Lycopene is more bioavailable from tomato paste than from fresh tomatoes[1–3]

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ABSTRACT Lycopene bioavailability from a single dose of fresh tomatoes or tomato paste (23 mg lycopene) ingested together with 15 g corn oil was compared by analyzing carotenoid concentrations in the chylomicron fraction. The lycopene isomer pattern was the same in both fresh tomatoes and tomato paste. The triacylglycerol response in chylomicrons was not significantly different after both treatments. Ingestion of tomato paste was found to yield 2.5-fold higher total and *all-trans*-lycopene peak concentrations ($P < 0.05$ and $P < 0.005$, respectively) and 3.8-fold higher area under the curve (AUC) responses ($P < 0.001$) than ingestion of fresh tomatoes. The same was calculated for lycopene *cis*-isomers, but only the AUC response for the *cis*-isomers was significantly higher after ingestion of tomato paste ($P < 0.005$). No difference was observed in the α- and β-carotene response. Thus, in humans, the bioavailability of lycopene is greater from tomato paste than from fresh tomatoes. *Am J Clin Nutr* 1997;66:116–22.

KEY WORDS Carotenoids, *all-trans*-lycopene, lycopene *cis*-isomers, chylomicrons, bioavailability, fresh tomatoes, tomato paste

INTRODUCTION

Lycopene, the predominant carotenoid in tomatoes, exhibits the highest antioxidant activity and singlet oxygen quenching ability of all dietary carotenoids (1–3). Its potential cancer-preventing properties are beginning to be investigated (4). Giovannucci et al (5) found that the dietary intake of lycopene is epidemiologically correlated with diminished risk for prostate cancer. Other carotenoids, lutein, β-cryptoxanthin, and α- and β-carotene showed no correlation in their study. Likewise, lycopene was superior to α- and β-carotene in inhibiting cell proliferation in various human epithelial cancer cell lines (6). Initiation and progression of 7,12-dimethyl-benz[a]anthracene–induced rat mammary tumors were suppressed by lycopene but not by β-carotene (7), and lycopene has been shown to protect efficiently against mammary tumorigenesis in a high-mammary-tumor strain of mice (8).

Few epidemiologic data on the relation between cancer risk and dietary intake of tomatoes or tomato products are available, and these studies have shown equivocal results (9–15). However, when serum concentrations of lycopene were investigated instead of dietary tomato intake, a lower cancer risk was correlated with higher serum lycopene concentrations throughout (16–19). Giovannucci et al (5) discussed whether differences in lycopene bioavailability from tomatoes and tomato products might account for this effect. They found consumption of tomato sauce and not of fresh tomatoes or tomato juice to be the strongest predictor for higher lycopene serum concentrations and diminished risk for prostate cancer.

The uptake of lycopene was found to be greater from heat-processed than from unprocessed tomato juice. Ingestion of tomato juice cooked in an oil medium resulted in a two- to threefold increase in lycopene serum concentrations 1 d after ingestion, but an equivalent consumption of unprocessed tomato juice caused no rise in plasma concentrations (20). Cooking or chopping are believed to enhance bioavailability by breaking down sturdy cell walls, thus making carotenoids more accessible.

Here we investigated the uptake of lycopene into human chylomicrons after a single dose of lycopene from fresh tomatoes and from tomato paste.

SUBJECTS AND METHODS

Subjects

Five subjects, three females and two males, took part in the study. The volunteers had no history of any chronic disease, bleeding disorder, hypertriglyceridemia, hyperlipoproteinemia, lipid malabsorption, or diabetes. They did not use any supplements of vitamins, minerals, or carotenoids in the 3 mo before the study and they had normal dietary habits. All volunteers signed an informed consent form. The study was conducted in accord with the Helsinki Declaration of 1975 as revised in 1983.

Study design

The study was conducted on 2 experimental days 2 wk apart. The volunteers were instructed to consume a diet low in carotenoids 3 d before the experimental days; tomatoes and tomato

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Received October 3, 1996.

Accepted for publication February 10, 1997.

products were to be avoided in particular. Compliance was checked by daily interview. On the days of the study, after fasting overnight, volunteers consumed either 400 g fresh tomatoes (day A) or 40 g tomato paste (day B) together with 15 g corn oil and 100 g bread. The experimental meals were served at 0830 in the morning after a fasting blood sample had been drawn. A crossover design was not used because we supposed it to be difficult to find, over a 2-wk span, two batches of fresh tomatoes with exactly the same texture and content of lycopene, carbohydrate, and fiber. The amount of total and *all-trans*-lycopene was the same in both tomato meals. The fresh tomatoes were cut into slices and served as tomato salad together with corn oil. For the tomato paste meal, the corn oil was stirred into the tomato paste. On both days, the same low-carotenoid lunch was served at 1300 (4.5 h after the tomato meal), and only black coffee and water were allowed during the experiment. Fresh tomatoes, corn oil, and bread were purchased from local distributors.

Sample preparation

Blood samples were drawn into evacuated containers without anticoagulant before (0 h) and 2, 4, 5, 6, 7, 9, and 12 h after ingestion of the tomato meal. To avoid isomerization of carotenoids, all further operations were performed under dim light. After clotting, serum was prepared by centrifugation at 16 °C for 10 min at 2000 × *g*. An aliquot was frozen at −70 °C until analyzed, and another was used directly for chylomicron preparation (21). Briefly, 2 mL serum was mixed carefully with 50 mg sucrose, 770 mg KBr, and 200 mL ethylene glycol, resulting in a serum density of ρ_{20} = 1.250 kg/L. The serum was overlaid with 2 mL KBr solution (ρ_{20} = 1.225 kg/L), 4 mL KBr solution (ρ_{20} = 1.100 kg/L), and 3 mL H_2O. After ultracentrifugation at 20 °C for 40 min at 155 000 × *g* in an SW 41 rotor (Beckman, Munich, Germany), the chylomicron fraction floating on top of the gradient was collected with a Pasteur pipette and immediately frozen at −70 °C.

Analysis and chromatography

Triacylglycerol and cholesterol were measured by using commercially available colorimetric test kits (CHOD-PAP and GPO-PAP, respectively, Boehringer Mannheim, Mannheim, Germany). The carotenoid content in tomatoes and tomato paste was analyzed according to Hart and Scott (22). Extraction of carotenoids from serum and chylomicrons was performed as described (23).

Extracts from vegetable samples were diluted appropriately in HPLC solvent A (CH_3OH:CH_3CN:2-propanol, 54:44:2 by vol) and analyzed on a 5-μm Suplex pKb 100 column (250 × 4.6 mm) from Supelco (Bellefonte, PA), by using a step gradient: 0–10 min 97% solvent A and 3% H_2O and 10–25 min 100% solvent A with a flow rate of 1 mL/min and detection at 450 nm. Dry carotenoid residues from serum and chylomicron extraction were redissolved in HPLC solvent A directly before analysis. The same HPLC system was used as above with a slightly modified gradient: 0–5 min 94.5% solvent A and 5.5% H_2O and 5–15 min a linear gradient running from 94.5% to 100% solvent A, which was held for 12 min. Peaks were identified spectrophotometrically by diode array detection (model 168; Beckman) and by coelution with synthetic reference carotenoids.

Reference carotenoids were either a gift from Z Nir, Makhteshim Chemical Works (lycopene; Beer Sheva, Israel) and J Bausch, Hoffmann-La Roche (lutein, zeaxanthin; Basel, Switzerland), or purchased from Sigma (α-carotene; Deisenhofen, Germany) or Fluka (β-carotene, ethyl-β-apo-8′-carotenoate, β-apo-8′-carotenal; Buchs, Switzerland). All other chemicals were obtained from E Merck (Darmstadt, Germany). The internal standard used for serum and chylomicron carotenoid analysis, β-apo-8′-carotenol, was synthesized from β-apo-8′-carotenal according to Khachik and Beecher (24) and purified by HPLC.

Response factors determined for our HPLC system were used to calculate the carotenoid contents in tomatoes, tomato paste, and other foods. Carotenoid concentrations in serum and chylomicrons were calculated from calibration curves generated from peak height ratios of carotenoid standards to the internal standard.

Statistics

Results are expressed as means ± SDs. Area under the curve [(AUC) 0–12 h] responses were calculated by trapeziodal rule after subtraction of fasting concentrations. Peak concentrations (*cmax*) were adjusted for fasting concentrations likewise. Effects of treatment, time, and treatment and time interactions on the triacylglycerol and carotenoid response were analyzed by two-factor repeated-measures analysis of variance. Differences in baseline serum concentrations, AUC responses, and peak concentrations between the 2 experimental days were assessed by two-sided paired Student's *t* test. All statistical calculations were done by using Excel 5.0 (Microsoft Corp, Unterschleissheim, Germany).

RESULTS

Volunteer characteristics are given in **Table 1**. Fasting serum triacylglycerol and cholesterol concentrations were in the normal range for all subjects on both experimental days when applying generally accepted cutoffs (< 2.3 mmol/L for triacylglycerol and < 5.2 mmol/L for cholesterol). Fasting serum carotenoid concentrations were around the lower limit of reported values in all volunteers (Table 1). There was no significant difference in fasting serum carotenoid concentrations between the experimental days. The higher serum concentra-

TABLE 1
Characteristics of the volunteers[1]

	Fresh tomatoes (Day A)	Tomato paste (Day B)
Age (y)	32.2 ± 7.3	
BMI (kg/m^2)	23.3 ± 4.0	
Fasting serum concentrations		
all-trans-Lycopene (nmol/L)	127 ± 12	165 ± 65
Total lycopene (nmol/L)	282 ± 36	360 ± 148
α-Carotene (nmol/L)	49 ± 34	48 ± 31
β-Carotene (nmol/L)	220 ± 122	219 ± 76
Lutein (nmol/L)	320 ± 100	297 ± 97
Zeaxanthin (nmol/L)	83 ± 42	81 ± 36
Triacylglycerol (mmol/L)	0.76 ± 0.16	1.13 ± 0.25
Cholesterol (mmol/L)	5.00 ± 0.54	5.03 ± 0.78

[1] $\bar{x}$ ± SD; *n* = 3 females and 2 males; day A and day B were 2 wk apart.

tions of *all-trans*- and total lycopene on day B were due to higher serum concentrations of these carotenoids in only one volunteer.

The lycopene content of the experimental meals was the same on both days of the study (**Figure 1**, A and B, and **Table 2**). No lycopene isomerization was observed in the tomato paste compared with fresh tomatoes. Biological variation might account for the somewhat higher β-carotene content in the fresh tomatoes.

The triacylglycerol response in chylomicrons after consumption of the tomato paste meal was not significantly different from that observed after consumption of the fresh tomato meal (**Figure 2**C and **Tables 3** and **4**). An early peak in chylomicron triacylglycerol concentrations was seen 2 h after ingestion of both tomato meals, and a second, higher peak again 1.5–2.5 h after lunch (6–7 h after ingestion of the experimental meals).

After both experimental meals, an increase in lycopene concentrations was observed in chylomicrons but not in serum of all volunteers. This chylomicron lycopene response was significantly higher ($P < 0.05$) after consumption of tomato paste than after consumption of fresh tomatoes as assessed by chylomicron lycopene concentrations, AUC responses (0–12 h), and peak concentrations (*cmax*) (Figure 2, A and B, and Table 4). Analysis of variance also revealed a combined effect of treatment and time on the chylomicron lycopene response (Table 3). Because of the small number of volunteers, these data should not be overemphasized. *all-trans*-Lycopene, the isomer almost exclusively present in tomatoes and tomato paste, accounted predominantly for the total lycopene response

TABLE 2
Carotenoid content in tomatoes and tomato paste per dose administered in this study[1]

	Tomatoes (400 g)	Tomato paste (40 g)
	mg	
Lycopene		
Total	22.2 ± 0.6	23.6 ± 0.2
all-trans-	21.1 ± 0.5	22.8 ± 0.2
cis-	1.16 ± 0.12	0.78 ± 0.05
β-Carotene	1.32 ± 0.08	0.50 ± 0.02

[1] $\bar{x}$ ± SD; $n = 3$.

(*all-trans*- and *cis*-lycopene) in chylomicrons (Figure 2, A and B, and Table 4).

In serum, no distinct changes in lycopene concentrations were observed (data not shown). After consumption of the tomato paste meal, total and *all-trans*-lycopene concentrations showed a slight time-dependent increase, but this increase was not significant, the values being not significantly different from 0-h concentrations at each time point. After consumption of the fresh tomato meal, total and *all-trans*-lycopene concentrations remained constant throughout the day of study with a tendency to decline, as did lutein, zeaxanthin, and α- and β-carotene serum concentrations on both experimental days. This was confirmed by analysis of variance, revealing no significant effect of time on serum concentrations of all carotenoids. An effect of treatment was observed only for *all-trans*- and total lycopene ($P < 0.005$ and $P < 0.05$, respectively).

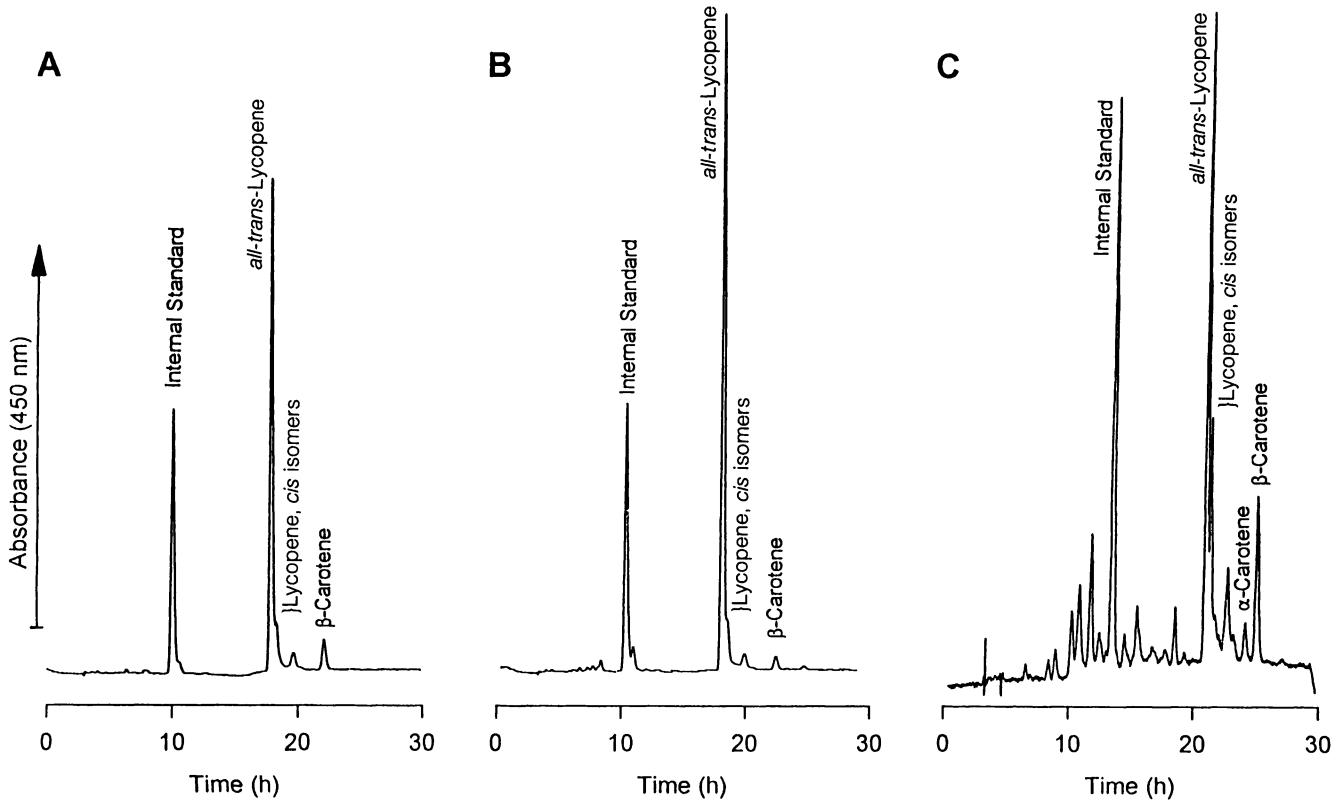

FIGURE 1. Carotenoid pattern in fresh tomatoes (A), in tomato paste (B), and in the chylomicron fraction (C) of one volunteer 4 h after consumption of tomato paste.

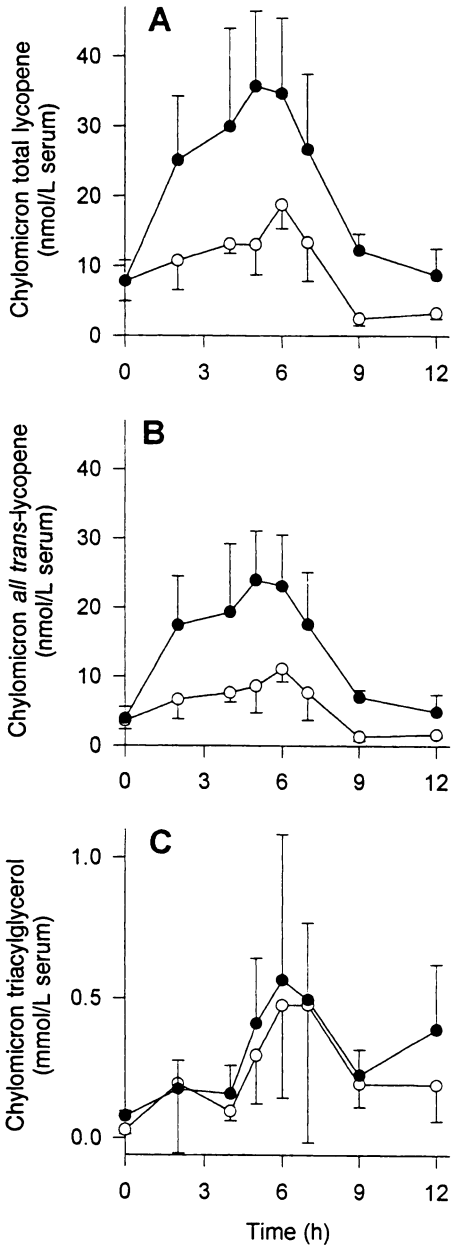

FIGURE 2. Total lycopene (A), *all-trans*-lycopene (B), and triacylglycerol (C) concentrations in the chylomicron fraction before (0 h) and after consumption of fresh tomatoes (○, day A) and tomato paste (●, day B). $\bar{x}$ ± SD; n = 5.

In chylomicrons we observed a slight increase in β-carotene concentrations after ingestion of tomato paste (data not shown). However, mean values were only significantly different ($P < 0.01$) from the 0-h value at 6 h after the tomato meal. No significant effect of treatment on β-carotene concentrations in chylomicrons was observed by analysis of variance (Table 3). On both experimental days, a small amount of α-carotene was found in the chylomicrons of all volunteers, which was not significantly different on both days and which did not change over time (Table 3). The AUC for β-carotene tended to be higher after consumption of tomato paste (Table 4). Nevertheless, the difference was not significant, and higher β-carotene availability from tomato paste might have been balanced by the lower β-carotene content in the paste.

TABLE 3
Effect of time and treatment on the carotenoid and triacylglycerol response in chylomicrons after ingestion of fresh tomatoes and tomato paste as shown in Figure 2[1]

	Effect of		
	Treatment *P*	time *P*	Treatment × time *P*
Triacylglycerol	NS	< 0.005	NS
Lycopene			
Total	< 0.0001	< 0.0001	< 0.05
all-trans-	< 0.0001	< 0.0001	< 0.05
cis-	< 0.0001	< 0.0001	< 0.05
α-Carotene	NS	NS	NS
β-Carotene	NS	< 0.05	NS

[1] Results of two-factor repeated-measures analysis of variance (treatment: fresh tomatoes versus tomato paste).

DISCUSSION

To compare lycopene bioavailability from fresh tomatoes and tomato paste we measured the lycopene response in the chylomicron fraction of volunteers because chylomicrons have been shown to be a more appropriate tool for studying intestinal absorption kinetics of carotenoids than are concentrations in plasma (23, 25–28).

In response to single carotenoid doses, peak concentrations in plasma are reached 24–48 h postdose (25–27, 29), whereas in chylomicrons they occur between 4–6 h and decline to near-basal concentrations within 12 h (23, 25–28, 30). Thus, carotenoid concentrations in chylomicrons mainly reflect absorption kinetics. A major part of the plasma response has been attributed to resecretion of newly absorbed carotenoids by the liver as constituents of other lipoproteins with half-lives longer than those of chylomicrons, thus leading to accumulation of the absorbed carotenoids in plasma (25, 27, 31). The lack of response in plasma, which has also been reported in other studies (28), might be due to the short period investigated, although Wingerath et al (23) observed a clear increase in β-cryptoxanthin plasma concentrations beginning 6 h after a single dose of β-cryptoxanthin.

The lycopene dose in this study was 23 mg. Single doses of carotenoids with this order of magnitude might not yield any effect on carotenoid plasma concentrations when derived from vegetables and not from purified supplements (29). In addition, large interindividual variation in the plasma response to single carotenoid doses, or even nonresponse, have been reported (26, 29, 32, 33). In studies that used chylomicrons to investigate carotenoid absorption, except for two (26, 34), no nonresponders were reported, as in the present study, and a response to single carotenoid doses sometimes as low as 1 mg was seen (23, 25–28, 30).

Constant study conditions on all days of the study are essential for investigating influences of different treatments on carotenoid bioavailability. Recently, van Vliet et al (28) reported differences in triacylglycerol and carotenoid responses to the same experimental meal between different days of their study and therefore used the ratio of carotenoid AUC response

TABLE 4
Area under the curve (AUC) responses and peak concentrations (*C*max) in chylomicrons after ingestion of fresh tomatoes and tomato paste[1]

	Fresh tomatoes (day A)		Tomato paste (day B)	
	AUC (0–12 h)	*C*max	AUC (0–12 h)	*C*max
	nmol · h/L	nmol/L	nmol · h/L	nmol/L
Lycopene				
Total	28.4 ± 15.7	11.0 ± 3.6	109.3 ± 26.6[2]	27.9 ± 9.3[3]
all-trans-	22.6 ± 11.1	7.5 ± 2.0	79.5 ± 18.8[2]	20.1 ± 6.1[4]
cis-	7.3 ± 4.9	3.4 ± 2.8	29.9 ± 8.5[4]	7.8 ± 3.4
α-Carotene	0.8 ± 0.6	0.4 ± 0.5	1.3 ± 1.1	0.4 ± 0.4
β-Carotene	7.0 ± 5.6	3.2 ± 3.3	10.9 ± 6.7	2.8 ± 2.4
Triacylglycerol	1.22 ± 1.01[5]	0.48 ± 0.33[6]	1.38 ± 0.71[5]	0.57 ± 0.52[6]

[1] $\bar{x}$ ± SD; n = 5. AUCs and peak concentrations were calculated after subtracting fasting concentrations.
[2,3,4] Significantly different from day A (Student's t test): [2] $p < 0.001$, [3] $p < 0.05$, [4] $p < 0.005$.
[5] mmol · h/L.
[6] mmol/L.

to the triacylglycerol AUC response as a reproducible measure between different days. In the present work, the triacylglycerol responses were not significantly different on the two experimental days. Therefore, a correction for triacylglycerol response was neither necessary nor did it change the results when performed (data not shown).

Triacylglycerol concentrations in chylomicrons peaked 2–3 h after both the tomato meal and the lunch, as has generally been observed (28, 35). A high proportion of the increase in chylomicron triacylglycerol after lunch has been reported to consist of fat ingested for breakfast 5 h earlier (35). The time-dependent response in chylomicron triacylglycerol concentrations to fat-containing meals was found to be highly variable between subjects, and sometimes more than one peak in triacylglycerol concentrations was observed (36, 37). The high SD in chylomicron triacylglycerols at most time points might be due to this effect.

Peak lycopene concentrations in chylomicrons were reached between 5 and 6 h postdose. This is in accordance with chylomicron kinetics reported for β-carotene (25–28) and β-cryptoxanthin (23). In studies using single carotenoid doses between 10 and 20 mg, peak concentrations of 30–50 nmol/L were reported (23, 28). In the present study, the total lycopene content in the tomato meals was 22.2 mg from fresh tomatoes and 23.6 mg from the tomato paste. As shown in Figure 2A, total lycopene peak concentrations of 35.6 nmol/L were reached in the chylomicron fraction after consumption of tomato paste and of 18.8 nmol/L after consumption of fresh tomatoes, the increments over 0-h concentrations being of 27.9 and 11.0 nmol/L, respectively (Table 4). Thus, ingestion of tomato paste resulted in 1.9- to 2.5-fold higher total lycopene peak concentrations ($P < 0.05$), whereas the total lycopene AUC response was even 3.8-fold higher after ingestion of tomato paste compared with ingestion of fresh tomatoes ($P < 0.001$). The same difference is calculated when comparing *all-trans*-lycopene and lycopene *cis*-isomer absorption kinetic parameters.

Thus, with a constant content of fat and other meal ingredients, lycopene bioavailability from tomato paste was significantly higher than that from fresh tomatoes. This lends experimental support to the epidemiologic observation regarding lycopene bioavailability. As mentioned above, tomato sauce was found to be the major predictor of lycopene plasma concentrations, followed by fresh tomatoes (5), whereas intake of tomato juice was not correlated with lycopene plasma concentrations. This is in line with data from our group (20) showing no increase in lycopene serum concentrations with ingestion of tomato juice. The observed increase in lycopene serum concentrations after heating the juice in an oil medium was suggested to be attributable to extraction of lycopene into the lipophilic phase during the boiling process. Carotenoids are known to be readily absorbed from lipophilic matrixes (29, 38). Therefore, carotenoid bioavailability from vegetables might be enhanced in two ways: extraction of carotenoids from the food matrix into a lipophilic phase (20) and mechanical disruption of cells, as was shown in the present study. Heat treatment might also affect the structure of vegetable tissue, yielding the same effect as mechanical disruption. Accordingly, Poor et al (39) reported higher carotenoid bioavailability from steamed than from raw carrot slurries in preruminant calves. On the other hand, heat treatment had no effect on β-carotene bioavailability from carrot juice in calves (39). In vegetable juice the cell matrix has already been disrupted, rendering any further effect of heat treatment on the cell matrix unlikely.

Apart from matrix effects, carotenoid absorption from foods is influenced by other factors, namely by coingestion of high amounts of dietary fiber (33) or by coingestion of fat (40). It might be assumed that tomato juice is usually not consumed together with any fat, resulting in poor lycopene bioavailability. This might explain the observation by Giovannucci et al (5) that intake of tomato juice was not correlated with lycopene plasma concentrations in their study.

About 95% of total lycopene in the study tomatoes and tomato paste was *all-trans*-lycopene. This isomer accounted for ≈65% of total lycopene in chylomicrons, but only for 45% in serum (41, 42, data not shown). This confirms results by Clinton et al (43), who reported that 90% of total lycopene was *all-trans*-lycopene in tomatoes, 32% in serum, and 17% in benign and malign prostate tissue. In other tissues (liver, kidney, and adrenal gland) the percentage of *all-trans*-lycopene is similar to that in serum or even higher, eg, 60% in testes (41). Thus, it appears that lycopene is absorbed into chylomicrons mainly in the form that it is present in foods and is isomerized in vivo to yield the typical pattern found in serum and tissues.

The biochemical or physiologic mechanisms leading to this possibly tissue-specific isomer pattern as well as the biological consequences remain to be elucidated.

In conclusion, lycopene bioavailability is higher from tomato paste than from fresh tomatoes. Thus, in light of the epidemiologically defined cancer-preventing properties of carotenoids, the factors affecting their bioavailability should be taken into account.

We thank B de Boer and K van het Hof, Unilever Research Laboratory, Vlaardingen, Netherlands, for helpful discussions; Clemens Fritsch and Olga Briviba for the blood drawings; and Ilka Römer (Diabetes Forschungsinstitut, Düsseldorf, Germany) for the triacylglycerol and cholesterol analyses.

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