

Prospective observational study on the efficacy and tolerability of a complex of phytochemicals versus dutasteride in the treatment of Lower Urinary Tract Symptoms due to Benign Prostatic Hyperplasia

Giuseppe Saitta¹, Franco A. Mantovani¹, Benedetto Calabrese^{1,2}, Camilla Aliboni^{1,2}, Giuseppe Di Paola¹, Attilio L. Meazza¹, Mauro Seveso¹

¹ ICCS Istituto Clinico Città Studi, Milan, Italy;

² Humanitas University, Pieve Emanuele, Milan, Italy.

Summary

Introduction: The aim of our study was to treat 2 similar groups of patients suffering from benign prostatic hyperplasia (BPH): one group with a complex of phytochemicals based on phycocyanin, Palmitoylethanolamide (PEA) and selenium; the other group with dutasteride. The effectiveness of these treatments was checked, especially regarding the improvement of lower urinary tract symptoms (LUTS) and the reduction of prostatic specific antigen (PSA) and prostate volume.

Materials and methods: We included 104 patients in the study. All patients were aged between 50 and 70 years, with PSA values between 4 and 10 ng/ml, prostate volume, as calculated by transrectal ultrasound between 50 and 70 cc, maximum flow value greater than or equal to 10 ml/s at flowmetry, no suspicious nodules on digital rectal examination (DRE), no suspicious lesions on magnetic resonance imaging MRI (PI-RADS 1-2), negative previous prostatic biopsies or never biopsied, moreover absence of diabetes mellitus or chronic renal failure (blood creatinine > 2 mg/dl). We considered: Group A of 54 men who used the complex of phytochemicals; Group B of 50 patients treated with dutasteride. We followed all the patients for 6 months after starting therapy, considering the following parameters: PSA, prostate volume, and flowmetry.

Results: Our results showed that both dutasteride and the phytochemicals complex decreased PSA levels ($p < 0.0001$ for both), with a more significant effect of dutasteride (mean decrease of -2.743 ng/ml vs -0.971 ng/ml). Uroflowmetry also improved in both groups ($p < 0.0001$) with a mean increase in maximum flow of urine of + 3.03 ml/min for the dutasteride group and + 13.02 ml/min for phytochemicals complex group. Lastly, dutasteride proved to be highly effective on reducing the prostate volume on transrectal ultrasound (TRUS) (-22.14 ml, $p < 0.0001$) compared to the complex of phytochemicals, which showed a mean decrease of -10.04 ml ($p < 0.0001$). Moreover, the reduction in prostate volume obtained through the use of dutasteride proved to be more consistent than the one obtained by using the complex of phytochemicals even at statistical analysis ($p < 0.0001$).

Conclusions: Both the complex of phytochemicals and dutasteride showed reduction of PSA values after 6 months of treatment. The complex based on phycocyanin, PEA and selenium showed a statistically significant improvement in urinary flow, while dutasteride acted more on the volume of the prostate.

However, the natural complex is a product with good efficacy on the phlogistic component and does not have the side effects of dutasteride (eg gynecomastia, reduced libido). Therefore, we believe it can be used by a large part of the population with BPH, in order to reduce LUTS and PSA and improve urinary flow, without side effects.

KEY WORDS: Benign Prostatic Hyperplasia; Lower Urinary Tract Symptoms; Prostate Specific Antigen; Prostate volume; Urinary flow.

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INTRODUCTION

Benign Prostatic Hyperplasia (BPH) is a common urological disease among older men. It consists of a progressive enlargement of the prostatic tissue, especially its central portion. The resulting bladder outlet obstruction, coupled with increased muscle tone of the bladder and secondary dysfunction of the detrusor, produce lower urinary tract symptoms (1).

Medical treatment is the first-line therapeutical option for this condition. Commonly administered drugs are alpha-blockers, 5-Alpha Reductase Inhibitors (5-ARIs) and phosphodiesterase 5-Inhibitors (PDE5-I). If men have persistent irritative storage symptoms after first line BPH therapy then OverActive Bladder (OAB) medications can be added or used as a replacement.

Combination therapies usually allow to increase the efficacy of medical treatments and delay the need for corrective surgery (2, 3). Most said drugs, however, show a consistent rate of side effects in those who use them. This is why there is a massive increase of interest for herbal and nutraceutical treatments. *Serenoa Repens*, for instance, is one of the oldest and most effective nutraceutical drugs used to treat BPH-related symptoms. *In vitro*, *Serenoa repens* extract (320 mg once a day) has demonstrated anti-inflammatory, antiandrogenic, and estrogenic effects along with a decrease in sexual hormone-binding globulin; inhibition of 5 α -reductase, muscarinic cholinoreceptors, dihydropyridine receptors, and vanilloid receptors; neutralization of free radicals. As of today, *Serenoa Repens* is considered

equally effective compared to the alpha-blocker tamsulosin for what concerns the improvements on *International Prostate Symptom Score* (IPSS), *Quality of Life* (QoL), maximum urinary flow rate, postvoid residual volume and *Prostate Specific Antigen* (PSA) levels (4, 5).

Combination therapy of alpha-blockers and *Serenoa Repens*, furthermore, proved even more effective than monotherapy (6).

Palmitoylethanolamide (PEA) is an endogenous fatty acid amide-signaling molecule with anti-inflammatory and neuroprotective effects that has an interesting role in the management of chronic pelvic pain syndrome and chronic urological pain (7). PEA exerts its clinical effects through different mechanisms: the down-regulation of mast cell activation; the direct activation of at least two different receptors: the peroxisome *proliferator-activated receptors-alfa* (PPAR- α) and the orphan *G-protein coupled receptors 55* (GPCR 55): GPR55; more recently, it has also been demonstrated that PEA can activate *transient receptor potential vanilloid 1* (TRPV1) channels or increase the expression of *cannabinoid receptor 2* (CB2) receptors, of which PEA has been demonstrated to be a weak agonist, via PPAR- α receptors. This results in a neuroprotective and anti-nociceptive effect of PEA, decreasing hyperalgesic responses in the *chronic constriction injury* (CCI) model of neuropathic pain (8, 9). In a female rat model of cyclophosphamide-induced cystitis, it has been reported that pain behavior, bladder inflammation and voiding dysfunction were associated with increased bladder levels of PEA, up-regulation of *cannabinoid receptor 1* (CB1) receptor expression and down-regulation of PPAR- α expression. Oral administration of ultra micronized PEA produced both anti-inflammatory and analgesic effects (10). Such results suggest that PEA could also be used in BPH-related voiding dysfunctions and irritative *lower urinary tract symptoms* (LUTS). In fact, *D'Amico et al.* demonstrated that daily administration of PEA in BPH-affected rats considerably reduced the levels of testosterone and *dihydrotestosterone* (DHT), main characters of BPH. Also, it substantially reduced 5 α -reductase-2 expression and obtained a significant decrease in *tumor growth factor-beta* (TGF- β) expression, leading to a better cellular growth/apoptosis ratio (11).

Phycocyanin (PC) is a protein that derives from spirulina. It has been widely demonstrated that PC exerts its anti-inflammatory and antioxidant activity through the inhibition of *cyclooxygenase-2* (COX-2) enzymatic activity. The same inhibitory effect of COX-2 was observed in the model of human prostate epithelial cells, in which PC also showed a synergic effect with PEA by abating the synthesis of *prostaglandin E2* (PGE2) (12, 13).

Selenium (Se) and *Tomato Extracts* (TE) are important trace elements in health, and their role has been widely evaluated even for BPH and prostate cancer. Se may be able to prevent, inhibit or reverse the transition of the epithelial cells to the mesenchymal phenotype. Both Se and TE proved to modify anatomopathological results when comparing a hyperplastic hypertrophic prostate treated with both elements and a healthy one. In particular, mild hyperplasia with predominance of no presence of glandular hyperplasia and stromal restructuring and decrease in the thickness of the epithelium was observed. Furthermore, the combination

on Se and TE proved to be synergic. In the oxidative stress markers of the BPH group, there was a significant increase in *malondialdehyde* (MDA) and *nitrites* (NO₂) with respect to the control group. Oral administration of Se and TE, especially when combined, proved to significantly decrease the levels of those markers, thus showing an antioxidant effect (14, 15).

The aim of our study was to compare two groups of patients affected by BPH: the first was treated with the 5-ARI Dutasteride, the second, instead, with a combination of nutraceuticals: *Palmitoylethanolamide* (200 mg), *Phycocyanin* (250 mg) and *Selenium* (55 mcg).

Although synergic effects between such elements have been hypothesized and, to some extent, demonstrated, our aim is to contribute to the present literature by describing the results in this cohort of patients.

MATERIAL AND METHODS

We included in the study 104 patients who presented to the *Istituto Clinico Città Studi* (ICCS) in Milan, Italy, complaining of symptoms related to BPH.

All patients were aged between 50 and 70 years, with *Prostate Specific Antigen* (PSA) values between 4 and 10 ng/mL, prostate volume, calculated through *transrectal ultrasound* (TRUS), between 50 and 70 ml, a maximum flow of urine value greater than or equal (4) to 10 ml/s at uroflowmetry, no suspicious nodules on *digital rectal examination* (DRE), no suspicious lesions on MRI (*Prostate Imaging - Reporting and Data System score: 1-2*), negative previous prostatic biopsies or never biopsied. Patients with diabetes mellitus or chronic renal failure were excluded.

We divided our patients into two groups: group A including 54 men who were treated using a complex containing phycocyanin, palmitoylethanolamide and selenium [*Ficopea (F)*, by KURA®], and group B including 50 men who were treated using *Dutasteride* alone (D). We re-evaluated all patients after 6 months of therapy, considering the following parameters: PSA levels, *uroflowmetry* (UFM), prostate volume.

Statistical analysis

Data were collected using Microsoft Excel (v. 12.2.4) and analyzed using the SPSS Statistics v.29 software (*IBM Corporation New York, USA*). Statistical analysis of data was performed using ANOVA test with Tukey's post-hoc correction. P values < 0.05 were considered significant. All data are expressed as mean \pm *Structural Equation Models* (SEM).

RESULTS

Our results showed a significant decrease in PSA value both for the dutasteride (-2.743 ng/mL after 6 months of treatment) and phytochemicals complex (-0.9712 ng/mL after 6 months of treatment) groups (Figure 1). There was a significant difference among the PSA values between the two groups after 6 months of treatment (+1.865 ng/mL higher for the phytochemicals complex group) (Figure 1). Regarding UFM, there was a slight but significant increase in the flow of urine (ml/s) for the dutasteride group (mean increase of +3.029 ml/s after 6 months of treat-

Figure 1. Difference of basal and 6-month follow up PSA values in dutasteride and phytochemical complex groups: significant decrease in both groups *. Lower mean PSA in dutasteride group at 6 month follow up.

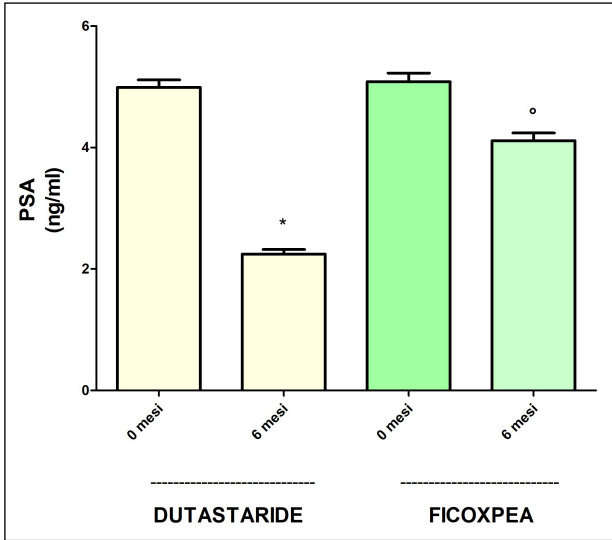
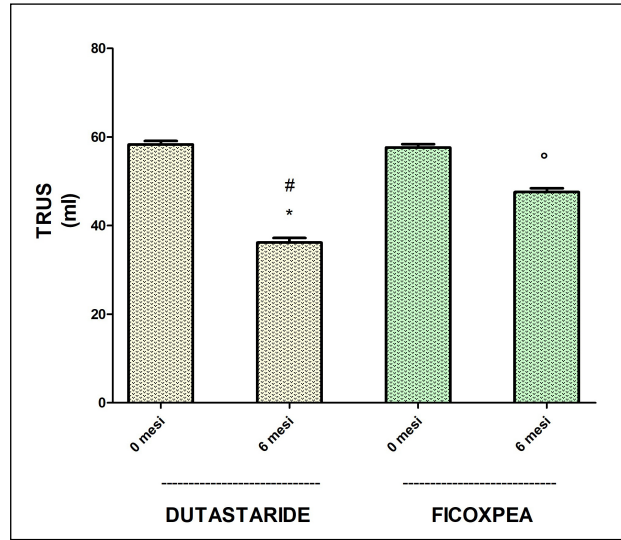
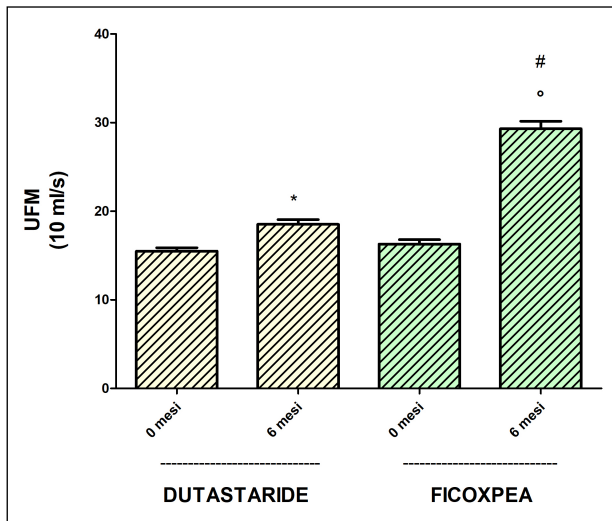


Figure 3. Difference of basal and 6-month follow up prostate volume values in dutasteride and phytochemical complex groups: significant decrease in both groups *. Lower mean volume in dutasteride group at 6 month follow up #.



ment). The phytochemicals complex group, on the other hand, showed a greater improvement after the administration of the complex with a mean increase of +13.03 ml/s ($p < 0.001$) after 6 months of treatment (Figure 2). The improvement in the flow of urine was statistically higher than that of the dutasteride group (+13.03 ml/s vs +3.029 ml/s, $p < 0.001$) (Figure 2). The mean voided volume (VV) was greater than 150 ml (154-347 ml) at the first observation and also after the medical therapy (157-418 ml). The post void residual

Figure 2. Difference of basal and 6-month follow up uroflowmetry values in dutasteride and phytochemical complex groups: significant improvement in both groups *. Higher mean Q_{max} values in the phytochemical complex group at 6-month follow up #.



(PVR) volume was greater than 50 ml (55-165 ml) before treatment and slightly decreased in both groups after 6 months (45-150 ml). No particular differences were found between the 2 groups regarding these parameters. Lastly, prostate volume evaluated through TRUS showed significant improvements in both groups. For the dutasteride group, a mean volume decrease of -22.14 ml ($p < 0.001$) after 6 months of treatment was found; for the phytochemicals complex group, despite being still significant from a statistical point of view, the mean decrease was much lower: -10.04 ml ($p < 0.001$) after 6 months of treatment (Figure 3). The difference in mean volume decrease was much higher in the dutasteride group, when compared to the phytochemicals complex group (-22.14 ml vs -10.04 ml, $p < 0.001$) (Figure 3).

DISCUSSION

The efficacy of nutraceuticals for the treatment of BPH-related urinary symptoms is a wide field of interest in urology. Our study aims to enriching the present literature for what concerns the comparison between commonly used drugs, like 5-ARI Dutasteride, and a combination of nutraceuticals like Palmitoylethanolamide, Selenium and Phycocyanin. Our results show that both the alternatives are valid for the treatment of such symptoms and suggest that treating BPH does not necessarily require the administration of drugs, such as 5-ARIs, that usually heavily impact the QoL because of their side effects. 5-ARI Dutasteride is well-known for its capability in reducing PSA values, the prostate volume and improving UFM parameters and our results agree with this. However, 5 α -reductases (5 α -Rs), a family of several isozymes whose activity is inhibited by the administration of 5-ARIs, play an important role in human physiology by

regulating cellular metabolism of androgens, glucocorticoids and other steroids. Along with hypoactive sexual desire, erectile dysfunction, gynecomastia and psychiatric side effects such as a higher risk of major depression, some studies suggest that such treatments may result in development of *non-alcoholic fatty liver diseases* (NAFLD), *insulin resistance* (IR), *type 2 diabetes* (T2DM), dry eye disease, potential kidney dysfunction, among other metabolic dysfunctions (16, 17).

Not many studies in literature have evaluated the role of less known nutraceuticals in the treatment of BPH (PEA, Selenium, Phycocyanin, etc.). However, based on the biochemical activities of such molecules, it is reasonable to suppose that their main action is towards inflammation and its pathways. Today, it is only possible to estimate the effects of such chemicals on the prostate function. For instance, PEA has been demonstrated to play a significant neuroprotective effect on chronic pelvic pain, but it may also play an important role in reducing inflammation by interfering with the androgenic pathways. As previously said, daily administration of PEA is capable of reducing the levels of testosterone, DHT and decreasing the expression of markers like PSA and 5 α -reductases in the prostate tissue (11). This mechanism may lead to the reduction in prostate weight and inflammation markers that eventually is responsible for the improvement of BPH-related LUTS that we have observed in our results.

According to our data, even if analysis is biased by the low number of patients taken into consideration, our results show that the complex was able to improve the maximum flow of urine by +13.03 ml/s after 6 months of treatment without dramatically reducing the prostate volume in the meantime. Not only is this evidence significant, but it is also very puzzling when compared to the +3.029 ml/s increase in patients treated with dutasteride. Even though this result may be paradoxical to some extent, it is possible to deduce that this combination of nutraceuticals may have a stronger impact on UFM parameters than on prostate weight or PSA serum levels, where dutasteride seemed to perform better, because of their effect on inflammation.

This result supposedly highlights the importance of inflammation pathways in determining urinary symptoms and the fact that such combination of nutraceuticals may have an equal or even slightly stronger anti-inflammatory effect compared to that of 5-ARI Dutasteride in BPH, thus undermining the importance of the absolute value of the prostate volume, main target of 5-ARIs, in causing BPH-related LUTS.

However, it is important to acknowledge the intrinsic limits of this study. The limited number of patients, and the fact that most of them had seen a urologist prior to the inclusion in the study, hence probably being exposed to *Serenoa Repens* and/or modifications of their lifestyle, could have affected the astonishing result that we have obtained regarding the UFM parameters.

The role of prostate inflammation in determining BPH-related LUTS is controversial and many studies are being conducted as to explain its exact role in the pathophysiology of BPH. It is well known that prostate tissue affected by BPH carries a particular kind of inflammatory infil-

trate (CD3+ T lymphocytes, CD19 or CD20 B lymphocytes, and macrophages). Most T cells in the inflammatory areas are CD4+ that are not present in normal prostate tissue (scattered stromal and intraepithelial T, 70% of which are CD8+, and B lymphocytes, macrophages, and mast cells). However, the stimulus for an inflammatory response in the prostates of older males is not fully understood and it is likely to be multifactorial (18). In an interesting clinical study, *Kwon et al.* observed that in patients with high-grade prostatic inflammation, the use of α -blockers with 5-ARIs can be insufficient to reduce symptom severity. Patients with high-grade chronic inflammation reported significantly lower changes in IPSS and storage symptom scores compared to patients with low-grade inflammation (19). A meta-analysis of three randomized controlled trials showed that *non-steroidal anti-inflammatory drugs* (NSAIDs), when given over periods of 4-24 weeks, improved symptoms by 2.9 IPSS points and flow by 0.89 ml/second (20).

These studies suggest the need to treat inflammation accordingly, a field in which nutraceuticals seem to have convincing possibilities.

CONCLUSIONS

Both nutraceutical complex and dutasteride showed reduction of PSA values after 6 months of treatment. The complex based on phycocyanin, PEA and selenium showed a statistically significant improvement in urinary flow, while dutasteride acted more on the volume of the prostate.

However, the natural complex is a product with good efficiency on the phlogistic component and does not have the side effects reported for dutasteride (such as gynecomastia, reduced libido). Therefore, we believe it can be used by a large part of the BPH population, in order to reduce LUTS and PSA and improve urinary flow, without side effects.

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DECLARATION

The introduction of *Ficoxpea*[®] in the commerce was ethically approved and officially notified at the *Italian Ministry of Health* on 16th October 2020.

All patients followed by us accepted anonymous data collection and agreed on its possible use for scientific purposes.

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Correspondence

Giuseppe Saitta, MD (Corresponding Author)

gsaitta@hotmail.it

ICCS Istituto Clinico Città Studi, Milan (Italy)

Viale Sabotino 19, 20135, Milan (Italy)

Franco A Mantovani, MD

mantovanifranco@yahoo.it

Benedetto Calabrese, MD

calabrese.benedetto98@gmail.com

Camilla Aliboni, MD

camilla.aliboni@gmail.com

Giuseppe Di Paola, MD

giuseppe.dipaola@ic-cittastudi.it

Attilio L Meazza, MD

attilio.meazza@ic-cittastudi.it

Mauro Seveso, MD

mauro.seveso@ic-cittastudi.it

ICCS Istituto Clinico Città Studi, Milan (Italy)

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