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SHORT-TERM EFFECTS OF A DIETARY SUPPLEMENT ON LOWER URINARY TRACT SYMPTOMS

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Benign prostatic hyperplasia (BPH) is one of the most common conditions affecting men over 40 years of age, typically manifesting itself with lower urinary tract symptoms (LUTS). Recently, research interest has focused in discovering a viable nutraceutical alternative to the drugs that are currently the first line of treatment for BPH. The aim of this study was to investigate the efficacy and safety of a dietary supplement containing curcumin, beta-sitosterol and oligomeric proanthocyanidins in a group of BPH/LUTS patients. One-hundred men with LUTS caused by BPH were enrolled in this study and agreed to take one tablet a day of the test dietary supplement for three months. Several parameters, such as International Prostate Symptom Score (IPSS), degree of urinary obstruction and average urinary flow were evaluated at different time points. Significant improvement in LUTS was seen after one month of treatment and a significant decrease in mean IPSS index was evident after three months of treatment. Moreover, a comparison of the mean urinary flow and of the number of subjects with bladder obstruction at three months versus one month of treatment shows a significant improvement. The study results suggest that the dietary supplement is effective for almost all the symptoms investigated, including the reduction of IPSS score and the increase of urinary flow. Moreover, the dietary supplement proved to be safe and well tolerated by the great majority of the enrolled subjects.

To the Editor,

Benign prostatic hyperplasia (BPH) is a disorder that affects 15% to 60% of men above 40 years of age (1), characterized by enlargement of the prostate and a decreased maximum urinary flow rate (Q_{max}), and clearly related to lower urinary tract symptoms (LUTS) (2). LUTS are a variety of symptoms that can be obstructive (e.g., hesitancy, poor and/or intermittent stream, straining, prolonged micturition), irritating (e.g., frequent urination, urgency, urge incontinence, nocturia), and/or related to post-micturition (e.g., feeling of incomplete emptying and post-micturition dribble). The main risk factors for BPH are age, genetic factors, high levels of dihydrotestosterone (DHT), lifestyle and inflammatory events (3). Currently, the approach used to limit LUTS is mainly symptomatic, and consists of treatment with α-adrenergic receptor blockers or 5-α reductase inhibitors (4). These drugs can cause several side effects, such as impotence, libido reduction, ejaculation disorders and gynecomastia. Since BPH is a chronic disease requiring long-term treatment, alternatives are much needed. Curcumin, an active compound contained in turmeric, is a good candidate, orally bioavailable and highly safe in humans. Its natural chemical components can block

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the inflammation processes acting on tumor necrosis factor-alpha (TNF-α) (5): β-sitosterols act as a well-tolerated 5-α reductase inhibitor (6) and Oligomeric proanthocyanidins (OPC) are oligomeric flavonoids with powerful antioxidant properties, especially useful in improving erectile and sexual performance dysfunctions (7, 8). These natural substances can slow down the hypertrophic process, hence reducing the associated LUTS without significant side effects. The aim of this study was to investigate the efficacy and the safety of a dietary supplement composed by curcumin, β-sitosterols and OPC in BPH/LUTS subjects.

MATERIALS AND METHODS

Study design

An observational, prospective, multicenter study was conducted in accordance with the Harmonized Tripartite Guidelines for Good Clinical Practice (ICH-GCP) and the set of ethical principles laid down in the Declaration of Helsinki. Study subjects were enrolled in three different Italian Clinical Centers, after signing and endorsing the informed consent form for the study participation.

All subjects underwent clinical and instrumental assessments as per standard clinical practice, such as an urological visit with digital rectal examination (DRE), ultrasound of the urinary tract with post-voiding residual (PVR), total PSA and PSA ratio evaluation, LUTS evaluations, in addition to filling in the International Prostate Symptom Score (IPSS) questionnaire. The presence of the following LUTS was assessed: difficulty in micturition, poor and/or intermittent stream, straining, frequent urination, urgency, urge incontinence, nocturia, feeling of incomplete emptying and post-micturition dribble. The IPSS questionnaire asks seven questions concerning urinary symptoms, each answer with a 0-5 score, resulting in a total score ranging from 0 (asymptomatic) to 35 (severe symptoms) (9). Based on their IPSS index, study subjects were classified into three groups according to their symptom severity: mild (IPSS 0-7 points), moderate (8-20 points), and severe (20-35 points); the effect of the test food supplement was then evaluated on each of those symptom severity groups.

After enrollment, all subjects were instructed to take one tablet of the study product daily, for 3 months.

The primary objectives of this study were the efficacy and the safety of a new dietary supplement in patients with BPH. The primary outcomes were the improvement of both the IPSS questionnaire score and the urinary flow rate. Secondary outcomes were the improvement of the above-mentioned symptoms (i.e., their presence/absence in the following visits) and the evaluation of efficacy and tolerability of the product.

In this observational study only within-subjects comparisons were planned, and a sample size of one hundred patients was considered large enough to obtain reliable information on the effect of the study product on LUTS.

Inclusion and exclusion criteria

The eligible population were men aged between 45 and 85 years, with clinical diagnosis of BPH related LUTS. An essential selection criterion was that subjects were included in the study at the first observation of disease, as such, they were drug-naïve for LUTS.

Patients with BPH complications (e.g., bladder calculus, bladder diverticulitis disease, prostatitis, bladder neck obstruction, PVR higher than 80 cc) were excluded from the study.

Study and treatment

One hundred men, aged 59±9 years, diagnosed for the first time with LUTS due to BPH, were enrolled in three Italian Clinical Centers in an outpatient setting. Study subjects were observed for three months, during which they were taking one tablet a day of a dietary supplement called LENITUS (formulated by UROBASP® technology to make the active ingredients bioavailable). Each tablet was composed of 135 mg of pine bark (*Pinus ssp.*), with a minimal beta-sitosterol content of 94.5 mg, 105 mg of turmeric, with a curcuminoid content of 99.75 mg and 21 mg of pine bark (*Pinus massoniana*), with an oligomeric proantocianidine content of 19.95 mg.

During the study each subject attended three clinical visits. During the first visit, the patients' baseline conditions were assessed as per standard clinical practice. Moreover, the IPSS questionnaire was administered and the study treatment was dispensed to the patients.

The second visit was performed after 30 days of treatment, to evaluate the efficacy and safety of the dietary supplement: the presence of the symptoms was

reassessed and, in case of need, the Investigators could decide to prescribe an alpha-lytic drug in addition to the study product.

The final visit was performed at the end of the treatment period to evaluate the product tolerance and effectiveness, by newly administering the IPSS questionnaire to the patients, measuring the urinary flow and assessing the presence of LUTS. These symptoms can be grouped into three types: obstructive (hesitancy, poor and/or intermittent stream, straining, prolonged micturition, feeling of incomplete bladder emptying), irritating (frequent urination urgency, urge incontinence, and nocturia) and post-micturition (feeling of incomplete emptying and post-micturition dribble).

Table I. *Improvement of main symptoms between Visit 1 (V1) and Visit 2 (V2).*

Symptom	V1			V2			Improved /worsened	p-value[a]
	Occurence	No.	%	Occurence	No.	%		
Frequent urination	N	25	25.00	N	32	32.99	9 / 1	**0.0114**
	Y	75	75.00	Y	65	67.01		
Nocturia	N	41	41.00	N	50	51.02	10/ 0	**0.0016**
	Y	59	59.00	Y	48	48.98		
Urgency	N	39	39.00	N	52	53.06	15 / 1	**0.0005**
	Y	61	61.00	Y	46	46.94		
Urge incontinence	N	96	96.00	N	85	92.39	0 / 3	0.0833
	Y	4	4.00	Y	7	7.61		
Hesitancy	N	48	48.00	N	57	58.76	13 / 1	**0.0013**
	Y	52	52.00	Y	40	41.24		
Dysuria	N	41	41.00	N	51	53.68	12 / 0	**0.0005**
	Y	59	59.00	Y	44	46.32		
Poor and/or intermittent stream	N	24	24.00	N	34	34.69	11 / 0	**0.0009**
	Y	76	76.00	Y	64	65.31		
Feeling of incomplete bladder emptying	N	47	47.47	N	60	64.52	16/ 1	**0.0003**
	Y	52	52.53	Y	33	35.48		
Post-micturition dribble	N	36	36.00	N	44	46.32	10 / 1	**0.0067**
	Y	64	64.00	Y	51	53.68		

[a] *McNemar's test. Bolded values are statistically significant at p<0.05.*

Table II. *Improvement of urinary flow and obstruction between Visit 2 (V2) and Visit 3 (V3).*

Urinary obstruction[a]	V2		V3		Improved/worsened	
	No.	%	No.	%		p-value[b]
Obstructed	7	7.22	4	4.49	*24 / 1*	**<0.0001**
Borderline	62	63.92	42	47.19		
Not obstructed	28	28.87	43	48.31		

[a] *Obstructed: "maximum urinary flow rate < 10 ml/sec."*
Borderline: "maximum urinary flow rate between 10 and 15 ml/sec."
Not obstructed: "maximum urinary flow rate > 15 ml/sec."
[b] *Bowker's test of symmetry. Bolded values are statistically significant at p<0.05.*

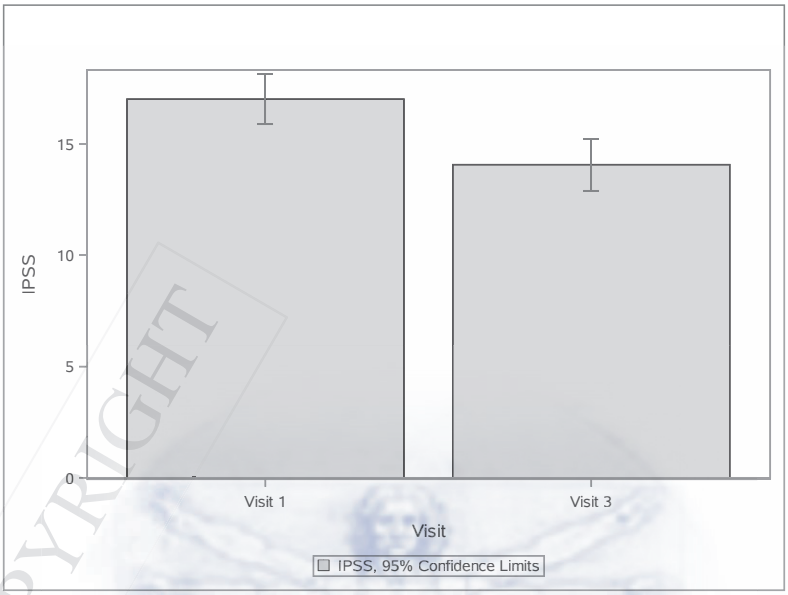

Fig. 1. *International Prostate Symptom Score (IPSS) values at Visit 1 and Visit 3.*

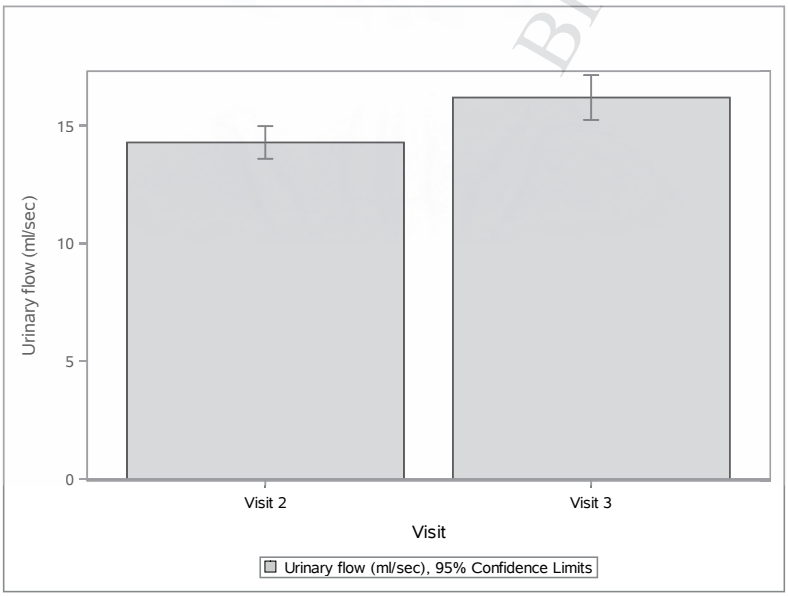

Fig. 2. *Urinary flow at Visit 2 and Visit 3.*

During the treatment period, the side effects were recorded to evaluate the safety of the study product.

Statistical analysis

Mean and standard deviations were calculated for continuous variables, and frequencies and percentages for discrete variables. Changes in continuous variables between visits were assessed using paired *t*-test. Changes in dichotomous variables between visits (2X2 tables) was assessed using McNemar's test. For square tables that have more than two response categories (levels, example 3X3), Bowker's test of symmetry was used. Statistical tests were considered statistically significant when p was lower that 0.05 ($p < 0.05$). Exact p-values are reported.

RESULTS

In this study, 100 men took one tablet a day of the test dietary supplement. Eight patients discontinued the study product before the study end: four subjects withdrew due to the adverse event reported below and four for personal reasons.

The following baseline features were evaluated in the study population: familiarity for prostate cancer (PCa) (30.61% had positive familiarity) and BPH (45.36% had positive familiarity); erectile dysfunction (55% was positive); premature ejaculation (11% was positive) and decreased libido (44% positive).

Several LUTS were evaluated and compared between Visit 1 (V1) and Visit 2 (V2). Significant improvement was observed in most of the symptoms investigated. For instance, frequent urination was present in 75% of the patients at V1 and in 67% of the patients at V2: in detail, 9 patients improved (i.e. frequent urination disappeared) while 1 patient worsened (i.e. previously absent frequent urination appeared during the study). Significant improvement was observed also for nocturia, urgency, hesitancy, dysuria, poor and/or intermittent stream, feeling of incomplete bladder emptying, and post-micturition dribble. Each of these symptoms disappeared in ten to sixteen patients. Urgency, hesitancy, feeling of incomplete bladder emptying, and post-micturition dribble appeared at V2 in one patient for each symptom, when they were not present at baseline, while urge incontinence appeared in three patients, who did not report it at baseline (Table I).

Mean IPSS decreased by 3.20 points between V1 and Visit 3 (V3) (from 17.02±5.72 to 14.07±5.70) and the difference was statistically significant ($p<0.0001$) (Fig. 1). Analyzing the improvement for each IPSS severity group separately, IPSS decreased by 0.8 points (from 6.29±0.49 to 5.40±1.82, not statistically significant), by 3.23 points (from 14.28±3.81 to 11.15±4.44, $p<0.0001$) and by 3.46 points (from 21.95±2.66 to 18.56±3.43, $p<0.0001$) in the mild, moderate and severe category, respectively.

Mean urinary flow increased by 2.06 ml/sec between V2 and V3 (from 14.28±3.41 to 16.18±4.49 ml/sec) and the increase was statistically significant ($p<0.0001$) (Fig. 2). Looking at each IPSS severity group, mean urinary flow increased by 1.83 ml/sec (from 18.23±2.13 to 19.90±5.10 ml/sec, not statistically significant), by 1.94 ml/sec (from 15.24±3.70 to 17.12±5.43 ml/sec, $p<0.0001$) and by 2.22 ml/sec (from 12.65±2.16 to 14.82±2.55 ml/sec, $p<0.0001$) in the mild, moderate and severe category, respectively. Even when categorizing the patients in obstructed, borderline and not obstructed, the improvement was statistically significant: 24 patients improved their urinary flow and only one worsened (Table II). In particular, obstruction was present in 7 patients at V2 and in 4 patients at V3. Borderline was present in 62 patients at V2 and in 42 patients at V3. 28 patients were not obstructed at V2 and 43 at the end of the treatment.

Subjective evaluation of the efficacy of the food supplement showed an increase in the confidence in the product between V2 and V3, with 45% of the subjects considering the study product effective or very effective.

Looking at the safety of the product, its tolerability was positively judged by the majority of the patients: only three patients did not tolerate well the product, while for the others the tolerability evaluated at V3 was at least good (excellent for 65% of the patients).

During the study, only eight subjects out of 100 experienced an adverse event: decreased libido (3), diarrhea/dysentery (2), gastrointestinal disturbances (2) and urticaria (1). Four events were considered as related to the study treatment: urticaria, two

events of decreased libido and one event of diarrhea/dysentery. The four subjects experiencing these events withdrew from the study. The relationship with the study product of the other events was considered unlikely.

Twenty-eight patients (28%) used 5-alpha reductase inhibitors after V2, as the improvement of the symptoms was judged by the Investigator not satisfactory.

DISCUSSION

In this observational, prospective, multicenter study, the administration of a dietary supplement containing curcumin, β-sitosterols and OPCs led to a decrease of mean IPSS and an increase of urinary flow in BPH/LUTS patients. In addition, almost all LUTS improved and only eight subjects reported an adverse event. Curcumin is known to have mainly anti-inflammatory and antioxidant properties (10). β-sitosterols act as 5-α reductase inhibitors, resulting in a decrease of circulating DHT, the increase of which is associated with BPH. According to the literature, β-sitosterols play a role in counteracting the hyperplasia of prostate cells (11) and improve urinary symptoms and urinary flow (12). The intake of OPCs can lead to an improvement of erectile dysfunction and sexual performance (7, 8). Thanks to the effects of the dietary supplement administered, BPH/LUTS patients enrolled in this study have experienced several improvements. First, the Q_{max} increased between one and three months of treatment. Several LUTS improved after only one month of treatment. In addition, the limited use of 5-alpha reductase inhibitors (28%) can be considered a proof of the efficacy of this dietary supplement. The urinary symptoms were evaluated also through IPSS, resulting in improvement after three months of intake of the dietary supplement. Overall, the clinical pattern of the patients enrolled in this study improved considerably, showing that curcumin, β-sitosterols and OPC are good candidates for BPH/LUTS treatment. The study had a number of limitations that could have led to uncontrolled bias: the small population, the lack of a control group and the concomitant use of alpha-lythic drugs. Despite these limitations, the study product had a positive effect on all the symptoms investigated, reduced the IPSS score and increased the urinary flow, and it was considered efficient and tolerable by both patients and investigators.

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