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Note

Beneficial Effect of Honeybee-collected Pollen Lump Extract on Benign Prostatic Hyperplasia (BPH) — A Double-blind, Placebo-controlled Clinical Trial —

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A double-blind, placebo-controlled clinical trial was performed to investigate the efficacy and safety of 12-week intake of honeybee-collected pollen lump extract (HPLE)-supplemented food in 47 patients with benign prostatic hyperplasia (BPH). The participants were randomly assigned to 3 study food trial groups: a placebo group (0 mg HPLE per day); a lower-dose group (160 mg HPLE per day); and a high-dose group (320 mg HPLE per day) (Groups P, L, and H, respectively). Outcome measures were the change during the 12-week intervention period in subjective symptom scores and 2 urodynamic parameters, maximum flow rate (Q_{max}) and residual urine volume. Q_{max} values were significantly increased in Group H ($P<0.05$) but not in Groups L or P. While residual urine volume was significantly increased in Groups L and P ($P<0.05$ each), the level in Group H decreased, although the difference between Groups H and P did not reach statistical significance ($P=0.052$). No HPLE-related health hazards or laboratory abnormalities of clinical significance were encountered.

Keywords: honeybee-collected pollen lump extract (HPLE), benign prostatic hyperplasia (BPH), lower urinary tract symptoms, efficacy, safety

Introduction

Benign prostatic hypertrophy (BPH) is a non-malignant enlargement of the prostate due to excessive cellular growth of both the glandular and the stromal elements of the gland. The morbidity associated with urination-related symptoms and referred to as symptomatic BPH is one of the most common medical conditions in aging adult men of all nations in the world. In Japan, the incidence of symptomatic BPH has increased rapidly in recent years; the number of patients with symptomatic BPH who visited medical institutions increased from 200,000 in 1987 to more than 500,000 in 1996 (Terai *et al.*, 2000). Since several urination-related symptoms, particularly obstructive symptoms (weak stream, hesitancy, intermittency, and incomplete emptying) and irritative symptoms (urgency, frequency, and nocturia) lower the quality of life (QOL) of such patients, they should receive treatment to relieve these bothersome lower urinary tract symptoms.

Currently, major treatment options for symptomatic BPH include lifestyle modification and minimally invasive or surgical treatment, as well as pharmaceutical therapy with 5α-reductase–inhibiting drugs and α-adrenergic antagonist drugs. Besides these modern drugs, several plant and pollen extracts have also been used as registered medicines or dietary supplements for the treatment of mild or moderate BPH-related symptoms, mainly because most phytotherapeutic agents are inexpensive and have virtually no untoward side effects (Hald, 1994; Marwick, 1995; Lowe and Ku, 1996; McDonald *et al.*, 1999).

Honeybees have the habit of making a lump of pollen that they have collected from flowers, to use as the feed for their larvae and as the material for producing royal jelly. Recently, such honeybee-collected pollen lumps have attracted interest as a functional food with health benefits. The existing

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reports dealing with the medical usefulness of cernitin pollen extract for the symptomatic relief of BPH suggested the possibility that honeybee-collected pollen lump extract (HPLE) may also have a similar beneficial efficacy. The present study was carried out to evaluate the effectiveness and safety of HPLE-supplemented food in Japanese patients with outflow obstruction symptoms due to BPH.

Patients and Methods

HPLE Honeybee-collected pollen lumps, mainly composed of *Citrus* pollen, were extracted with 95% ethyl alcohol. The solvent was removed under vacuum and the resulting precipitate was collected by filtration and dried in vacuum tray driers. The obtained materials were referred to as HPLE and used for preparing test foods for the present study.

Study food and placebo High-dose and lower-dose study foods were prepared as round tablets, 305 mg in weight and 9 mm in diameter, containing 32 and 16 mg per tablet of HPLE, respectively, along with crystalline cellulose and lubricant as vehicles. Placebo tablets consisted of crystalline cellulose and lubricant only.

Patients Forty-seven male patients aged 40 to 83 years with mild-to-moderate symptomatic BPH who visited the Jishyukai Ueda Kidney Clinic (Ueda, Japan) during the period between June 2005 and December 2005 were enrolled into this prospective, randomized, placebo-controlled study. Before enrollment, the study protocol approved by the Internal Review Board of the institution was explained to the patients and written informed consent was obtained. All potential candidates were evaluated by medical history and physical and laboratory examinations, including urinalysis, outflow obstruction symptoms, quality of life (QOL), peak urinary flow rate, and post-void residual urine volume. Patients with prostatic cancer, prostatitis, neurogenic bladder, bladder-neck sclerosis, urethral stricture, bladder stone, or primary urinary tract infection (other than infection secondary to BPH), and those who had undergone resection of the prostate were excluded from the study. Also patients with marked extra-prostate disorders, such as cardiovascular, renal, or hepatic insufficiency; orthostatic hypotension; or dementia; and those with pollen allergy were excluded.

Study design The study was designed as a double-blind, placebo-controlled trial. Forty-seven patients were randomized to receive high-dose study food (10 high-dose HPLE tablets a day, 320 mg HPLE/day) (n=15), lower-dose study food (10 lower-dose HPLE tablets a day; 160 mg HPLE/day) (n=17) or placebo (n=15), once to 3 times daily after meals over a 12-week period. The 3 trial groups were designated high-dose group (Group H), lower-dose group (Group L), and placebo group (Group P), respectively.

Subjective assessment was made using the International Prostate Symptom Score (IPSS) system, in which the severity of 7 major BPH symptoms, *viz*., incomplete emptying, daytime frequency, intermittency, urgency, hesitancy, dysuria, and nocturia, were rated, with a score of 0–5 for each of these symptoms (0 being an absence of symptoms and 5 being the most severe). Objective assessment was based on the peak uroflow rate (Q_{max}) determined by uroflowmetry and the residual urine volume as measured by abdominal ultrasound imaging. In addition, for safety evaluation, physical and laboratory examinations were performed regarding vital signs/physical parameters (systolic and diastolic blood pressures, pulse rate, and body weight), blood counts (white blood cells, red blood cells, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and blood platelet count), blood chemistry profile (total protein, albumin, albumin/globulin ratio, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine kinase, gamma-glutamyl transpeptidase, blood urea nitrogen, creatinine, uric acid, Na, K, Cl, Ca, P, total cholesterol, high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, total triglycerides, and blood sugar), and urinalysis (urinary protein, urinary glucose, urinary urobilinogen, urinary bilirubin, ketone bodies in urine, urinary occult blood, and urinary pH). All investigations and examinations were carried out before the start and at the end of the 12-week intervention period.

Statistical methods and analysis Statistical analysis was designed with consideration of the following: (i) homogeneity of demographic distribution including baseline symptomatic and urodynamic parameters; (ii) assessment of efficacy; and (iii) assessment of safety and tolerance. The unpaired *t* test was used to check the comparability of the baseline demographic characteristics of the 3 trial groups. The paired *t* test was used to assess changes in self-reported symptoms (IPSS), urodynamic parameters, and physical and laboratory parameters of the 3 trial groups. The x^2 test was used for comparison between each of the 2 study food groups (Group H and Group L) and the placebo group (Group P) with regard to symptomatic improvement rate. Analysis of variance by *t* test was used to compare the changes in urodynamic parameters for Group H and Group L with the values for Group P. All tests were performed using 5% as the level of significance. Numerical values are presented as the mean±S.E..

Results

Of the 47 patients entered into the study, 3 in Group L were excluded during the course of the study: one voluntarily

withdrew from the study, one was admitted to a hospital with an accidental bone fracture, and one had fever with perspiration and palpitations that was considered to be unrelated to the study food intake. The other 14 patients in Group L and all 15 patients each in Group H and Group P, 44 patients in total, were evaluated for efficacy and safety of the study food at the end of the 12-week intervention period. The rates of the study food (or placebo) intake in all 44 patients, estimated on the basis of their diaries, were in the range of 89.3 to 100%, and therefore no patient was excluded from the evaluation for reason of insufficient intake of the study food (or placebo). There was no significant difference in the baseline characteristics such as age, IPSS, QOL score, Q_{max}, and residual urine volume among the 3 trial groups.

IPSS values before and after the 12-week intervention were recorded for the 44 patients, comprising 15, 14, and 15 patients in Group P, Group L, and Group H, respectively. In all of the 3 trial groups IPSS decreased significantly during the intervention period: from 13.8 to 6.5 in Group P ($P<0.01$), from 12.6 to 8.2 in Group L ($P<0.05$), and from 11.1 to 8.1 in Group H ($P<0.05$). The severity of subjective symptoms improved in 13 of 15 patients (86.7%) in Group P, 10 of 14 patients (71.4%) in Group L, and 10 of 15 patients (66.7%) in Group H. There were no significant differences in response rate between Group L or Group H and Group P.

The results for Q_{max} and residual urine volume in the 3 trial groups before and after the 12-week intervention are shown in Table 1. In Group P and Group L, there was no significant change in Q_{max} (both groups showed a slight increase). In contrast, in Group H the Q_{max} values increased significantly from 8.7±1.0 to 13.3±1.4 mL per second ($P<0.05$).

Unexpectedly, residual urine volume significantly worsened in Group P and Group L (from 41.6±29.9 mL to 69.3±27.7 mL and from 10.6±4.1 mL to 13.4±5.2 mL, respectively) after the 12-week intervention period. In contrast, the value for Group H improved, though not to a significant extent, from 35.1±13.4 mL to 27.5±6.7 mL ($P>0.05$). Comparison of variance in residual urine volume for Group H (-7.6±14.4 mL) with the value for Group P (27.7±9.9 mL) showed that daily intake of the high-dose study food is likely to improve residual urine volume ($P=0.053$).

The safety and tolerability of the study food taken in the two different doses for 12 weeks were evaluated, in comparison with those of placebo, on the basis of frequency and severity of adverse events as well as physical and laboratory abnormalities. Six of 14 patients in Group L and 10 of 15 patients in Group H experienced 6 and 10 intervention-emergent adverse events, respectively. In Group L, transient diarrhea (or soft stool) and transient abdominal pain were experienced by 4 and 2 patients, respectively. In Group H, transient diarrhea/soft stool, transient abdominal pain, and allergic coryza were experienced by 8, 1, and 1 patients, respectively. All of these adverse events were mild in severity, and no patients discontinued the study as a result of an adverse event. Transiently-occurring diarrhea/soft stool and abdominal pain were considered by the investigators to be possibly related to the study food intake. In Group P, no patient experienced any adverse event. Significant mean changes during the interven-

Table 1. Urodynamic data obtained before and after the 12-week intervention in the 3 trial groups.

Parameter	Trial group	Values (mean±S.E.)		Change from baseline[1)]		
		Before intervention (baseline)	After intervention			
Q_{max} (mL/s)	Group P (n=15)	9.8±1.2	13.4±2.1	3.5±2.0	P=0.464	P=0.717
	Group L (n=14)	9.9±2.1	11.6±2.3	1.7±1.5		
	Group H (n=15)	8.7±1.0	13.3±1.4*	4.5±1.8		
Residual urine Volume (mL)	Group P (n=15)	41.6±29.9	69.3±27.7*	27.7±9.9	P=0.223	P=0.053
	Group L (n=14)	10.6±4.1	24.0±5.5*	13.4±5.2		
	Group H (n=15)	35.1±13.4	27.5±6.7	-7.6±14.4		

* $P<0.05$ against baseline (paired *t* test).

1) P-values calculated by unpaired *t* test.

tion period in values of some vital signs and/or laboratory tests were observed in the 3 trial groups (Table 2). However, all of them changed within the reference interval, and the changes were not clinically significant.

Discussion

Surgical resection or minimally invasive therapy represented by thermotherapy remains the most effective treatment of BPH but is associated with complications in both the short and longer terms, while symptomatic improvement and patient satisfaction after the surgical intervention appear to be lower in patients who have only mild-to-moderate symptoms than in those with severe symptoms or retention (Fowler *et al.*, 1988). Therefore, there is a place for therapeutic agents that are of proven benefit and free of untoward side effects for the treatment of mildly or moderately symptomatic BPH patients, or even more severely symptomatic BPH patients who are unfit for surgery.

Our current major concern is the development of a dietary supplement that is useful for relieving BPH-associated symptoms. In the course of searching for appropriate dietary supplements, we found HPLE to be a promising candidate. The present double-blind, placebo-controlled clinical trial was conducted to evaluate the therapeutic usefulness of HPLE based on the efficacy and safety for patients with mild-to-moderate BPH who are or are not under medical treatment.

The results of the study showed substantial subjective and objective improvement with a positive response in Group H. A concern about the result of this study was the occurrence of subjective improvement in the placebo group (Group P), possibly due to the so-called "placebo effect," which created difficulty in evaluating the symptom-relieving effectiveness of the study food. However, the beneficial effect of the study food was more clearly demonstrated in the two urodynamic parameters: in Group H Qmax was significantly ($P<0.05$) and residual urine volume likely ($P=0.053$) improved in Group H as compared with before intervention and Group P,

Table 2. Vital signs and laboratory tests with group mean values that showed statistically significant changes during the 12-week intervention period.

Vital signs/laboratory tests	Reference interval	Trial group[1)]	Values (mean±S.E.)	
			Before intervention (baseline)	After intervention
Pulse rate (beat/min)	---	Group H	66.9±1.8	71.5±1.7*
Body weight (kg)	---	Group H	61.29±1.81	62.31±1.86*
MCV (fL)	83 – 102	Group H	96.6±1.3	94.1±1.0*
Blood platelets ($10^4/\mu L$)	13.0 – 36.9	Group P	24.59±2.74	26.27±2.78*
Creatinine (mg/dL)	0.61 – 1.04	Group H	0.949±0.049	0.890±0.049*
Uric acid (mg/dL)	2.6 – 7.0	Group L	5.49±0.33	5.13±0.33*
Na (mEq/L)	134 – 147	Group H	143.8±0.5	141.7±0.5**
K (mEq/L)	3.6 – 5.0	Group L	4.02±0.17	4.44±0.17*
Ca (mEq/L)	8.2 – 10.4	Group P	9.11±0.06	9.32±0.09*
P (mg/dL)	2.5 – 4.6	Group H	6.61±0.68	3.71±0.37**
Total cholesterol (mg/dL)	150 – 220	Group H	189.8±7.2	202.1±8.1*
Total triglycerides (mg/dL)	35 – 149	Group P	191.0±29.6	140.1±20.5*

* $P<0.05$ and ** $P<0.01$ against baseline (paired *t* test).

1) Numbers of participants in each trial group were the same as those in Table 1.

respectively.

Although several gastrointestinal adverse events probably related to the study food, such as diarrhea/soft stool and abdominal pain, were reported by patients in both Groups L and H, all the events were mild, occurred only temporarily, and resolved without any medical treatment. Moreover, no laboratory abnormalities of clinical significance ware observed in either of the study food groups.

The present clinical study suggests the possibility that intake of a sufficient dose of HPLE could be effective in improving some BPH-associated symptoms, although the active component(s) and action mechanism(s) of HPLE remain to be determined. A population study performed in the United Kingdom demonstrated that the frequency of lower urinary tract symptoms was 8-31% among men in their fifth decade and up to 44% in the seventh decade (Bosch *et al.*, 1995). In the United States, the annual cost of caring for elderly patients with such symptoms has been estimated to exceed 4 billion US dollars per year (Korrt and Bootman, 1996). The advent of HPLE-containing food readily available as a non-prescription dietary supplement would be beneficial for the self-management of symptomatic BPH and have the potential to lower the expense of medical treatment of this clinical condition.

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