A global clinical view on vitamin A and carotenoids[1–3]

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ABSTRACT

The clinical importance of vitamin A as an essential nutrient has become increasingly clear. Adequate vitamin A is required for normal organogenesis, immune competence, tissue differentiation, and the visual cycle. Deficiency, which is widespread throughout the developing world, is responsible for a million or more instances of unnecessary death and blindness each year. β-Carotene is an important, but insufficient, source of vitamin A among poor populations, which accounts for the widespread nature of vitamin A deficiency. It has only recently become apparent that the bioconversion of traditional dietary sources of β-carotene to vitamin A is much less efficient than previously supposed. The other major carotenoids, particularly lycopene, lutein, and zeaxanthin, have been found to have important biological properties, including antioxidant and photoprotective activity, and high intake has been linked in observational studies with reduced risk of a number of chronic diseases. But, to date, no clinical trials have proven the clinical value of ingested carotenoids individually or in combination, in either physiologic or pharmacologic doses, with the excepton of the provitamin A activity of carotene. Indeed, several trials have suggested an increased risk of lung cancer among high-risk individuals (smokers and asbestos workers) who were given high doses of β-carotene alone or in combination with other antioxidants. Much more evidence is needed before commonly encountered claims of the value of ingesting high doses of non–provitamin A carotenoids are validated. *Am J Clin Nutr* 2012;96(suppl):1204S–6S.

INTRODUCTION

The publication of McLaren's critique, "The Great Protein Fiasco" (1), greatly reduced, for a considerable period, global concern for nutrition-focused strategies and interventions, except for efforts to alleviate protein-energy malnutrition accompanying famines. This neglect began to change, in part, because of increased interest in the high prevalence of vitamin A deficiency among preschool-age children, which was first documented by Oomen et al (2), and because of evidence that this deficiency was responsible for an estimated 5–10 million cases of xerophthalmia and a half million instances of irreversible blindness each year (3). Whereas the nutrition community and international donors developed a renewed interest in micronutrient deficiencies in general, and vitamin A deficiency in particular (4), local and global policymakers only began to take the problem seriously when it was shown that even mild degrees of deficiency, preceding the onset of clinical ocular disease, reduced resistance to severe infection (principally measles and diarrhea) and dramatically increased morbidity and mortality (5). Vitamin A deficiency received global recognition, and its alleviation was enshrined in the Convention on the Rights of Children and, more recently, in the Millennium Development Goals. Real progress has been made in reducing vitamin A deficiency, through a global initiative led by UNICEF (6) and largely funded by Canadian and US foreign assistance.

Although now receiving the recognition and response it deserves, vitamin A deficiency and its associated deficiency disorders still remain all too common. An estimated 10 million preschool-age children and pregnant women develop potentially blinding xerophthalmia each year (7). Whereas UNICEF has estimated that vitamin A intervention programs, principally periodic high-dose supplementation, save the lives of $\geq$350,000 children each year, it still leaves at least twice that many who die unnecessarily from deficiency. More than 50 countries are estimated by UNICEF to now reach at least 80% of their target children at least once (with the recommended twice-annual supplements) per year. But many countries do not approach this level of coverage, and even for those that do the missing 20% are likely to be children in greatest need and the ones who would benefit from supplemental vitamin A the most. In addition, pregnant women from these same populations, particularly those in whom deficiency is severe (night blindness rates during pregnancy $>$10%) and where the maternal mortality rate is high, are also likely to die unnecessarily (8).

Periodic supplementation (size of dose and timing dependent on age and fertility status) (5, 9) remains the most widely implemented intervention. Other potential interventions, particularly vitamin A fortification of centrally processed foods, could well be effective. Indeed, there is growing evidence that vitamin A sufficiency in the west depends, at least in part, on this practice (10). But most poor populations cannot afford centrally processed foods. Alternative, local, and home-based fortification strategies are under active investigation.

Improved diets could, theoretically, be valid and effective interventions. But vitamin A deficiency has largely disappeared only in relatively wealthy populations, where higher cost animal products and relatively expensive fruit are consumed in large amounts. Recent claims that periodic supplementation and even

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First published online October 10, 2012; doi: 10.3945/ajcn.112.034868.

fortification are unnatural and unnecessary and that increasing vegetable and fruit production and consumption by poor communities would be far preferable (11) remain unsupported by evidence that such approaches are practical, effective, sustainable, or scalable in poor, traditional, cereal-consuming societies.

Indeed, there is a reason why vitamin A deficiency is so prevalent in the developing world: the populace, particularly young children, is largely dependent on the consumption of provitamin A carotenoids (primarily β-carotene) in vegetables and fruit to satisfy their vitamin A needs. Globally, preformed vitamin A provides only 30% of all dietary vitamin A activity, and this varies considerably by region, socioeconomic class, and age (12). Recent research has shown that the bioavailability of traditional dietary sources of β-carotene is considerably lower (by one-half to one-fourth) than was previously assumed (13, 14). At these lower rates, the food supplies of Asia and sub-Saharan Africa can supply only half of the vitamin A required per capita. Many, of course, receive even less than that, when one considers that the poorest, most-deficient individuals never receive their fair "per capita" share.

Although a number of developing countries, such as Indonesia, have improved their vitamin A status (as judged by dramatic declines in xerophthalmia rates), such improvements do not necessarily mean that clinically significant deficiency has been eliminated and excess mortality controlled. Only a sustained shift to the right in serum retinol concentrations (so that $\leq$5% of individuals have concentrations that are $<$0.7 μm/L, and most have concentrations $>$1.05 μm/L) among those at greatest risk of deficiency supports that conclusion. Even so, such changes can prove fragile: vitamin A deficiency and xerophthalmia reappeared in Indonesia in epidemic proportions during the Asian financial crisis of the late 1990s. Unfortunately, despite occasional data-free claims to the contrary (11, 15), xerophthalmia and concomitant excess morbidity and mortality remain common throughout much of the developing world, especially in South Asia and sub-Saharan Africa (16).

This does not mean that changes in dietary practices, even vegetable-based interventions, will never prove effective or adequate. Increased cultivation and consumption of β-carotene–rich foods, better storage and preparation methods, and the use of new cultivars containing higher concentrations of more bioavailable β-carotene (eg, sweet potato) might well offer important new tools for effective intervention. A radical approach includes genetically bioengineered crops, such as "golden rice," which contains highly bioavailable β-carotene (17) in a food in which it does not naturally occur, or those that offer a dramatic increase in β-carotene, such as tomatoes (18). Whether this will prove a popular and practical solution remains to be seen: locally adapted varieties will have to provide the same (or higher) yields and profits that farmers will find attractive, and the populace will need to appreciate, or at least remain neutral, to any alterations in their organopleptic qualities.

CAROTENOIDS

Carotenoids have become a major area of scientific inquiry and big business, with sales projected to reach $1.2 billion by 2015.

The major carotenoids of current medical research interest, found in colored fruit and vegetables, include carotenes (that animals, including humans, can convert to vitamin A), lycopene, lutein, and zeaxanthin. Carotenoids occur widely throughout the vegetable kingdom and are readily accumulated by vegetable-consuming animals, including humans.

Adequate intake of carotenoids is purportedly important for the prevention of all manner of disease (19–24). Yet, whereas supplies of vegetables and fruit vary dramatically around the world (12), there is little clinical evidence that any sizeable population consumes inadequate amounts for normal physiologic function. In other words, these are not "essential nutrients" in the traditional sense, and, as matters now stand, their "deficiency" does not result in clinically recognizable disease. Of course, we must remain open to the possibility that such deficiency disease or diseases might exist: only relatively recently was vitamin A deficiency definitively recognized to influence immune competence and increase infectious morbidity and mortality (5), despite previous suspicions that this might be the case (25, 26). Until such time as true, carotenoid "deficiency"–related clinical entities are discovered, the only natural physiologic role recognized to be important is that of the provitamin A activity of carotenes, especially β-carotene.

Unusually large dietary consumption of various carotenoids has been linked to a reduction in the risk of various chronic diseases, particularly cancer of the lung, gastrointestinal tract, and pancreas; cardiovascular disease; and both cataract and age-related macular degeneration (19–22). Most supportive data arise from observational epidemiologic studies, which compared the risk (prevalence or incidence) of these conditions among individuals consuming few if any vegetables (often the bottom decile or quintile in the study population) with those consuming the most (27–30). Other analyses and observational studies have failed to support these purported relations (31, 32).

More worrisome still are the outcomes of several large, particularly well-conducted randomized clinical trials. Randomized trials are the "gold standard" for proving the value of reversing a "deficiency" or of increasing the intake of a particular substance in pharmaceutical amounts. These have failed to find any consistent reduction in the incidence of cancers or cancer deaths, or of cardiovascular disease, among individuals randomly assigned to receive β-carotene, with or without α-tocopherol or retinol (33–35). Worse still, in 2 of these trials, which specifically enrolled participants at high risk of lung cancer (smokers and/or asbestos workers) the active agents appeared to increase the risk of developing lung cancer (34, 35). Subsequent systematic reviews of the literature confirm the potential for increased cancer risks from β-carotene supplementation (36, 37).

Why these apparently conflicting clinical and epidemiologic results? The most obvious reason is that purely observational studies are prone to suffer from bias. People who eat the most salad are likely to differ in many other ways from those who eat much less. Whereas these studies purportedly "adjust" for other differences in lifestyle and known risks, they cannot "adjust" for them all, nor necessarily for the most important. No study can collect data on every potentially important variable, and the most important variables may not even be known. Even if frequent consumption of salad, by itself, reduces the risk of certain diseases, salads contain an enormous number of different compounds, not just β-carotene or carotenoids in general.

Clearly, new and very different research designs are needed to begin to dissect out which dietary carotenoids (or combinations of carotenoids) are important for promoting health and preventing

disease, if indeed there are diseases that increased carotenoid intake can help to prevent. The fact that lutein and zeaxanthin are highly concentrated in the macula strongly suggests that they might play a vital physiologic role (38). In the meantime, most carotenoid scientists will continue to work at the molecular level, elucidating the mechanisms by which carotenoids might affect health, whether through their antioxidant, light-absorbing, or other qualities. But, we must remain mindful that other nutrients thought to have antioxidant qualities, such as vitamins E and C for example, and that are associated in observational studies with a reduced risk of cataract formation in humans have failed to show any such benefit when tested in tightly controlled randomized trials (39).

Until definitive clinical evidence becomes available, we can only conclude that humans accumulate a variety of carotenoids, but their importance and roles remain uncertain. The only well-established pathophysiologic consequence of dietary carotenoid "deficiency" remains the provitamin A activity of carotene, especially β-carotene.

The authors' responsibilities were as follows—AS: conceived of the study and prepared the manuscript; and KSV: assisted in data collection and in review of the manuscript. Neither of the authors reported a conflict of interest.

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