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The role of provitamin A carotenoids in the prevention and control of vitamin A deficiency

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SUMMARY. That ß-carotene is the main source of vitamin A in fruits and vegetables has been known for many years. Many studies have been conducted to assess bioconversion of ß-carotene to vitamin A in animals. More recently, bioconversion studies using stable-isotopically labeled ß-carotene have been used to assess bioconversion in humans. The efficiency of the bioconversion of ß-carotene to vitamin A has been accepted to be six but this value may vary depending on vitamin A status and the amount of ß-carotene consumed. This paper reviews the human studies on purified ß-carotene supplements and/or consumption of fruits and vegetables conducted to ascertain whether ß-carotene can alter the vitamin A status of deficient populations. The conclusion is that data are lacking from well-designed studies to show that, with the possible exception of red palm oil, ß-carotene-rich foods are as effective as vitamin A supplements for eliminating vitamin A deficiency. Nevertheless, the data do show that ß-carotene-rich foods may be important for preventing vitamin A deficiency.
Key words: Provitamins A, vitamin A deficiency.

RESUMEN. El papel de los carotenoides provitamina A en la prevención y control de la deficiencia de vitamina A. El hecho de que el ß-caroteno es la fuente principal de la vitamina A en frutas y vegetales ha sido conocido por muchos años. Varios estudios han sido conducidos para evaluar la bioconversión del ß-caroteno en vitamina A en animales. Más recientemente, estudios de bioconversión con ß-caroteno marcado con isótopos estables han sido utilizados para evaluar la bioconversión en humanos. La eficiencia de la conversión de ß-caroteno en vitamina A aceptada es seis, sin embargo este valor puede variar dependiendo del status en vitamina A. Este articulo discute los estudios en humanos con suplementos de ß-caroteno puro o consumo de frutas y verduras, efectuados para averiguar si el ß-caroteno puede alterar el estado de vitamina A de poblaciones deficientes. La conclusión es que faltan datos de estudios bien diseñados para mostrar que, con la posible excepción del aceite de palma roja, los alimentos ricos en ß-caroteno son tan efectivos como los suplementos de vitamina A en la eliminación de la deficiencia de vitamina A. Sin embargo, los datos muestran que alimentos ricos en carotenoides pueden ser importantes para la prevención de la deficiencia de vitamina A.
Palabras clave: Provitamina A, deficiencia de vitamina A.

INTRODUCTION

The only proven physiological function of carotenoids in humans is as provitamin A (1). ß-carotene is the primary provitamin A in fruits and vegetables and is found naturally as the all-*trans* isomer. *Cis*-isomers, which exist both naturally and are formed during food preparation, have lower biological activity (2).

The average total vitamin A intake by region of the world, the percentage from provitamin A carotenoids and the prevalence of vitamin A deficiency is shown in Table 1. Provitamin A carotenoids account for between 60 and 90% of vitamin A intake with dependency on them as a source of vitamin A being particularly high in South East Asia, Africa and the Western Pacific (3). Although the prevalence of vitamin A deficiency is high throughout the developing world, its association with provitamin A carotenoid intake is complex due to the various factors that affect the bioavailability and bioconversion of carotenoids, which depend on both the food matrix and host-related factors (4).

TABLE 1
Vitamin A intake, percent from carotenoids and vitamin A deficiency by region (3)

Region	Total vitamin A (µg RE/d)	% Provitamin A carotenoids	Prevalence of vitamin A deficiency (%)
Africa	776	84	49
Americas	814	64	20
South East Asia	431	88	69
Europe	738	63	0
Eastern Mediterranean	936	63	22
Western Pacific	997	78	27

Studies have been conducted to assess the bioconversion of ß-carotene to vitamin A in animals (5). More recently, studies using stable-isotopically labeled ß-carotene have been carried out to assess bioconversion in humans. The efficiency of the bioconversion of ß-carotene to provitamin A has been accepted to be six (6) although this value may vary depending on vitamin A status, which data (7-9) suggests may be:

- more efficient when status is lower
- less efficient the more ß-carotene consumed.

Several human studies involving ß-carotene supplementation and/or consumption of fruits and vegetables have been conducted to find out whether ß-carotene can alter vitamin A status, particularly in the vitamin A deficient. Most of these studies have been conducted among children or pregnant/lactating women in developing countries.

Intervention studies

The information presented here summarizes intervention studies on children and women that were comprehensively reviewed by de Pee and West (4), and include more recent articles or abstracts. Thirty-two studies have been conducted that are divided into five groups namely, studies among children that included (a) no effective control groups, (b) a positive control group, (c) a negative control group, and (d) both a negative and positive control group; and studies among pregnant and lactating women.

Ideally, both negative and positive control groups should be included in intervention studies as the results will be more reliable, but minimally a negative control group should be included. A negative control group shows whether vitamin A status would change without the intervention due to the Hawthorn effect or seasonal variation in dietary practices. The positive control, in which the subjects receive the same amount of purified ß-carotene or vitamin A, will show the maximum effect of the intervention.

Intervention studies among children

The intervention studies that did not include adequate control groups (10-18) are listed in Table 2. The first column lists the study and site where it was conducted; the second column shows the age group studied; the third column shows baseline retinol level, where < 20 µg/dL is the cut off to define more than marginal deficiency; the fourth column states the intervention; the fifth column shows the duration of the study; and the final column shows the effect defined as "+" or "0".

TABLE 2
Studies with inadequate control groups

Study/Source/Site	Age	Retinol µg/dL	Intervention	Time	Effect
1. Pereira & Begun (10), India	2-5 y	22	GLV (1.5-2.25 MG ßC) No control	3 m	+
2.Lala & Reddy (11), India	2-6 y	na	Amaranth (1.2 mg ßC) -ve control,	15 d	+
3. Devadas & Murthy (12), India	3-5 y	21	Vegetables (1.2 mg ßC) then purified ßC (1.2 mg) No control	3 m	+
4. Devadas et al. (13), India	4-5 y	12 - 14	GLV (1.2 mg) or purified ßC (1.2 mg) -ve control,	2.5 m	+
5. Jayarajan et al. (14), India	2-6 y	20-21	Spinach (1.2 mg ßC) ± groundnut oil (5 or 10 g) No control	4 w	+
6. Charoenkiatkul et al. (15), Thailand	> 6 m	na	Ivy gourd (1.1 mg ßC) or VA (450 RE) No control	2 w	+
7. Mariath et al (16), Brazil	3-12 y	xerop-thalmic	Buriti sweet (0.8 mg ßC) No control	20 d	+
8. Hussein & El-Tohamy (17), Egypt	11-13 y	34.2	Carrots (4.75 mg ßC), carrot juice (3.35 mg ßC), spinach (12.7 mg ßC) No control	2 w	0
9.Nasoetion et al. (18), Indonesia	10-13 y	23-25 37-38	Carrot soup or carrot juice (1.8 mg ßC) -ve control,	3 m	0

GLV-green leafy vegetables; ßC-ß-carotene; VA-vitamin A; na-not available; -ve control- diet without intervention

Seven of the nine studies reported an improvement in vitamin A status, but this should be interpreted with caution due to the design weaknesses:

- Study 5 did not have a control group for the effect of vegetables, but it did have one for the effect of fat intakes. The results showed a greater impact on vitamin A status when 5 or 10 g of oil was included with the spinach, although there was no difference between these two levels, suggesting that as little as 5 g oil can improve ß-carotene absorption;

- Only three of the studies (studies 2, 5, and 6) gave adequate information on fat intakes as both the fat content of the intervention and the content of the daily diet. Five of the studies did not provide information on the fat content of the intervention (studies 1, 3, 4, and 8) and two on the fat content in the daily diet (studies 7 and 9);
- There were large differences in energy and fat intake between groups in two studies (studies 2 and 4);
- In study 7, the sweets were given as take-home supplements and no data were provided on compliance;
- Study 6 subjects were their own control who had been receiving routine vitamin supplements until the study; thus, the baseline retinol levels were variable;
- In study 3, the effects of the vegetable could not be separated from that of the ß-carotene because baseline vitamin A levels were not measured;
- In studies 2 and 4, the sample was not randomized. Moreover, in study 2 the sample size differed between the groups, while in study 4 the number in each group was only 4-5 individuals.

Of the two studies showing no effect, one (study 8) included children whose baseline retinol was on average 34 µg/dL; thus, as a group they were not vitamin A deficient. The other study (study 9) divided the sample into those having retinol levels below and above 30 µg/dl but no improvement was seen in either group.

The studies that included only a positive control (19-23) are listed in Table 3. Four of the five studies showed an improvement in vitamin A status. The positive controls included fortified salt (study 10), mega dose vitamin A (study 11) and vitamin A (studies 12-14). Besides the design limitation,

- Study 10 was not randomized, had different sample sizes among the groups, and had a large drop out rate (25%);
- The sample size in study 11 was very small (n=4-5/group) and no information was provided on the daily diet.

TABLE 3
Studies with a positive control group

Study/Source/Site	Age	Retinol µg/dL	Intervention	Time	Effect
10. Muhilal & Karyadi (19), Indonesia	3-5 y	19-20	DGLV (1.9 mg ßC) or VA (0.3 mg)	75 d	0
11. Hussein & El-Tohamy (20), Egypt	6-13 y	17	Spinach (3.7 mg ßC) + Oil (10 g) or carrots (2.4 mg ßC) or VA (200 mg)	40 d/ 21 serv	+
12. Carlier et al. (21), Senegal	2-15 y	abn CIC	Purified ßC, VA	7 w	+
13. Rukmini (22) India	7-9 y	21-23	Red palm oil or VA (? 0.7 mg)	60 d	+
14. Manorama et al. (23)	7-9 y	24	Red palm oil (2.4 mg ßC) or VA (0.6 mg)	60 d	+

DGLV-dark green leafy vegetables; ßC-ßcarotene; VA-vitamin A; abn CIC-abnormal conjunctival impression cytology

The studies that included only a negative control (24-29) are listed in Table 4. Five of the six studies showed an improvement in vitamin A status (studies 15, 16, 18, 19, 20) and, in one study, the intervention prevented vitamin A deficiency (study 17). Yin et al's (26), Solon et al's (27), Takyi and Owusu's (28) and Persson et al's (29) results are available only in abstracts.

- Study 16 did not provide detail of the fat content of the intervention;
- Study 16 did not collect baseline data on status; thus, the difference could have existed at the outset;
- Study 17 showed serum retinol levels were maintained with the intervention, unlike in the control group, i.e., the intervention prevented vitamin A deficiency. Moreover, the study included children who were not vitamin A deficient at the baseline, which may explain why there was no improvement in vitamin A status per se;
- Study 20 did not provide detail of the fat content of the intervention. The study included children who were marginally subclinically deficient at baseline. Retinol levels increased significantly only among the group that received dark green leafy vegetables, who also had the lowest baseline retinol levels. The rise in serum ß-carotene was significant in both intervention groups and the control group.

The six studies that included both a negative and positive control group (30-35), which provide the most reliable results, are listed in Table 5. In these studies, the positive control included, vitamin A (studies 22,23,24 and 26) or purified ß-carotene (studies 21 and 25). The caveats in these studies include:

- Studies 21 and 24 had small sample sizes;

- Study 24 also had a large drop out rate (30%);
- Study 24 did not provide detail on the fat content of the intervention although the diet had 5-7 g fat, which would have helped absorption.
- The one study showing no effect (study 25) included children who were not vitamin A deficient.

TABLE 4
Studies with a negative control group

Study/Source/Site	Age	Retinol µg/dL	Intervention	Time	Effect
15. Jalal (24), Indonesia	2-7 y	17	ßC-rich foods (5.1 mg ßC), fat (25 g), deworming	24 d	+
16. Wadha et al. (25), India	7-12 y	not done	Carrots/papaya/coriander (2.3-3.3 mg ßC)	1 m	+
17. Yin et al. (26), China	5.5-6.5 y	33	DGLV (200 g/d)	10 w	+
18. Solon et al. (27), Philippines	Sch c'dren	VAD	Yellow fruits/veg (5 mg ßC)	5 d/w/ 12 w	+
19. Takyi and Owusu (28), Ghana	2-6 y	17-22	DGLV (2.4 mg ßC) or purified ßC (2.4 mg)	12 w	+
20.Persson et al. (29), Bangladesh	8-12 y	24-27	DGLV (3.5 mg ßC) or sweet pumpkin (1.6 mg ßC)	6 d/w/ 6w	+ 0

DGL-dark green leafy vegetables; ßC-ß-carotene; VAD-vitamin A deficiency.

TABLE 5
Studies with both a negative and positive control group

Study/Source/Site	Age	Retinol µg/dL	Intervention	Time	Effect
21. Roels et al. (30), Rwanda	9-16 y	32-36	Carrots (19 mg ßC) ± fat (18 g) or purified ßC (28 mg) + fat	31 d	+
22. Roels et al. (31), Indonesia	3-13 y	Mgnal	Palm oil (7.8 mg) or VA (0.6 mg)	22 d	+
23. Lian et al. (32), Indonesia	1-5 y	13-18	Palm oil (1.8 mg ßC) or VA	11-14 m	+
24. Devadas et al. (33), India	3-5 y	13-14	Papaya or amaranth (1.2 mg ßC) or VA (0.3 mg)	2 m	+
25. Bulux et al. (34), Guatamala	7-12 y	34	VA (1.0 mg), purified ßC (6 mg) + fat (10 g), or carrots (6 mg ßC)	20 d	0
26. de Pee et al. (35)	7-11 y	20-21	Vegetables (684 RE), fruit (509 RE), retinol-rich (556 RE), low carotene/low retinol (44 RE)	9 w	+

ßC-ß-carotene; VA-vitamin A; RE-retinol equivalent; mgnal-marginal

The impact of ß-carotene or ß-carotene-rich foods on vitamin A status

Although the rigor of the experimental designs in the 26 studies varied, only four did not show an improvement in vitamin A status after consumption of either purified ß-carotene or ß-carotene-rich foods.

Of the four that showed no effect, two studies included children who were overall not vitamin A deficient at the baseline: serum retinol was 33-34 µg/dL in the study by Bulux et al. in Guatemala (study 25) and in the Hussein and El Thomamy study in Egypt (study 8).

Of the remaining 22 studies:

- 16 showed an improvement in vitamin A status after consuming 0.8 to 19 mg ß-carotene as ß-carotene-rich foods (studies 1,2,3,4,5,6,7,11,15,16,18,19,20,21,24 and 26);
- 4 showed an improvement in vitamin A status after consuming 1.8 to 2.4 mg ß-carotene as red palm oil (studies 13,14,22 and 23);
- 4 showed an improvement in status after consuming 1.2 to 2.4 mg ß-carotene as purified ß-carotene (studies 3,4,12 and 19);
- 1 showed the vitamin A status of children who did not consume ß-carotene-rich foods worsened during the intervention; thus, ß-carotene-rich foods prevented vitamin A deficiency in the intervention group (study 17);

- 1 showed an improvement in vitamin A status after consuming 3.5 mg ß-carotene but not 1.6 mg ß-carotene from ß-carotene-rich foods (study 20). The baseline vitamin A status of the former group, however, was worse than the latter.

Yin et al's (study 17) and Solon et al's (study 18) studies used stable isotopes to determine vitamin A status, which is a more accurate assessment method than blood retinol levels.

Impact of ß-carotene versus vitamin A on vitamin A status

Among the studies with a positive control, a comparison can be made of the benefit of ß-carotene, be it purified or provided as foods, with vitamin A supplements. Any difference in vitamin A status between the ß-carotene and the vitamin A supplemented groups would be due to the efficiency of bioconversion and the presence of ß-carotene absorption enhancers and inhibitors. Of the 26 studies on children, nine included a positive control using vitamin A (studies 10,11,12,13,14,22,23,24 and 25) and one using retinol-rich food (study 26).

- 4 of the 10 studies compared red palm oil with vitamin A and palm oil was shown to have a benefit similar to vitamin A (studies 13,14,22 and 23);
- 1 study (study 25), showed no improvement in vitamin A status from either vitamin A or purified ß-carotene. As mentioned before, the children in this study were not deficient at the baseline;
- 1 study compared ß-carotene from vegetables and ß-carotene from fruit with retinol-rich food. Serum retinol improved in all three groups and the increase was larger in the retinol-rich group than the fruit and vegetable groups (study 26).

Of the remaining four studies that included comparisons between ß-carotene and vitamin A:

- Study 11 in Egypt, showed that ß-carotene-rich foods had a similar effect to a mega dose vitamin A supplement in improving vitamin A status;
- Study 12 in Senegal, showed that purified ß-carotene and vitamin A supplements similarly reduced the prevalence of abnormal eye cytology;
- Study 24 in India, showed that both ß-carotene and vitamin A improved vitamin A status but the improvement was greater after intervening with vitamin A than with ß-carotene;
- Study 10 in Indonesia, showed no effect on vitamin A status.

Impact of purified ß-carotene versus ß-carotene rich foods on vitamin A status

Purified ß-carotene can also be used as a positive control to evaluate the contribution of provitamin A foods to vitamin A status. Four of the 26 studies (studies 3,4,19,25) attempted to include purified ß-carotene as a control.

In the Devadas and Murthy study (Study 3), vitamin A status improved after the consumption of both amaranth and purified ß-carotene but they did not distinguish the effects of the amaranth from that of the purified ß-carotene.

The Ghana study (Study 19) found that vitamin A status improved after the consumption of ß-carotene-rich vegetables (± fat) and purified ß-carotene and the results are preliminary.

The Guatemala study (Study 25), as mentioned earlier, included children who were not deficient; thus, there would be little room for improvement in status.

Only one study, conducted in India (Study 4), which included vitamin A deficient children, has shown that ß-carotene-rich foods and purified ß-carotene improved vitamin A status to the same extent. These children were quite deficient in vitamin A having baseline retinol levels of 12-14 µg/dL.

Intervention studies among pregnant and lactating women

Six studies have been conducted among pregnant and lactating women (Table 6) (36-41) and their experimental designs have been more rigorous than those for children; all the studies have at least a negative control.

In Table 6, time refers to the duration of the regimen. For example, de Pee et al. (Study 27) gave the intervention 5 days/week for 12 weeks. Rice et al. (Study 28) gave one group a mega dose of vitamin A post partum and the other group a purified ß-carotene supplement daily for eight months. Effect refers to the intervention by group. For example, de Pee et al. (Study 27) showed a positive effect using purified ß-carotene but not with vegetables, while Yamini et al. (Study 29) showed a positive effect among both pregnant and lactating women.

Collectively, five of the six studies (Studies 28,29,30,31 and 32) showed that ß-carotene and/or ß-carotene-rich foods can improve vitamin A status and, more important, can reduce the clinical symptoms of a deficiency. Yamini et al (Study 29) found that vitamin A and purified ß-carotene improved the vitamin A status of pregnant and lactating women by 32% and 11%, respectively. Similarly, Christian et al. (Study 30) found that vitamin A and purified ß-carotene reduced the incidence of night blidness by 50-60% and 30-40% in pregnant and lactating women, respectively.

Wasantwisut et al. (Study 32) found that both serum and breast milk retinol levels increased in the intervention and control groups 12 weeks post intervention. The ß-carotene-rich foods group, however, consumed one-half to one-third less vitamin A from animal foods at baseline and during the intervention compared with the control groups. Serum and breast milk retinol levels increased the most in the purified ß-carotene group followed by the ß-carotene-rich foods group, and then the low ß-carotene control group. Isotope analysis to assess body vitamin A stores is in progress.

Canfield et al. (Study 31) found that retinol levels in Honduran mothers did not increase, but they did in their infants after consuming ß-carotene-rich fruits and vegetables and synthetic ß-carotene compared with the placebo.

Rice et al's Bangladesh study (Study 28) showed the importance of the duration of an intervention. They found that it took nine months for a daily ß-carotene supplement to improve milk vitamin A levels, whereas it took two months to see an effect from a single high dose of vitamin A but the effect was not sustained; hence the brackets in the table for effect. The levels of both vitamin A and ß-carotene were not sufficient, however, to correct the underlying subclinical deficiency nor bring the infants to adequate status.

Only de Pee et al. have found that vitamin A status did not improve from ß-carotene-rich foods alone (Study 26). The women, however, were marginally vitamin A deficient and the dose of ß-carotene provided in this study was about 50% of that given in Honduras (Study 30).

TABLE 6
Studies with both a negative and positive control group among pregnant/lactating women

Study/Source/Site	µg/dL	Group	Intervention	Time	Effect
27. de Pee et al. (36),	25	Preg	Purified ßC (3.5 mg)	5d/w/12 w	+
Indonesia			Vegetables (3.5 mg ßC)		0
28. Rice et al. (37),	na	Lact (pp)	VA (60 mg)	Once	(+)
Bangladesh			Purified ßC (7.8 mg)	d/8 m	+
29. Yamini et al. (38),	na	Preg	VA (7 mg) or purified ßC	d/3.5+y	+
Nepal		Lact	(42 mg)		+
30. Christian et al. (39),	XN	Preg	VA (7 mg) or purified ßC	d/3.5+y	+
Nepal		Lact	(42 mg)		+
31. Canfield et al. (40),	31.3	Lact	ßC-rich foods (7.5 mg) or	3x/w/4 w	+
Honduras	16	Infants	purified ßC (7.5 mg)		+
32. Wasantwisut et al.	na	Lact	ßC-rich foods (4.7 mg)	5d/w/	+
(41), Thailand			or purified ßC (3.6 mg)	12w	+
					+

ßC-ß-carotene; VA-vitamin A; na-not available; pp-post partum;XN-night blindness

CONCLUSIONS

Based on the studies cited here, there is clearly a dearth of data from well-designed studies to argue that, except for red palm oil, ß-carotene-rich foods are effective in eliminating vitamin A deficiency. The evidence, however, leans toward ß-carotene-rich fruit and vegetable intake improving vitamin A status in deficient children and women. Vitamin A is more effective than ß-carotene in preventing vitamin A deficiency because there are many factors that affects the bioconversion of ß-carotene (4). Nevertheless, increasing the consumption of fruits and vegetables that are widely available in developing countries is a viable and sustainable approach to preventing vitamin A deficiency, especially where coverage of pharmaceutical supplements and vitamin A-fortified foods are limited.

The FAO RDA for vitamin A for children one to 10 years old is 400 RE (42), which is equivalent to about 3.4 mg ß-carotene. Data compiled by West and Poortvliet (43), showed that in develping countries:

- 100 g of uncooked or cooked carrots, which is equivalent to about one cup of grated carrots or two-thirds of a cup of diced carrots, contains between 1.6-64 mg ß-carotene;
- 100 g or just over one-half cup of cooked spinach contains between 2.5-5.8 mg. A similar amount of amaranth contains between 0.25-31.6 mg ß-carotene.
- 100 g or just over one-half cup of mango contains between 0.3-2 mg ß-carotene.

Thus, where varieties of ß-carotene-rich foods are available, manageable amounts of these foods can be eaten to meet requirements.

The challenge for programs is to encourage households to change their eating habits so that those most vulnerable to vitamin A deficiency have better access to both vitamin A-rich and ß-carotene-rich fruits and vegetables. At a minimum, this requires that such foods are available at a price that people can afford which, in turn, is dependent on climatic conditions and market infrastructure. In addition, the foods to promote must not be regarded as inferior foods and they must be palatable to the target groups.

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