Human Studies on Bioavailability and Plasma Response of Lycopene

ELIZABETH J. JOHNSON[1]

Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts 02111

Lycopene is a major carotenoid in human plasma, tissue, and diet. It is unique among the carotenoids in that it has one major food source: tomatoes and tomato products. While similar to β-carotene in its chemical composition, lycopene has several unique biological properties of its own. For example, lycopene possesses exceptionally high antioxidant activity compared to other carotenoids (1) and, therefore, may be useful in chemoprevention of cancer. Therefore, it is important to understand factors that influence concentrations in the body and to evaluate the metabolism and biological function of lycopene and its metabolites. This is essential for the understanding of the protective effects of this carotenoid.

Human Metabolism of Lycopene

Absorption. Many of the factors known to influence the absorption of lycopene have been recently reviewed (2). Lycopene, being fat soluble, follows the same intestinal absorption path as dietary fat. Lycopene is released from food matrices and solubilized in the gut. This is done in the presence of fat and conjugated bile acids. The efficiency of release is influenced by such factors as disposition of lycopene in the food matrix, particle size after mastication and stomach action, and the efficiency of digestive enzymes. Heating of plant foods before ingestion improves the bioavailability of lycopene from food (3). This is probably a result of weakening of protein-carotenoid complexes. Absorption is affected by the same factors that influence fat absorption. Thus, absence of bile or any generalized malfunction of the lipid absorption system will interfere with absorption of lycopene.

Transport. After absorption into the intestinal mucosal cells, lycopene is transported in the plasma exclusively by lipoproteins. Chylomicrons are responsible for the transport of lycopene from the intestinal mucosa to the blood stream *via* the lymphatics. It is thought that hydrocarbons, such as lycopene, exist in the hydrophobic core of the particle. Lycopene is primarily transported in low-density lipoproteins (LDL). Approximately 75% of the hydrocarbons (β-carotene and lycopene) are associated with LDL and the remaining 25% with the high density lipoproteins and very-low density liproteins (4). The distribution of lycopene among lipoproteins is similar to that of β-carotene and similar between men and women (Fig. 1) (5, 6).

Lycopene is a predominant carotenoid in human plasma. Other major plasma carotenoids include β-carotene, α-carotene, lutein, zeaxanthin, and β-cryptoxanthin. In the United States, lycopene accounts for approximately 40% of the total blood carotenoids compared to less than 10% in Asians (Fig. 2) (7). Lycopene is also a major carotenoid in a variety of human tissues (8, 9), indicating that there is effective transfer from plasma lipoproteins to tissues. Lycopene is predominantely found in testes and adrenals, but significant amounts are also found in the liver, adipose tissue, prostate, kidney, and ovary (8, 9). Testes and adrenals are known to exhibit a high rate of LDL uptake (10), which may explain lycopene deposition in these tissues.

Plasma Response to Supplements and Diet. It is generally accepted that the plasma carotenoid concentration reflects the immediate dietary intake. However, compared to other carotenoids, plasma levels of lycopene appear to be less influenced by dietary intakes. Lycopene supplements are less certain to increase plasma concentrations. No increase in lycopene plasma concentrations were found after the intake of 700 ml of tomato juice (70 mg lycopene; see Ref. 3). This is in agreement with another study in which the consumption of tomato juice (containing 12 mg lycopene) did not increase plasma concentrations of lycopene (11). In a continuous dosing study examining the effect of feeding subjects 180 g of tomato juice (containing 12 mg lycopene) for 6 weeks, mean plasma values were increased by only 44 nmol/l (12). The low plasma response observed in these studies using tomato juice may be due to the availability of lycopene in this food matrix.

A correlation between 7-day food diary lycopene intake and plasma lycopene has been reported (13). In contrast, it has also been found that there does not appear to be a correlation between plasma lycopene and total fruit and vegetable intake (14). Given that lycopene has one major food source (tomatoes and tomato products), high fruit and vegetable intake may not indicate a high lycopene intake.

[1] To whom requests for reprints should be addressed at Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111. E-mail: johnsone_cn1@hnrc.tufts.edu

0037-9727/98/2182-0115$10.50/0

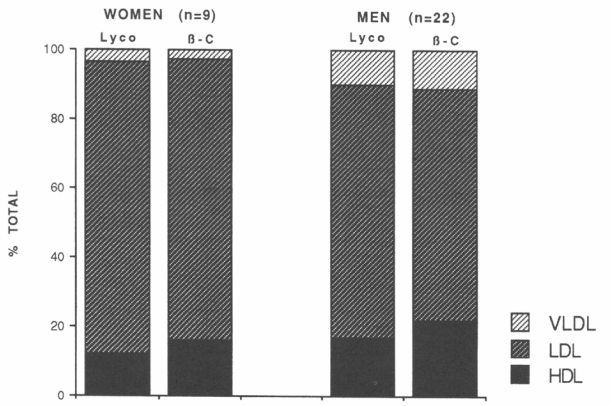

Figure 1. Distribution of β-carotene and lycopene among lipoproteins in women and men. Adapted from References 5 and 6.

This concept is demonstrated in a study conducted in vegetarians and nonvegetarians in which plasma and dietary carotenoids were measured (15). The vegetarians were found to have higher intakes of fruits and vegetables as assessed by food-frequency questionnaires. This higher fruit and vegetable intake was reflected in a higher mean plasma concentration of β-carotene in the vegetarian group (Fig. 3). Unlike β-carotene, a difference in the mean concentration of plasma lycopene was not found (Fig. 3).

Given the low plasma lycopene responses in the above studies, the question arises: Can increased intake of dietary lycopene increase plasma lycopene concentrations? This question was examined in a controlled diet study that measured the plasma carotenoid responses in healthy men and women before and after being fed controlled diets with high carotenoid content (16 mg/day; 3.3 mg/day lycopene) (16). The food source of lycopene in this study was a commercially avaiable, heat-processed vegetable juice. The concentration of plasma lycopene significantly increased after 2 weeks of the high fruit and vegetable diet (Fig. 4), indicating that plasma lycopene can be increased in a relatively short time by increasing the dietary intake of this carotenoid.

Keeping in mind the dietary source of lycopene in these various plasma response studies, it appears that heat processing of the dietary source of lycopene may be an important consideration when examining plasma lycopene relationships with lycopene intakes.

Physiologic Factors

Sex Differences. In contrast to β-carotene, plasma concentrations of lycopene are not found to be higher in women than in men (Fig. 5) (17, 18). These observations remain after adjusting for other factors (smoking, supplement use, alcohol consumption, age, BMI, HDL- and non-HDL-cholesterol) (17). For both men and women, plasma concentrations of lycopene were significantly correlated to dietary intakes (17), suggesting that there is no sex difference in the absorption or utilization mechanism of lycopene.

Age. Increasing age has been found to be significantly associated with all plasma carotenoids except lycopene, to which it was found to be inversely related (17). Similar, but weaker, associations were seen between age and intake of carotenoids. Because dietary lycopene is derived primarily from tomatoes and tomato products, an explanation to this observation is that younger individuals consume more of such lycopene-rich foods as pizza and ketchup. However, diet may only partially explain the inverse relationship between age and plasma lycopene. After adjusting for other

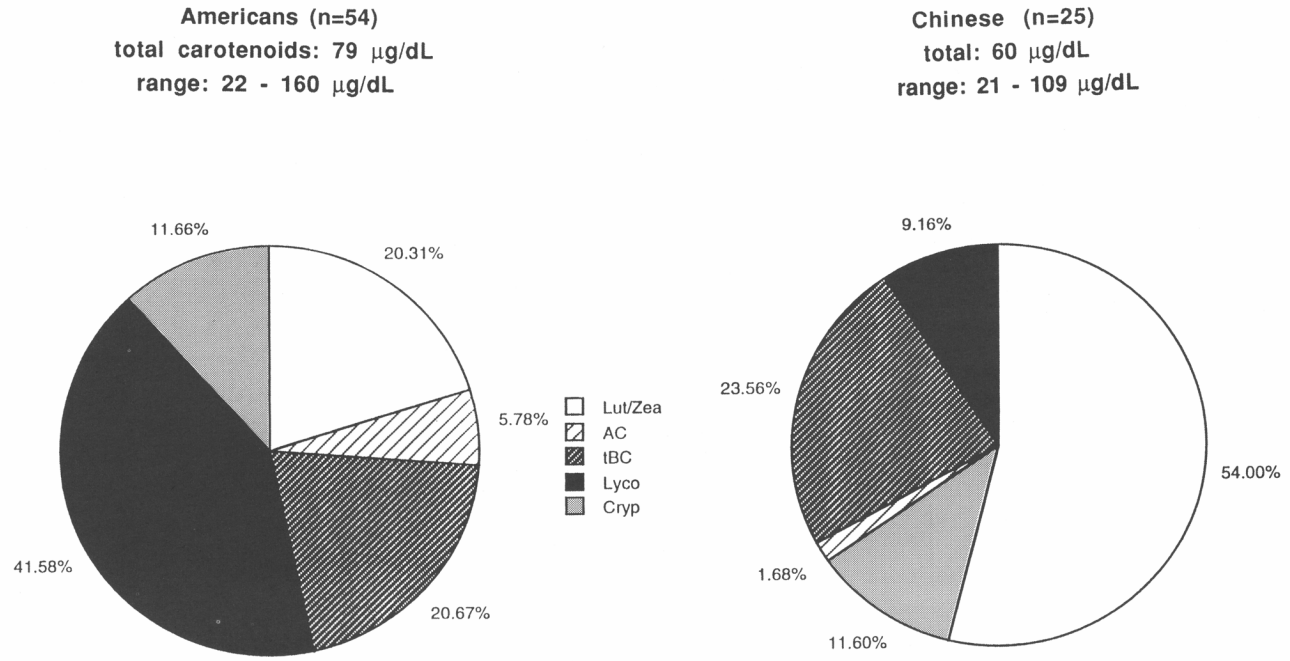

Figure 2. Distribution of plasma carotenoids in plasma of healthy adult Americans and Chinese. Data adapted from Reference 7.

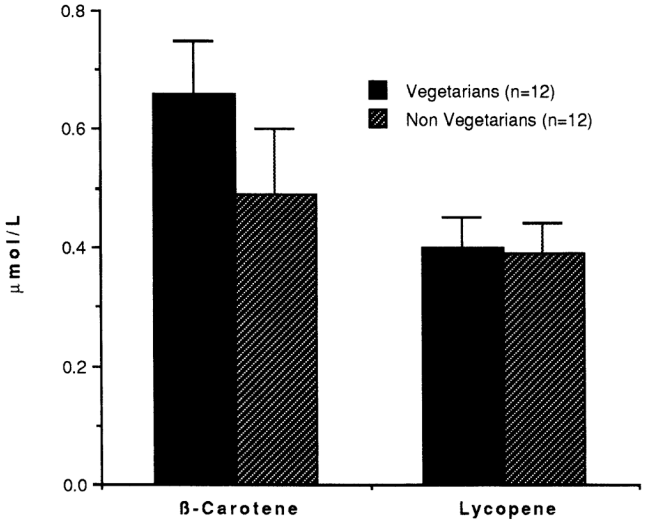

Figure 3. Plasma concentration of β-carotene and lycopene (mean ± SE) in vegetarians and nonvegetarians. Adapted from Reference 15.

factors, the relationship between age and lycopene remained significant (17).

Smoking and Alcohol Use

Smoking. Smokers have been shown to have lower plasma concentrations of β-carotene than do nonsmokers in several studies (Fig. 6) (17, 19, 20). In part, this was related to dietary intake (17). Cigarette smoke is known to contain a large number of oxidants (21). The suppression of concentrations of circulating antioxidants, such as β-carotene, may be one of the pathways through which cigarette smoking increases cancer risk. However, the effect of smoking on plasma lycopene was also examined in these studies. It was found that, compared to nonsmokers, there was no decrease of plasma lycopene concentrations in smokers. These results are difficult to interpret. It would be expected that the plasma concentration of lycopene, a stronger antioxidant than β-carotene, would decrease with smoking. It is possible that smokers eat more dietary lycopene, but this seems unlikely. It appears that smoking affects plasma concentrations of lycopene less than that of β-carotene.

Alcohol. Similar to cigarette smoking, alcohol consumption can be a source of oxidative stress. Therefore, plasma concentrations of carotenoids, being antioxidants, may be reduced in the presence of alcohol. However, the findings among carotenoids have not been consistent. That is, lycopene appears to be less influenced by alcohol consumption than the other major plasma carotenoids. Low drinkers of alcohol (<33 g/day) have been reported to have greater plasma concentrations of β-carotene than that of moderate drinkers but no differences in plasma lycopene were measured (Fig. 7) (22). In a study on healthy women consuming a controlled diet with 30 g alcohol daily for approximately 3 months, α- and β-carotene plasma levels increased, lutein and zeaxanthin decreased, and lycopene was unchanged (23). Similar to these findings, in a population-based study of 400 individuals, alcohol intake was inversely related to all plasma carotenoids except lycopene (17). In this study, the associations of ethanol consumption with plasma carotenoid were similar to those seen with carotenoid intake indicating that plasma carotenoids may reflect the influence of alcohol intake on carotenoid intake.

Relationships between plasma concentrations of lycopene and physiologic and lifestyle factors are probably re-

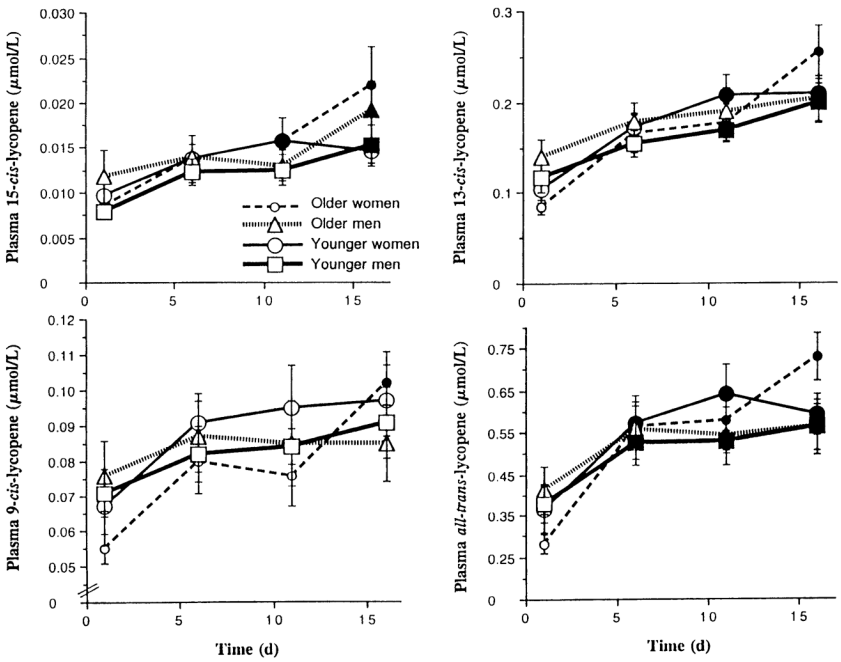

Figure 4. Plasma *cis*- and *trans*-lycopene responses to high carotenoid diets (16 mg/day; 3.3 mg/day lycopene). Mean ± SE; $n = 9$ per group. Filled-in symbols specify significant differences from baseline, $P < 0.05$. Adapted from Reference 16.

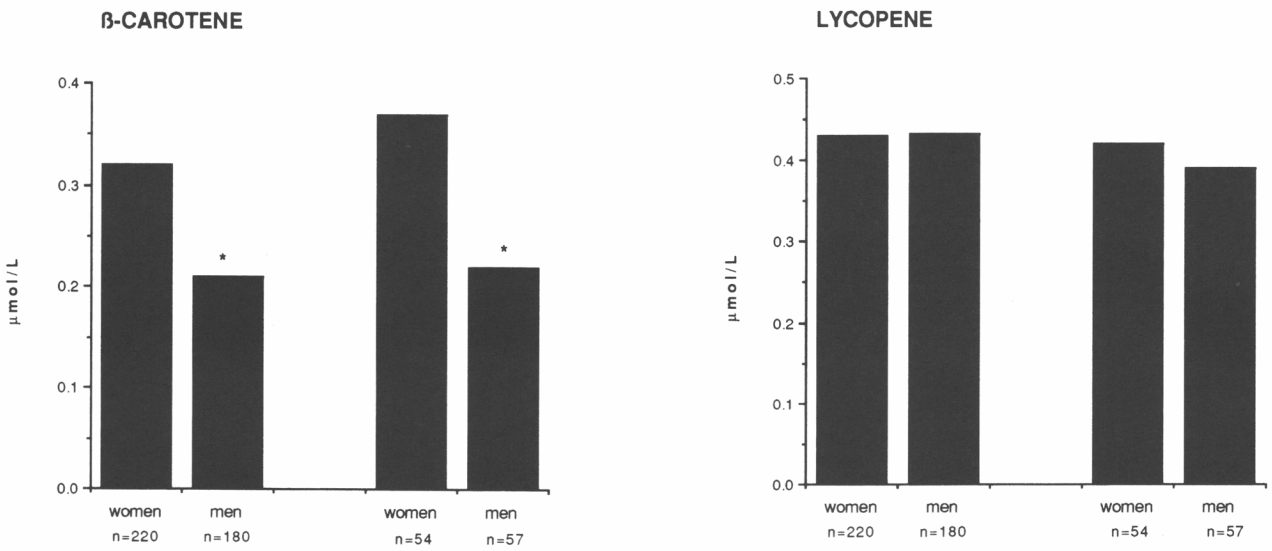

Figure 5. Plasma β-carotene and lycopene in healthy adult men and women. Data from References 17 and 18. *Significantly different from women ($P < 0.05$).

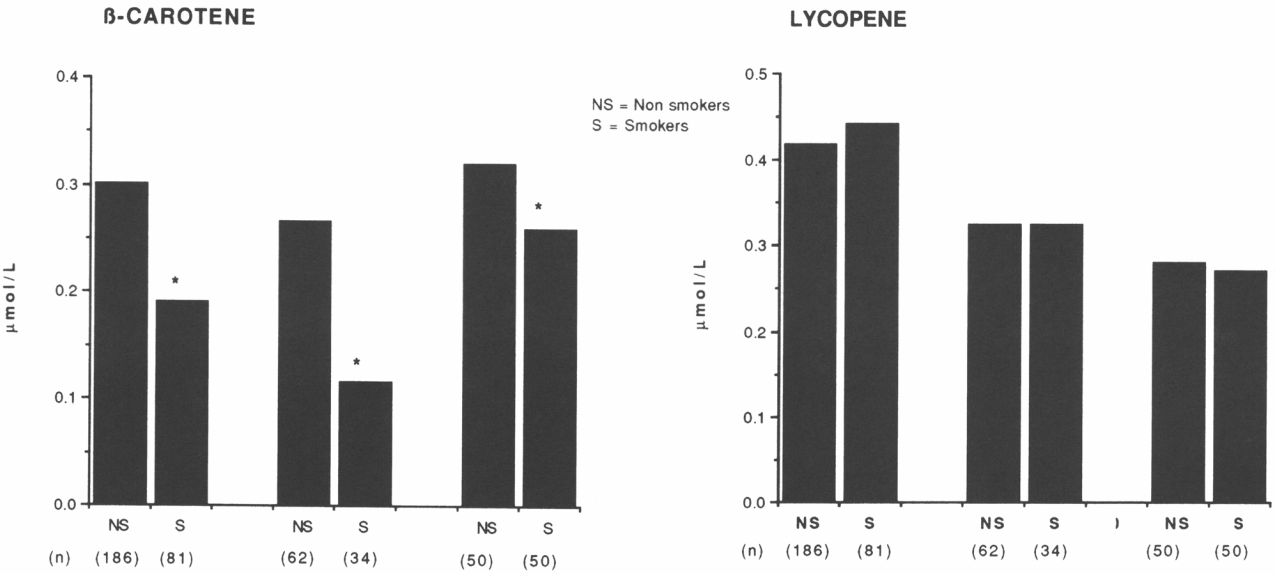

Figure 6. Plasma β-carotene and lycopene in smokers and nonsmokers. Data from References 17, 19, and 20. *Significantly different from nonsmokers ($P < 0.05$).

lated to dietary intake of lycopene. In view of this, dietary lycopene intake may be an important factor in the planning of studies designed to evaluate various aspects of lycopene metabolism and status. However, relationships between plasma concentrations and dietary intakes of lycopene may be difficult to assess given that there may be differences in the bioavailability of lycopene in heat-processed and unprocessed foods (3).

Interactions Between Lycopene and β-Carotene

It has been proposed that high-dose intake of a carotenoid may antagonize the bioavailability and absorption of

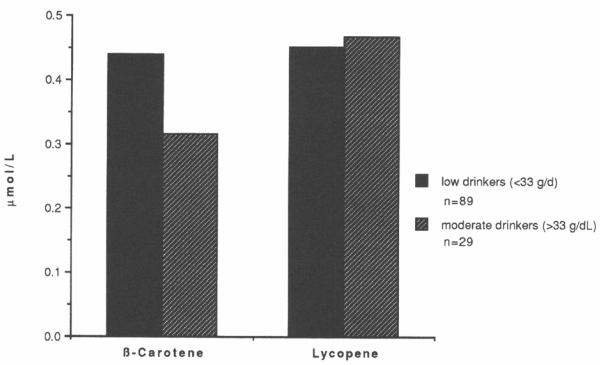

Figure 7. Plasma β-carotene and lycopene in low and moderate drinkers of alcohol. Adapted from Reference 22.

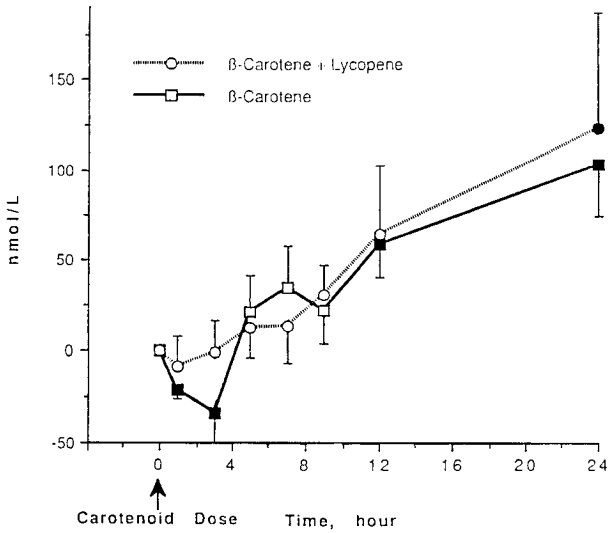

Figure 8. Change in serum β-carotene concentrations after either a single dose of β-carotene or a combined dose of β-carotene and lycopene in men consuming a diet low in vitamin A and carotenoids. Solid points are significantly different ($P < 0.05$) from baseline (0 h). Serum concentrations were adjusted by subtraction of the baseline (0 h) serum concentrations. Results are expressed as means ± SE, $n = 10$.

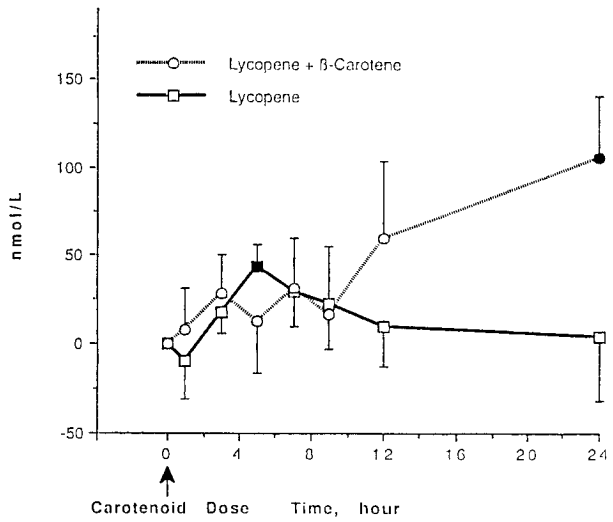

Figure 9. Change in serum lycopene concentrations after either a single dose of or a combined dose of β-carotene and lycopene in men consuming a diet low in vitamin A and carotenoids. Solid points are significantly different ($P < 0.05$) from baseline (0 h). Serum concentrations were adjusted by subtraction of the baseline (0 h) serum concentrations. Results are expressed as means ± SE, $n = 10$.

other carotenoids. In a study designed to investigate the plasma response to individual and combined doses of β-carotene and lycopene crystals dispersed in corn oil, volunteers were given either 30 mg of β-carotene, 30 mg of lycopene, or a combined dose of each (24). Subjects were tested with each of the three doses. Ingestion of the individual carotenoid resulted in significant increases in plasma concentrations of the ingested carotenoid. Ingestion of a

Table I. Serum β-Carotene and Lycopene Responses in Men Given an Oral Dose of β-Carotene, Lycopene, or a Combined Dose[a]

Dose	Baseline	AUC[b]
	nmol/L	*nmol/(L · h)*
Serum β-carotene		
β-Carotene, 60 mg	252 ± 47	11234 ± 3745
β-Carotene, 60 mg + lycopene, 60 mg	248 ± 73	13041 ± 7452
Serum lycopene		
Lycopene, 60 mg	481 ± 67	3074 ± 4043[c]
β-Carotene, 60 mg + lycopene, 60 mg	443 ± 75	12668 ± 6427[c]

[a] Values are means ± SEM, $n = 10$. Adapted from Ref. 24.
[b] Area under the curve calculated by the trapezoidal rule after adjusting for fasting concentrations.
[c] Significantly different ($P < 0.05$).

combined dose resulted in a significant increase in plasma concentrations of both β-carotene and lycopene (Figs. 8, 9). However, the 24-hr areas under the curve (AUC) for β-carotene were not different when β-carotene was ingested alone or with lycopene (Table 1). The 24-hr AUC for lycopene was significantly greater when lycopene was ingested with β-carotene than when ingested alone. These data suggest that ingestion of a combined dose of β-carotene and lycopene has little effect on the absorption of β-carotene but improves that of lycopene. An explanation of the finding of an improved lycopene absorption with β-carotene is that some components in the β-carotene suspension enhanced the solubilization of lycopene and, thereby, provided a better plasma response.

Lycopene and β-carotene are primarily transported in LDL (4). A recent study investigated the possible interactions between the transport of β-carotene and lycopene (25). Healthy human subjects received high-dose, β-carotene supplements starting with loading doses of 100 mg β-carotene daily for 6 days followed by 50 mg every other day for 23 days. Compared to the magnitude of β-carotene uptake into LDL, the concentration of lycopene in LDL reduced (12% and −25%, respectively). This may indicate that β-carotene and lycopene are competing for the same transport mechanism.

Summary

Lycopene is a major carotenoid in human plasma, tissue, and diet. It is unique among the carotenoids in that it has one major food source: tomatoes and tomato products. In contrast to other carotenoids: 1) plasma lycopene concentrations are not higher in women than in men; 2) increasing age is associated with decreasing plasma lycopene concentrations; 3) plasma lycopene concentrations are not inversely related to alcohol intake. Relationships between plasma concentrations of lycopene and physiologic and lifestyle factors are probably related to dietary intake of lyco-

pene. However, relationships between plasma concentrations and dietary intake of lycopene may be difficult to assess given that there may be differences in the bioavailability of lycopene in heat-processed and unprocessed foods. High intake of β-carotene may improve the absorption of lycopene but may also interfere with the transport of lycopene in LDL.

Conclusion

Given that lycopene is a major dietary and plasma carotenoid in the U.S. population, and that there is an inverse association between lycopene intake or plasma concentrations and cancer of the prostate, pancreas, and possibly stomach, it is important to understand factors that influence concentrations in the body and evaluate the metabolism and biological function of lycopene and its metabolites. This is essential for the understanding of the protective effects of this carotenoid.

1. DiMascio P, Kaiser S, Sies H. Lycopene as the most efficient biological carotenoid singlet oxygen quencher. Arch Biochem Biophys **274:**532–538, 1989.
2. Erdman JW Jr, Bierer TL, Gugger ET. Absorption and transport of carotenoids. Ann NY Acad Sci **691:**76–85, 1993.
3. Stahl W, Sies H. Uptake of lycopene and its geometrical isomers is greater from heat-processed than from unprocessed tomato juice in humans. J Nutr **122:**2161–2166, 1992.
4. Krinsky NI, Cornwell, DG, Oncley JL. The transport of vitamin A and carotenoids in human plasma. Arch Biochem Biophys **73:**233–246, 1958.
5. Reddy PP, Clevidence BA, Berlin E, Taylor PR, Bieri JG, Smith JC. Plasma carotenoids and vitamin E profile of lipoprotein fractions of men fed a controlled typical U.S. diet. FASEB J **3:**A955, 1989.
6. Forman MR, Johnson EJ, Lanza E, Graubard BI, Beecher GR, Muesing R. Distribution of individual carotenoids in lipoproteins of premenopausal women: A controlled dietary study. Am J Clin Nutr **67:**81–87, 1998.
7. Yeum KJ, Lee-Kim YC, Zhu S, Xiao S, Mason J, Russell RM. Serum concentrations of antioxidant nutrients in American, Chinese, and Korean healthy adults (in press).
8. Kaplan LA, Lau JM, Stein EA. Carotenoid composition, concentrations, and relationships in various human organs. Clin Physiol Biochem **8:**1–10, 1990.
9. Clinton SK, Emenhiser C, Schwartz SJ, Bostwick DG, Williams AW, Moore BJ, Erdman JW Jr. Cis-trans lycopene isomers, carotenoids, and retinol in the human prostate. Cancer Epidemiol Biomarkers Prev **5:**823–833, 1996.
10. Spady DK, Turley SD, Dietschy JM. Receptor-independent low-density lipoprotein transport in the rat *in vivo*. J Clin Invest **76:**1113–1122, 1985.
11. Brown ED, Micozzi MS, Craft NE, Bieri JG, Beecher G, Edwards BK, Rose A, Taylor PR, Smith JC, Jr. Plasma carotenoids in normal men after a single ingestion of vegetables or purified beta-carotene. Am J Clin Nutr **49:**1258–1265, 1989.
12. Micozzi MS, Brown Ed, Edwards BK, Bieri JG, Taylor PR, Khachik F, Beecher GR, Smith JC. Correlations of vitamin A and E intakes with the plasma concentrations of carotenoids and tocopherols among American men and women. Am J Clin Nutr **55:**1120–1125, 1992.
13. Forman MR, Lanza E, Yong L-C, Holden JM, Graubard BI, Beecher GR, Melitz M, Brown ED, Smith JC. The correlation between two dietary assessments of carotenoid intake and plasma carotenoid concentrations: Application of a carotenoid food-composition database. Am J Clin Nutr **58:**519–524, 1993.
14. Campbell DR, Gross MD, Martini MC, Grandits GA, Slavin JL, Potter JD. Plasma carotenoids as biomarkers of vegetable and fruit intake. Cancer Epidemiol Biomarkers Prev **3:**493–500, 1994.
15. Johnson EJ, Suter PM, Sahyoun N, Ribaya-Mercado JD, Russell RM. The relationship between β-carotene intake and plasma and adipose tissue concentrations of carotenoids and retinoids. Am J Clin Nutr **62:**598–603, 1995.
16. Yeum KJ, Booth SL, Sadowski JA, Liu C, Tang G, Krinsky NI, Russell RM. Human plasma carotenoid response to the ingestion of controlled diets high in fruits and vegetables. Am J Clin Nutr **64:**594–602, 1996.
17. Brady WE, Mares-Perlman JA, Bowen P, Stacewicz-Sapuntzakis M. Human serum carotenoid concentrations are related to physiologic and lifestyle factors. J Nutr **126:**129–137, 1996.
18. Olmedilla B, Granado F, Blanco I, Rojas-Hidalgo E. Seasonal and sex-related variations in six serum carotenoids, retinol, and α-tocopherol. Am J Clin Nutr **60:**106–110, 1994.
19. Peng YM, Peng YS, Lin Y, Moon T, Roe DJ, Ritenbaugh C. Concentrations and plasma-tissue diet relationships of carotenoids, retinoids, and tocopherols in humans. Nutr Cancer **23:**233–246, 1995.
20. Ross MA, Crosley LK, Brown KM, Duthie SJ, Collins AC, Arthur JR, Duthie GG. Plasma concentrations of carotenoids and antioxidant vitamins in Scottish males: Influences of smoking. Eur J Clin Nutr **49:**861–865, 1995.
21. Church DF, Pryor WA. Free-radical chemistry of cigarette smoke and its toxicological implications. Environ Health Perspect **64:**111–126, 1985.
22. LeComte E, Grolier P, Herbeth B, Pirollet P, Musse N, Paille F, Braesco V, Siest G, Artur Y. The relation of alcohol consumption to serum carotenoid and retinol levels: Effects of withdrawal. Int J Vitam Nutr Res **64:**170–175, 1994.
23. Forman MR, Beecher GR, Lanza E, Reichman ME, Graubard BI, Campbell WS, Marr T, Yong LC, Judd JT, Taylor PR. Effect of alcohol consumption on plasma carotenoid concentrations in premenopausal women: A controlled dietary study. Am J Clin Nutr **62:**131–135, 1995.
24. Johnson EJ, Qin J, Krinsky NI, Russell, RM. Ingestion of a combined dose of β-carotene and lycopene does not affect the absorption of β-carotene but improves that of lycopene. J Nutr **127:**1833–1837, 1997.
25. Gaziano JM, Johnson EJ, Russell RM, Manson JE, Stampfer MJ, Ridker PM, Frei B, Hennekens CH, Krinsky NI. Discrimination in absorption or transport of β-carotene isomers after oral supplementation with either all-*trans*- or 9-*cis* β-carotene. Am J Clin Nutr **61:**1248–1252, 1995.