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Use of selenium–silymarin mix reduces lower urinary tract symptoms and prostate specific antigen in men

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ABSTRACT

The aim of this double-blind, placebo controlled clinical trial was to assess the effects of a combination of selenium and silymarin in men with lower urinary tract symptoms, benign prostatic hyperplasia and a prostate specific antigen (PSA) ≤2.5 ng/ml. The volunteers were randomized to two groups: the first one ($n = 26$) received 240 μg selenium (in the form of yeast L-selenomethionine) plus 570 mg silymarin daily for 6 months and the second ($n = 29$) received placebo. Outcome measures were changes in the International Prostate Symptom Score (IPSS), bladder volume (V), urinary flow rate, ultrasound estimated postvoid residual urine volume (RV), serum PSA, testosterone and selenium levels, safety clinical biochemistry, hematology and oxidative stress parameters at baseline and on day 180. The results showed statistically significant differences ($p < 0.05$) between treatment and control groups for the following parameters: IPSS score, urodynamic parameters: maximal rate of urine flow (Q_{max}), average flow (Q_{ave}), V and RV, total PSA value and serum selenium levels. There was a significant reduction in PSA in the selenium–silymarin group but no effect on blood testosterone level. Overall the treatment was well-tolerated with no adverse effects.

Introduction

Prostate health is increasingly important in older men. Two of the most common prostate conditions affecting men older than 40 years are benign prostatic hyperplasia (BPH) and chronic prostatitis (Wang et al., 2012). They are associated with bothersome lower urinary tract symptoms (LUTS) and can lead to a number of medical complications such as untreated acute urinary retention, gross hematuria, repeated urinary tract infections, obstructive uropathy and cystolithiasis. Conventional treatments are α-andrenergic receptor blockers, 5-α-reductase inhibitors or antibiotics (Oesterling, 1995). Recent years however have seen increasing interest in natural therapies which support prostate health and show prophylactic effects on LUTS. Protective effects are generally confirmed in clinical trials for the micronutrients selenium, vitamins D and E, curcumin, resveratrol, lycopene, omega-3 polyunsaturated fatty acids (omega-3 PUFA), and phytoestrogens (genistein and daidzein). In dietary supplements, containing powdered whole plant/plant extract or seed oil, the prominent active components are from green tea (*Camellia sinesis*), saw palmetto berries (*Serenoa repens*), pumpkin seeds (*Cucurbita pepo*), flax seeds (*Linum usitatissimum*), roots of stinging nettle (*Urtica dioica*) and silymarin (*Silybum marianum*) (Demark-Wahnefried, 2008; Ma and Chapman, 2009; Syed et al., 2007). The latter is often used as a supplement by prostate cancer patients (Kren and Walterova, 2005; Vidlar et al., 2010). Silibinin, the major flavonolignan of silymarin, has demonstrated interesting preventive and anticancer properties in prostate cancer animal models (Klempner and Bubley, 2012). Recently two studies were published on the influence of selenium or omega-3 PUFA on PSA in healthy men. Zhang et al. (2011) reported that a 3-month supplementation with 200 μg selenium (in the form of glycinate) per day increased plasma and erythrocyte glutathione peroxidase (GPX) and lowered serum PSA. Twelve weeks daily consumption of omega-3 PUFA (1.12 g of eicosapentaenoic and 0.72 g docosahexaenoic acids) or coenzyme Q_{10} (100 mg) significantly reduced serum PSA level in healthy men with a PSA ≤ 2.5 ng/ml (Safarinejad et al. 2012).

The randomized, double-blind pilot trial reported here was based on the hypothesis that a 6-month daily supplementation with a selenium and silymarin combination will reduce (i) voiding symptoms, (ii) improve urodynamic parameters and (iii) lower

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values for serum PSA more than the components singly. The daily dose of selenium–yeast (240 μg) and silymarin (570 mg) was used based on Vidlar et al. (2010), the selenium dose was based on serum levels of selenium according to the U-shaped dose response curve (Dennert et al., 2011).

Materials and methods

Selenium–silymarin mix and placebo

The selenium–silymarin mix (Se–SM) and placebo tablets were supplied by FAVEA (Kopřivnice, Czech Republic). The Se–SM tablets contained a combination of 80 μg selenium as L-selenomethionine in inactivated whole cell yeast (Lalmin® Se2000, Lallemand Human Nutrition A/S, Birkerød, Denmark) and 190 mg of silymarin (SM) of the following composition (%; w/w): taxifolin 4.13, silychristin 17.00, silydianin 7.70, silibinin A 23.66, silibinin B 29.01, isosilibinin A+B 11.38, and undefined polymeric components 7.11 (silymarin; lot 040105, Teva Pharmaceuticals Industry LTD, Opava, Czech Republic), microcrystalline cellulose (250 mg), isomalt (60 mg), and hydroxypropyl cellulose (10 mg). The placebo tablets consisted of microcrystalline cellulose (250 mg), isomalt (250 mg), and hydroxypropyl cellulose (10 mg). The verum and placebo tablets were coated with hypromellose. The appearance and organoleptic characteristics of verum and placebo tablets were identical. The tablets were provided in blister packs labeled Selenium–Silymarin.

Study volunteers and inclusion/exclusion criteria

Recruitment was carried out between November 2011 and February 2012 at the Department of Urology, University Hospital in Olomouc, Czech Republic. A total of 55 non-smoking and non-alcohol dependent men aged 45–70 years were invited to participate in the study. All subjects were relatively healthy but had LUTS and BPH. At the beginning of the study the serum PSA_{tot} level was 0.18–2.53 ng/ml. None of the volunteers had food allergies, chronic liver or kidney diseases, gastrointestinal or metabolic disorder or any other chronic health condition such as diabetes mellitus identified from the findings of the interview. They were instructed not to change diet or lifestyle during the study. Exclusion criteria included clinically and/or histopathologically proven prostate cancer, histological findings of acute or chronic non-bacterial prostatitis, pathological urinary sediment and positive bacterial cultures of urine. Exclusion criteria also included: consumption of food rich in soy isoflavonoids, dietary supplements of any kind, medication with possible effects on prostate health such as antibiotics, anti-inflammatory drugs, alpha-1-adrenoreceptor antagonist and 5-alpha-reductase inhibitors.

Study design

The study was conducted according to the guidelines laid down in the Declaration of Helsinki. All procedures involving human subjects were approved by the Ethics Committee of the University Hospital and the Faculty of Medicine and Dentistry, Palacký University in Olomouc, Czech Republic. The participants signed an informed consent and were aware of the study goals from the outset. They were assigned to placebo ($n = 29$, aged 55.0 ± 10.0 years) and Se–SM ($n = 26$, aged 55.0 ± 5.8 years) groups by the simple (unrestricted) randomization. In the Se–SM group, three tablets daily were taken at approximately equal intervals throughout the day for a 6-month period. The placebo group took placebo tablets (3 tablets/day) for the same duration.

Health investigation, participant compliance and withdrawals

During the health examination on the first day, after 3-months, and on the last day of the trial the following parameters were routinely assessed: (i) detailed medical history; (ii) assessment of all concurrent medical drugs and therapies; (iii) digital rectal examination; (iv) dietary habits; (v) filling of International Prostate Symptom Score (IPSS); (vi) urine analysis; (vii) uroflowmetry with postvoidal residual urine (RV); (viii) kidney and bladder ultrasound; and (ix) a blood laboratory analysis. All blister packs were collected at the second visit and at the end of trial to check patient compliance. All subjects completed the 6 month period.

Assessment of LUTS

The volunteers completed the IPSS questionnaire. In addition to the total IPSS score, each of the seven components of the questionnaire (feeling of incomplete emptying, frequency, intermittency, urgency, weak stream, hesitancy, and nocturia) and quality of life (QoL) were used. Uroflowmetry data: maximal urinary flow rate (Q_{max}), average urinary flow rate (Q_{ave}) and bladder volume (V) were measured using FlowMic (Medkonsult, Czech Republic). RV was assessed using a BK Medical Viking 2400 with abdominal probe 3.5–5 MHz. RV was calculated using the formula for a prolate ellipsoid (width × length × height × 0.523).

Clinical biochemistry and hematology

Basic biochemical and hematological parameters were determined in all samples immediately after sampling: sodium, potassium, chloride, total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols (TAG), apoA1, apoB, C-reactive protein (CRP), lactate dehydrogenase (LD), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GMT), alkaline phosphatase (ALP), urea, creatinine, bilirubin, and testosterone (TST) using a HITACHI Modular Evo P analyzer (Hitachi, Japan). PSA in serum was determined using an Architect type LEIA analyzer (Abbott Laboratories, Abbott Park, IL, USA). Selected parameters for evaluation of oxidative stress were determined as total antioxidant capacity (TAC) and total SH groups in plasma (T-SH), lipid peroxidation products such as malondialdehyde in plasma (PMDA) and erythrocytes (MDA), advanced oxidation protein products (AOPP) in plasma; glutathione (GSH); glutathione peroxidase (GPX); catalase (CAT); glutathione reductase (GSR); glutathione transferase (GST); superoxide dismutase (SOD) in erythrocytes as described by Vidlar et al. (2010). Selenium in plasma was determined by atomic absorption spectrometry using the AA6300 instrument (Shimadzu, Japan). Hemoglobin (Hb), hematocrit (Htc), erythrocytes (RBC), thrombocytes (PLT) and leukocytes (WBC) were measured in Na_2EDTA blood.

Urinanalysis

Urine samples were collected from a midstream clean catch and analyzed using the IQ200 Automated Urinanalysis System (IRIS International, Inc., USA).

Statistical methods

Nonparametric Wilcoxon two-sided tests (paired and unpaired) were used to determine the statistical significance between parameter values on day 0 and after 6 months and between the placebo and Se–SM groups. The level of significance was set at 5%. Values