

A physiological pharmacokinetic model describing the disposition of lycopene in healthy men

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Abstract A physiological pharmacokinetic model was developed to describe the disposition of lycopene, delivered as a tomato beverage formulation in five graded doses (10, 30, 60, 90, or 120 mg), for a phase I study in healthy male subjects (five per dose). Blood was collected before dose administration (0 h) and at scheduled intervals until 672 h. Serum concentrations of carotenoids and vitamins were measured by high performance liquid chromatography analysis. The model was comprised of seven compartments: gastrointestinal tract, enterocytes, chylomicrons, plasma lipoproteins, fast-turnover liver, slow-turnover tissues, and a delay compartment before the enterocytes. As predicted, the percent absorption at the 10 mg dose ($33.9 \pm 8.1\%$) was significantly greater than at the higher doses; however, the amount of lycopene absorbed (mg) was not statistically different (mean: 4.69 ± 0.55 mg) between doses, suggesting a possible saturation of absorptive mechanisms. The slow-turnover tissue compartment served as a slow-depleting reservoir for lycopene, and the liver represented the fast-turnover pool. Independent of dose, 80% of the subjects absorbed less than 6 mg of lycopene. This may have important implications for planning clinical trials with pharmacological doses of lycopene in cancer control and prevention if absorption saturation occurs at levels that are already being consumed in the population.—Diwadkar-Navsariwala, V., J. A. Novotny, D. M. Gustin, J. A. Sosman, K. A. Rodvold, J. A. Crowell, M. Stacewicz-Sapuntzakis, and P. E. Bowen. A physiological pharmacokinetic model describing the disposition of lycopene in healthy men. *J. Lipid Res.* 2003. 44: 1927–1939.

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The growing interest in lycopene as an agent for cancer control and prevention can be attributed to recent epide-

miological evidence which suggests that the intake of tomato sauce, the most bioavailable source of lycopene, may be associated with a reduced risk for prostate cancer in men (1). It is speculated that this effect is likely due to the antioxidant properties of lycopene. In vitro studies suggest that lycopene is the most potent singlet oxygen quencher among the carotenoids (2); however, conclusive evidence in vivo is still lacking. Lycopene is the primary serum carotenoid in men and women in the United States, and is also found in various tissues, including the prostate gland (3–7). Recent studies have demonstrated lower prostate cancer risk in men with elevated plasma lycopene levels (8), and significantly lower serum and tissue lycopene levels in prostate cancer patients compared with controls (9). Supplementation with 30 mg/day lycopene in the form of a tomato sauce pasta entree for 3 weeks in 32 prostate adenocarcinoma patients produced significantly higher lycopene levels in serum (2-fold) and prostate tissue (3-fold), and resulted in concomitant decreases in DNA damage in both leukocytes and prostate, along with a reduction in serum prostate specific antigen (PSA) (10). Lycopene supplementation as capsules (30 mg/day for 3 weeks) in patients with localized prostate cancer resulted in 47% higher tissue lycopene levels, and although not significant, smaller tumors and lower plasma PSA levels were found in the intervention group compared with control subjects (11). These human studies point to a possible role for lycopene in prostate cancer control and prevention, although the likelihood that other components in tomatoes may afford a protection is also being considered. The mechanism by which lycopene may affect prostate carcinogenesis is still under investigation. In vitro and animal studies suggest that it may affect cell cycle progres-

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sion (12), levels of antioxidant enzymes (13), gap junctional communication (14), and cell proliferation (15) in different cancer cell lines.

Although several investigations have focused on elucidating the mechanisms of lycopene action in vitro, human studies investigating lycopene metabolism, particularly at graded doses, are scarce. A suitable animal model that mimics lycopene metabolism has not been identified, limiting the extrapolation of results from animal studies to humans. Unlike β -carotene, understanding the dynamics of lycopene metabolism has also been hampered by the slow progress in the synthesis of stable isotope-labeled lycopene. At this point human metabolism studies seem to be the best approach to examining lycopene bioavailability.

The increasing interest in lycopene as a potential anticancer agent has initiated a formal evaluation of this compound. As part of such an evaluation, we recently completed a phase I clinical trial in 25 healthy male subjects (18–45 years) designed to evaluate the pharmacokinetics of a dose range of lycopene delivered as a tomato beverage formulation, and to determine three doses for a 3 month chronic-dosing study that is now ongoing. The pharmacokinetics of lycopene was determined in healthy male subjects after the oral administration of a single dose of 10, 30, 60, 90, and 120 mg. Serial blood samples were collected up to 672 h (28 days) to determine serum lycopene concentrations. All lycopene *cis* and *trans* isomers eluted together and were quantitated as total lycopene in one peak. In order to describe the disposition of lycopene, a physiological model was developed using WinSAAM, a differential equation solving package, which allows the mathematical prediction of nutrient metabolism based on experimentally measured serum values. The kinetics of *cis* and *trans* lycopene will be addressed in a separate paper. Most bioavailability studies apply indirect measures of absorption such as plasma response or area under the concentration time curve (AUC). These provide limited quantitative and qualitative information. Using the modeling approach, we were able to quantify several critical parameters of lycopene absorption and hypothesize the process of lycopene assimilation, clearance, and transport in the body. Novotny et al. (16) have developed a similar compartmental model to describe the kinetics of stable isotope-labeled β -carotene uptake and removal from whole plasma in an adult volunteer. Using this model, they were able to predict the percentage of β -carotene dose that was absorbed, the percentage of total retinoid formed from β -carotene in the liver and intestine, and also the percentage of β -carotene converted to retinoids while passing through the liver (16). Here we report results from the physiological pharmacokinetic analysis of lycopene disposition at graded doses in 25 healthy male subjects.

EXPERIMENTAL PROCEDURES

Subject selection

Twenty-five informed, consenting, healthy male volunteers between the ages of 18 and 45 years were recruited for the study.

The study protocol was approved by the Institutional Review Board (IRB) of the University of Illinois at Chicago (UIC). Subjects were recruited through IRB-approved advertisements posted at the UIC campus. Potential subjects were identified by prescreening via a telephone interview. Eligibility was confirmed after determining the prestudy serum lycopene concentration and following physical evaluation by the study clinician. Eligibility was limited to subjects with serum lycopene concentrations less than 700 nM, because previous investigations suggested that subjects with high serum lycopene concentrations were less likely to demonstrate significant changes with a single-dose administration (17). All participating subjects were within 15% of ideal body weight (IBW), in good health based on history and physical examination, were nonsmokers, or had quit smoking within the 3 months prior to study entry, had no known malabsorption problem or other condition that could affect nutrient absorption, did not have a history of alcohol abuse, and were willing to refrain from alcohol consumption for 72 h prior to study entry and during the study period. Five subjects were enrolled per dose level.

Rationale for dose selection

Five doses of lycopene were selected for the study: 10, 30, 60, 90, and 120 mg. All dose levels were considered low risk for adverse reactions. The minimum dose of 10 mg was selected based upon prior epidemiological evidence, which indicated that a decrease in prostate cancer risk was associated with intakes of over 6.4 mg/day of lycopene from food sources (1). Lycopene studies conducted in our laboratory have demonstrated that 30–50 mg of lycopene administered daily for 4 weeks produced no apparent toxicity (18). One case study of lycopene toxicity reported yellow skin coloration and liver enlargement with large chronic intake of tomato juice, equivalent to a lycopene dose of 180 mg/day, which was well above the 120 mg dose in this study (19). Therefore, the dose range in our study provided a safe increase and also a wide range of doses to evaluate (12-fold).

Tomato beverage formulation

Standardized concentrations of total lycopene were delivered as a tomato beverage formulation. Thirty grams of commercially available tomato paste (Hunt-Wesson, Inc., Fullerton, CA) was combined with 5 ml of olive oil (extra virgin olive oil, Bertolli USA, Secaucus, NJ), mixed to a smooth paste, made up to 100 ml with distilled water, and blended again to give a uniform consistency. The addition of oil to tomato paste improved palatability of the beverage. Because different batches of tomato paste may vary in their lycopene content, every batch was analyzed separately, and standardized to the total lycopene content. Volumes of the tomato beverage were adjusted to reflect this variability in lycopene content from batch to batch, so that the intended dose of total lycopene was delivered. The different doses of total lycopene corresponded to the following volumes: 79 ml = 10 mg, 238 ml = 30 mg, 476 ml = 60 mg, 769 ml = 90 mg, and 797 ml = 120 mg.

Administration of lycopene dose and blood draw

All subjects were instructed to follow a low-carotenoid eating plan 1 week prior to dose administration. On the day of lycopene dosing, subjects came to the Clinical Research Center (CRC) at UIC in a fasting state. Following the baseline blood draw, the appropriate dose of lycopene was administered orally. All subjects were allowed to drink up to 250 ml of water, which was provided with the tomato beverage. A maximum time period of 15 min was permitted to complete consumption of the beverage. Subjects then immediately consumed a breakfast negligible in carotenoids, which provided 30% of the calories as fat and consti-

tuted 25% of the subjects' energy needs for the day. Lunch was fed after the 4 h blood draw and dinner after the 10 h draw. These meals also contained negligible amounts of carotenoids and provided 30% of calories as fat. Lunch provided 40% and dinner 30% of each subject's energy requirements. A late-evening snack constituted 5% of the energy requirement. The nutrient content of the meals and olive oil used in the tomato beverage formulation is presented in **Table 1**. The same meals were fed to the subjects on the second day of the study. The energy requirement for all subjects was calculated using the Harris-Benedict equation (20), assuming an activity factor of 1.7 during their stay at the CRC. When subjects left the CRC, they were instructed to follow a low-carotenoid eating plan until completion of the trial. Subjects were given a list of foods to avoid, specifically those containing lycopene, and were instructed to ingest sparingly foods that contained other carotenoids. All subjects completed 24 h dietary records and were asked to report the ingestion of significant amounts of any of the listed carotenoid-rich foods on all days during the week prior to the start of the study and for 3 days/week throughout the study period of 4 weeks. Record days for each week of the 4 week study period included two week days and one weekend day.

One 7 ml blood sample was collected from each subject before dose administration [time zero (0)] and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 36, 48, 72, 96, 120, 168, 240, 336, 408, 504, 576, and 672 h thereafter, into vacutainers without anticoagulant substances. The extensive blood-sampling schedule (28 days) after lycopene administration was needed to characterize both its absorption and elimination phases. Subjects remained in the CRC for up to 48 h and had hourly vital signs monitored for the initial 4 h.

Analysis of serum carotenoids and vitamins

After clotting of blood samples, serum was prepared by centrifugation for 15 min at 3,000 g. Serum collected at each sam-

TABLE 1. Nutrient content of the menus and olive oil

Nutrient	Energy Level		Olive Oil
	5 ml		
Primary energy sources	3,000 Kcals	3,200 Kcals	40 Kcals
Total fat (g)	97.17	101.08	4.57
Total carbohydrate (g)	443.23	469.49	0
Total protein (g)	102.72	111.47	0
% Calories from fat	28.84	28.35	100
% Calories from carbohydrate	58.47	58.53	0
% Calories from protein	13.55	13.90	0
Total fiber (g)	18.26	17.95	0
Vitamins			
α -Tocopherol (mg)	11.52	11.61	0.56
γ -Tocopherol (mg)	20.92	21.14	0.03
Retinol (μ g)	471	492	0
Ascorbic acid (mg)	58.07	57.67	0
Carotenoids			
β -Carotene (μ g)	165	202	4
α -Carotene (μ g)	16	15	0
β -Cryptoxanthin (μ g)	32	47	0
Lutein + zeaxanthin (μ g)	719	755	12

Following dose administration, subjects were given low carotenoid foods during 36 h of their stay at the Clinical Research Center. The energy requirement for each subject was calculated by the Harris-Benedict equation, assuming an activity factor of 1.7. Nutrient content for the most frequently consumed energy levels is shown [analyzed by Nutrient Database System (NDS version 4.03_31)]. The five doses of lycopene were delivered as a tomato beverage formulation. The basic formulation contained 30 g tomato paste combined with 5 ml olive oil and made up to 100 ml volume with distilled water. Volume of the formulation was adjusted to meet the dose requirement. The nutrient content of 5 ml olive oil in the basic formulation is presented in the table.

pling time point (0 h to 672 h) was assayed in duplicate for levels of lycopene, lutein/zeaxanthin, β -cryptoxanthin, α -carotene, β -carotene, α - and γ -tocopherols, and retinol.

The carotenoid and vitamin concentrations in all serum samples were measured by a high-performance liquid chromatography (HPLC) method (21). Briefly, 200 μ l of serum was mixed with 200 μ l of ethanol containing retinyl acetate as an internal standard and was extracted twice with 2 ml hexane (containing 0.01% BHT to prevent oxidation). The combined hexane layers were evaporated to dryness in vacuo (Speed-Vac centrifuge) and the residue reconstituted to the original serum volume of 200 μ l with 50 μ l stabilized ethyl ether and 150 μ l mobile phase (methanol-acetonitrile-stabilized tetrahydrofuran, 50:45:5, v/v/v). Ten microliters of the extract were injected onto a Waters Novapak C18 reverse phase column and eluted isocratically with the mobile phase at a flow rate of 1 ml/min. The peaks were detected by a Waters 490 Programmable Multiwavelength Detector with 4 channels, each analyte at its specific maximum absorbance (325 nm for vitamin A compounds, 295 nm for vitamin E compounds, 450 nm for carotenoids). The peak area and height of these analytes were measured using the Millennium software (Waters, MA), which calculates the carotenoid concentrations in serum samples on the basis of the standard concentrations. Peak height measurements were used for the calculation of concentrations of all vitamins and carotenoids except lycopene. Lycopene isomerization affects the shape of a single lycopene peak, leading to underestimation of total lycopene content if measured by height. Hence, lycopene concentrations were calculated by peak area. All peaks were visually inspected and corrected if miscalculated by the software.

The within- and between-days variability for lycopene measurement by our method was 2.7% and 7.4%, respectively. These are based on multiple assessments of lycopene concentration in individual control serum. Our laboratory is a reference laboratory for the National Institute of Standards and Technology (Gaithersburg, MD) quality assurance program for carotenoids (22).

Physiological pharmacokinetic model

A physiological pharmacokinetic model was developed for lycopene based on current knowledge of the metabolism of carotenoids in humans (23, 24). The initial model was constructed identically to an earlier published model of β -carotene metabolism (16), except the β -carotene conversion to vitamin A was excluded from the model, and the connectivity of the slow-turnover tissue lycopene pool was modified. In the β -carotene model, the slow-turnover β -carotene pool was interpreted as part of the liver, while in the present lycopene model the slow-turnover lycopene pool was connected to the lipoprotein compartment independent from the liver. This change was made because it allowed a broader interpretation of the slow-turnover lycopene pool. When connected directly to the lipoprotein compartment, the slow-turnover lycopene pool may be interpreted as any body tissue containing lycopene and turning it over at a slow rate, including but not limited to the adipose tissue and liver. Because this initial lycopene model fit the data well, the structure was not changed during model fitting, and this was also the final model structure. The model was constructed using the Windows version of WinSAAM software, a general equation-solving package that has been developed and supported by the National Institutes of Health (<http://www.winsam.com>). A detailed description of the model is provided in the Results section.

Initial conditions for compartmental lycopene contents were based on literature values. Weighted averages from three studies were used (4–6). Because our study included only male subjects, tissue data for men only were included in the calculations. Tissue

masses were calculated using data from HPLC measurements of lycopene concentration in autopsied human tissues multiplied by the mass of each tissue of the ICRP No. 23 reference man (25). Based on these calculations the initial tissue reserves in the fast-turnover liver compartment were set to be 5.9 μmol . The initial reserve of lycopene in the slow-turnover tissue pool was approximated by the lycopene content of adipose tissue, because comparison of other extra-hepatic concentrations showed that the adipose tissue, due to its larger mass, contributed the largest amount of lycopene to the total body pool. Therefore, initial reserves of slow-turnover lycopene pool were calculated for each subject as reported adipose concentrations (4, 6) times an assumed fat mass of 20% of body weight. Thus, the assumed initial mass of lycopene varied among subjects, ranging from 10.11 to 16.09 μmol with a mean mass of $12.55 \pm 0.32 \mu\text{mol}$.

Calculation of lycopene mass in the plasma compartment

The plasma volume for each subject was estimated by the following equation (26): plasma volume (l) = [IBW (kg) \times 0.045] + [excess weight (EW) (kg) \times 0.01]. IBW was calculated from the Metropolitan Life Insurance tables (27) using the equation: IBW = $-47.41 + 0.649 \times \text{height (cm)}$ (no shoes). EW was calculated as total body weight - IBW. The factor 0.045 assumes that the plasma volume for IBW is 4.5%. The factor 0.01 assumes that the plasma volume in the excess adipose tissue is 1% of its mass (26). Baseline concentrations of total lycopene in the plasma were multiplied by the subjects' estimated plasma volume to give the total initial mass of lycopene in the plasma compartment for kinetic modeling.

Fractional transfer coefficients, flow rates, percent absorption, and steady state masses in tissues

The fractional transfer coefficient (FTC) is the kinetic constant that is derived by fitting the model to the experimental data. In WinSAAM, the FTC is referred to as L(I,J) and is the fraction of analyte transferred from compartment J (donor compartment) to compartment I (recipient compartment) per unit of time. The FTC multiplied by the mass in the donor compartment gives the rate of flow (e.g., $\mu\text{mol/day}$) of the analyte from the donor to the recipient compartment (16).

Initial FTCs in our model were estimated by extrapolating information on the turnover rates for β -carotene from the scientific literature (16). For each subject, transfer coefficients were adjusted in physiologically meaningful ways until the model pre-

dictions provided a close fit for the experimentally measured data as determined visually, and then the final parameters were generated using WinSAAM's iterative process, which is based on the least squares procedure that minimizes the sums of squares between the model predicted values and the experimental data. Variance in the model predicted parameters are reported as fractional standard deviations (FSDs) and are equal to SD/mean.

The percent absorption of lycopene and the steady state masses in the fast-turnover liver pool and the slow-turnover tissues were predicted by WinSAAM based on calculations inherent in the software (28). The mass of lycopene absorbed in all subjects at each dose level was calculated as percent lycopene absorbed multiplied by dose (mg).

Model constraints

We set loose constraints to certain FTCs in order to ensure the physiological relevance of our model. Therefore, the FTC of lycopene from the chylomicron compartment to the fast-turnover liver compartment was constrained to 59.77 days^{-1} based on a chylomicron half-life of $15 \pm 10 \text{ min}$ in healthy adult men (29). Similarly, the FTC for LDL turnover was constrained to 0.225 days^{-1} (30).

Statistical analysis

All data are expressed as mean \pm SE. Between-group comparisons were analyzed by one-way ANOVA. Data that failed the normality test were assessed following log transformation. Post hoc analyses for all pairwise multiple comparisons were performed using the Tukey test. All statistical analyses for ANOVA and post hoc analysis were performed using SigmaStat version 2.0 (SPSS Inc., Chicago, IL). Relationship between variables was tested by exponential regression analysis using Microcal Origin version 5.0. A value of $P < 0.05$ was considered significant.

RESULTS

Baseline characteristics of subjects

The mean baseline characteristics of subjects included in the study are presented in **Table 2**. There were no significant differences in any of the baseline characteristics between groups. Our study population was a young and

TABLE 2. Mean^a baseline characteristics of subjects in each of five dose groups^b

	10 Mg	30 Mg	60 Mg	90 Mg	120 Mg
Age (years)	25.8 \pm 2.1	26.0 \pm 2.1	30.8 \pm 1.9	23.2 \pm 2.0	30.2 \pm 3.8
BMI (kg/m ²)	24.5 \pm 0.80	24.1 \pm 1.2	24.4 \pm 1.2	22.4 \pm 0.54	24.5 \pm 1.3
Serum triglycerides (mg/dl)	128.2 \pm 41.7	82.0 \pm 22.2	123.2 \pm 34.1	92.2 \pm 22.4	84.8 \pm 13.2
Serum cholesterol (mg/dl)	166.8 \pm 13.5	167.6 \pm 14.2	174.8 \pm 6.7	177.2 \pm 16.3	166.4 \pm 13.6
Baseline serum carotenoid concentration ($\mu\text{mol/l}$)					
Lutein	0.251 \pm 0.062	0.328 \pm 0.101	0.374 \pm 0.057	0.263 \pm 0.057	0.336 \pm 0.049
β -Cryptoxanthin	0.118 \pm 0.015	0.163 \pm 0.046	0.262 \pm 0.051	0.211 \pm 0.038	0.329 \pm 0.116
Lycopene	0.300 \pm 0.030	0.370 \pm 0.040	0.310 \pm 0.030	0.330 \pm 0.030	0.340 \pm 0.050
α -Carotene	0.036 \pm 0.012	0.061 \pm 0.014	0.102 \pm 0.023	0.061 \pm 0.011	0.109 \pm 0.045
β -Carotene	0.157 \pm 0.025	0.284 \pm 0.107	0.254 \pm 0.042	0.219 \pm 0.023	0.409 \pm 0.184
Baseline serum vitamin concentration ($\mu\text{mol/l}$)					
Retinol	1.7 \pm 0.08	1.9 \pm 0.17	1.6 \pm 0.11	1.6 \pm 0.13	1.6 \pm 0.10
γ -Tocopherol	3.8 \pm 0.60	4.2 \pm 0.82	6.0 \pm 0.60	3.8 \pm 0.72	4.0 \pm 0.36
α -Tocopherol	17.3 \pm 1.9	18.9 \pm 1.5	23.1 \pm 2.0	20.1 \pm 2.4	19.7 \pm 1.3

BMI, body mass index.

^a Values are mean \pm SE.

^b Each dose group includes data from five subjects.

healthy group of men with a mean age of 27.2 ± 1.17 years and mean body mass index of $23.97 \pm 0.46 \text{ kg/m}^2$.

The mean baseline serum lycopene, β -carotene, and α -carotene concentrations were 2.5-, 1.7-, and 1.5-fold lower, respectively, compared with values reported in the general US population (3). A review of the food frequency questionnaires showed that most subjects in the study consumed either moderate or high amounts of lycopene from tomato products in their usual diet. Therefore, the lower carotenoid levels observed at baseline could be attributed to the carotenoid-deplete diet that subjects were instructed to follow for 1 week prior to dose administration in order to ensure a detectable serum lycopene response. Mean retinol and α -tocopherol concentrations were 1.2- and 1.4-fold lower, respectively, while mean γ -tocopherol concentrations were 3-fold higher in our group of men compared with the reported values (3).

Physiological pharmacokinetic model of lycopene disposition

A schematic representation of the physiological pharmacokinetic model developed to predict lycopene disposition at graded doses is shown in **Fig. 1**. The proposed model was comprised of seven compartments that included one for the lumen of the gastrointestinal tract (GIT) into which the dose of lycopene is administered, one for the enterocyte at which absorption occurs, a total plasma compartment subdivided into chylomicron and lipoprotein compartments, one compartment for the fast-turnover liver pool, and one for the slow-turnover tissue pool.

The single dose of lycopene was detected in the serum after a short lag time, which represents the time required by lycopene to pass through the stomach, enter the intestinal lumen, and transfer from the tomato beverage formulation to the mixed micelles before passing through the enterocytes. Therefore, a delay compartment was added between the GIT and the enterocytes. Each compartment was assumed to be homogenous and to be kinetically distinct from the other compartments. All irreversible loss was modeled to occur from the GIT and the lipoprotein compartment of the model. This simplification was necessary because liver and extrahepatic tissues of subjects were not experimentally sampled, and we were therefore unable to discern lycopene lost directly from the tissues from lycopene reentering the circulation before irreversible loss.

Physiological pharmacokinetic model fit to experimental data

Figure 2A–E show the model predictions and experimentally measured serum lycopene concentrations as a function of time in representative subjects from the five dose cohorts. The closed circles represent the measured values of lycopene and the line shows the model fit using the physiological pharmacokinetic model in **Fig. 1**. The same physiological model provided an excellent fit for the experimentally measured concentrations of lycopene at various doses in different subjects despite variability in

shapes of their absorptive curves. In most subjects, the concentration of serum lycopene peaked twice following dosing. The mean time for appearance of the first peak was $6.7 \pm 0.83 \text{ h}$, followed by a transient fall, and then a second peak at $28.2 \pm 1.6 \text{ h}$. The maximum concentration of lycopene was achieved by $22.1 \pm 2.7 \text{ h}$. A slow decline in serum lycopene concentration observed thereafter was predominantly maintained by the flow of lycopene out of the slow-turnover tissue pool into the lipoprotein compartment and by the irreversible loss from the lipoprotein compartment.

Predicted FTCs for lycopene between compartments

FTCs are the rate constants that were obtained by fitting our model to the measured serum lycopene values. An FTC describes the rate at which a fraction of lycopene is transferred from a donor compartment to an acceptor compartment per day. The FTCs were not statistically different between groups, with the exception of those for intestinal absorption; therefore, the mean population FTCs were calculated for all five dose levels combined, as presented in **Table 3**. In our model, the mean FTC from the chylomicron to the fast-turnover liver compartment was the largest ($61.93 \pm 2.45/\text{day}$), followed by the mean FTCs from the lipoprotein to the slow-turnover tissues ($7.97 \pm 3.17/\text{day}$), and that from the enterocyte to the chylomicron compartment ($4.27 \pm 0.976/\text{day}$). The FTC from the lipoprotein to fast-turnover liver compartment ($0.222 \pm 0.003/\text{day}$) and that from the slow-turnover tissues to lipoprotein compartment ($0.351 \pm 0.145/\text{day}$) were the two lowest rates.

The lag time between the delivery of the lycopene dose to the stomach and its absorption into the blood stream was not significantly different between dosing groups. The mean population lag time was predicted to be $2.93 \pm 0.24 \text{ h}$ and ranged from 0.4 h to 6.5 h, indicating that a time delay of $\sim 3 \text{ h}$ occurred between lycopene dose administration and the onset of absorption and appearance of measurable serum lycopene concentrations. This is in accord with the expected delay for stomach emptying (31).

All parameter FSDs, a measure of variance in the model, were below 0.65. However, there was one case where the parameter estimate for the FTCs from the lipoprotein compartment to irreversible loss [L(0,4)], and from the slow-turnover tissue to lipoprotein compartment [(L(4,17))] were characterized by higher FSDs than desired. This was due to a large rise in lycopene at very late time points, suggesting noncompliance to a low-lycopene self-selected diet.

Predicted flow rates for lycopene between compartments

The model was able to predict flow rates of lycopene through the body and its mass in compartments from the pharmacokinetic data, combined with an estimate of the steady-state mass of lycopene in the serum compartment. Flow rates are the product of the mass of lycopene in the donor compartment multiplied by the FTC to a recipient compartment. For this study, the steady-state value for serum lycopene was estimated by the baseline serum lycopene

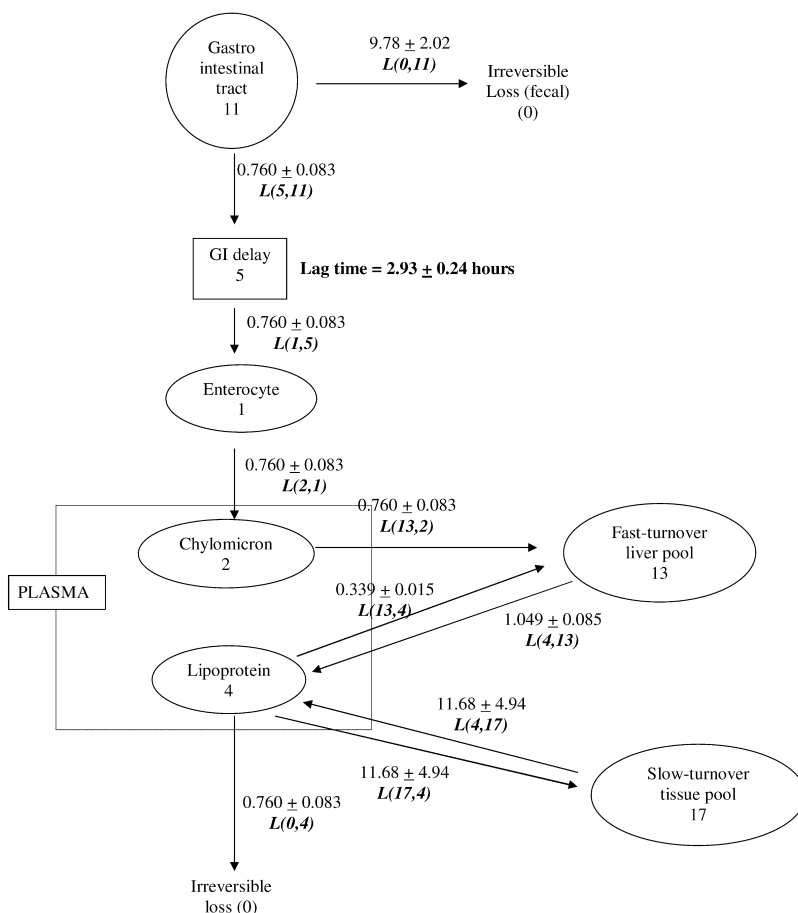


Fig. 1. A physiological pharmacokinetic model describing the disposition of lycopene in healthy men at five dose levels (10 mg, 30 mg, 60 mg, 90 mg, 120 mg). Each compartment contains a kinetically distinct form of lycopene. Arrows represent the connectivity between compartments. The fractional transfer coefficients (FTCs), $L(I,J)$, depicted in bold italics, are the kinetic constants derived by fitting the model to the experimental data. They refer to the rate at which lycopene is transferred from compartment J to compartment I per unit of time. The numbers alongside the arrows are the mean steady state flow rates (flow out = flow in) at all doses ($\mu\text{mol}/\text{day}$) between compartments, which are calculated by multiplying the steady state mass in the donor compartment by the FTCs from the donor to acceptor compartment.

lycopene concentration of subjects before they began the experimental treatment period. The predicted flow rates for our compartmental model did not vary significantly with dose. Figure 1 shows the mean flow rates of lycopene from donor to recipient compartments for a steady state simulated with the transfer coefficients resulting from this model.

For our physiological pharmacokinetic model, the flow rates ranged from 0.339 ± 0.015 $\mu\text{mol}/\text{day}$ to 11.68 ± 4.94 $\mu\text{mol}/\text{day}$. The high flow rate indicates that a considerable amount of lycopene exchange occurs between the lipoprotein and slow-turnover tissue compartments.

Predicted mass and flow of lycopene in the fast-turnover liver pool and slow-turnover tissues

Figure 3A presents a representative graph of the predicted change in mass of lycopene in the fast-turnover liver and slow-turnover tissue compartments following the intake of a 30 mg lycopene dose in a representative subject consuming a lycopene-free diet. A similar pattern of

change was observed in subjects at other dose levels. The fast-turnover liver stores of lycopene depleted to a greater extent than the slow-turnover stores. The fast-turnover liver lycopene mass peaked on day 1 and was almost completely depleted by days 8–12, whereas the slow-turnover lycopene mass peaked between 4 and 8 days with slow losses thereafter. Figure 3B is a representative graph showing the flow of lycopene out of the fast-turnover liver and slow-turnover tissues following administration of the 30 mg dose. On average, at the early time points, the flow of lycopene out of the liver (4.75 ± 1.62 $\mu\text{mol}/\text{day}$) and slow-turnover tissues (4.44 ± 1.93 $\mu\text{mol}/\text{day}$) was predicted to be similar. However, by 28 days the flow out of the liver had dropped to an average of 0.142 ± 0.008 $\mu\text{mol}/\text{day}$, while the slow-turnover tissue flow averaged at 6.31 ± 3.31 $\mu\text{mol}/\text{day}$. The drop in lycopene flow out of the liver occurred because this tissue compartment, which represents the fast-turnover liver pool, was severely diminished during the low-lycopene diet. The rise in flow out of the slow-turnover tissue occurred because a substantial portion of the ly-

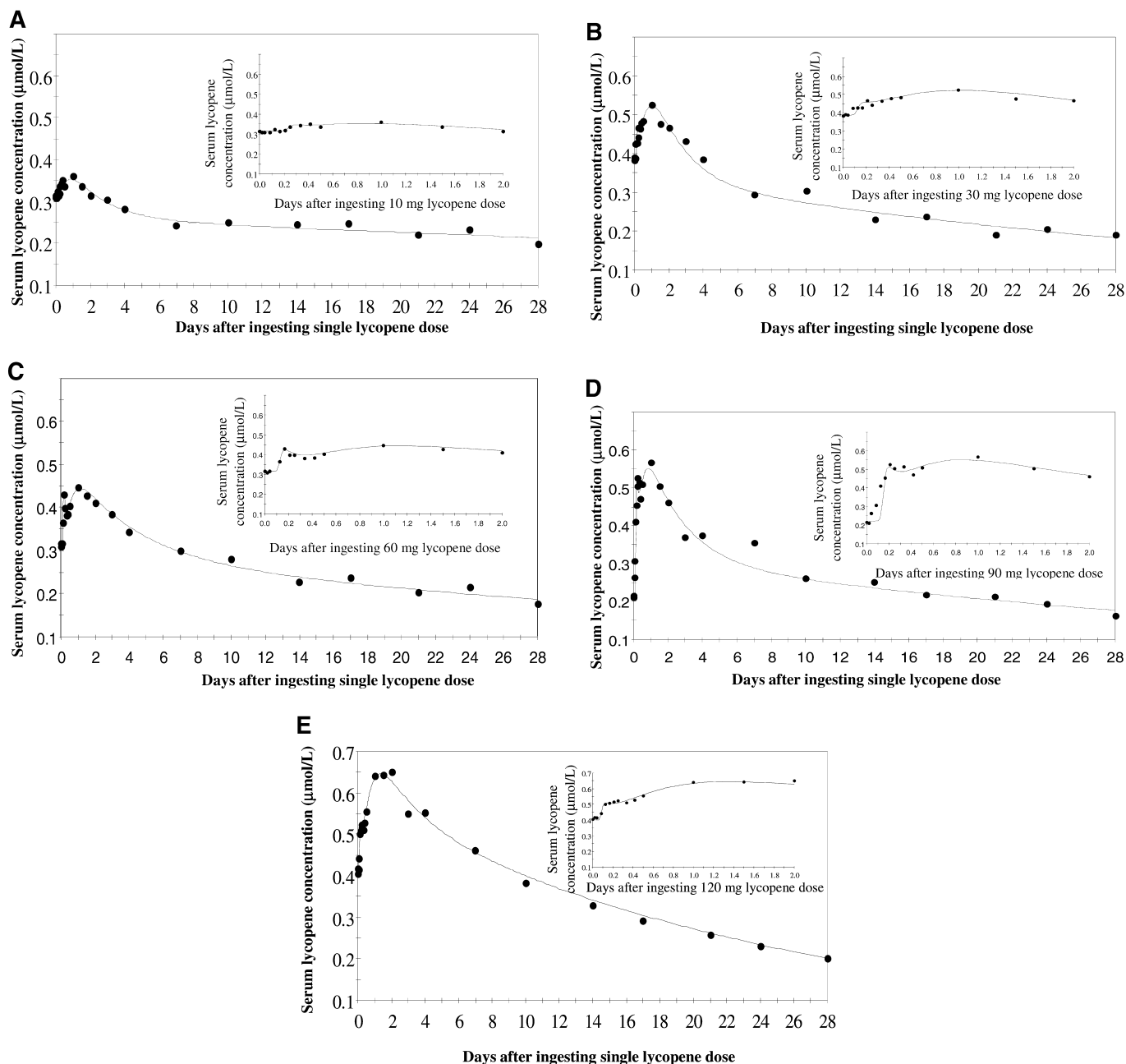


Fig. 2. Pharmacokinetic model fit (line) for the serum lycopene concentrations (closed circles) in representative subjects at five dose levels. The insets show the model fit for the first 2 days (48 h) after dosing: After dosing, the first lycopene peak was observed at around 6 h (0.25 days), followed by a temporary decline and a second peak at around 24 h (1 day). A: Model fit for 10 mg dose, B: model fit for 30 mg dose, C: model fit for 60 mg dose, D: model fit for 90 mg dose, and E: model fit for 120 mg dose. All predictions are based on the physiological compartmental model in Fig. 1.

copene test dose was deposited in this tissue, supplying more lycopene to ultimately flow out. The slower turnover pool would include not only adipose tissue lycopene, but also any slow-turnover pool, including longer-term liver lycopene. Therefore, a steady flow of lycopene from the slow-turnover tissue into the serum was established during the elimination phase of the study, indicating that the slow-turnover tissue pool may serve as a reservoir for lycopene storage, while the fast-turnover liver pool may supply lycopene to the circulation on a shorter time scale.

Predicted absorption and tissue reserves of lycopene using the physiological compartmental model at five dose levels

Specific model predictions are presented in **Table 4**. The predicted mean percentage absorption at the 10 mg dose was $33.9 \pm 8.1\%$, which was significantly higher than the predicted percent absorption at the 60 mg, 90 mg, and 120 mg doses. There was also a significant difference in the percent absorption of lycopene at the 30 mg compared with the 120 mg dose ($P = 0.017$), but not be-

TABLE 3. Mean population fractional transfer coefficients from donor to recipient compartments of the physiologic compartmental model of lycopene metabolism

Donor Compartment	Recipient Compartment	FTC \pm SE/Day
Independent FTCs		
Enterocyte	Chylomicron	4.27 \pm 0.976
Fast turnover liver	Lipoprotein	0.805 \pm 0.273
Lipoprotein	Slow turnover tissues	7.97 \pm 3.17
Slow turnover tissues	Lipoprotein	0.351 \pm 0.145
Lipoprotein	Irreversible loss	0.508 \pm 0.060
Dependent FTCs		
Chylomicron	Fast turnover liver	61.93 \pm 2.45
Lipoprotein	Fast turnover liver	0.222 \pm 0.003
Lag time, subdivisions/delay compartment		
Lag time in hours		2.93 \pm 0.240
Subdivisions of delay compartment		2

FTC, fractional transfer coefficient. FTC is a rate constant that refers to the rate of transfer of lycopene from a donor to a recipient compartment per unit time. Values are expressed as day⁻¹. All values apply to the compartmental model in Fig. 1 and represent the average FTCs for all 25 subjects.

tween the other pairwise comparisons. Furthermore, the percent absorption showed an exponential decrease with linearly increasing dose (Fig. 4), suggesting a dose-dependent saturation in absorption. Therefore, the lower physi-

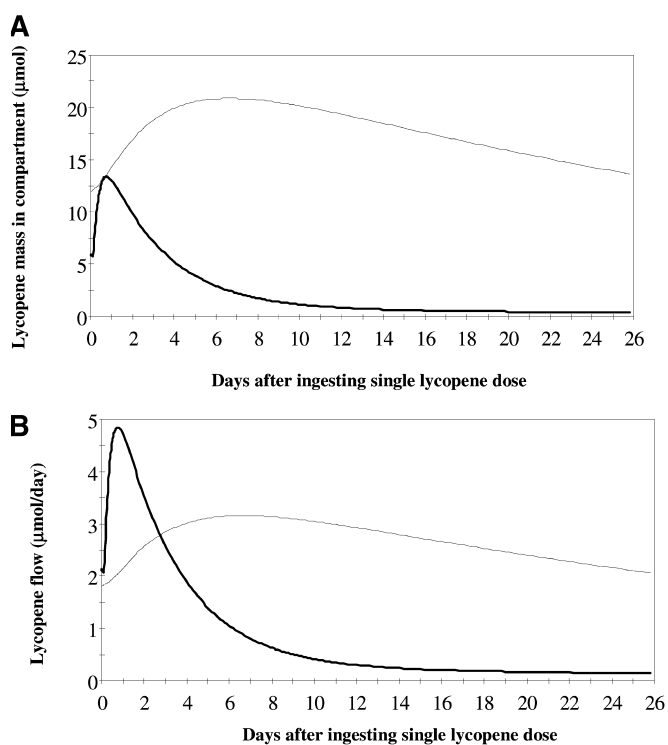


Fig. 3. A: Physiological pharmacokinetic model predicted changes in mass of lycopene in fast-turnover liver (thick line) and slow-turnover tissue compartments (thin line) in a representative subject who received 30 mg of lycopene dose. The mass of lycopene in the liver depleted to a greater extent than the lycopene mass in the slow-turnover tissues. B: Physiological pharmacokinetic model predicted changes in flow of lycopene in fast-turnover liver (thick line) and slow-turnover tissue compartments (thin line) in the same subject who received 30 mg of lycopene dose.

ological doses were absorbed more efficiently than the pharmacological doses. However, of particular interest was the finding that, although percent absorption of lycopene decreased significantly at higher doses, the absolute amount of lycopene absorbed, calculated as dose multiplied by percent of lycopene absorbed, was only slightly higher at the two higher doses but not statistically different from the lower doses (Table 4). There was a slight linear increase in the average mass of lycopene absorbed from 10 mg to 120 mg; however, due to the small sample size at each dose level and the substantial variability in response between subjects (Fig. 5), we hesitate to draw any conclusions about this dose related linear rise. The mean mass of lycopene absorbed at all five doses was 4.69 \pm 0.55 mg.

The mean initial lycopene content in the slow-turnover tissue pool and the fast-turnover liver for all subjects was 12.5 \pm 0.322 μ mol and 5.9 μ mol, respectively, and the model-predicted steady state lycopene mass was 36.5 \pm 2.4 μ mol in the slow-turnover tissue pool and 2.4 \pm 0.29 μ mol in the liver. There were no statistical differences in the predicted steady state mass of lycopene in the liver and the slow-turnover tissues for subjects consuming the different doses of lycopene.

Change in other carotenoids following lycopene dose administration

Change in other serum carotenoids was determined by comparing the concentrations at specific time points with baseline levels using the paired *t*-test for two sample means. Specific time points were selected by observing the time-mean concentration graphs for each carotenoid in order to ascertain the time points at which significant rises or falls were apparent.

There was a significant (7.8%, $P < 0.001$) rise in mean serum lutein concentration at 5 h compared with baseline. No significant changes were seen thereafter, although there was a small decline in concentration at 24 h. β -Carotene concentrations showed a significant rise of 4.9% at 5 h ($P = 0.006$) and of 5.9% at 24 h ($P = 0.003$), followed by a significant decrease in concentration until the end of the study. β -Cryptoxanthin concentrations were significantly lower at 5 h and 24 h, and showed no change from baseline thereafter. α -Carotene concentrations were not significantly different from baseline. In general, our subjects complied well with the recommended low-carotenoid diet. The initial rise in lutein and β -carotene could be due to the presence of small amounts of these carotenoids in the olive oil and also in the meals that were provided during their stay at the CRC (Table 1).

DISCUSSION

We developed a physiological pharmacokinetic model to describe the disposition of lycopene, administered as a tomato beverage formulation at five graded doses in healthy men. The tomato beverage formulation was prepared from tomato paste, a bioavailable source of lycopene, and olive oil that enhances absorption due to the

TABLE 4. Model predicted absorption and estimated steady-state tissue reserves of lycopene at five dose levels

Model Predicted Parameters ^a	10 Mg	30 Mg	60 Mg	90 Mg	120 Mg
% Lycopene absorption ^b	33.9 ± 8.1 ^c	13.6 ± 2.2 ^e	6.9 ± 0.56 ^d	6.1 ± 1.4 ^d	5.3 ± 1.8 ^{d,f}
Mass of lycopene absorbed (mg) ^g	3.4 ± 0.81	4.1 ± 0.65	4.1 ± 0.34	5.5 ± 1.3	6.4 ± 2.2
Fast-turnover liver lycopene content (μmol)	1.8 ± 0.52	3.0 ± 0.90	3.0 ± 0.80	1.6 ± 0.40	2.8 ± 0.44
Slow-turnover tissue lycopene content (μmol)	34.8 ± 4.5	28.3 ± 1.3	42.0 ± 3.8	35.9 ± 5.2	41.4 ± 8.4

^a Values are mean ± SE; n = 5 per dose level.

^b The data for percent absorption of lycopene was not normally distributed and was log transformed prior to statistical analysis.

^{c,d} Significantly different (single factor ANOVA) $P < 0.001$.

^{e,f} Significantly different (single factor ANOVA) $P < 0.017$.

^g Calculated as dose times percent of lycopene absorbed.

lipid-soluble nature of lycopene. The administered lycopene doses ranged from 10 mg to 120 mg. The 50th and 75th percentile mean 1 day intake of lycopene from foods in men aged 19–30 years is estimated to be 5.1 mg and 16.0 mg/day, respectively (32). The lowest dose of 10 mg in our study lies between these intake levels. The 30 mg dose in our study is equivalent to the 90th percentile intake of 33.4 mg/day, and the three high doses (60 mg, 90 mg, and 120 mg) are above the 95th percentile intake of 47.5 mg/day in the same age group of men. Therefore, the administered doses in our study included the usual intake in the population (10 mg and 30 mg) and also covered pharmacological levels (60 mg, 90 mg, and 120 mg).

The physiological pharmacokinetic model for lycopene was constructed to be consistent with known aspects of carotenoid metabolism. The GIT and the enterocytes were represented by one compartment each. A delay compartment was added between these two compartments to allow for the transit time before the single dose of lycopene appeared at the enterocyte for absorption. Following absorption in the enterocyte, carotenoids are packaged into tri-

glyceride-rich chylomicron particles for transport to the liver (23); therefore, the enterocyte compartment in our model was connected to the chylomicron compartment, which then transferred lycopene to the fast-turnover liver compartment. A lipoprotein compartment showing a bidirectional exchange with the fast-turnover liver compartment was included, which represents secretion of VLDL particles from the liver along with any associated lycopene to undergo exchange with other lipoproteins in the blood circulation. Also included in the model was a slow-turnover tissue compartment exchanging lycopene with the lipoprotein compartment, based on the suggestion that any transfer of carotenoids between lipoproteins may be occurring via transfer in and out of other tissues (23, 33). Therefore, our model included two tissue pools for lycopene, similar to the fast and slow turnover pools proposed by Rock et al. (34), who observed that the rate of decline in carotenoids was more marked during the early periods of depletion compared with later days in subjects who were on a low-carotenoid diet. From Fig. 3, it is apparent that the slow-turnover tissue compartment in our model represents the tissue pool that is resistant to depletion and helps maintain serum levels during a low-carotenoid supply.

Therefore, our proposed model was simple, physiological, and provided a good fit with the experimentally measured lycopene concentrations at five dose levels. To the best of our knowledge, this is the first study that has inves-

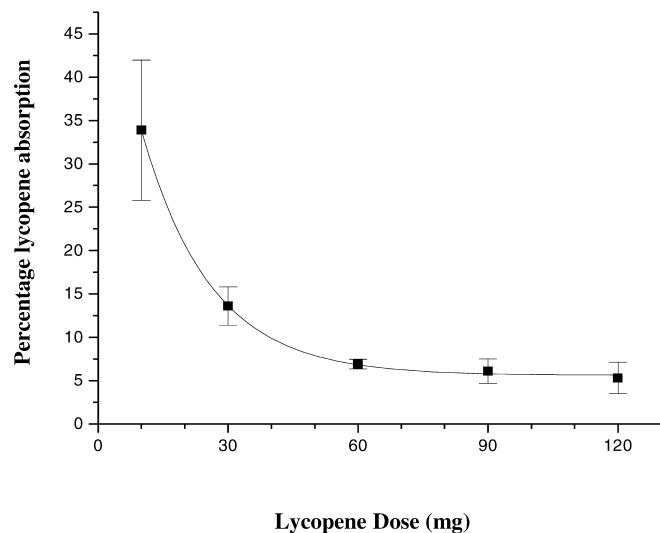


Fig. 4. Exponential decrease in percent absorption (mean ± SE) with increasing dose (mg), suggesting a dose-dependent saturation in absorption. The data points were fit with an exponential decay function of the form $y = 5.6 + 28.3 \exp [(10 - x)/15.9]$.

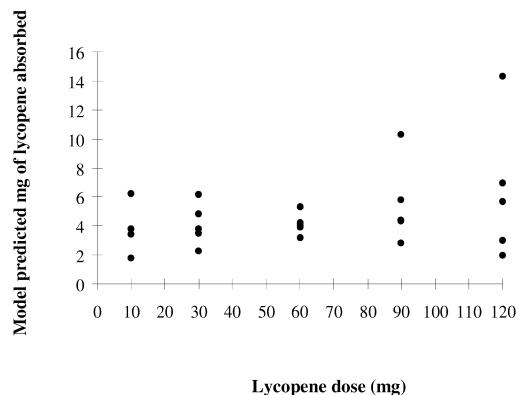


Fig. 5. Dose versus model predicted mass of lycopene absorbed in all subjects. The figure shows a wide variation in the absorption of lycopene between subjects at different dose levels.

tingated the physiological process of lycopene at a wide range of doses using mathematical analysis.

Using our physiological pharmacokinetic model, we were able to estimate the percent of lycopene absorbed from the five doses. Interestingly, although the predicted percent absorption was significantly different between the 10 mg and the 60, 90, and 120 mg doses (Table 4), the absolute amount (mg) of lycopene absorbed was not statistically different between dose levels. Independent of dose, the mean mass of lycopene absorbed in all subjects was 4.69 ± 0.55 mg and ranged from 1.78 mg to 14.28 mg. The interindividual variability for absorption was high and varied by the dose. The coefficient of variability (CV) was greatest at the highest dose of 120 mg (CV = 76.5%) and lowest at the 60 mg dose (CV = 18.4%). It was similar at the 10 mg (CV = 53.6%) and 90 mg (CV = 51.9%) doses. At the 30 mg dose, the CV was 35.4%. High interindividual variability in plasma response to lycopene has been observed in other studies (35, 36, 37).

Distribution of subjects based on amount of lycopene absorbed (Fig. 6) showed that, independent of the dose administered, 80% of the subjects absorbed less than 6 mg of lycopene, while only 20% of the subjects absorbed more. We also classified subjects as low (0–2 mg), moderate (2–6 mg), or high (>6 mg) accumulators, depending on the amount of lycopene absorbed regardless of the dose level. Based on this classification, two subjects at the 10 mg dose and one subject at the 120 mg dose (total of three subjects) were identified as low accumulators of lycopene. One subject each at the 10 mg, 30 mg, and 90 mg dose, and two at the 120 mg dose (total of five subjects) were identified as high accumulators, while rest of the 17 subjects were moderate absorbers. This distribution pattern suggests that most individuals may be able to absorb modest quantities of lycopene (2–6 mg) within the dose range investigated in this study, but in the majority of the population lycopene absorption may plateau at less than 6 mg, with high accumulators representing only a small fraction. The wide range of lycopene absorption observed in our study (1.78 mg to 14.28 mg) could have important implications for human health. It is likely that a certain

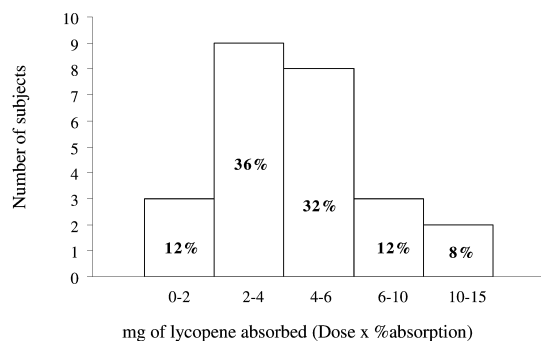


Fig. 6. Distribution of subjects based on the amount (mg) of lycopene absorbed independent of the dose administered. Amount of lycopene absorbed was calculated as dose (mg) \times percentage of lycopene absorbed. The percentage of subjects is indicated within each bar.

segment of the population may consistently accumulate low levels of lycopene despite pharmacological dosing, and therefore hypothesized health benefits may not be available from supplementation. On the other side, in some high accumulators large doses of lycopene could possibly produce adverse effects, although no such effects were observed in our group of men.

The observation that the mass of lycopene absorbed at the different dose levels was neither statistically nor physiologically meaningfully different may suggest that escalating doses do not improve lycopene assimilation by the body and indicates a possible saturation of the absorptive processes in the GIT with increasing dose. Only one subject at the 90 mg dose had grade 1 diarrhea, possibly associated with the dose or volume of the beverage; however, subjects at the highest lycopene dose of 120 mg did not complain of any intestinal discomfort related to the larger volume (797 ml) of the tomato beverage. Furthermore, subjects consumed breakfast immediately after the tomato beverage intake, which would have slowed gastric emptying, especially with increased quantities of fat in the beverage. Therefore, the possibility that absorption saturation was related to the volume of the tomato beverage is unlikely. Instead, saturation could have occurred either at the enterocytes (at the brush border or in the cell cytosol) or during incorporation into chylomicrons. Absorption of carotenoids at the brush border has been proposed to occur by passive diffusion based on an early study in which the rate of β -carotene absorption was found to be linear at concentrations of 0.5–11 $\mu\text{mol/l}$ in a micellar perfusate circulated through the jejunal and ileal intestinal loops of unanaesthetized rats (38). In another study, addition of metabolic inhibitors did not retard β -carotene uptake by rat everted gut sacs with no evidence for saturation kinetics (39). Passive diffusion in these studies was limited by the thickness of the unstirred water layer, the saturation of fatty acids in the micelles, high pH, and the absence of optimal concentration of bile salts to achieve a critical micellar concentration (38). Inadequate fat in the diet could be another limiting factor in carotenoid absorption. In our study, although the amount of fat provided at breakfast was similar at all five doses (23.2 ± 0.26 g), the quantity of olive oil in the tomato beverage formulation increased proportional to the dose. Therefore, the amount of fat consumed at breakfast, including the olive oil from tomato beverage, ranged from 27.2 g at the 10 mg dose to 60.3 g at the 120 mg dose; hence, insufficient fat is unlikely to have impaired lycopene absorption at higher doses.

The possible saturation pharmacokinetics observed in this study seem to be consistent with the findings of During et al. (40), who, using an *in vitro* Caco-2 cell culture system, observed a linear increase in β -carotene absorption into cells and secretion into basolateral membrane up to the physiological concentration of 6 μM (3.2 mg), and a plateau thereafter for initial concentrations greater than 10 μM (5.4 mg). Percentage of β -carotene incorporated into chylomicrons also increased with time in a curvilinear manner at an initial concentration of 1 μM . Based

on the saturation observed, they proposed the presence of specific intestinal epithelial transporters for β -carotene absorption. Our observation of a decline in the percentage of lycopene absorption above the physiological dose of 10 mg is in accordance with the suggestion by During et al. (40) of facilitated transport for carotenoids, although it remains unknown if this saturable phenomenon is related to a specific transport system or particular binding proteins for lycopene. Saturation in lycopene kinetics has also been reported by Stahl and Sies (35), who observed a greater efficiency in lycopene absorption at lower doses in a single subject fed heated tomato juice with 1% corn oil at doses equivalent to 13 mg, 45 mg, and 90 mg in a 70 kg man.

Due to their poor solubility in aqueous milieu, the existence of cytosolic binding proteins for carotenoids has been postulated (41). Recently, a carotenoid binding protein was isolated from the silk worm (*Bombyx mori*) localized in the villi of the midgut epithelium, indicating that these proteins may be involved in the absorption of carotenoids (42). Carotenoid-specific binding proteins have also been identified in mammalian systems. A cellular carotenoid binding protein was recently purified from the liver of ferrets fed β -carotene (43) and showed a specific affinity for carotenoids such as α -carotene and β -cryptoxanthin, with at least one unsubstituted β -ionone ring. Lycopene, however, did not competitively inhibit the binding of β -carotene. To date, intestinal binding proteins for carotenoids have not been identified in mammals, although it is possible that they exist and may be involved in the facilitated absorption of some carotenoids. The saturation of lycopene absorption in our study supports this possibility.

Our study addressed absorption and metabolism of single doses of lycopene, and response to chronic doses could vary because of the frequent supply of lycopene. Due to differences in the methods of assessment for absorption (AUC vs. compartmental modeling), direct comparison of lycopene absorption in our study with other studies was not feasible. However, comparison of plasma responses with other single dose studies showed that the increase in serum lycopene concentration from baseline at the 90 mg dose ($0.2 \pm 0.043 \mu\text{mol/l}$) was similar to a $0.26 \mu\text{mol/l}$ rise seen by Stahl and Sies (35) at an equivalent single dose (90 mg for 70 kg person), but an increase of $0.173 \pm 0.035 \mu\text{mol/l}$ at our 60 mg dose was about 3-fold higher than that detected by Johnson et al. (37). The better response in our study could be attributed to the 2-fold higher amount of fat in our breakfast (44.6 g including fat from olive oil) compared with the 21 g fat provided in their study. In another study (44), single ingestion of 180 g tomato juice providing 12 mg of lycopene had no effect on plasma lycopene concentration, which again was in contrast to an appreciable response of $0.075 + 0.019 \mu\text{mol/l}$ we observed at the 10 mg dose. The substantially high baseline levels of lycopene in their subjects ($0.842 \pm 0.33 \mu\text{mol/l}$) may have impaired additional increases in plasma lycopene levels following dosing (44).

Serum lycopene concentration in our study peaked twice following dosing in most subjects. The initial 6 h rise was predicted by the flow of lycopene from the enterocyte

to the chylomicron compartment, while the flow out of the fast-turnover liver pool into the lipoprotein compartment was associated with the second lycopene peak at 27 h. Two peaks in serum concentrations have also been observed for β -carotene by Kostic et al. (45) and Novotny et al. (16) following a single-dose administration. However, lutein and canthaxanthin, oxocarotenoids related to β -carotene, show only a single peak after dosing (45, 46, 47). These variations in serum response patterns could be related to the differences in rate of exchange of the polar versus apolar carotenoids between lipoproteins.

The majority of our subjects absorbed less than 6 mg of lycopene despite the dose administered. The mean one-day intake of lycopene in the 19–30 year age group of men as included in our study is 12.7 mg/day (median intake = 5.1 mg/day) (32), which is comparable to the dose at which we observed a saturation in lycopene absorption (10 mg). The mean intake of lycopene in the age range of men at a risk for prostate cancer (51–70 years) is 6.6 mg/day (median intake = 1.6 mg) (32). The median lycopene intake associated with a significant reduction in the risk for prostate cancer (RR = 0.84, CI (0.73–0.96)) was found to be 18.8 mg/day (48). Therefore, with a large number of men already consuming amounts of lycopene at which we observed saturation, the question arises whether an intervention trial with pharmacological doses may have additional beneficial effects for a majority of participants. This is of importance considering the potential chemopreventive role for lycopene in prostate cancer.

However, our results are based on lycopene absorption from the single-dose administration of a specific tomato beverage formulation; additional analysis with chronic doses and different sources of lycopene in a diverse population may help identify aspects of lycopene metabolism related to gender, age, nutritional status, and disease conditions. Furthermore, more conclusive evidence of absorption saturation at higher lycopene doses may be obtained if a greater number of subjects is included at each dose level. Nevertheless, the data presented here have important implications for planning clinical trials with multiple doses of lycopene in cancer control and prevention. In conclusion, the experimental design of the present study offered an excellent opportunity for a comprehensive investigation of lycopene metabolism at a wide range of doses. We developed a physiological pharmacokinetic model that allowed us to elucidate key aspects of lycopene disposition. The proposed physiological pharmacokinetic model predicted a possible dose-dependent saturation in the absorption of lycopene. Optimal percentage absorption of lycopene occurred at the physiological dose of 10 mg; however, the quantity of lycopene assimilated at all five doses was similar. Our data support the proposition that lycopene absorption may occur via a saturable mechanism. Compartmental analysis offers the advantage of providing quantitative information of nutrient disposition, and because carotenoids are emerging as promising preventive and therapeutic agents in diseases, a detailed investigation of their metabolism is central to our understanding of these effects. ■

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