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β-Carotene and α-tocopherol in healthy overweight adults; depletion kinetics are correlated with adiposity

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Abstract

Healthy overweight subjects (24 males, 68 females; mean age = 48.8 years; body mass index = 27.1 ± 4.9) participated in a randomized, double-blind, placebo-controlled crossover study with two periods of 28-day supplementation using a nutritional product composed primarily of dehydrated juice concentrates from mixed fruits and vegetables (JuicePlus+®). Compared with placebo, supplementation for 28 days increased concentrations of serum β-carotene by 264% ($P < 0.001$) and α-tocopherol by 14% ($P < 0.01$). After crossover of the active group to placebo, β-carotene and α-tocopherol declined via first-order kinetics, with serum half-lives ($t_{1/2}$) for β-carotene and α-tocopherol determined to be 22.8 ± 3.1 and 4.6 ± 2.3 days, respectively. Depletion rates for β-carotene correlated with adiposity (quartile 1, body mass index = 21.96, $t_{1/2}$ = 17.6 days vs. quartile 4, body mass index = 37.87, $t_{1/2}$ = 26.3 days; $P < 0.05$). In conclusion, the supplementation period resulted in significantly elevated levels of β-carotene and α-tocopherol, indicating bioavailability. These increased levels persisted 2–4 weeks after supplementation was discontinued, and the rates of depletion were correlated with the levels of general adiposity.

Keywords: *β-Carotene, α-tocopherol, half-life, body mass index, fruit, vegetable*

Introduction

Being overweight or obese has been shown to affect serum levels of various micronutrients (Olusi 2002; Kimmons et al. 2006). In particular, serum concentrations of β-carotene and α-tocopherol have been reported to be correlated with obesity as assessed by body mass index (BMI) (Wallstrom et al. 2001; Anderson et al. 2006; Kimmons et al. 2006). Furthermore, when β-carotene was supplemented, the magnitude of increase in serum levels was significantly and inversely related to BMI (Constantino et al. 1988; Zhu et al. 1997). Increased BMI may cause a decrease in serum carotenoids due to generation of oxidative stress by adipose tissue (Higdon and Frei 2003; Keaney et al. 2003; Lasheras et al. 2002; Olusi 2002).

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Because carotenoids and vitamin E play a recognized role in combating oxidative stress and conferring human health benefits, there has been major interest in factors that influence the absorption, utilization and metabolism of these antioxidants (Lotito and Fraga 2000; Schwedhelm et al. 2003; Burri and Clifford 2004). Several studies have examined the depletion of serum carotenoids after feeding low-carotenoid diets (Rock et al. 1992 ; Burri et al. 2001; Granado et al. 2004). Increased interest in the metabolism and biokinetics of vitamin E in humans has been reflected in current studies using deuterium-labeled α-tocopherol (Hall et al. 2005; Leonard et al. 2005) and a conference focusing on vitamin E (Lodge et al. 2004; Ekanayake-Mudiyanselage et al. 2004). It should be noted that the above-cited studies were conducted on average weight individuals, and there is currently little information on the effect of BMI on the depletion kinetics of serum β-carotene and α-tocopherol. With the increase in obesity worldwide (Darnton-Hill et al. 2004) it is important to have a better understanding of the association between varying levels of adiposity and the uptake and depletion of these important micronutrients. Previous studies in normal weight subjects (BMI <24.9) that employed this encapsulated nutritional supplement consisting primarily of fruit and vegetable juice powder concentrates also showed significant increases in serum carotenoids and α-tocopherol (Samman et al. 2003; Kawashima et al. 2007).

The aim of the present study was to assess the effects of this nutritional supplement on serum levels of antioxidant nutrients in a mostly overweight population and comparing groups of subjects that were normal weight, overweight, and obese. By employing a cross-over design, a secondary aim was to determine the depletion characteristics of these antioxidant nutrients after discontinuation of supplementation, and the correlation of turnover rate to BMI.

Methods and materials

Study design

Subjects participated in a double-blind, randomized, placebo-controlled trial with a cross-over design consisting of two intervention periods of 28 days. They were randomly assigned to receive either the active nutritional supplement or a placebo. At 28 days, subjects were crossed-over from active to placebo (Group 1) or from placebo to active (Group 2) without a washout period. Blood samples were taken at day –7 and 0 to establish baseline values and at 14, 28, 35, 42, 49 and 56 days for both Group 1 and Group 2. Subjects were asked to maintain their normal dietary and exercise patterns, and not to use any dietary supplements during the study period.

Subjects

The present study was Institutional Review Board approved and each subject provided written informed consent. Subjects were generally healthy non-smokers with no reported severe or chronic illness, no history of metabolic disease, and no use of nutritional supplements. Subject characteristics are indicated in Table I.

Table I. Subject baseline characteristics.

	Group 1 ($n=45$)	Group 2 ($n=47$)
Age (years)	43.9±10.9	43.3±11.3
Male (n)	13	11
Female (n)	32	36
Weight (kg)	77.0±15.9	78.0±16.9
Height (m)	1.69±0.08	1.63±0.08
BMI (kg/m^2)	26.4±4.6	27.8±5.4
Cholesterol (mg/dl)	198.3±33.3	195.9±44.3
LDL (mg/dl)	123.4±26.9	120.2±36.5
High-density lipoprotein (mg/dl)	53.4±13.4	51.9±9.9
Triglycerides (mg/dl)	107.4±58.6	126.4±92.6

Data expressed as the mean±standard error of the mean.

Study capsules

The two treatment groups were: active fruit and vegetable juice concentrate (FVC) capsules (Juice Plus+®; NSA, LLC, Collierville, TN, USA), which contained primarily juice concentrate powder from apple, orange, pineapple, cranberry, peach, acerola cherry, papaya, carrot, spinach, broccoli, kale, cabbage, parsley, beet, and tomato; and placebo capsules similar in appearance, containing microcrystalline cellulose. The active phytonutrient supplement provided 7.5 mg β-carotene and 45 IU D-α-tocopherol, along with other micronutrients. Supplements were provided in opaque two-piece hard gelatin capsules, and subjects consumed two capsules twice daily with meals. Compliance was estimated from the returned capsule count.

Blood samples

Fasting blood samples were taken at each scheduled time from the antecubital vein of subjects. Blood was collected into untreated vacutainer tubes (Becton Dickinson, Franklin Lakes, NJ, USA) for the analysis of serum β-carotene and α-tocopherol. Blood samples were kept on ice and centrifuged within 1 h at 1,500 $\times g$ for 8 min. Aliquots of serum were removed and frozen on dry ice and then stored at -80°C until analysis.

Biochemical analysis

Serum β-carotene and α-tocopherol were measured by high-performance liquid chromatography. An internal standard was incorporated into each sample before analysis on a Hewlett Packard HPLC (1090M) Series II with diode array detector (β-carotene) (Agilent Technologies, Santa Clara, CA, USA) and a HP 1045A fluorescence detector (α-tocopherol) (Agilent Technologies, Santa Clara, CA, USA) using an isocratic mobile phase and a C-18 reversed-phase column.

Statistical and data analysis

The data were analyzed by SAS statistical software (SAS Institute, Inc., Cary, NC, USA). Repeated-measures analysis utilized Proc Mixed. Adjusted least-square means and their standard errors were calculated at each time point within groups, and

between groups at each time point. Also, data from Group 1 at baseline, 14 and 28 days were paired with data from Group 2 at baseline 42 and 56 days for analysis as combined active. Significance was set at $P<0.05$.

Serum carotenoid and tocopherol concentrations in Group 1 subjects were plotted for samples taken at 28, 35, 42, 49 and 56 days. Plots of the natural log (ln)-transformed data versus time showed that the serum concentration of each compound over time followed apparent first-order kinetics. Therefore, the half-life ($t_{1/2}$) of each compound in each subject was calculated by dividing 0.693 ($\ln_2$) by the slope of each plot for each subject (Burri et al. 2001). The mean $t_{1/2}$ and its mean standard error of the mean were calculated for β-carotene and α-tocopherol. Comparison of $t_{1/2}$ with BMI quartiles was analyzed by one-way analysis of variance, and differences of means between quartiles were analyzed by mixed analysis of variance.

Results

Subject characteristics are presented in Table I. No significant differences were noted between the active and placebo groups. The study population was overweight, with a mean BMI of 26.4 for males and 27.8 for females. Supplementation with FVC for 28 days resulted in significant increases in serum levels β-carotene and α-tocopherol. Combined data from the active FVC phase of supplementation (Group 1, 0–28 days + Group 2, 28–56 days) compared with the placebo (Group 2, 0–28 days) showed significant elevations in β-carotene (263.5%; $P<0.001$) (Figure 1a) and α-tocopherol (14.1%; $P<0.01$) (Figure 1b).

In the Group 1 subjects who received active supplementation during the initial 28 days of the study, the time course of the decline of each analyte serum concentration during the subsequent 28 days (with placebo supplementation) could be assessed. Concentrations of β-carotene and α-tocopherol declined with apparent first-order kinetics as reflected in Figure 1a,b. The $t_{1/2}$ of decline was calculated to be 22.8 ± 3.1 days and 4.6 ± 2.3 days for β-carotene and α-tocopherol, respectively.

Table II shows Group 1 subjects divided by quartiles based on BMI. The first quartile included normal weight subjects who had an average BMI of 21.96. The second quartile of subjects was overweight (BMI = 26.35), while the third quartile was borderline obese (BMI = 30.17). Obese subjects comprised the fourth quartile, with an average BMI of 37.87. When the BMI of subjects was compared with the apparent $t_{1/2}$ of serum analytes, only β-carotene showed a significant correlation (Table II), with an increased $t_{1/2}$ ($P<0.05$) confined to individuals in the highest BMI quartile (37.87 ± 0.93).

Baseline levels for β-carotene and α-tocopherol in each BMI quartile did not show significant differences, although β-carotene showed a trend with serum levels in the first quartile being higher than the other three quartiles (Table III). Comparing supplementation with time showed significant increases in serum β-carotene at 14 and 28 days in all four quartiles, although the magnitude of change was significantly lower with increasing BMI (Table III). For example, after 14 days on active supplementation for quartiles two, three and four, serum β-carotene levels were only 68.2%, 57.5% and 49.9%, respectively, of those achieved by quartile one, and this relative differential in serum values was maintained at 28 days and during the decline after cessation of supplementation with FVC capsules (Table III). Similar analysis of α-tocopherol levels between BMI quartiles did not show significant differences at any time point.

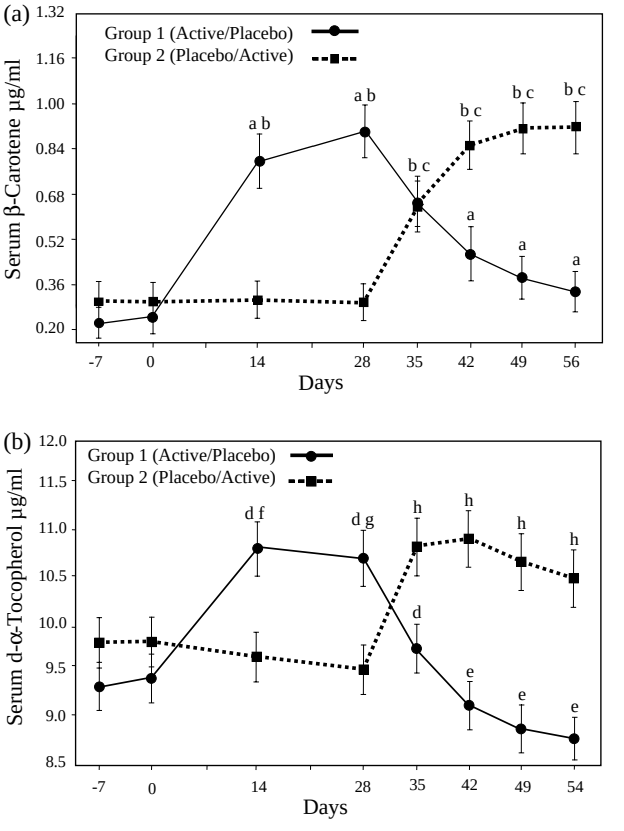

Figure 1. Changes in serum levels of β-carotene and α-tocopherol after supplementation with FVC or placebo. Group 1 ($n=45$) consumed the active FVC supplement for 28 days followed by the placebo supplement for an additional 28 days. Group 2 ($n=47$) consumed the placebo supplement first, followed by the active FVC supplement. Bars represent the mean ± standard error of the mean. (a) Changes in serum β-carotene: [a]different from Group 2 ($P<0.001$), [b]different from baseline ($P<0.001$), and [c]different from baseline ($P<0.001$). (b) Changes in serum α-tocopherol: [d]different from Group 2 ($P<0.05$), [e]different from Group 2 ($P<0.01$), [f]different from baseline ($P<0.001$), [g]different from baseline ($P<0.05$), and [h]different from baseline ($P<0.01$).

Discussion

More than 60% of Americans are overweight or obese, conditions that are associated with increased risk for hypertension, dyslipidemia, type 2 diabetes, coronary heart

Table II. Comparison of BMI by quartile with the β-carotene $t_{1/2}$.

	First quartile	Second quartile	Third quartile	Fourth quartile
Subjects (n)	11	12	13	9
Male	2	5	4	2
Female	9	7	9	7
BMI (kg/m^2)	21.96 ± 0.60	26.35 ± 0.31	30.17 ± 0.61	37.87 ± 0.93
$t_{1/2}$ (days)	17.58 ± 2.45	17.71 ± 2.34	19.72 ± 2.34	26.33 ± 2.87*

Data for $t_{1/2}$ are from Group 1 subjects during the 28-day placebo phase and are expressed as the mean ± standard error of the mean. *$P<0.05$.

Table III. Changes in serum β-carotene levels in Group 1 subjects after supplementation with mixed fruit and vegetable concentrates (0–28 days) followed by a placebo (29–56 days).

Days	First quartile	Second quartile	Third quartile	Fourth quartile
0	0.295 ± 0.05	0.230 ± 0.04	0.258 ± 0.07	0.179 ± 0.03
14	1.190 ± 0.17[a]	0.811 ± 0.10[ab]	0.685 ± 0.12[abc]	0.594 ± 0.07[abc]
28	1.288 ± 0.17[a]	1.010 ± 0.14[a]	0.804 ± 0.13[ade]	0.584 ± 0.11[ade]
35	0.887 ± 0.11[a]	0.759 ± 0.16[a]	0.543 ± 0.10[afg]	0.419 ± 0.09[afg]
42	0.660 ± 0.12[a]	0.491 ± 0.08[a]	0.394 ± 0.08[hi]	0.317 ± 0.06[h]
49	0.569 ± 0.11[a]	0.378 ± 0.05	0.364 ± 0.08[j]	0.287 ± 0.05[j]
56	0.459 ± 0.08	0.319 ± 0.04	0.354 ± 0.07	0.226 ± 0.04

Data expressed as the mean (μg/ml) ± standard error of the mean. [a]Different from baseline (0 day) ($P < 0.005$). [b]Different from quartile one at 14 days ($P < 0.001$). [c]Different from quartile two at 14 days ($P < 0.003$). [d]Different from quartile one at 28 days ($P < 0.0001$). [e]Different from quartile two at 28 days ($P < 0.001$). [f]Different from quartile one at 35 days ($P < 0.0001$). [g]Different from quartile two at 35 days ($P < 0.01$). [h]Different from quartile one at 42 days ($P < 0.01$). [i]Different from quartile two at 42 days ($P < 0.05$). [j]Different from quartile one at 49 days ($P < 0.05$).

disease, stroke, and certain cancers (Centers for Disease Control and Prevention 2006; Kimmons et al. 2006). The overweight or obese are known to alter the absorption, distribution, metabolism and/or excretion of β-carotene and α-tocopherol (Wallstrom et al. 2001; Anderson et al. 2006; Kimmons et al. 2006).

Multiple studies, including several with rather large population cohorts have shown an independent and inverse relationship between BMI and α-tocopherol and β-carotene concentrations in blood. This correlation between obesity as measured by BMI, and carotenoids and α-tocopherol, has been reported from analysis of 15,145 individuals in the NHANES III database (Kimmons et al. 2006), 3,071 participants in the CARDIA study (Anderson et al. 2006), 3,128 subjects in the SU.VI.MAX French study and the 529-person sample from the Malmo population registry (Wallstrom et al. 2001). In all cases, increased BMI was reflected in decreased levels of β-carotene and α-tocopherol. In the present study, we observed a trend showing an inverse relationship between BMI and baseline β-carotene ($P = 0.056$).

The independent negative correlation between general obesity and serum β-carotene and α-tocopherol may be attributable to several etiologies. One is related to the lipophilic nature of carotenoids and α-tocopherol, with adipose tissue acting as a reservoir that actively takes up these compounds from plasma (Van Vliet 1996; Wallstrom et al. 2001). Thus, a person with a high fat mass would have a larger portion of ingested β-carotene and α-tocopherol absorbed by fat tissue than would a lean person if all other metabolic factors were equal. Increased BMI may also cause a decrease in serum carotenoids due to generation of oxidative stress by adipose tissue (Higdon and Frei 2003; Keaney et al. 2003; Lasheras et al. 2002; Olusi 2002). In addition, the basic diet could differ from lean subjects, who may consume diets richer in β-carotene and α-tocopherol.

Any of these general mechanisms offer explanations for the observations in the current study, which showed increases in serum β-carotene in response to supplementation were blunted with increasing levels of general adiposity. Furthermore, the rate of β-carotene decline in serum after cessation of supplementation was significantly slower in individuals with the highest BMI.

Only a few studies have examined the influences of BMI on changes in β-carotene during supplementation and/or depletion. Zhu et al. (1997), followed two groups for 28 days on a low-carotenoid diet, with one group receiving a β-carotene supplement (30 mg/day). In the supplemented group, the magnitude of increase in plasma β-carotene was significantly and negatively associated with body weight, BMI and fat-free mass. In the placebo group (low-carotenoid diet only), the decrease in β-carotene was significantly positively associated with BMI, body weight and fat-free mass. Therefore, subjects with greater BMI exhibited smaller decreases in plasma β-carotene concentration accompanying dietary carotenoid deprivation. A similar result was reported by Constantino et al. (1988), who studied β-carotene supplementation in elderly men for 10 months, showing the magnitude of plasma β-carotene increase was significantly and inversely related to BMI.

In a third study (Tulley et al. 2005), 45 men were assigned to three groups stratified by age and BMI—consisting of a control group, a low-fat-diet group and an olestra group—and were followed for 36 weeks during a weight-loss program. All subjects received a supplement containing 3 mg β-carotene daily, with the control and low-fat groups showing significant increases in plasma β-carotene, while the olestra group had a significant reduction in β-carotene. When changes in β-carotene levels were compared with BMI, the increases in the control and low-fat groups and the decreases in the olestra group correlated with BMI.

In the present study, significant increases in serum β-carotene and α-tocopherol were observed after 28 days of the active supplement, indicating effective absorption. This degree of bioavailability is consistent with previous studies employing this FVC (Samman et al. 2003; Nantz et al. 2006; Kawashima et al. 2007).

With respect to metabolism and clearance of carotenoids, several studies have examined the depletion of serum carotenoids after feeding subjects low-carotenoid diets. Depletion kinetics in women fed low-carotenoid diets were carefully measured by Burri et al. (2001). These investigators reported that the decrease in each serum carotenoid over time followed apparent first-order kinetics with half-lives for β-carotene of 37 ± 5 days, lycopene 27 ± 3 days, and lutein/zeaxanthin 66 ± 10 days. In another depletion study (Granado et al. 2004), ten type 1 diabetic individuals and eight healthy control subjects consumed a low carotenoid diet for 21 days. The authors reported no difference between depletion rates in diabetic individuals and non-diabetic individuals. Accordingly, data from the groups were combined and showed non-linear (apparent first-order) decreases calculated as estimated $t_{1/2}$ values of 16 days and 13 days for β-carotene and lycopene, respectively.

In the present study, the $t_{1/2}$ for β-carotene was estimated at 22.8 ± 3.1 days. Although this result is similar to the above-cited studies, they are not entirely comparable since those subjects were fed low-carotenoid diets that depleted serum carotenoids to artificially low levels. In contrast, the decline in β-carotene concentration in the present study was measured after discontinuing supplementation. Particularly in the study by Burri et al. (2001), the longer half-lives may be reflective of a mechanism of conservation of nutrients under conditions of deprivation.

A study employing β-carotene supplementation (Thürman et al. 2002), involved four groups of four subjects each, receiving 6 mg, 7.2 mg, 18 mg or 21.6 mg β-carotene in juice or powder form for 40 days, which then measured the kinetics of increase in plasma levels from baseline to steady state. By analyzing the pattern of plasma increase approaching the plateau state, a turnover rate and therefore an

apparent $t_{1/2}$ of between 6 and 11 days for β-carotene was determined. The substantially shorter $t_{1/2}$ reported for β-carotene in this supplementation study compared with the present study could be explained by the different methodologies employed, in which turnover kinetics were calculated without measuring actual depletion from plasma. In the present study, the population was markedly overweight, which probably also contributed to the longer $t_{1/2}$ of β-carotene. And while this pattern of decline is consistent among studies, the differences in estimated $t_{1/2}$ values could be related to several variables (Burri and Clifford 2004; Faulks and Southon 2005). These include differences in the experimental depletion diets, number of subjects and their characteristics, including BMI, frequency of blood collection and study duration.

A more specific mechanism involving lipid metabolism may also be operating, which affects β-carotene accumulation and clearance. The very low-density lipoprotein particles initially incorporate β-carotene, followed by conversion to low-density lipoprotein (LDL) particles that are carriers for ~87% of serum β-carotene (Ziouzenkova et al. 1996; Burri and Clifford 2004). Obese subjects were shown to have a significantly decreased percentage conversion of very low-density lipoprotein to LDL, while the fractional catabolic rates of LDL particles were greatly reduced (Chan et al. 2002, 2004). In addition, a 50% reduction in LDL receptors was reported in obese subjects (Mamo et al. 2001).

The inverse relation between BMI and serum β-carotene levels observed in the cited studies, and in this study the blunting effect of increased BMI on β-carotene response due to supplementation (Table III), could be due to reduced production and catabolism of LDL. In addition, the increased $t_{1/2}$ of β-carotene in the highest BMI quartile (Table II) could be attributable in part to a reduction in LDL receptors, which would slow the removal of β-carotene carrying LDL particles from circulation.

The kinetics of vitamin E metabolism have been reported during and after vitamin E supplementation (Traber et al. 2001). Smokers ($n=6$) and non-smokers ($n=5$) with normal lipid profiles were supplemented with deuterated α-tocopherol (150 mg) daily for 7 days, followed by 21 days without supplementation. The calculated $t_{1/2}$ for α-tocopherol in smokers was 55.6 ± 7.4 h and for non-smokers was 72.1 ± 17.3 h. This compares with 110.4 h (4.6 days) in the present study. Another study employed a single dose of deuterated α-tocopherol (150 mg) given to 25 subjects with varying blood lipid profiles (Hall et al. 2005). Kinetic analysis showed an α-tocopherol $t_{1/2}$ of 51.8 ± 17.5 h for nine subjects with normal lipid profiles, 67.9 ± 22 h for ten hypercholesterolemic subjects, and 136.8 ± 43.9 h for six hypercholesterolemic/hypertriglyceridemic subjects. In a third study (Leonard et al. 2005) a single dose of 50 mg deuterated α-tocopherol was administered to 14 participants with normal lipid profiles. The $t_{1/2}$ for α-tocopherol was 56.9 ± 18.5 h.

The longer $t_{1/2}$ for α-tocopherol reported in this study (4.6 days; 110 h), when compared with the results above, apparently cannot be attributed to elevated blood lipids since cholesterol and triglyceride levels were in normal ranges (Table I), and we did not observe a relationship between general adiposity and α-tocopherol concentrations. More probably, this extended $t_{1/2}$ might be ascribed to the complex nature of phytonutrient components of the FVC nutritional supplements utilized in this investigation. Carotenoids function as powerful antioxidants (DiMascio et al. 1991), and β-carotene increased in our subjects during the FVC supplement phase of the study. In addition, other compounds such as bioflavonoids, anthocyanins and

polyphenols are found in plant foods and have demonstrated antioxidant functions (Svilaas et al. 2004). Due to complex interactions between different antioxidants and the ability of these compounds to exhibit a sparing effect in biological systems (Lotito and Fraga 2000; Schwedhelm et al. 2003; Burri and Clifford 2004), it is possible that depletion of serum α-tocopherol in this study was delayed.

Subjects in the present study were on average overweight, with more than 30% being considered obese (BMI $\geq$30). Since serum levels of β-carotene have been found to be inversely correlated with BMI (Zhu et al. 1997; Wallstrom et al. 2001; Anderson et al. 2006), this is consistent with results from our subject population. Supplementation showed differential increases in serum β-carotene, with peak levels attained in BMI quartiles two, three and four being, respectively, 22%, 38% and 55% less than BMI quartile one (Table III, day 28), and a significantly increased $t_{1/2}$ of β-carotene (26.3 days) in subjects with the greatest BMI. This may be due to a greater portion of β-carotene being stored in adipose and other tissue compartments versus the serum in obese individuals compared with lean, or altered metabolism of carrier lipoproteins.

Conclusion

Supplementation with Juice Plus+® significantly increased serum levels of β-carotene and α-tocopherol. Levels remained elevated after cessation of the FVC supplementation phase and were depleted at differential rates with apparent first-order kinetics. For β-carotene, the magnitude of uptake was inversely correlated with BMI and the depletion rate was extended in subjects with the highest BMI and greatest adipose stores.

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