curved. Saturated fats and trans fats are considered to be unhealthy [10,11]. A polyunsaturated fatty acid is one with many double bonds.

FREE RADICALS

A free radical is a highly reactive chemical with an unpaired electron in the outer orbit. Free radicals can damage molecules with double bonds, such as long-chain, polyunsaturated fatty acids; they can also damage proteins and DNA [10]. The body's free radical scavenging enzymes help prevent damage from free radicals. Some of these enzymes contain trace metals as intrinsic components of the enzyme. Examples include glutathione peroxidase, which contains selenium; two different forms of superoxide dismutase contain either copper or zinc. A person who is deficient in selenium cannot make adequate amounts of glutathione peroxidase. Some vitamins have antioxidant properties. These include vitamin E and vitamin A, which are fat soluble; vitamin C, another antioxidant vitamin, is water soluble [12].

VITAMIN A

Vitamin A has long been known as the *anti-infective* vitamin [13]. Vitamin A is essential for maintaining the integrity and function of the epithelium. In developing countries, vitamin A is used to prevent complications of measles. Severe vitamin A deficiency leads to metaplasia, in which the epithelium of the bronchi and urinary bladder is transformed into stratified squamous epithelium. Vitamin A is essential for the eye. Severe deficiency leads to blindness; in developing countries, in-hospital death rates for children with vitamin A deficiency blindness are 15%–25% [14]. Milder vitamin A deficiency causes night blindness and Bitot spots. Even mild deficiency can decrease epithelial function [15]. Severe vitamin A deficiency is uncommon in the United States. However, we found that 15% of young children had suboptimal levels of plasma retinol [16].

VITAMIN D

Vitamin D is known as the "sunshine vitamin," because ultraviolet B rays in sunshine produce vitamin D in the skin. Inadequate vitamin D levels are common in the United States because of indoor lifestyles and avoidance of the sun to prevent certain skin cancers. Circulating 25-hydroxyvitamin D [25(OH)D] is the measure of the body's vitamin D status. In the kidney, 25(OH)D is hydroxylated again to form 1,25-dihydroxyvitamin D, the active circulating hormone that is important for calcium metabolism and bone and muscle health. New research has shown that many tissues in the body can make their own 1,25-dihydroxyvitamin D for their own use; these include prostate cells, breast cells, colon cells, and immune cells [17].

After 1,25-dihydroxyvitamin D enters the nucleus of the cell, it binds to the vitamin D receptor (VDR). The latter binds to the RXR receptor (retinoid-X receptor); this complex then binds to the vitamin D response element (VDRE), which recruits transcription factors to the complex, leading to gene transcription [18].

The level of plasma or serum 25(OH)D considered to be acceptable and healthy is higher than it was years ago; it is also controversial. In addition, this level can vary with the assay used. Vitamin D deficiency is associated with rickets in growing children and osteomalacia in adults. Neither is usually present with a 25(OH)D level over 10 ng/mL (25 nmol/L). In adults, as a result of new research on chronic conditions and vitamin D, a level less than 20 ng/mL (50 nmol/L) is now considered deficient, while levels from 21 through 29 ng/mL (52–72 nmol/L) are considered insufficient. The optimal range is now 30–60 ng/mL (75–150 nmol/L) [17,18].

The seasonal decrease in 25(OH)D levels in winter has been linked to epidemic influenza A [19]. Recent reports document that vitamin D is essential for the production of endogenous antimicrobial peptides [18]. As reviewed by Holick, *in vitro* studies have demonstrated that when serum levels of 25(OH)D fall below 20 ng/mL (50 nmol/L), monocytes and macrophages

are prevented from initiating the innate immune response to *Mycobacterium tuberculosis* [17]. In a small study of 16 subjects with a median age of 2.9 years, we found that 50% had plasma 25-hydroxyvitamin D levels less than 20 ng/mL (50 nmol/L) [20]. The blood level of vitamin D needed to protect young children from upper respiratory tract infection has not yet been defined.

OUR RESEARCH

Our group is interested in the role of nutritional substances in influencing the immune, inflammatory, and antioxidant systems. We have had promising results with the clinical use of cod liver oil (which contains long-chain omega-3 fatty acids, as well as vitamins A and D), other vitamins, and trace metals in the prevention of upper respiratory tract infection in young children [1,16,21,22].

Cod liver oil is not regulated or standardized in the United States; therefore, it is important to read the label carefully for the lower age limit and the contents of vitamins D and A, as well as omega-3 fatty acids. The current tolerable daily intake (TDI) of polychlorinated biphenyls and dioxins, expressed as *WHO-TEQ,* or World Health Organization toxic equivalents, is 2 WHO-TEQ/kg/day [23]. It may be necessary to contact the manufacturer to obtain purity information about a particular brand of cod liver oil.

We used a "randomized sites" or "cluster randomization" design for several reasons [21]. We did not have a matched placebo for liquid cod liver oil (infants and young children do not swallow capsules); cod liver oil can be purchased without a prescription; and families told about the supplements wanted them for their children and refused randomization to a "no supplements" group.

We performed this study at 2 sites in northern Manhattan in New York City that were part of a larger pediatric group and had similar patient populations (Medicaid, Latino) [21]. The sites were randomized to the Supplementation Site or the Medical Records Control Site [21]. A limitation of the study is that the control group was recruited first because the Norwegian cod liver oil (reformulated with less vitamin A per the Norwegian government) was delayed in U.S. Customs. Children with a known allergy to fish, feeding disorders, or epilepsy were excluded for medical reasons. Also excluded were children who routinely received medical care at other practices or medical centers, as well as children with life-threatening diseases.

Children from 1 to 5 years of age received 1 teaspoon of Carlson's lemon-flavored cod liver oil per day and one-half tablet of Carlson's chewable multivitamin/mineral tablet with selenium. For children from 6 months to 1 year of age, the starting dose was halved. For the youngest children, cod liver oil and a crushed tablet were mixed with a small amount of food such as yogurt. This resulted in a total daily dose of vitamin D of 600 to 700 IU/d: 400–500 IU from cod liver oil, and 200 IU from the tablet. The total daily dose of eicosapentaenoic acid (EPA) was 460–500 mg/d, and that of docosahexaenoic acid (DHA) was 500–550 mg/d. However, the total daily dose of pre-formed vitamin A was less than that used in our original pilot study [16] because the Norwegian government had stipulated that the amount of pre-formed vitamin A in cod liver oil should be reduced because of concern about vitamin A and hip fracture in older women. The total daily dose of pre-formed vitamin A was 3500–3750 IU/d: 1000–1250 IU from cod liver oil, and 2500 IU from the tablet. Current formulations of these products contain even less pre-formed vitamin A [24].

A total of 47 children were included in each of the Supplementation and Medical Records Control Groups. The age range was 6 months–5 years; mean age was slightly greater than 2 years in both groups. In the Supplementation Group, a statistically significant decrease in the mean number of pediatric visits for upper respiratory tract infection was noted over the course of the winter and early spring ($p = 0.042$), using an intention-to-treat analysis. However, in the Medical Records Control Group, no statistically significant change was seen in this parameter ($p = 0.999$).

The supplements also had a clinically significant effect; mean visits/subject/month decreased by 36%–58% in the Supplementation Group. Thus, the number-needed-to-treat was 2–3, meaning that 2–3 children would have to receive the supplements to prevent 1 pediatric visit for an upper respiratory tract illness. In contrast to medication, these are nutritional supplements that provide many other health benefits.

CONCLUSION

Future areas of potential research include asthma, particularly the prevention of exacerbation due to upper respiratory tract illness [25], pertussis, dental caries, the metabolic syndrome, and aortic stiffness. Cod liver oil is culturally valued and has been used as a folk remedy by low-income minorities in the United States [26,27]. Nutritional supplements cannot be purchased with SNAP benefits (formerly called food stamps) [28]. Inclusion of cod liver oil in state Medicaid formularies would make it available to low-income children, whose families may not be able to pay for it out-of-pocket.

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