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ORIGINAL CONTRIBUTION

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Synthetic and tomato-based lycopene have identical bioavailability in humans

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Summary *Background* Bioavailability studies with lycopene have focused on natural sources. A synthetic source has recently become available. *Aim of the study* To determine the relative bioavailabilities of synthetic and tomato-based lycopene in free living volunteers in a single-blind, randomized, placebo-controlled, parallel trial. *Methods* Three groups (n = 12/group) of healthy, normolipemic male and female subjects with a mean baseline serum lycopene concentration of 0.36 µmol/L took a dose of 15 mg/day total lycopene for 28 days from either Lycovit 10 % (beadlets, BASF, Germany) or Lyc-O-Mato (beads, LycoRed Natural Products, Israel) or a placebo (without lycopene) together with the main meal. The increase in serum lycopene from baseline was used as the parameter of bioavailability. *Results* Synthetic and tomato-lycopene resulted in significant increases above baseline of serum total lycopene by 0.58 and 0.57 µmol/L, trans-lycopene by 0.34 and 0.41 µmol/L, and total-cis-lycopene by 0.24 and 0.16 µmol/L, whereas no significant changes were found in the placebo treatment. The mean serum total lycopene response to synthetic and natural lycopene was not significantly different. Neither lycopene source affected the other serum carotenoids, viz. α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin and lutein. *Conclusion* We conclude that synthetic and natural lycopene are equivalent sources of lycopene and that there is no interaction with other circulating carotenoids.

Key words lycopene – serum carotenoids – bioavailability – human

Introduction

Lycopene occurs almost exclusively in tomatoes [1]. In many Western populations it is a prominent carotenoid in blood [16, 23, 50], lymphocytes [38, 42], buccal cells [43], adrenal glands, lungs, testes, prostate gland, liver, and skin [2, 14, 16, 17]. Lycopene has attracted much interest because of its ability to quench singlet oxygen [5, 20, 36], to inhibit the growth of human endometrial, mammary, or lung cancer cells grown in culture [15, 21] and because of its potential anticancer effects [18, 19, 27]. A possible association between lycopene and myocardial infarct has also been investigated [13]. Epidemiological studies have indicated that low intake of tomato products or low plasma lycopene concentration are associated with a higher risk of various cancers including prostate cancer [11, 27]. According to a recent review, 57 out of 72 studies reported such inverse associations of which 35 were statistically significant [19]. In these studies the sources of dietary lycopene were tomatoes and tomato-based products that also contained, *in-*

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ter alia, phytoene, phytofluene, ε-carotene, neurosporene, γ-carotene and β-carotene [1]. Hence, as reviewed earlier [19], there is a possibility that lycopene accounts for or contributes to the reported health benefits, but this is not yet proven and requires further studies. Reviews on the potential role of lycopene for human health and disease have been published [14, 15, 18, 19, 22].

Studies relating to lycopene bioavailability in humans have been reported and reviewed previously [3–6, 8–10, 12, 16, 20, 23, 25, 29]. The sources were raw tomatoes and tomato paste [6, 33], tomato juice, tomato oleoresin, beadlets made from tomato oleoresin [24], a whey-based formulation of lycopene extract from tomato [48] and fruit and vegetable concentrate [8, 9]. Consumption of heat-processed tomato juice resulted in a greater plasma lycopene response than consumption of unprocessed juice [31]. A recent pilot study comparing the plasma response to synthetic and tomato-based deuterated lycopene in two subjects each found that synthetic lycopene was more bioavailable than lycopene from cooked and pureed tomatoes [25]. Preliminary data from a human study using synthetic lycopene were reported recently [28].

The aim of the present paper was to compare the relative bioavailability of a synthetic beadlet preparation (LycoVit 10 %, BASF), and of Lyc-O-Mato (LycoRed, Israel), a beadlet preparation containing tomato-oleoresin.

Materials and methods

Objective. Bioavailability was assessed as the concentration of serum total lycopene after 28 days supplementation. The study design was a single-blind, randomized, placebo-controlled, parallel trial in free living volunteers. Treatments consisted of the ingestion of one capsule each day for 28 days.

The study was conducted at TNO, Zeist, The Netherlands, according to Good Clinical Practice guidelines. The protocol was approved by the TNO Medical Ethics Committee and all volunteers gave their written informed consent.

Lycopene sources. LycoVit 10 % (BASF) containing synthetic lycopene as gelatin beadlets had an analyzed content of 11.45 % total lycopene (77 % all-trans-, 23 % total-cis-lycopene). Lyc-O-Mato™ Beads 5 % (natural tomato lycopene in beadlets, LycoRed Natural Products Industries Ltd, Israel) was purchased. The analyzed content was 4.3 % total lycopene (85 % all-trans- and 15 % total-cis-lycopene). The material contains further carotenoids, e. g., lutein, β-carotene, γ-carotene, ξ-carotene, phytofluene, phytoene and neurosporene [1, 24]. Study substances were given in acid-soluble gelatin capsules that contained either 15 mg total lycopene or placebo. The placebo capsules contained beadlets formulated with the same ingredients as in LycoVit 10 % except for lycopene.

Inclusion criteria were good health as assessed by questionnaire, physical examination and clinical laboratory tests; age from 18 to 60 years, body mass index 19–28 kg/m^2, fasting serum lycopene from 0.1 to 0.4 μmol/L, fasting serum β-carotene below 1.0 μmol/L, regular food pattern; and willingness to abstain from the use of supplements containing vitamins C, E, or A or carotenoids.

Exclusion criteria were, cigarette smoking, alcohol consumption > 28 units/week for male subjects and > 21 units/week for female subjects (one unit being equivalent to ca. 10 g of alcohol), abnormal fat absorption, frequent (> once/week) use of supplements containing vitamins E, A or carotenoids within 1 month before the pre-study screening, more than 8 hours/week strenuous exercise, reported unexplained weight loss or gain of > 2 kg in the month prior to the pre-study screening, reported slimming or medically prescribed diet, reported vegan, vegetarian or macrobiotic, and pregnancy or lactation or wish to become pregnant during the study.

Randomization (n = 12 subjects/treatment) was based on serum total lycopene at pre-screening (–18 d). Parameters determined at randomization are given in Table 1. Treatments were blinded for the subjects only.

Blood sampling. Blood was collected at pre-study screening (d –18), on d 1 (baseline) and at the end of the study (d 29). Blood samples were taken from an antecubital vein after an overnight fast in tubes containing clot activator and gel (Vacutainer® systems). The tubes were immediately stored in a closed box to avoid breakdown of carotenoids by UV light. Tubes were centrifuged within 15–30 min after collection, and serum was stored at –70 °C. All sample handling was done under subdued light.

Compliance. Subjects were instructed to take one capsule per day during the main meal, regardless whether this was at lunch or dinner time, and to store the study substances in a refrigerator. Compliance was monitored by handing out a number of capsules that exceeded the number to be taken during the study. The capsules remaining were counted after two and four weeks. In addition, subjects had to enter into a list, the time of capsule intake each day.

Adverse events were established by a trained medical investigator and on the basis of spontaneous reporting.

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Table 1 Results of pre-study screening (d–18): age, body mass index (BMI), and total cholesterol, β-carotene and total lycopene in serum. Data are treatment means ± SD

Treatment	Lyc-O-Mato™ 5%	LycoVit 10%	Placebo	Overall	ANOVA P-value
Number (n)	12	12	12	36	
Male/female	4/8	3/9	5/7	12/24	
Age [years]	43±14	43±13	37±11	41±13	0.39
BMI [kg/m^2]	22.9±2.6	23.6±2.1	23.6±2.8	23.4±2.5	0.63
Total cholesterol [mmol/L]	5.7±1.0^A	5.2±0.9^{A,B}	4.7±0.7^B	5.2±0.9	0.06
β-Carotene [μmol/L]	0.50±0.19^A	0.38±0.12^B	0.31±0.21^B	0.39±0.18	0.02
Total lycopene [μmol/L]	0.27±0.07	0.25±0.09	0.27±0.06	0.25±0.07	0.59

^{A,B} Values within a row not sharing the same superscript are significantly different ($p < 0.05$)

Carotenoid profile. In fasting serum samples collected at d –18, β-carotene and total lycopene were measured. In samples of d 1 and 29, α-carotene (all-trans), β -carotene (all trans), β-cryptoxanthin, lycopene (total, total-cis, all-trans), zeaxanthin and lutein were measured. In addition, in the samples of d 1 and 29 phytoene and phytofluene were measured using a non-validated HPLC method. Peak height was measured at the relative position of these compounds in the HPLC chromatogram. However, because there were no calibrated standards available for phytoene and phytofluene and no complete baseline separation was achieved, only indicative values for phytoene and phytofluene could be derived from the HPLC chromatogram using a phytoene standard (kindly supplied by Dr. W. Stahl, Düsseldorf).

Carotenoid analysis was done as described [49]. Briefly, samples were deproteinized using ethanol with tocol added as internal standard, and subsequently extracted using hexane. Separation was done using two C18 reversed-phase columns in series and a gradient of methanol, acetonitrile, 2-propanol and milliQ® purified water for elution. Carotenoids were detected by diode array. The quality of measurements was assessed by analyzing plasma quality control samples in each series.

Statistical analysis. The data are expressed as means ± standard deviation. Differences in serum parameters between treatments were evaluated by analysis of variance (ANOVA) with gender and treatment and their interaction as factors in the model. In case of an overall significant F-test, individual groups were compared using the student t-test. In all statistical tests performed, the null hypothesis was rejected at the 0.05 level of probability.

Results

General

Compliance was very good. Out of a total of 1008 (36 x 28) doses, 10 doses were not consumed (with a maximum of 2 per subject) and 14 doses were taken after the meal (with a maximum of 3 per subject). Non-compliance was equally distributed over treatment groups. No adverse events occurred after the use of any of the supplements.

Thirty-six subjects (12 males, 24 females) completed the study. Pre-study screening data are given in Table 1. Total serum lycopene was similar in the three treatment groups, with a mean value of 0.25 μmol/L across treatments and gender. Serum β-carotene was significantly higher in the group given Lyc-O-Mato compared with the other treatment groups.

Serum carotenoids

Values on d 1 and d 29 (the day following the last dose) are given in Table 2. Supplementation resulted in a 2–3-fold increase in serum total lycopene (trans plus total-cis) over baseline without significant differences between sources (0.91 vs. 0.95 μmol/L, Lycovit 10% vs Lyc-O-Mato). There was no significant increase in serum total lycopene in the placebo group (d 1 vs d 29). On d 29 serum trans-lycopene was higher for Lyc-O-Mato than for Lycovit ($p \leq 0.02$), whereas total-cis lycopene did not significantly differ between lycopene sources.

No significant differences in serum concentrations between d 1 and 29 were found for α-carotene, β-carotene, β-cryptoxanthin, zeaxanthin, lutein, phytoene and phytofluene.

The changes in serum carotenoids (d 29 – d 1) are shown in Table 3. The increments in total lycopene were almost identical for both lycopene sources (0.58 vs. 0.57 μmol/L, Lycovit 10% vs Lyc-O-Mato) and significantly greater than for the placebo group. For both lycopene sources, the increase of total lycopene was due to a significant rise in total-cis and all-trans-lycopene. In contrast to the significant difference in trans-lycopene *concentrations* between Lyc-O-Mato and LycoVit on d 29, there was no significant difference in *response* (d 29 – d 1).

Table 2 Serum α-carotene, β-carotene, β-cryptoxanthin, lycopene (total, total-cis, all-trans), zeaxanthin, lutein, phytoene and phytofluene (μmol/L) on d 1 and d 29 per treatment group. Data are treatment means ± SD

Treatment	Day 1				Day 29			
	Lyc-O-Mato™ 5%	LycoVit 10%	Placebo	P-value ANOVA	Lyc-O-Mato™ 5%	LycoVit 10%	Placebo	P-value ANOVA
α-Carotene	0.07±0.04	0.10±0.09	0.07±0.04	0.32	0.07±0.04	0.09±0.09	0.07±0.04	0.71
β-Carotene	0.43±0.18	0.39±0.19	0.32±0.21	0.45	0.47±0.19	0.42±0.22	0.33±0.21	0.32
β-Cryptoxanthin	0.32±0.13	0.27±0.17	0.22±0.11	0.18	0.27±0.10	0.30±0.28	0.18±0.09	0.33
Total lycopene	0.38±0.18	0.33±0.12	0.36±0.14	0.32	0.95±0.20^{A}	0.91±0.30^{A}	0.46±0.18^{B}	**0.0000**
Total-cis lycopene	0.16±0.08	0.15±0.06	0.16±0.06	0.58	0.32±0.07^{A}	0.39±0.13^{A}	0.20±0.07^{B}	**0.0000**
All-trans lycopene	0.22±0.10	0.19±0.07	0.20±0.09	0.21	0.63±0.14^{A}	0.53±0.17^{B}	0.26±0.11^{C}	**0.0000**
Zeaxanthin	0.07±0.03	0.08±0.04	0.07±0.03	0.84	0.07±0.04	0.09±0.04	0.07±0.03	0.64
Lutein	0.22±0.10	0.28±0.22	0.21±0.08	0.60	0.20±0.09	0.29±0.20	0.21±0.06	0.26
Phytoene*	141±90	96±45	148±249	0.69	129±81	107±68	127±106	0.68
Indicative values	0.08±0.05	0.06±0.03	0.08±0.05		0.08±0.05	0.06±0.05	0.08±0.06	
Phytofluene*	242±129	253±163	192±60	0.60	254±137	231±151	198±99	0.61
Indicative values	0.15±0.08	0.15±0.13	0.15±0.05		0.15±0.08	0.14±0.09	0.12±0.06	

$^{A, B, C}$ Values within a row not sharing the same superscript are significantly different ($p < 0.05$)
* Data are presented as peak height (*Absorption units* AU), whereby 100 AU is close to a phytoene concentration of 0.06 μmol/l

Table 3 Changes in serum carotenoids (μmol/L), day 29 – day 1. Data are treatment means ± SD

Treatment	Change			
	Lyc-O-Mato™ 5%	LycoVit 10%	Placebo	P-value ANOVA
α-Carotene	–0.00±0.03	–0.02±0.04	0.00±0.03	0.39
β-Carotene	0.04±0.07	0.03±0.12	0.01±0.07	0.77
β-Cryptoxanthin	–0.05±0.06	0.03±0.13	–0.03±0.03	0.06
Total lycopene	0.57±0.26^{A}	0.58±0.32^{A}	0.10±0.15^{B}	**0.0001**
Total-cis lycopene	0.16±0.09^{A}	0.24±0.14^{A}	0.04±0.06^{B}	**0.0003**
All-trans lycopene	0.41±0.18^{A}	0.34±0.18^{A}	0.06±0.09^{B}	**0.0000**
Zeaxanthin	0.00±0.03	0.01±0.01	0.00±0.02	0.56
Lutein	–0.02±0.03	0.01±0.05	–0.00±0.05	0.24
Phytoene*	–12±44	11±45	–21±155	0.82
Indicative values	–0.01±0.02	0.01±0.02	–0.01±0.09	
Phytofluene*	12±57	–23±96	6±84	0.45
Indicative values	0.01±0.03	–0.01±0.06	0.00±0.05	

$^{A, B}$ Values within a row not sharing the same superscript are significantly different ($p < 0.05$)
* see footnote in Table 2

No significant differences in serum response between the three treatments were found for α-carotene, β-carotene, β-cryptoxanthin, lutein, zeaxanthin, phytoene and phytofluene.

On d 01 and d 29 serum concentrations for cryptoxanthin, lycopene (total- total-cis and trans), zeaxanthin and phytofluene differed between gender (p-<0.0001–0.019). However, there was no significant interaction between gender and treatment. Also, the changes in serum concentrations (d 29–d1) did not differ between males and females.

Discussion

In this study the relative bioavailability of a synthetic source and a common natural source of lycopene was compared under conditions typical of supplement intake, viz over a prolonged period of time. Supplementation with both sources resulted in clear and similar increases of serum lycopene.

The study design was aimed at ensuring a serum response with a high probability of detecting a possible

difference between sources. This approach constrained the selection of volunteers to reduce variability. First, normolipemic subjects with serum lycopene below 0.4 μmol/L were selected by pre-study screening on d –18. This was done because high serum lycopene at baseline appears to be associated with a low or no response upon supplementation [10, 26, 40], whereas most supplementation studies resulted in significant increments [8, 10, 20, 24, 36, 37, 40, 41]. Mean serum total lycopene of the subjects selected was 0.25 μmol/L (n = 36). About two wk later, at baseline (d 1), mean total lycopene was 0.36 μmol/L. This is at the low end of the range of serum lycopene concentrations reported for many countries [8, 50, 53]. Second, in order to eliminate the confounding effect of dietary fat that is required for efficient carotenoid absorption, the daily dose was taken with the main meal of the day. This lowers the likelihood that any one subject may take the dose outside a meal and possibly with a fat-free drink resulting in a low or failing serum response even though total daily fat intake is normal. It is noteworthy that the majority of bioavailability studies with isolated carotenoids in free-living humans failed to specify if the dose was ingested together with food and this may be one factor contributing to the large variation in plasma response that has been reported [41, 45]. Third, a long duration of 4 wk supplementation was used so as to attain the steady state. In a previous study the latter was apparently reached after 7 to 14 d [20]. Finally, in order to achieve a high compliance, subjects were instructed to record each day the exact time when the dose was taken. These precautions resulted in a coefficient of variation for mean serum total lycopene (n = 36) of 28 % (pre-screening), 41 % (d 1) and 31 % (d 29), respectively. For comparison, in epidemiological studies the CV is normally > 50 %.

We have no explanation for the difference in serum lycopene concentrations between d –18 and d 1. It may be due to large day-to-day variation and regression to the mean in the subjects selected for a relatively low serum lycopene concentration.

In this study, there was a significant gender effect on lycopene concentrations, i. e., women had higher serum concentrations than men (not shown). However, no interaction between gender and treatment was observed, indicating that men and women showed comparable responses to the treatments. Indeed, no gender difference was observed in the changes of serum lycopene from d 1 to 29. Likewise, there was no gender effect on serum total lycopene in a recent study involving control subjects from five European countries [53] and on the serum response to lycopene supplementation in the same subjects [55].

In this study lycopene from the synthetic beadlet preparation had the same bioavailability as lycopene from the natural beadlet formulation, based on the response of serum total lycopene to a supplement of 15 mg total lycopene for 28 d. Thus, in terms of providing lycopene, both sources were equivalent at this dosage. However, it is unknown if this is also the case with other doses. On an individual basis, a marked increase in serum total lycopene was found in 23 out of the 24 subjects. We have no explanation for the single case of non-responder as his reported compliance was 100 % and none of the measured parameters was outside the range. The highest value following 28 d supplementation was 1.42 μmol/L and the highest individual increase (d 29 – d 1) was 1.05 μmol/L. As observed previously, plasma concentrations rarely exceed 1 μmol/L, irrespective of the dose and the duration of application (W. Stahl, Düsseldorf, personal communication).

The difference in isomer composition of the supplements (23 % vs 15 % cis-isomers, synthetic vs natural) was not associated with a difference in serum response of cis- and total lycopene. Studies with lymph-cannulated ferrets showed a preferential absorption of cis-lycopene; 77 % of lycopene in lymph was in the cis-form compared with 8 % in the dose [47]. However, tissues and serum contained about 50 % cis-lycopene, indicating that a state of equilibrium between trans and cis-isomers exists [47]. Likewise, in a recent European multicenter supplementation study using 13.3 mg total lycopene/d (15 % cis), no change from baseline was found in the plasma cis/trans proportion [55]. This agrees with earlier studies on smaller groups of subjects that also did not detect a change in plasma cis/trans proportion [6, 56, 57]. Our study was not aimed at investigating the differential response between cis and trans-lycopene but the results seem to be in agreement with the other studies in that the ratio in serum is higher than in the supplement and is not affected by supplementation. Whether a preferential absorption of cis-lycopene over trans-lycopene results in a higher serum total lycopene response to supplements with a high cis-content has yet to be studied. In most human studies natural lycopene sources low in cis-lycopene (about 5 % of total lycopene [54]) were used, and plasma analysis rarely separated between cis- and trans-lycopene. It has recently been concluded that the isomer distribution in blood is independent of that in the diet/supplement [55].

In a human trial that used the same material as in this study, the serum response was only about one-half the response we found [24]. This discrepancy cannot yet be explained, but may be related to the higher baseline plasma lycopene (about 0.59 μmol/L) compared with this study (0.36 μmol/L).

Apart from lycopene, tomatoes contain also lutein, β-carotene, phytoene and phytofluene [24]. In spite of their low concentration in tomato oleoresin and beadlets, the latter two carotenoids have been reported to elicit marked plasma responses [8, 24]. This contrasts with our results where the tomato-based lycopene

source did not elevate serum lutein or β-carotene. Likewise, no apparent effect was detected on serum phytoene and phytofluene, albeit by a non-validated HPLC method. This indicates that in tomato-based lycopene preparations, the bioavailability of the accompanying carotenoids is equivocal.

In tomatoes and tomato products, about 79 to 91 % of total lycopene are present as all-trans lycopene [46]. A higher proportion of cis-isomers is found after heating lycopene in oil [46]. Thus, the isomeric composition of synthetic lycopene in LycoVit is similar to that of heated tomato products. Isomerization is the result of the micronization process where crystalline all-trans lycopene derived from synthesis is diminished in size to render it bioavailable. One such process of micronization has been described [44]. Briefly, the carotenoid is dissolved in organic solvent at elevated temperature resulting in a molecular solution. The latter is mixed with an aqueous solution of gelatin at low temperature resulting in precipitation of carotenoid nanoparticles and spontaneous adsorption of the gelatin onto the nanoparticles thus limiting their growth. The resulting hydrosol is subsequently formulated into beadlets by spray-drying. By varying the thermal input and duration of micronization the proportion of cis-isomers and potentially, bioavailability, can be modified.

In our study, synthetic lycopene and the natural source did not affect other circulating carotenoids. There are very little data on interactions between lycopene and other carotenoids, particularly β-carotene, in human subjects [30, 33, 34, 52]. They indicate that β-carotene might affect the absorption of lycopene but lycopene does not affect the bioavailability of β-carotene [30]. This is supported by our study.

In conclusion, a daily supplement of 15 mg lycopene given for 4 wk as beadlet preparations containing synthetic lycopene (Lycovit 10 %) or tomato oleoresin (Lyc-O-Mato) resulted in a marked and identical serum cis-, trans- and total lycopene response. This indicates that both sources had the same bioavailability. Other circulating carotenoids were not affected by lycopene. Because the synthetic source contains lycopene only whereas tomato oleoresin contains *inter alia* other carotenoids, synthetic lycopene is a potential tool to investigate the effects of a defined, single carotenoid on human health.

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