JGG 2018;66:211-215

Short Communication

A lycopene and olives vegetation water compound improves lower urinary tract symptoms in men with histologically-proven benign prostatic hyperplasia and inflammation

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Background and aims. There is evidence for the ability of antioxidants to counteract the effects of inflammation. We aimed to determine whether the administration of a lycopene/olives vegetation water compound might reduce prostatic inflammation and consequent lower urinary tract symptoms in patients with histologically proven prostatic inflammation.
Methods. Over a month period, patients having undergone prostate biopsy and having been diagnosed with benign prostate were given lycopene/olives vegetarian water compound (Group A). Data were compared with those of a matched population of patients who did not receive such treatment (Group B). International prostate symptom score, peak flow rate and post-void residual were recorded before and at the end of treatment.
Results. The 17 patients in group A and the 17 in group B, had similar age, PSA, prostate volume, peak flow rate and post-void residual, but patients in Group A had lower median international prostate symptoms score than those in group B (7 *vs* 12; p = 0.012). All patients in group A successfully completed treatment with no side effect. Group B experienced no difference in international prostate symptoms score, peak flow rate and post-void residual whereas group A experienced no difference in peak flow rate, a slight reduction in post-void residual and a decrease in international prostate symptoms score. Most important, reduction in international prostate symptoms score was significantly higher in group A than in group B (-2.0 *vs* 0, respectively; p = 0.0004).
Conclusions. The lycopene/olives vegetation water compound seems to be effective in counteracting lower urinary tract symptoms due to prostatic inflammation.

Key words: Lycopene, Olives vegetation water, Prostatic inflammation, LUTS, Benign prostatic Hyperplasia

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a chronic disease widely diffused between the elderly population. Indeed, its incidence increases with age, reaching 80% of males aging 70 to 80 years [1]. It develops as a simple micronodular hyperplasia and then progress to macroscopic volume enlargement and clinical expression.
There is emerging evidence that prostatic inflammation plays a key role, since BPH evolves through early and late inflammatory modifications. Indeed, the prostate is an immunocompetent organ populated by T and B-lymphocytes, macrophages and mast cells [2]. Regulatory T cells (CD-4) are located into the fibromuscolar stroma whereas Cytotoxic T cells (CD-8) are more distributed around periglandular area creating the so-called Prostate associated Lymphoid Tissue (PALT).
There are two main clinical manifestations of prostatic

Received: October 29, 2018 - Accepted: December 09, 2018
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inflammation, namely lower urinary tract symptoms (LUTS) and increase in serum PSA often leading to prostate biopsy (PBx).

Data suggest that a potential mechanism by which inflammation promotes prostate enlargement is local hypoxia, which is responsible for the release of reactive oxygen species (ROS). Such ROS promote neovascularization and further release of vascular endothelial growth factors (VEGFs), interleukin-8 (IL-8), fibroblast growth factor 7 (FGF-7), transforming growth factor (TGF-b), and fibroblast growth factor (FGF-2). All of them contribute to prostatic enlargement and further inflammation [3].

There is also evidence that, apart from promoting prostatic enlargement, prostatic inflammation may also promote prostate cancer (PCa). Like BPH, PCa is common among elderly males. The median age of PCa diagnosis is 66 years, and nearly 20% of patients are diagnosed when they age 75y or more [4]. The immune cells can stimulate tumor cell proliferation and angiogenesis by the production of reactive oxygen species and by inflammatory processes that result into tissue damage and permanent DNA damage [5]. A recent meta-analysis, however, pointed out that the presence of inflammation on prostate needle biopsy was associated with a lower PCa risk [6].

In the absence of a standard treatment for prostatic inflammation [7], the use of substances like antioxidants that may stop or potentially reverse the deleterious effects of inflammation is particularly attractive. Lycopene and olives vegetation water are well-known strong antioxidants, with properties potentially useful in protecting DNA from oxidation [8 9].

The present study therefore aimed to determine whether the administration of a lycopene and olives vegetation water compound might reduce inflammation and therefore LUTS in patients with histologically proven prostatic inflammation.

PATIENTS AND METHODS

Over a one-month period, consecutive patients having undergone prostate biopsy (PBx) at our institution and having been diagnosed with benign prostate were given lycopene/olives vegetarian water compound (Group A). Data were compared with those of a matched population of patients having undergone prostate biopsy and having been diagnosed with benign prostate (Group B). All data were prospectively entered into our dedicated Institutional Review Board-approved database on prostate biopsy.

Indications for trans-rectal ultrasound (TRUS)-guided PBx were increased serum PSA (≥ 4 ng/mL) and/or abnormal digital rectal examination (DRE). All patients underwent International prostate symptom score (IPSS) and uroflowmetry (UFM) before PBx, as we have demonstrated that BPO-related parameters such as peak flow rate (PFR), post-void residual (PVR) and IPSS [10-12] are independent predictors of the risk of being diagnosed with PCa. Recently, we also developed a novel BPO-related parameters nomogram [13] that may help reducing the number of unnecessary PBxs, thus reducing the risk of over diagnosis and consequent overtreatment with possible procedure-related complications [14].

Following local non-infiltrative anaesthesia [15 16], TRUS was used to determine prostate and transition zone volume and to guide trans-rectal prostate sampling according to our systematic 18-core biopsy scheme [17]. A senior uropathologist evaluated the specimens according to contemporary diagnostic criteria for high-grade prostatic intraepithelial neoplasia (HGPIN), atypical small acinar proliferation (ASAP) of prostate [18] and PCa.

Patients in group A, unless reporting a history for allergies or hypersensitivity to tomato, inflammatory diseases of the urogenital tract (i.e. orchitis, epididymitis or both) and malabsorption syndrome, were given lycopene/olives vegetarian water compound in the form of 5 gr medical bags to be dissolved in water or other liquid once-a-day for 2 months. The intake could take place before, during or after meals. Patients in Group B did not receive any treatment. All patients were seen after 2 months for IPSS questionnaire, clinical evaluation and uroflowmetry to assess PFR and PVR.

The study protocol was approved by the University of Foggia Ethics Committee and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent to take part was given by all participants.

Statistical analysis

The primary study endpoint was assessing changes in IPSS, PFR and PVR; the secondary endpoint was to assess safety.

Continuous variables are reported as median and interquartile range; they were compared by the Mann-Whitney U-test. Rates were tested by Fisher's exact test or chi-square test, as appropriate. Statistical significance was set at $p < 0.05$. Statistical calculations were carried out using STATA-SE software, version 14.0 for Mac OS X.

RESULTS

The study population consisted of 34 patients, 17 in Group A and 17 in Group B; their characteristics are summarized in Table I. Overall, the two groups had similar age, PSA, prostate volume (PVol), PFR and PVR,

Table I. Patients baseline characteristics.

	Group A = 17	Group B = 17	P-value*
Age (y)*	67.0 (63.0, 70.0)	65.5 (62.5, 67.0)	0.4
PSA (ng/mL)*	7.3 (5.2, 11.7)	5.6 (4.7, 7.1)	0.2
Prostate volume (mL)*	55.0 (50.0, 66.4)	60.0 (50.0, 85.0)	0.3
IPSS*	7.0 (5.0, 12.0)	12.0 (9.0, 16.0)	0.012
PFR (mL/s)*	14.4 (11.0, 17.7)	14.9 (12.7, 17.3)	0.8
PVR (mL)*	35.0 (0.0, 50.0)	35.0 (0.0, 45.0)	0.9

*Data are expressed as median and Interquartile range.

but patients in group A had lower median IPSS score than those in group B (7 *vs* 12; p = 0.012).

All patients in group A successfully completed treatment with no side effect. Patients in group B experienced no difference in their median PFR and PVR (Tab. II) but a slight increase in median IPSS, which might however be due to the impact of the procedure itself on voiding symptoms. Patients who received the lycopene/olives vegetation water compound (Group A), experienced no difference in their median PFR, a slightly lower PVR and, above all, a decrease in their median IPSS. Comparing the two groups, median reduction in IPSS was significantly higher in group A than in group B (-2.0 *vs* zero, respectively; p = 0.0004).

DISCUSSION

The present study pointed out that, in men with histologically-proven prostatic inflammation and benign prostate, the administration of a lycopene/olives vegetation water compound after PBx provided a statistically significant reduction in IPSS as compared to no treatment. In both groups, there was no significant change in PFR, but patients in group A experienced a slight reduction in their PVR. These findings would support a role for the lycopene/olives vegetation water compound in reducing prostatic inflammation and consequent LUTS.

The correlation between prostatic inflammation and LUTS has been strongly pointed out by Nickel et al. [19] who evaluated 8224 men aged 50-75 years with BPH undergoing prostate biopsy and included in the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial. Patients were classified according to the presence of acute and chronic inflammation at biopsy. Interestingly, 77.6% of patients presented with chronic inflammation. These patients had higher prostate volumes than those without inflammation (46.5 *vs* 43.4 mL, respectively; p < 0.001). Interestingly, older age and higher degree of chronic inflammation were significantly associated with higher IPSS (8.8 *vs* 8.2, respectively; *p* < 0.001), particularly the storage IPSS sub-scores (frequency, nocturia, urgency). Similarly, Robert et al. [20] found, in 282 patients treated with surgery for complicated or symptomatic BPH, that the grade of prostatic inflammation was strongly associated with LUTS severity, and patients with chronic inflammation had higher IPSS than those without inflammation (21 *vs* 12, respectively; p = 0.02).

Counteracting inflammation is relevant not only to reduce symptoms but also to slowing development and progression of BPH. Indeed, Tuncel et al. [21] have shown that the presence of prostatic inflammation is a risk factor for the development of BPH complications such as acute urinary retention. The Medical Therapy of Prostatic Symptoms (MTOPS) study [22], whereby 3000 patients with LUTS due to BPH were treated for 5 years, highlighted that the percentages of disease progression, urinary retention and need for surgery were higher in patients with chronic inflammatory status than in those without it. It has also been pointed out

Table II. Treatment outcomes.

	Variable	Pre-treatment	Post-treatment	P-value
Group A = 17	IPSS*	7.0 (5.0, 12.0)	4.0 (3.0, 9.0)	0.14
	PFR (mL/s)*	14.4 (11.0, 17.7)	14.4 (12.4, 19.4)	0.5
	PVR (mL)*	35.0 (0.0, 50.0)	28.5 (0.0, 41.5)	0.3
Group B = 17	IPSS*	12.0 (9.0, 16.0)	14.0 (9.0, 16.0)	1
	PFR (mL/s)*	14.9 (12.7, 17.3)	14.1 (11.6, 17.3)	0.7
	PVR (mL)*	35.0 (0.0, 45.0)	35.0 (15.0, 50.0)	0.8

*Data are expressed as median and Interquartile range.

that, like smoking in bladder cancer [23], inflammation has a negative impact on response to conventional BPH treatments therapy such as alpha-blockers and 5-alfa reductase inhibitors.

The clinical relevance of prostatic inflammation and consequent LUTS is further highlighted by the fact that LUTS and cardiac symptoms have the same impact on the general state of health and quality of life [24].

Counteracting inflammation could be relevant also to reduce the risk of developing PCa. If it is true that inflammation on prostate needle biopsy is associated to benign prostate more frequently than to PCa risk [6], it is also true that several studies supports the role of chronic inflammation in malignant transformation. Interleukin (IL)-8 and IL-6 have been reported to promote PCa [25 26]. A recent preclinical investigation showed that IL-17 might promote the development of PCa through the activation of the matrix metalloproteinase-7 expression [27]. A large prospective study on 68.675 patients demonstrated that a personal history of prostatitis, as well as symptom duration, were significantly associated with an increased risk of PCa [28].

While searching for novel molecular markers and pathways potentially involved in prostatic inflammation [29-31] up to representing potential therapeutic targets, the main issue remains what do we already have to counteract inflammation. ROS involvement in prostatic inflammation make antioxidants an attractive means of counteracting them. Indeed, lycopene is a powerful antioxidant with proven antinflammatory effect [32]. Pannellini et al. [33] showed that tomato-based preparations optimized to maximize lycopene and other carotenoids bioavailability were able to significantly increase the antioxidant serum activity and, at the same time, to reduce biomarkers inflammation in the mouse TRAMP. Another interesting antioxidant is 3,4-dihydroxyphenyl ethanol or hydroxytyrosol (HT) [34], a simple phenol predominantly found in Olea europea also known as the olive plant. Specifically, HT is most abundant in the aqueous fraction of olive pulp with trace amounts in the olive oil fraction and in the leaves. Olive vegetation water and HT have been found to exploit anti-inflammatory activity in mice by inhibiting the production of tumor necrosis factor-alpha (TNF-alpha), a pivotal cytokine in inflammation [34]. Our findings of a relatively short course of these two substances reducing IPSS seem to provide a proof of concept for their effect against prostatic inflammation.

This study is not devoid of limitations. One is the small patients' number but this aimed to be a pilot study in this field. Others include is the relatively short time-frame of treatment and the absence of another control group receiving other substances potentially active against prostatic inflammation, but again this was beyond the scopes of a small pilot study.

In conclusion, there seems to be a clear link between prostatic inflammation, BPO and LUTS. In view of the postulated immunocompetent nature of the prostate, modulators of the immune response, which are opening new pathways in several urological cancers [35 36], are attractive but probably too costly. Antioxidants conversely stand as a potential simple means of counteracting prostatic inflammation and this small study seems to be a proof of such concept.

Conflict of Interest

The authors declare no conflict of interest.

References

1 Kramer G, Mitteregger D, Marberger M. *Is benign prostatic hyperplasia (BPH) an immune inflammatory disease?* Eur Urol 2007;51:1202-16.

2 Steiner G, Gessl A, Kramer G, et al. *Phenotype and function of peripheral and prostatic lymphocytes in patients with benign prostatic hyperplasia*. J Urol 1994;151:480-4.

3 Gandaglia G, Briganti A, Gontero P, et al. *The role of chronic prostatic inflammation in the pathogenesis and progression of benign prostatic hyperplasia (BPH).* BJU Int 2013;112:432-41.

4 Siegel RL, Miller KD, Jemal A. *Cancer statistics* 2017;67:7-30.

5 Amara S, Tiriveedhi V. *Inflammatory role of high salt level in tumour microenvironment (review)*. Int J Oncol 2017;50:1477-81.

6 Vasavada SR, Dobbs RW, Kajdacsy-Balla AA, et al. *Inflammation on prostate needle biopsy is associated with lower prostate cancer risk: a meta-analysis*. J Urol 2018;199:1174-81.

7 Gravas S, Cornu JN, Drake MJ, et al. *EAU Guidelines on Management of non-neurogenic male lower urinary tract symptoms*. 5.2 *Pharmacological treatment*. Eur Urol 2018;17-25.

8 Wertz K, Siler U, Goralczyk R. *Lycopene: modes of action to promote prostate health*. Arch Biochemical Biophys 2004;430:127-34.

9 Kouka P, Chatzieffraimidi GA, Raftis G. *Antioxidant effects of an olive oil total polyphenolic fraction from a Greek Olea europaea variety in different cell cultures*. Phytomedicine 2018;47:135-42.

10 Cormio L, Lucarelli G, Netti GS, et al. *Post-void residual urinary volume is an independent predictor of biopsy results in men at risk for prostate cancer*. Anticancer Res 2015;35:2175-82.

11 Cormio L, Lucarelli G, Selvaggio O, et al. *Absence of bladder outlet obstruction is an independent risk factor for prostate cancer in men undergoing prostate biopsy*. Medicine 2016;95:2551-6.

12 Cicione A, Cormio L, Cantiello F, et al. *Presence and severity of lower urinary tract symptoms are inversely correlated with the risk of prostate cancer on prostate biopsy*. Minerva Urol Nefrol 2017;69:486-92.

[13] Cormio L, Cindolo L, Troiano F, et al. *Development and internal validation of novel nomograms based on benign prostatic obstruction-related parameters to predict the risk of prostate cancer at first prostate biopsy.* Front Oncol 2018;8:438.

[14] Cormio L, Massenio P, Lucarelli G, et al. *Hem-o-lok clip: a neglected cause of severe bladder neck contracture and consequent urinary incontinence after robot-assisted laparoscopic radical prostatectomy.* BMC Urology 2014;14:21-7.

[15] Cormio L, Lorusso F, Selvaggio O, et al. *Non infiltrative anesthesia for transrectal prostate biopsy: a randomized prospective study comparing lidocaine-prilocaine cream and lidocaine-ketorolac gel.* Urol Oncol 2013;31:68-73.

[16] Cormio L, Pagliarulo V, Lorusso F, et al. *Combined perianal-intrarectal (PI) lidocaine-prilocaine (LP) cream and lidocaine-ketorolac gel provide better pain relief than combined PI LP cream and periprostatic nerve block during transrectal prostate biopsy.* BJU Int 2012;109:1776-80.

[17] Cormio L, Scattoni V, Lorusso F, et al. *Prostate cancer detection rates in different biopsy schemes. Which cores for which patients?* World J Urol 2014;32:341-6.

[18] Sanguedolce F, Cormio A, Musci G, et al. *Typing the atypical: diagnostic issues and predictive markers in suspicious prostate lesions.* Cril Rev Clin Labor Sci 2017;22:1-17.

[19] Nickel JC, Roehrborn CG, O'Leary MP, et al. *The relationship between prostate inflammation and lower urinary tract symptoms: examination of baseline data from the REDUCE trial.* Eur Urol 2008;54:1379-84.

[20] Robert G, Descazeud A, Nicolaiew. *Inflammation in benign prostatic hyperplasia: a 282 patients immunohistochemical analysis.* Prostate 2009;69:1774-80.

[21] Tuncel A, Uzun B, Eruyar T, et al. *Do prostatic infarction, prostatic inflammation and prostate morphology play a role in acute urinary retention*? Eur Urol 2005;48:277-84.

[22] McConnell JD, Roehrborn CG, Bautista OM, et al.; Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. *The long-term effect of doxazosin, finasteride, and combination therapy on the clinical progression of benign prostatic hyperplasia*. N Engl J Med 2003;349:2387-98.

[23] Serretta V, Altieri V, Morgia G, et al. *Cigarette smoking status atdiagnosis and recurrence in intermediate-risk non muscle invasive bladder carcinoma*. Urology 2013;81:277-81.

[24] Blanker MH, Driessen LF, Bosch JL, et al. *Health status and its correlates among Dutch community-dwelling older men with and without lower urogenital tract dysfunction*. Eur Urol 2002;41:602-7.

[25] Thapa D, Ghosh R. *Chronic inflammatory mediators enhance prostate cancer development and progression.* Biochem Pharmacol 2015;94:53-62.

[26] Chi N, Tan Z, Ma K, et al. *Increased circulating myeloid-derived suppressor cells correlate with cancer stages, interleukin-8 and -6 in prostate cancer*. Int J Clin Exp Med 2014;7:3181-92.

[27] Zhang Q, Liu S, Parajuli KR, et al. *Interleukin-17 promotes prostate cancer via MMP7-induced epithelial-to-mesenchymal transition*. Oncogene 2017;36:687-99.

[28] Cheng I, Witte JS, Jacobsen SJ, et al. *Prostatitis, sexually transmitted diseases, and prostate cancer: the California Men's Health Study.* PLoS One 2010;5:e8736.

[29] Sanguedolce F, Cormio A, Brunelli M, et al. *Urine TMPRSS2: ERG fusion transcriptas a biomarker for prostate cancer: literature review.* Clin Genit Urin Cancer 2016;14:117-21.

[30] Falzarano SM, Ferro M, Bollito E, et al. *Novel biomarkers and genomic tests in prostate cancer: a critical analysis.* Minerva Urol Nefrol 2015;67:211-31.

[31] Stallone G, Cormio L, Netti GS, et al. *Pentraxin 3: a novel biomarker for predicting progression from prostatic inflammation to prostate cancer*. Cancer Res 2014;74:4230-8.

[32] de la Taille A, Descazeaud A, Robert G et al. *How to prevent LUTS due to BPH development and progression.* Prog Urol 2018 24:30517-27.

[33] Pannellini T, Iezzi M, Liberatore M, et al. *A dietary tomato supplement prevents prostate cancer in TRAMP mice.* Cancer Prev Res 2010;3:1284-91.

[34] Bitler CM, Viale TM, Damaj B, et al. *Hydrolyzed olive vegetation water in mice has anti-inflammatory activity.* J Nutr 2005;135:1475-9.

[35] Caratozzolo MF, Valletti A, Gigante M, et al. *TRIM8 anti-proliferative action against chemo-resistant renal cell carcinoma.* Oncotarget 2014;5:7446-57.

[36] Gigante M, Pontrelli P, Herr W, et al. *miR-29b and miR-198 overexpression in CD8+ T cells of renal cell carcinoma patients down-modulates JAK3 and MCL-1 leading to immune dysfunction.* J Transl Med 2016;14:84-9.