The Journal of Nutrition
Nutrition and Disease

Lycopene Inhibits Disease Progression in Patients with Benign Prostate Hyperplasia[1,2]

Silke Schwarz,[3,4] Ute C. Obermüller-Jevic,[3,5] Eva Hellmis,[6] Winfried Koch,[7] Günther Jacobi,[6] and Hans-Konrad Biesalski[3]*

[4]University of Hohenheim, Institute of Biological Chemistry and Nutrition, 70593 Stuttgart, Germany; [5]BASF Aktiengesellschaft, 67117 Limburgerhof, Germany; [6]Urologic-Andrologic Medical Practice, Prof. Dr. med. Jacobi and Dr. med. Eva Hellmis, 47179 Duisburg, Germany; and [7]HaaPACS GmbH, 69198 Schriesheim, Germany

Abstract

Lycopene is a promising nutritional component for chemoprevention of prostate cancer (PCa). A possibly beneficial role of lycopene in patients diagnosed with benign prostate hyperplasia (BPH), who are at increased risk of developing PCa, has been suggested, although clinical data are lacking. Therefore, this pilot study aimed to investigate the effects of lycopene supplementation in elderly men diagnosed with BPH. A total of 40 patients with histologically proven BPH free of PCa were randomized to receive either lycopene at a dose of 15 mg/d or placebo for 6 mo. The effects of the intervention on carotenoid status, clinical diagnostic markers of prostate proliferation, and symptoms of the disease were assessed. The primary endpoint of the study was the inhibition or reduction of increased serum prostate-specific antigen (PSA) levels. The 6-mo lycopene supplementation decreased PSA levels in men ($P < 0.05$), whereas there was no change in the placebo group. The plasma lycopene concentration increased in the group taking lycopene ($P < 0.0001$) but other plasma carotenoids were not affected. Whereas progression of prostate enlargement occurred in the placebo group as assessed by trans-rectal ultrasonography ($P < 0.05$) and digital rectal examination ($P < 0.01$), the prostate did not enlarge in the lycopene group. Symptoms of the disease, as assessed via the International Prostate Symptom Score questionnaire, were improved in both groups with a significantly greater effect in men taking lycopene supplements. In conclusion, lycopene inhibited progression of BPH. J. Nutr. 138: 49–53, 2008.

Introduction

Lycopene, a carotenoid mainly consumed from tomatoes, is a promising nutritional component for the chemoprevention of prostate cancer (PCa)[8] (1). In epidemiological studies, regular intake of lycopene and high blood levels of the carotenoid have been repeatedly associated with a reduced risk of developing PCa. Experimental studies have shown that lycopene inhibits progression of prostate tumor growth and PCa cell proliferation, respectively, as recently reviewed by Clinton et al. (2,3). Clinical evidence for prostate health benefits of lycopene has been limited to patients with PCa or high-grade prostatic intraepithelial neoplasia (4,5). To evaluate the chemopreventive potential of lycopene, clinical studies in men with no evidence of PCa or high-grade prostatic intraepithelial neoplasia but at high risk of the disease are warranted. A possibly beneficial role of lycopene in patients diagnosed with benign prostate hyperplasia (BPH), who are at elevated risk of developing PCa, has been suggested but not yet studied (6–9).

BPH is a common disease of elderly men and a risk factor for developing PCa later in life. It affects ~50% of men in their 50s with increasing prevalence up to 90% of men in their 80s and older. Clinical symptoms are reported to be manifest in ~25 and 50% of men in the respective age groups (10).

The aim of this randomized clinical pilot study was to investigate whether intake of lycopene supplements inhibits disease progression in patients with BPH, improving clinical diagnostic markers and symptoms of BPH.

Subjects and Methods

Subjects and study design. Forty patients with BPH were recruited from October 2004 through July 2005. Eligibility criteria included a serum prostate-specific antigen (PSA) concentration >4.0 μg/L, histologically confirmed BPH, age between 45 and 70 y, absence of acute illness, and written consent of willingness to participate in the study. Criteria for exclusion were histologically proven PCa or other malignancies, chronic diseases of the liver and kidneys, inflammatory diseases

[1] Supported by BASF Aktiengesellschaft, Ludwigshafen, Germany.
[2] Author disclosures: S. Schwarz, E. Hellmis, W. Koch, G. Jacobi and H.K. Biesalski, no conflicts of interest. U.C. Obermüller-Jevic is an employee of BASF Aktiengesellschaft.
[3] Both authors contributed equally to this work.
[8] Abbreviations used: BMC, buccal mucosa cells; BPH, benign prostate hyperplasia; DRE, digital rectal examination; IGF-1, insulin-like growth factor-1; IGF-BP-3, insulin-like growth factor binding protein-3; IPSS, International Prostate Symptom Score; PCa, prostate cancer; PSA, prostate-specific antigen; TRUS, trans-rectal ultrasonography.
* To whom correspondence should be addressed. E-mail: biesal@uni-hohenheim.de.

Manuscript received 12 April 2007. Initial review completed 19 May 2007. Revision accepted 22 October 2007.

of the urogenital tract, ongoing therapy with doxazosin, dutasterid, and/or finasterid, testosterone, or other substances that affect hormone status. Further criteria for exclusion were ongoing phytotherapy, chronic inflammatory bowel disease, fat malabsorption and maldigestion, known allergies and/or sensitiveness to lycopene intake, and participation in a clinical study 4 wk prior to and/or during the present study. Of the 327 patients screened who had visited the urologic-andrologic medical practice for routine voluntary PSA examination, 49 patients met the inclusion criteria and 9 patients self-selected not to participate in the study. The remaining 40 participants gave their informed consent before participation. They could withdraw from the study at any time.

The study was designed to be randomized, double-blind, placebo-controlled to determine whether intake of 15 mg/d lycopene from a dietary supplement can significantly alter the PSA level during a 6-mo intervention period. The participants were randomly assigned to receive either lycopene or placebo. The study clinician was informed to allocate the supplements to the patients after inclusion into the study using increasing randomization numbers. Neither the study clinician nor any patients had access to the computer-generated randomization plan. In case of an emergency, the treatment information was available at the center in sealed envelopes. The envelopes were returned after study termination and none of them had been opened. Participants were scheduled for 4 visits at the urologic-andrologic medical practice during the 6-mo study period at baseline (visit 1), after 1 mo (visit 2), after 3 mo (visit 3), and after 6 mo (visit 4). The study was approved by the regional ethics committee (Landesärztekammer Baden-Württemberg).

Supplements, dose, and treatment procedures. Lycopene supplements were provided by BASF as hard gelatin capsules containing 15 mg synthetic lycopene (77% all-*trans* and 23% total *cis*-lycopene) each. We used a commercially available powder formulation containing 10% lycopene embedded in a matrix of gelatin and sucrose (LycoVit) to fill the capsules. The placebo was a powder formulation without lycopene. The supplements were freshly manufactured at the beginning of the study and the stability of lycopene with proper handling of the supplements was guaranteed for at least 36 mo. Bioavailability of the lycopene supplement was demonstrated previously and was identical to a tomato-based supplement (11). The supplements were identical in form, taste, smell, and appearance for lycopene and placebo. The subjects were instructed to take 1 capsule per day with lunch.

Biochemical parameters and clinical examinations. The biochemical variables measured and clinical examinations conducted are summarized in **Table 1**. The primary endpoint was defined as inhibition of the delta increase or decreased PSA levels in blood. Secondary endpoints were increases in the lycopene concentrations in blood and tissue [buccal mucosa cells (BMC)], reduced circulating insulin-like growth factor (IGF-1), and increases in IGF-binding protein-3 (IGF-BP-3) concentrations in blood. Additional variables measured were circulating concentrations of testosterone (free and bound), LDL cholesterol and total cholesterol, and blood glucose concentrations and routine hemograms. Additional examinations were digital rectal examination (DRE), trans-rectal ultrasonography (TRUS) of the prostate and assessment of the International Prostate Symptom Score (IPSS). The American Urological Association's IPSS questionnaire was used to measure the clinical symptoms and quality of life index. During intervention, adjuvant therapy of BPH and intake of self-selected dietary supplements were not allowed. Patients were advised not to change their dietary habits, which were monitored via FFQ (EBISpro dietary assessment program, version 6.0, University of Hohenheim) modified to widely assess intake of foods rich in lycopene. A compliance check was done at each visit including a count of the remaining capsules, retrospective dietary protocols, and checking the compliance calendar.

Sample collection. Prostate tissue samples from men while under anesthesia as systematic sextant TRUS-guided biopsies in which 3 tissue samples each of the right and left prostate lobes were obtained. Blood samples were drawn from an antecubital vein of fasting subjects into evacuated containers containing EDTA. BMC were collected non-invasively using the PASCOE multivitamin test (Biotesys) according to the manufacturer's protocol. All sample collection procedures were conducted with a minimum of light exposure and samples were stored at −80°C.

Laboratory and clinical methods. We measured PSA and testosterone in serum using electrochemiluminesence immunoassays (ECLIAs) from Roche Diagnostics in combination with a Roche/Hitachi MODULAR ANALYTICS device. Serum IGF-1 and IGF-BP3 were analyzed using enzyme-labeled chemiluminescence immunoassays and the IMMULITE 2000 analyzer from DPC. Serum glucose, cholesterol, and LDL were measured using a Roche/Hitachi 917 analyzer and the following enzymatic colorimetric assays: Gluco-quant and HiCo Cholesterol CHOD-PAP from Boehringer and the LDL-C Plus second generation assay from Roche Diagnostics.

Extraction of carotenoids from plasma, BMC, and prostate and subsequent HPLC analysis was performed as published previously (12). All extraction procedures were conducted with a minimum of light exposure. Synthetic lycopene from BASF was used as a reference standard.

Prostate weight was determined via TRUS using a Falcon Type 2101 ultrasound device (B-K Medical). Prostate volume was estimated via DRE, i.e. manual (finger) palpation of the rectum performed by an experienced examiner.

Statistical analysis. The primary statistical analysis used a linear model to compare the change of total PSA in blood from visit 1 (baseline) to visit 4 at the end of 6 mo. Covariates in this model were total PSA at

TABLE 1 Study protocol: biochemical variables, clinical examinations, and nutritional assessment (schedule)

	Biochemical parameters[1]	Clinical examinations	Nutritional assessment
Screening	PSA (total)	Biopsy (prostate)	Lycopene (plasma) Lycopene (prostate)
Baseline (Visit 1)	IGF-1, IGF-BP-3, testosterone, LDL cholesterol, total cholesterol, glucose, hemogram	DRE, TRUS IPSS questionnaire	Lycopene (plasma) Lycopene (BMC) Dietary protocol
After 1 mo (Visit 2)	PSA	IPSS questionnaire	Lycopene (plasma) Dietary protocol
After 3 mo (Visit 3)	PSA	IPSS questionnaire	Lycopene (plasma) Dietary protocol
After 6 mo (Visit 4)	PSA, IGF-1, IGF-BP-3, testosterone, LDL cholesterol, total cholesterol, glucose, hemogram (whole blood)	DRE, TRUS IPSS questionnaire	Lycopene (plasma) Lycopene (BMC) Dietary protocol

[1] Analyzed in serum unless otherwise indicated.

TABLE 2 Anthropometric, dietary, and serum biochemical characteristics of BPH patients at baseline and after 6 mo of lycopene supplementation[1]

	Placebo		Lycopene	
Characteristic	Baseline	6 mo	Baseline	6 mo
n	18	18	19	19
Age, *y*	67.7 ± 5.6 (69.0)		67.0 ± 4.6 (67.0)	
Height, *m*	1.74 ± 0.06 (1.74)		1.77 ± 0.07 (1.78)	
Weight, *kg*	79.9 ± 8.8 (81.0)	78.6 ± 8.5 (80.5)	84.7 ± 9.7 (86.0)	84.6 ± 9.4 (84.5)
BMI, kg/m^2	26.3 ± 2.0 (27.0)	25.9 ± 2.1 (25.8)	27.0 ± 2.0 (26.7)	27.0 ± 1.8 (26.9)
Energy intake, *MJ/d*	11.6 ± 4.3 (10.5)	9.3 ± 3.4* (8.8)	12.4 ± 3.0 (13.0)	11.4 ± 2.9 (11.2)
Dietary lycopene intake, *mg/d*	6.2 ± 11.5 (4.1)	6.1 ± 6.6 (4.0)	6.2 ± 5.9 (3.8)	9.2 ± 15.5 (4.2)
Glucose, *mmol/L*	5.8 ± 1.1 (5.4)	6.0 ± 1.1 (5.5)	6.4 ± 1.6 (5.9)	5.9 ± 1.1 (5.4)
Total cholesterol, *mmol/L*	6.0 ± 1.3 (6.2)	5.4 ± 1.1** (5.5)	5.4 ± 0.9 (5.3)	5.3 ± 0.8 (5.3)
LDL cholesterol, *mmol/L*	4.0 ± 1.1 (3.9)	3.5 ± 1.1** (3.5)	3.3 ± 0.9 (3.3)	3.3 ± 0.7 (3.3)
Total testosterone, *nmol/L*	16.7 ± 5.6 (14.6)	16.7 ± 4.9 (16.3)	16.3 ± 4.9 (16.7)	16.7 ± 5.2 (17.0)
Free testosterone, *pmol/L*	47.9 ± 14.6 (46.2)	43.7 ± 14.2 (43.7)	39.9 ± 10.8 (41.0)	39.2 ± 10.4 (38.2)

[1] Values are means ± SD (median). Asterisks indicate different from baseline: * $P < 0.05$, ** $P < 0.01$ (Wilcoxon Signed-Rank Test).

baseline, BMI, and age. Covariates could be eliminated from the model if $P > 0.4$ and thus far from the usual limits of significance. The primary null hypothesis to be tested was that the changes from baseline do not differ between the lycopene and the placebo group after adjustment for baseline, BMI, and age. The predefined α level was 0.05 (2-sided).

The sample size estimation was based on a *t* test for independent samples. To detect a difference in PSA change between lycopene and placebo groups of 1.82 μg/L with a statistical power of 80% assuming an error SD of 2 μg/L, 20 patients per group were needed. At the time of planning, there was considerable uncertainty regarding the true size of the residual error SD. We anticipated that in this pilot study, the final statistical power might be lower than the planned 80% and therefore comparisons within groups in addition to comparisons between groups were planned.

No data were excluded from analyses and missing values were not replaced. Comparisons within groups used the robust Wilcoxon's Signed-Rank Test for paired samples with a 2-sided $\alpha = 0.05$. Considering the low power of this pilot study, 2-sided $P < 0.1$ are reported as statistical tendencies. The analyses described above for PSA were performed also for other variables. Baseline data were collected for all variables at visit 1 before randomization, with the exception of total PSA and free PSA. At visit 1, no PSA measurement was conducted due to increased risk of bias resulting from a recent biopsy; instead, the measurements of total PSA from the preceding screening examination were used as baseline covariates. No baseline data for free PSA were available for this study. Simple linear regression between target variables and baseline variables was performed to estimate pair wise correlation coefficients in addition to multiple regression coefficients. Statistical analyses were performed using SAS JMP version 6.0.2 from SAS Institute and SPSS version 11.5.

Results

Demographic data. A total of 40 patients entered the study. Two participants quit before beginning supplement intake. One participant in the placebo group was excluded after 50 d due to an unexpected hospitalization resulting from a family member's death. Nineteen subjects completed the study in the lycopene group and 18 subjects in the placebo group completed. Anthropometric, dietary, and biochemical characteristics of participants did not differ in the 2 groups at baseline (**Table 2**). After the 6-mo supplementation period, most anthropometric and biochemical characteristics, including blood glucose and testosterone, as well as the hemogram, did not change from baseline in either group and the groups did not differ from one another. However, serum total and LDL cholesterol

TABLE 3 Serum PSA, IGF-1, IGF-BP-3, and lycopene status in BPH patients at baseline and after 6 mo of lycopene supplementation[1]

	Placebo		Lycopene	
	Baseline	6 mo	Baseline	6 mo
n	18	18	19	19
Primary endpoints				
Serum total PSA,[2] $\mu g/L$	6.85 ± 2.3 (6.31)	6.81 ± 4.7 (5.07)	6.56 ± 2.3 (5.87)	5.82 ± 1.8* (5.57)
Serum free PSA, $\mu g/L$	—	0.98 ± 0.53 (0.87)	—	0.93 ± 0.33 (0.85)
Secondary endpoints				
Plasma lycopene, $\mu mol/L$	0.46 ± 0.24 (0.38)	0.54 ± 0.25 (0.60)	0.43 ± 0.22 (0.42)	1.24 ± 0.31**,## (1.23)
Prostate lycopene, $\mu mol/g$	0.45 ± 0.25 (0.43)	—	0.51 ± 0.30 (0.43)	—
BMC lycopene, $pmol/\mu g$ *DNA*	0.06 ± 0.07 (0.05)	0.17 ± 0.14* (0.11)	0.06 ± 0.1 (0.00)	0.59 ± 0.58**,# (0.38)
Serum IGF-1, *nmol/L*	20.8 ± 7.1(20.5)	19.5 ± 7.5 (19.2)	21.3 ± 8.0 (21.5)	21.4 ± 6.7 (20.9)
Serum IGF-BP-3, *nmol/L*	156.5 ± 34.8 (153.0)	146.1 ± 34.8 (146.1)	170.4 ± 41.7 (166.9)	166.9 ± 27.8 (166.9)

[1] Values are means ± SD (median). Asterisks indicate different from baseline, * $P < 0.05$, ** $P < 0.0001$ (Wilcoxon Signed-Rank Test). #, Change from baseline different from placebo group, # $P < 0.01$, ## $P < 0.0001$ (linear model with age, BMI, and plasma lycopene at baseline as covariates).

[2] Total PSA determined during screening instead of baseline (explanation in Subjects and Methods).

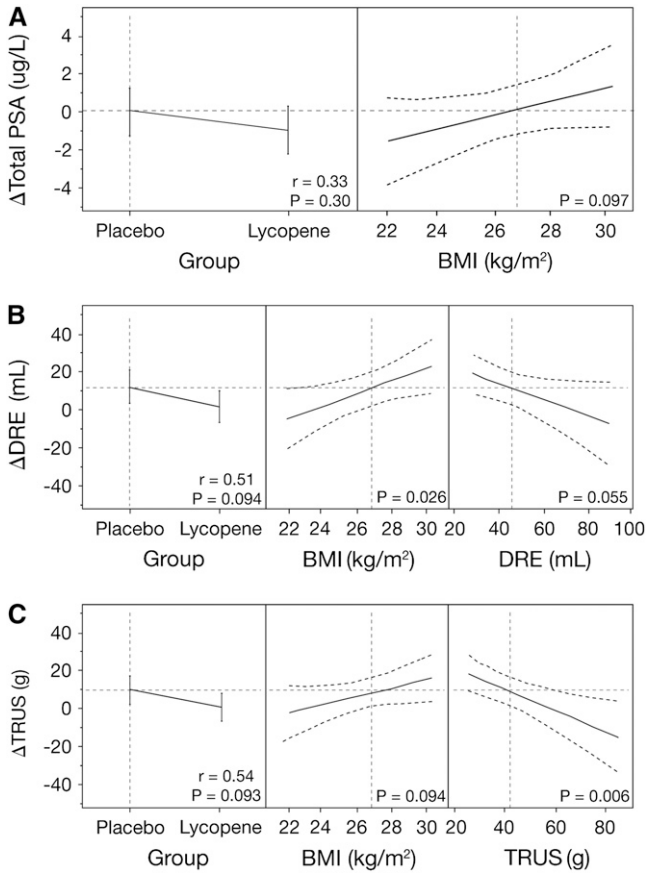

FIGURE 1 Changes in serum total PSA (*A*), DRE (*B*), and TRUS (*C*) in BPH patients supplemented with lycopene or placebo for 6 mo adjusted to relevant baseline covariates. For serum total PSA, the change was between screening and the end of the study (visit 4) and for other variables, between baseline (visit 1) and visit 4. *P*-values indicate the effect of each variable after adjustment for the other variables. The multiple correlation coefficient, *r*, for the model, the 95% confidence limits for treatment effects, and the 95% confidence bands are shown.

concentrations decreased in the placebo group ($P < 0.01$), which can be explained by reduced calorie intake in this group ($P < 0.05$).

PSA, IGF-1, and IGF-BP-3. In the lycopene group, the serum total PSA concentration decreased during the 6-mo supplementation period by 0.74 μg/L ($P < 0.05$), whereas there was no change in the placebo group and the change from baseline did not differ between groups (**Table 3**). The serum total PSA concentration in the lycopene group tended to be correlated with BMI ($r = 0.30$; $P = 0.097$) (**Fig. 1***A*). When free PSA concentrations at the end of study were statistically analyzed using the total PSA concentration at baseline as a covariate, the 2 groups did not differ. Changes in total and free PSA were not associated with baseline lycopene concentrations in plasma, BMC, or prostate.

The serum concentrations of IGF-1 and IGF-BP-3 tended to decrease in the placebo group ($P = 0.06$ and $P = 0.09$, respectively) (Table 3), which may be chance findings. These concentrations did not change in the lycopene group and changes did not differ between groups.

Lycopene in plasma, BMC, and prostate. Plasma and BMC concentrations of lycopene increased in the lycopene group during supplementation to 2.9-fold of the initial value in plasma and 9.8-fold of the initial value in BMC after 6 mo ($P < 0.0001$) (Table 3). In the placebo group, BMC lycopene increased to 2.8-fold of the baseline concentration ($P < 0.05$). The changes from baseline in both plasma and BMC lycopene differed between the 2 groups (plasma, $P < 0.0001$; BMC, $P < 0.01$).

The plasma baseline lycopene concentration correlated with the baseline concentration in prostate ($r = 0.66$; $P < 0.0001$) and tended to correlate with that in BMC ($r = 0.20$; $P = 0.059$). Changes in the plasma lycopene concentration during the intervention were inversely related to age ($r = -0.17$; $P < 0.05$) and the baseline concentration ($r = -0.16$; $P < 0.01$). The BMC lycopene concentration tended to be positively associated with age ($r = 0.19$; $P = 0.18$).

Plasma concentrations of other carotenoids, including β-carotene, lutein, zeaxanthin, and β-cryptoxanthin, were unaffected by supplementation with lycopene or placebo (data not shown).

DRE, TRUS, and IPSS. Clinical examinations for enlargement of the prostate, including DRE and TRUS, showed in the placebo group 24% ($P < 0.01$) and 27% ($P < 0.05$) increases in prostate volume and weight (**Table 4**). In contrast, in the lycopene group, slight and nonsignificant 5% ($P = 0.19$) and 3% ($P = 0.21$) increases in volume and weight occurred. Changes in DRE ($r = 0.29$; $P < 0.05$) and TRUS ($r = 0.19$; $P = 0.094$) were related to BMI and inversely related to their baseline values ($r = -0.32$; $P = 0.055$ and $r = -0.43$; $P < 0.01$, respectively). After

TABLE 4 Results from clinical examinations and IPSS in BPH patients at baseline and after 6 mo of lycopene supplementation[1]

	Placebo		Lycopene	
	Baseline	6 mo	Baseline	6 mo
n	18	18	19	19
DRE, *mL*	43.6 ± 12.1 (40.0)	55.3 ± 25.6** (50.0)	47.4 ± 15.2 (40.0)	49.7 ± 13.0 (50.0)
TRUS, *g*	40.5 ± 13.0 (36.9)	50.1 ± 21.1* (46.5)	42.2 ± 14.3 (37.0)	43.4 ± 11.9 (43.0)
IPSS, *points*	12.4 ± 2.0 (12.5)	10.1 ± 4.8* (9.5)	12.0 ± 2.4 (12.0)	10.3 ± 4.0** (10.0)
IPSS obstruction-related,[2] *points*	7.3 ± 0.9 (7.0)	5.6 ± 3.1* (5.0)	7.2 ± 1.6 (7.0)	5.9 ± 2.9** (6.0)
IPSS irritation-related,[3] *points*	5.2 ± 1.5 (5.0)	4.5 ± 2.2 (4.0)	4.8 ± 1.1 (4.0)	4.4 ± 1.5 (4.0)
IPSS quality of life, *points*	1.8 ± 0.7 (2.0)	2.2 ± 1.0 (2.0)	2.1 ± 0.6 (2.0)	2.1 ± 0.8 (2.0)

[1] Values are means ± SD (median). Asterisks indicate different from baseline:* $P < 0.05$,** $P < 0.01$ (Wilcoxon Signed-Rank Test).
[2] Includes IPSS question nos. 1, 3, 5, and 6.
[3] Includes IPSS question nos. 2, 4, and 7.

adjustment for BMI and baseline values, prostate enlargement tended to be slower in the lycopene group compared with the placebo group as assessed by changes in DRE ($P = 0.094$) (Fig. 1*B*) and TRUS ($P = 0.093$) (Fig. 1*C*). Baseline lycopene status did not affect prostate enlargement during the study.

The IPSS (total score and obstruction-related questions) decreased in the placebo group ($P < 0.005$) and in the lycopene group ($P < 0.01$) during the study ($P < 0.05$) and the changes did not differ between the groups. Quality of life, as assessed using the IPSS questionnaire, was unaffected in both groups.

Discussion

Lycopene supplementation for 6 mo at a dose of 15 mg/d was well tolerated by the participants; no adverse events or unusual symptoms occurred that may have been related to supplement intake. A daily dose of 15 mg lycopene was chosen based on our previous bioavailability study (11). Furthermore, consumption of 15 mg/d lycopene not only from dietary supplements but also from diet seems feasible for elderly men in the long term.

The primary aim of the study, to inhibit PSA increase in blood through lycopene intake, was achieved within the 6-mo study period. Clinical diagnostic markers for disease progression confirmed the favorable effect of lycopene in BPH patients based on within-group comparisons. The *P*-values of between-group comparisons in this pilot study were <0.1 for clinical examinations but not <0.05. There was no selective interference of lycopene with PSA levels, which is important to allow early detection of PCa during long-term intake of supplements. This is in contrast to the pharmaceutical 5-α-reductase inhibitors finasteride and dutasteride.

In our study, age and BMI had a significant influence on some indicators of disease progression and on the effects of lycopene supplementation. Interestingly, with increasing age, BPH patients had a significantly smaller increase in plasma lycopene concentration and tended to have higher lycopene concentrations in BMC. This suggests stronger accumulation of lycopene in cells and tissues. We speculate that lycopene accumulation increases with age as a biological mechanism, helping to protect against cellular and, subsequently, tissue damage. Obesity (BMI > 30 kg/m^2) was associated with increased progression of the disease; this was significant for DRE and borderline significant for TRUS. The lack of effect of lycopene on IGF-1 and IGF-BP-3 was unexpected, because lycopene is known to modulate IGF-1 signaling in experimental studies. We speculate that effects of lycopene on IGF-1 and IGF-BP-3 in humans may be detectable in prostate tissue rather than in plasma.

This pilot study is, to our knowledge, the first controlled clinical study reported on lycopene effects in BPH patients. Indications for potential inhibitory effects of lycopene on disease progression in BPH exist from a clinical pilot study in PCa patients showing induction of apoptosis by lycopene in cancer-free BPH tissue (6). From in vitro studies, it is known that lycopene inhibits proliferation of benign prostate epithelial cells (7). The underlying mechanism may be inhibition of 5-α-reductase and interleukin-6 signaling, as demonstrated in benign prostate tissue of rats (8). Moreover, because lycopene is an antioxidant (13), it may play a role in the oxidative stress-mediated cell proliferation and remodeling in benign prostate tissue (14).

In conclusion, this study indicates that lycopene at a dose of 15 mg/d for 6 mo, may inhibit disease progression and may ameliorate symptoms in BPH patients. Lycopene supplements are safe and well tolerated. Lycopene does not selectively interfere with PSA levels, which is important to allow early detection of PCa during long-term supplement intake. Analysis of lycopene in BMC may be suitable for routine screening and may serve as a basis for recommending supplementation with lycopene in the long-term management of prostate health.

Acknowledgment

We thank Christiane Schulz from Biotesys GmbH, Esslingen, Germany for carotenoid analyses in BMC.

Literature Cited

1. Chan JM, Gann PH, Giovannucci EL. Role of diet in prostate cancer development and progression. J Clin Oncol. 2005;23:8152–60.
2. Clinton SK. Tomatoes or lycopene: a role in prostate carcinogenesis? J Nutr. 2005;135:S2057–9.
3. Limpens J, Schroeder FH, de Ridder CM, Bolder CA, Wildhagen MF, Obermueller-Jevic UC, Kramer K, van Weerden WM. Combined lycopene and vitamin E treatment suppresses the growth of PC-346C human prostate cancer cells in nude mice. J Nutr. 2006;136:1287–93.
4. Stacewicz-Sapuntzakis M, Bowen PE. Role of lycopene and tomato products in prostate health. Biochim Biophys Acta. 2005;1740:202–5.
5. Mohanty NK, Saxena S, Singh UP, Goyal NK, Arora RP. Lycopene as a chemopreventive agent in the treatment of high-grade prostate intraepithelial neoplasia. Urol Oncol. 2005;23:383–5.
6. Kim HS, Bowen P, Chen L, Duncan C, Ghosh L, Sharifi R. Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer. 2003;47:40–7.
7. Obermuller-Jevic UC, Olano-Martin E, Corbacho AM, Eiserich JP, van der Vliet A, Valacchi G, Cross CE, Packer L. Lycopene inhibits the growth of normal human prostate epithelial cells in vitro. J Nutr. 2003;133:3356–60.
8. Herzog A, Siler U, Spitzer V, Seifert N, Denelavas A, Hunziker PB, Hunziker W, Goralczyk R, Wertz K. Lycopene reduced gene expression of steroid targets and inflammatory markers in normal rat prostate. FASEB J. 2005;19:272–4.
9. Kaplan SA. Lycopene: modes of action to promote prostate health. J Urol. 2005;174:679.
10. McVary KT. BPH: epidemiology and comorbidities. Am J Manag Care. 2006;12 Suppl 5:S122–8.
11. Hoppe PP, Krämer K, van den Berg H, Steenge G, van Vliet T. Synthetic and tomato-based lycopene have identical bioavailability in humans. Eur J Nutr. 2003;42:272–8.
12. Back EI, Frindt C, Nohr D, Frank J, Ziebach R, Stern M, Ranke M, Biesalski HK. Antioxidant deficiency in cystic fibrosis: when is the right time to take action? Am J Clin Nutr. 2004;80:374–84.
13. Krinsky NI, Johnson EJ. Carotenoid actions and their relation to health and disease. Mol Aspects Med. 2005;26:459–516.
14. Calo LA, Pagnin E, Davis PA, Lodde M, Mian C, Semplicini A, Pycha A. Effect of doxazosin on oxidative stress-related proteins in benign prostate hyperplasia. Urol Int. 2006;76:36–41.