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RESEARCH NEWS

Vitamin A, Bones, and Children

A review of: Michaelsson K, Lithell H, Vessby B, Melhus H 2003 Serum retinol levels and the risk of fracture. New Engl J Med 348:287–294

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A RECENT ISSUE of the *New England Journal of Medicine* included an interesting and concerning report linking higher than average vitamin A levels with fractures (1). The study prompts questions about the validity of routine vitamin A supplementation (2).

Karl Michaelsson and colleagues studied 2322 adult men in Sweden (1). They tested vitamin A levels at enrollment (age 49–51 years) and followed the men for 30 years. Fractures were identified in 266 men and were most common in men whose vitamin A levels were in the highest quintile. In fact, having a vitamin A level at or greater than the 99th percentile gave a sevenfold increased risk of fracture when compared to men with lower levels. This new study is similar to previous studies that linked higher fracture rates to hypervitaminosis A.

Retinoic acid, an active metabolite of vitamin A, prompts osteoclastic activity and bone resorption. Hypervitaminosis A would be expected to increase circulating levels of retinoic acid and thereby lead to bone resorption and more fractures.

How does this relate to children? Clearly, vitamin A insufficiency is common in many areas of the world, accounts for many cases of blindness, and is linked to high mortality (3). Community-based supplementation of vitamin A yields decreased mortality, and, in patients with measles, supplementation decreases morbidity (3). Dietary intake of vitamin A is associated with reductions in mortality, diarrheal and respiratory infections, and stunting (4). Even though there is inconsistency in results of studies of pharmacologic vitamin A supplementation (4), limitation of dietary vitamin A intake in developing countries could have markedly negative consequences on many children.

In fact, there is also evidence that low vitamin A intake is associated with decreased bone density, at least in older adults (5). As pointed out by Michaelsson's study (1), our goal should be to provide appropriate vitamin A intake for adults. Similarly, we should continue to strive to provide adequate vitamin A for children, being careful to avoid intakes that are either too high or too low. Michaelsson's report should heighten our efforts to provide appropriate vitamin A supplementation to children and should not hinder ongoing supplementation for children in areas of the world where vitamin A deficiency is common.

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Sudden Infant Death Syndrome Is Preceded by Hypoxia

A review of: Jones KL, Krous HF, Nadeau J, Blackbourne B, Zielke HR, Gozal D 2003 Vascular endothelial growth factor in the cerebrospinal fluid of infants who died of sudden infant death syndrome: evidence for antecedent hypoxia. Pediatrics 111:358–363

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NAEYE SHOWED IN a large autopsy series in 1980 that infants who succumbed to sudden infant death syndrome (SIDS) had morphological signs of antecedent hypoxia in several organs (1). Among the most important findings were brain stem gliosis, also described by Takashima *et al.* two years earlier (2), and confirmed by Kinney *et al.* (3), and Valdes-Dapena *et al.* (4). Since brainstem astrogliosis takes several days to develop, a search for biochemical hypoxia markers was initiated. The first biochemical evidence was demonstration of elevated hypoxanthine in vitreous humor in approximately 80% of SIDS cases (5, 6).

However, a substantial overlap was found between victims of SIDS and infectious deaths (7), a possible reason why others were not able to confirm these results (8).

Jones *et al.* (9) recently found evidence that SIDS is preceded by prolonged hypoxia. These authors measured vascular endothelial growth factor (VEGF) in the cerebrospinal fluid, vitreous humor, and serum of SIDS infants. SIDS was verified according to well-established criteria. A control group consisted of cases whose cause of death was clearly established.

VEGF is an important factor for neovascularization, and is upregulated by hypoxia and down regulated by hyperoxia (10–12). Therefore, a high level may indicate preceding hypoxia. In CSF, mean VEGF was 3.6 fold higher in the SIDS group than in controls. With a VEGF cut off point of 200 pg/dL, 60% of the SIDS cases had elevated levels compared with 6.5% of controls. The study by Jones *et al.* is important, although it contains some well-known weaknesses in SIDS research including the establishment of a proper control group and the biochemical post mortem changes. The causes of death in the control group were heterogeneous and several of these including pneumonia, sepsis, suffocation, and congenital heart diseases might also be preceded by hypoxia. In spite of this, Jones *et al.*'s data indicate that hypoxic episodes precede SIDS, pointing out as suggested earlier, that SIDS may not be as sudden as previously believed (5). The paper was strengthened in that rat experiments were added showing that VEGF increases in CSF after a hypoxic challenge peaking at 12 hours and returning to baseline after 24 hours. VEGF increased slowly in rat CSF during the first 36 hours after death, indicating that samples obtained in human infants after a mean post mortem time of 22 hours reflect the levels at time of death. Repeated sampling during the post mortem time in at least a few dead infants could have disclosed important additional information.

The etiology of hypoxia in SIDS is poorly understood. Further, it is not known whether SIDS victims undergo single or multiple hypoxic events before death. But the authors underline that it takes several hours for genomic transcription and expression of VEGF protein after activation and nuclear binding of the hypoxic sensing elements mediating VEGF gene regulation.

This study should prompt us to intensify research identifying possible triggering factors inducing hypoxia and the cascade of events leading to SIDS. If such trigger factors are found, screening methods to identify infants at risk may be established representing a first step to reduce SIDS even further by prevention.

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