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Daidzein plus isolase associated with zinc improves clinical symptoms and quality of life in patients with LUTS due to benign prostatic hyperplasia: Results from a phase I-II study

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Summary *Objective: In the last years there is a growing interest in nutraceutical substances that seems able to improve clinical symptoms in patients with lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH). In this paper, we evaluated both efficacy and safety of a combination of daidzein with isolase and zinc in patients with LUTS due to BPH.*

Materials and methods: In a phase I-II study clinical trial we enrolled patients with clinical and instrumental diagnosis of LUTS associated to BPH that received a six-month treatment with a combination of daidzein with isolase and zinc (1 tablet/day). Clinical, laboratory and instrumental analyses were carried out at the time of admission (T0) and 6 months after the ending of the treatment (T1). The Italian version of International Prostatic Symptom Score (IPSS), International Index of Erectile Function (IIEF-5) and Quality of Well-Being (QoL) questionnaires were used. The development of adverse drug reactions (ADRs) and drug interactions (DDIs) were recorded using the Naranjo scale and drug interaction probability scale. Student's t test and Anova test were used for statistical analysis, and the threshold of statistical significance was set at $P < 0.05$.

*Results: We enrolled 71 patients, 62 (87.3%) completed the follow-up and we documented a significant differences between T0 and T1 in terms of IPSS [21.5 ± 1.2 vs 16.2 ± 1.5 ; (-4.8); $p < 0.001$], C_{max} [9.7 ± 3.7 vs 15.3 ± 2.5 ; (+5.6); $p < 0.001$] and QoL [0.56 ± 0.15 vs 0.84 ± 0.19 ; (+0.28); $p < 0.001$]. In contrast, no significant difference were recorded in terms of IIEF-5 [$p = 0.50$] and PSA [$p = 0.67$]. Finally, we did not record any significant ADRs or DDIs during the study. **Conclusions: In this study, we documented that a combination of daidzein with isolase and zinc, reduces the clinical symptoms of LUTS and improves the quality of life in patients with BPH, without the development of ADRs or DDIs.***

KEY WORDS: BPH; Zinc; LUTS; Equol; Isoflavones; Medical treatment.

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is one of the most common diseases affecting the elderly male and is the most common clinical condition among all urological outpatients (1). BPH is characterized by clinically rele-

vant lower urinary tract symptoms (LUTS) that can reduce the quality of life (QoL) leading to serious clinical manifestations, e.g. acute urinary retention, urinary incontinence, recurrent urinary tract infection, obstructive uropathy, up to surgery (2). To date, two main categories of drugs are prescribed to treat patients with symptomatic BPH: 1) α 1-adrenoreceptor antagonists that improve the dynamic component of urination (activation of bladder smooth muscles) and relieve the symptoms (3); 2) 5-ARIs that block the conversion of testosterone to dihydrotestosterone, and deprive the prostatic tissue of trophic androgenic influence (3). The guidelines for BPH/LUTS recommend a combination therapy with α -blockers and 5ARI in patients with moderate-to-severe LUTS and enlarged prostates (3). Unfortunately, these treatments may be related with the development of ADRs that can induce the discontinuation of the current therapy with an impaired of both clinical symptoms and quality of life (4). Even if the current therapeutic strategies for the management of patients affected by LUTS associated to BPH are able to both control the progression of the disease and relieve the symptoms, their use is related with the development of adverse drug reactions (ADRs) particularly on sexual function (5). In a recent meta-analysis Liu and co-workers, evaluating the effects of 5 α -Reductase inhibitors (5ARIs) on sexual function in men with BPH, documented that both dutasteride and finasteride compared with placebo were associated with the development of sexual dysfunction (6). The development of ADRs represents a common problem during drug administration and represents the most common cause of low adherence to the treatment (7). In the last years, there is a growing interest for nutraceutical agents in several clinical manifestations for several reasons, e.g. low side-effect and costs, high level of adherence and a low rate of efficacy of standard treatments with subsequent patient disappointment and drop-out (8-9). Several nutraceutical products for the management of BPH have been commercialised in Italy (10) and between these, a new nutraceutical is MIGAR[®] MG, an association between daidzein, isolase and zinc. The effects of each component have been well-reported in literature.

Daidzein is a soy isoflavone, after oral intake it crosses the enterocytes, is reduced to S-(-)equol through the intermediate dihydrodaidzein, and then is converted by deoxygenation to yield the bioactive S-(-)equol by intestinal bacteria (11). Several bacteria are able to perform this reaction and one of these, *Lactococcus garvieae*, was found in some Italian cheeses and has been used to produce the first natural S-(-) equol-containing nutraceutical (12). The bioactivation of daidzein to S-(-)equol is related to gender, race and age and requires: specific equol-producing bacteria and an optimum intraluminal conditions in terms of redox potential for the above described reactions (13). Therefore, the aim of this study is to evaluate the efficacy and safety of MIGAR® MG Retard in patients affected by LUTS related to BPH.

METHODS

Study design

We performed a non-sponsored phase I-II study in a single urological institution between January to June 2016. The study was conducted according in line with *Good Clinical Practice guidelines* and with the ethical principles of the *Declaration of Helsinki*. Before the beginning of the study, all participants signed the written informed consent. No placebo run-in period was performed.

Experimental protocol

Patients with clinical and instrumental diagnosis of moderate-severe LUTS related to BPH were recruited. We considered patients with moderate-severe LUTS and with an *International Prostatic Symptom Score* (IPSS) score > 8. At the time of admission (T0), the patients underwent self-administered baseline questionnaire [IPSS, *International Index of Erectile Function* (IIEF-5) and *Quality of Well-Being* (QoL)], urological examination with history interview, prostate ultrasound and uroflowmetry (C_{max}) with evaluation of post-voided residual volume (PVR), in accordance with the procedure described in EAU guidelines (3). All patients who met the inclusion criteria were enrolled and received 1 tablet/day of a combination of daidzein with isolase and zinc (MIGAR® MG Retard). The follow-up was performed 6 months after the end of therapy (T1) when patients underwent IPSS, IIEF-5/QoL questionnaires and urological examination with laboratory and instrumental examinations.

Inclusion and exclusion criteria

Patients male who were > 45 years, sexually active, with a maximal urinary flow rate (C_{max}) < 15 mL/s and with a post-residual voided volume < 100 cc, with IPSS = 8 or greater, with Prostate Specific Antigen (PSA) < 4 ng/ml (or higher in presence of negative prostate biopsy) and IIEF-5 score > 21 were enclosed in this study. On the other hand, patients with diabetes, liver, and/or renal failure, cancer, prostatitis, active urinary tract infection, chronic retention or polycystic kidney disease were excluded from the study. Moreover, we also excluded patients with urethral stenosis or anatomical abnormality interfering with the evaluation of voiding function. Patients with a history of transurethral resections of the prostate, laser therapy, or thermo therapy

or with allergy to one or more compounds of MIGAR® MG Retard were also excluded. Finally, were also excluded from the study the patients that received a treatment for LUTS/BPH in the last 6 months.

Questionnaires and urological examinations

The validated Italian versions of the IPSS (14), IIEF-5 (15) and QoL (16) were self-administered to each patient at the arrival to the urological institution. The QoL scale was selected because it has been successfully applied to acute illnesses, whereas other quality of life scales, including the Short Form-36 (SF-36) Health Survey, are more suitable in chronic cases (17). Higher scores on the QoL scale reflect a higher quality of life (16). The IIEF-5 questionnaire was used for exclude all patients with concomitant erectile dysfunction and for evaluating the impact of treatment on sexual function at the end of the follow-up therapy.

Composition and characterization of the extracts used MIGAR® MG Retard

Each tablet contains *Daidzein* 20 mg, *Genistein* 20 mg, *Isolase*® 40 mg, *Zinc* 10 mg.

Instrumental, laboratory and urological evaluation

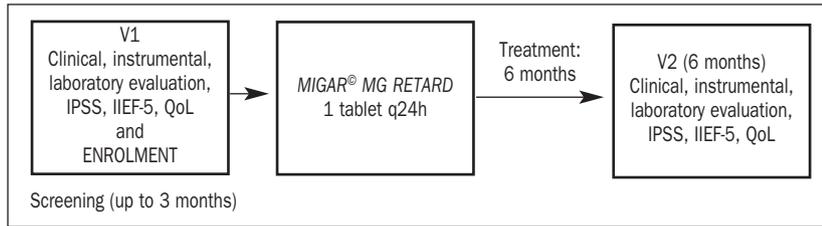
At the time of the enrolment (T0) and during the follow-up (T1), all patients underwent urological examinations with the prostate volume ultrasound evaluation. Ultrasound prostate evaluation was performed during the urological examination with a trans-abdominal approach. The trans-abdominal scan was performed with the patient's supine after applying ultrasonic gel to the suprapubic regions (3). Moreover, an uroflowmetry (C_{max}) with ultrasound evaluation of post-voided residual volume was performed by using *URODYN® 1000 System* (Medtronic Functional Diagnostics A/S.) (3). All patients were asked to do the PSA dosage. In order to exclude urinary tract infection, both leukocyte esterase and nitrite levels were measured in urine samples through dipstick assay (*Bayer Multistix Pro Reagent Strips*) (3).

Main outcome measure

The main outcome measure was the improvement of quality of life at the end of the whole study period, in terms of changes in IPSS, IPSS-QOL, C_{max} , PVR, and QoL from baseline to the evaluation point, that is, 6 months. As secondary endpoints we considered a change between T0 and T1 in the following parameters: PSA values, prostate volume, progression of disease, and surgical treatment. Clinical failure was defined as the persistence of symptoms after the treatment or the suspension of therapy for significant reported ADRs, in particular on sexual function (3). Finally, from the beginning of the study (T0) and up to its ending (T1), the development of ADRs or of drug-drug interactions (DDIs) were recorded in agreement with our previous paper (18) using the Naranjo scale and the Drug Interaction Probability Scale, in agreement with the common terminology criteria for adverse events (CTCAE) guidelines (19). Safety assessments included treatment-emergent adverse events (TEAEs) and serious AEs (SAEs). The study design is reported in Figure 1.

Figure 1.

The figure shows the study schedule. IPSS: International Prostatic Symptom Score; IIEF-5*: International Index of Erectile Function; QoL: Quality of Well-Being. V1: visit 1, at the enrolment; V2: visit 2 at the second follow-up (6 months).



Efficacy outcome

The efficacy outcome was identified as a statistically significant difference between clinical data recorded at the time of admission (T0) and those recorded at the end of the study (T1).

Drug adherence

At the end of the study, the adherence to the treatment was calculated using a formula based on the number of tablets consigned at the time of admission and on the number of tablets returned unused at the end of the study.

Statistical analysis

The required sample size for the present study was calculated under the following conditions: Difference between T0 and T1, 4 ± 1 score points in the IPSS score; α error level, 0.05 two-sided; statistical power, 80%; and

anticipated effect size, Cohen’s d = 0.5. The calculation yielded 45 individuals. At baseline, the independent sample 2-tailed t-test was used to compare variables. For categorical parameters, chi-square test was applied. Changes from baseline to end of therapy were analyzed using ranked one-way analysis of variance (ANOVA) with a term for treatment group. All data are expressed as mean ± standard deviation. The threshold of statistical significance was set at p < 0.05. All reported p-values are two-sided. All statistical analyses were performed by using SPSS 21.0 (IBM Corporation, Armonk, NY, USA), while G*Power (Institut für Experimentelle Psychologie, Heinrich Heine Universität, Dusseldorf, Germany) was used for power calculation.

RESULTS

During the study period, 71 patients were enrolled. Nine patients (12.7%) were lost during the follow-up and excluded from the analysis, while 62 patients (87.3%) completed the study (mean age 65.4 ± 5.6 years).

Baseline characteristics

History, clinical, laboratory, instrumental and questionnaires data at the time of admission are reported in Table 1.

Follow-up examination

At T1 we recorded a significant difference in terms of IPSS in all patients [21.5 ± 1.2 vs 16.2 ± 1.5; (-4.8); p < 0.001], and C_{max} [9.7 ± 3.7 vs 15.3 ± 2.5; (+5.6); p < 0.001], post-voiding residual volume [85 ± 20.6 vs 50 ± 18.5; (-35); p < 0.001], QoL [0.56 ± 0.15 vs 0.84 ± 0.19; (+0.28); p < 0.001]. We did not record any in terms of PSA evaluation [2.47 ± 5.6 vs 2.09 ± 4.3; p = 0.67], prostate volume [41.5 ± 5.8 vs 42.1 ± 7.5 p = 0.61] and IIEF-5 [22.1 ± 1.8 vs 22.3 ± 1.5 p = 0.50] between T0 and T1 (Table 2).

Table 1. Clinical, instrumental and laboratory patient’s data at the enrolment time.

Patients (n°)	62
Age (mean ± SD#)	65.4 ± 5.6
Marital status	
Married	56 (90.3)
Unmarried	6 (9.7)
Educational qualification	
Primary school	31 (50)
High school	20 (32.2)
University	11 (17.8)
Sexually active (past month)	62 (100)
Symptoms Score at baseline (mean ± SD#)	
IPSS†	21.5 ± 1.2
IIEF-5*	22.1 ± 1.8
QoL‡	0.56 ± 0.15
Charlson Comorbidity Index	
0-1	62 (100)
≥ 2	-
Laboratory	
Serum totale PSA (ng/ml)	2.47 ± 5.6
Serum creatinine (ng/ml)	1.0 ± 0.6
Urine dipstick	
negative	62 (100)
positive	-
Ultrasound and uroflowmetry data	
Prostate volume (ml)	41.5 ± 5.8
Post-voiding residual volume (ml)	85 ± 20.6
Maximal urinary flow rate (ml/sec)	9.7 ± 3.7

The table shows all anamnestic, clinical and questionnaires data at enrolment. SD#: Standard Deviation; IPSS†: International Prostatic Symptom Score; IIEF-5*: International Index of Erectile Function; QoL‡: Quality of Well-Being

Table 2. Questionnaire results at the first follow-up visit (6 months).

	Baseline values (SD* or %)	Follow-up values (SD* or %)
Efficacy outcomes		
IPSS†	21.5 ± 1.2	16.2 ± 1.5
Treatment difference	-4.8 ± 1.1 (p < 0.001)	
IIEF-5*	22.1 ± 1.8	22.3 ± 1.5
Treatment difference	0.1 ± 0.2 (p = 0.50)	
QoL‡	0.56 ± 0.15	0.84 ± 0.19
Treatment difference	0.28 ± 0.02 (p < 0.001)	
Maximal urinary flow rate (ml/sec)	9.7 ± 3.7	15.3 ± 2.5
Treatment difference	5.6 ± 0.8 (p < 0.001)	
Post-voiding residual volume (ml)	85 ± 20.6	50 ± 18.5
Treatment difference	-35 ± 1.9 (p < 0.001)	

The table shows the mean change differences from baseline to 6 months relative to main outcome measures. IPSS†: International Prostatic Symptom Score; IIEF-5*: International Index of Erectile Function; QoL‡: Quality of Well-Being.

ADRs

During the study period, 1 patient (1.6%) developed a mild ADRs (nausea) that did not require drug discontinuation or other treatments. Moreover, did not document the development of DDIs, while we recorded a 100% adherence to the treatment and a 100% compliance to the experimental protocol.

DISCUSSION

In this phase I-II clinical trial, we evaluated the efficacy and the safety of a new nutraceutical agent named MIGAR® MG containing daidzein, isolase and zinc in the treatment of LUTS related to BPH. It has been documented that in Italy, about 50% of treatment used in patients with BPH are phytotherapies, while in Germany and other European countries, these represent the first-line treatment for mild-to-moderate LUTS in patients with BPH. Isoflavones show a chemical structure similar to the estrogen which allows them to bind to both alpha and beta estrogen receptors, exerting estrogen-like effects and so also called as phytoestrogens (21). Whereas estrogen binds to and transactivates both estrogen receptors, isoflavones preferentially bind to and transactivate estrogen beta receptor exercising tissue-selective effects (22) that is expressed in prostate epithelial cells and plays a role in cellular homeostasis inducing anti-proliferative, pro-differentiative (23), and pro-apoptotic effects (23-24). In this concern, several clinical trials documented that isoflavones are able to suppress PSA expression in patients with prostate cancer cells. In a recent meta-analysis, Zhang *et al.*, evaluating the effects of isoflavones on prostate cancer risk, analyzed 11.346 cases and 140.177 controls and documented that daidzein, genistein, and glycitein were associated with a reduction of prostate cancer risk with an odds ratio: 0.85, 0.87 and 0.89, respectively (25). In agreement, in an experimental model performed in human prostate cancer cell lines Lu *et al.*, recorded that s-equol has significant anti-prostate cancer activities probably related to the activation of the transcription factor Forkhead box O3 via an Akt-specific pathway and inhibitory effects on MDM2 expression (26). Moreover, in an experimental animal model Bae *et al.* reported that genistein and equol are strong inhibitors of testosterone 5 α -reductase enzyme, suggesting that isoflavones could be used in the management of patients with LUTS (27). In fact, Wong *et al.* documented in elderly men that the dietary intake of genistein, glycitein or daidzein was related with a significant decrease of LUTS (28). In our study, we documented that oral intake of MIGAR® MG reduces LUTS with an improvement of uroflowmetry parameters, IPSS score and QoL. Probably these improvements could be related to a potentiating of daidzein induced by isolases that seems to be able to improve the action time of equol reducing its catabolism and increasing its clinical efficacy. On the other hand the presence of zinc in this studied formulation could play synergic effects with daidzein and isolases. In fact, a long period clinical study (4-year) documented that chronic prostate inflammation is related to both severity and progression of BPH and LUTS and zinc has antioxidant and anti-inflammatory activity and changes in prostate zinc

concentrations play a role in the improvement of BPH (29). Take together these published data confirm our results documenting the efficacy of this new nutraceutical formulation in patients with LUTS. However, nutraceuticals are dietary supplements, and it is not necessary to demonstrate data on efficacy or safety before marketing therefore could be possible the development of ADRs or DDIs during their use. In the present study, using the Naranjo probability scale and the Drug Interaction Probability Scale, we failed to report the development of severe ADRs or DDIs during the treatment with this compound. In particular, we recorded the development of a probable mild ADR in 1 patient only but this manifestation did not induce the discontinuation of the treatment, documenting the safety of this nutraceutical. Moreover, must be underlined that enrolled patients did not develop sexual dysfunction, and the optimal sexual activity should be considered as one principal aim in the management of patients with LUTS associated to BPH (30). Previously, we documented that a better sexual quality of life is correlated with a higher overall quality of life regardless of the urinary function in patients affected by LUTS due to BPH10. Finally, in our study we documented a complete adherence (100%) to the treatment and a complete compliance (100%) to the experimental protocol and it may be related to the improvement of QoL. The present study has two limitations: first, the lacks of placebo arm, because in Italy ethically patients must receive a treatment during a spontaneous study, as ours; second, we evaluated the safety and efficacy of this new compound for a short time that did not allow evaluating its effects for a long time.

CONCLUSIONS

In this study, we demonstrated that combination of daidzein plus isolase and zinc (MIGAR® MG Retard) reduces the symptoms and improves the quality of life in patients affected by LUTS due to BPH, without the development of ADRs.

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CONTRIBUTIONS

TC, DT, IT data collecting and analyzing; TC, DT, PV manuscript writing; GM, RB, AP, LG, VM supervision.

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