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ORIGINAL PAPER

Effect on prostatic specific antigen by a short time treatment with a Curcuma extract: A real life experience and implications for prostate biopsy

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Summary

Introduction and objectives: *PSA elevation is associated with prostate cancer and it is used in screening programs for its diagnosis. It is one of the most common indications for referral to an urologist. There's no consensus about what to do in PSA elevation management. Antibiotics, nutraceuticals or anti-inflammatories are commonly prescribed in daily practice. Our objective was to verify the effect on the PSA value of a short 30-day trial of a curcuma extract, than to discuss the implications in terms of reducing the number of prostate biopsies performed.*

Patients and methods: *We enrolled 50 consecutive patients admitted at our attention for a first PSA over the level of 4 ng/ml or for a suspected PSA rising defined as PSA velocity (PSAv) > 0.75 ng/ml/years. They received treatment with curcuma extract, 2 tablets per day for 30 day. All patients received a second PSA measurement and TRUS within 6 days from the end of the therapy. In case of PSA reduction below 4 ng/ml, patients were reassured and invited to repeat a PSA control over the time. When PSA level were persistently high over 4 ng/ml or in case of any rising, patients underwent a transrectal ultrasound guided 12-core prostatic biopsy (TRUSbx).*

Results: *Mean age of the patients was 64.56 ± 8.88 (range, 42-81 years). Prostate volume was 48.34 ± 15,77 ml (range, 18-80 ml). At visit 1, PSA value was in mean 6,84 ± 3.79 ng/ml (range 2.93-21ng/ml). Consequently, mean PSA density value was 0.16 ± 0.16 (range 0.05-1.11). PSA free and PSA total ratio at baseline was 16.85 ± 3.9% (range 8-26%). At visit 2, the prostate volume did not change. Total PSA was 4.65 ± 2,67 ng/ml (range 1-16.82 ng/ml). PSA free and PSA total ratio (PSAF/T) after treatment was 19.68 ± 5.35 % (range 7.8-29%). The differences of total PSA and PSAF/T between visit 1 and visit 2 were < 0.0001 and p < 0.0036, respectively. We performed 26 TRUSbx. Prostate cancer was diagnosed in 6 cases, PIN HG in 2 cases and non neoplastic findings in the remnants 18 patients.*

Conclusions: *Use of the Curcuma extract is able to lower the PSA value after a 30-day intake period. We are not able to state that the reduction of PSA after intake of this Curcuma extract may exclude a prostate cancer. We need further studies to evaluate that.*

KEY WORDS: *Prostatic specific antigen; Curcuma; Prostate biopsy; Prostate cancer; Nutraceuticals.*

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No conflict of interest declared.

INTRODUCTION

Prostatic specific antigen (PSA) may be raised as a result of prostate cancer, benign prostatic hyperplasia, prostatic infection or inflammation (1). A raised PSA, over a value considered as normal (i.e. 4 ng/ml), usually prompts an *ultrasound guided prostate biopsy* (TRUSbx) even in absence of an abnormal *digital rectal examination* (DRE). TRUSbx is a procedure performed in an ambulatory setting but it is characterized by a morbidity and a patient's discomfort (2). The scientific literature does not define with certainty what should be the attitude to be taken by the urologist when he is managing a PSA elevation, without symptoms and without anomalous findings to the DRE. Although the prescription of antibiotics or nutraceuticals or anti-inflammatories is widespread in daily practice, the guidelines recommend repeating PSA over time, but this does not protect against performing biopsies with negative results for neoplasia.

Our objective was to verify the effect on the PSA value of a short 30-day trial of a Curcuma extract and if this effect could have an implication in terms of reducing the number of prostate biopsies.

PATIENTS AND METHODS

Patients and study design

This was a prospective mono-institutional real-life study of 50 patients who were admitted at our attention for a first PSA raised over the level of 4 ng/ml or for a suspected PSA rising defined as *PSA velocity* (PSAv) > 0.75 ng/ml/years. The exclusions criteria were any previous surgical prostatic treatment, any prior prostate biopsy, any therapy with *5-alpha-reductase inhibitors* (5ARI); (finasteride or dutasteride), any abnormalities detected at DRE, any alterations in *transrectal ultrasound prostate study* (TRUS), any *low urinary tract symptoms* (LUTS) suggesting for *urinary tract infection* (UTI) or recognized physiologic or iatrogenic cause of PSA rising.

Patients enrolled received treatment with *PROSTAFLOG®*, 2 tablets per day for 30 day. They received a second PSA

measurement and TRUS within 6 days from the end of the therapy. In case of PSA reduction below 4 ng/ml, patients were reassured and invited to repeat a PSA control over the time. When PSA level were persistently high over 4 ng/ml or in case of any rising, patients underwent a transrectal ultrasound guided 12-core prostatic biopsy (TRUSbx).

Technical aspect and measurements

At first line visit, patients in each group underwent a clinical evaluation with a DRE and TRUS (end fire BK Medical probe, 8808). Prostate volume (ml) was measured according to the prostatic ellipsoid formula, multiplying the largest anteroposterior, transverse and cephalocaudal prostate diameters by 0.524. PSA density (PSAD) (ng/ml/g) was defined as PSA (ng/ml) at the enrolling visit time divided by prostate volume (ml). TRUS guided prostate biopsy was performed by a single experienced urologist and consisted in 12 cores of tissue targeting the peripheral zone at the apex, mid gland and the base on each side of the gland, whit an end fire needle access route. Prostatic cores were evaluated by a single dedicated genitourinary pathologist.

Herbal product

PROSTAFLOG® (*Naturmed srl*) is a food supplement based on plant extracts of *Curcuma, Boswellia, Nettle* and *Maritime Pine*, which promote the physiological functions of the prostate. Component quantitative are, per dose (2 tablets): *Curcumin* 500 mg, *Boswellia* 300 mg, *Nettle* 240 mg (Betasitosterol intake 1 mg), *Maritime Pine* 200 mg (Betasitosterol intake 150 mg), *Soy's Lecitine* 70 mg.

Statistical analyses

The statistical analysis was performed with Med Calc ver. 9.0.2.1 demo mode.

For quantitative parameters were determined: mean, standard deviation, median. For all quantitative parameters, the normality or less of the distribution was preliminarily verified with D'Agostino-Pearson test. If the normality was accepted, the data analysis was performed with parametric tests. Otherwise with non-parametric tests.

Results

As showed in Table 1, mean age of the patients was 64.56 ± 8.88 (range, 42-81 years). Prostate volume was 48.34 ± 15.77 ml (range, 18-80 ml). At visit 1, PSA value was in mean 6.84 ± 3.79 ng/ml (range, 2.93-21 ng/ml).

Consequently, mean PSA density value was 0.16 ± 0.16 (range 0.05-1.11).

PSA free and PSA total ratio at baseline was 16.85 ± 3.9% (range, 8-26%). At visit 2, the prostate volume did not change. Total PSA was 4.65 ± 2.67 ng/ml (range, 1-16.82 ng/ml). PSA free and PSA total ratio (PSAF/T) after treatment was 19.68 ± 5.35% (range, 7.8-29%).

The differences of total PSA and PSAF/T between visit 1 and visit 2 were calculated. Given the non-normal distribution of data, the analysis was performed with Wilcoxon tests for paired data.

The value of p was < 0.0001 for total PSA. For PSAF/T, p < 0.0036. The differences, therefore, between "*before and after*" were statistically significant. The power of the test was equal to 0.979 (used software *G*Power* 3.0.10).

Total PSA reduction was observed in 41 cases (82%).

Of 50 patients, 26 (52%) underwent TRUSbx because of persistent total PSA elevation (9/50, 18%) or PSA reduction but not under the cut off value of 4 ng/ml (17/50, 34%). Hystopathologic results showed prostatic adenocarcinoma in 6 cases (6/26, 23%), in 10 (10/26, 38.5%) acute and chronic flogosis, in 8 (8/26, 30.8%) atrophic findings. Monofocal PIN HG was detected in 7.69% (2/26). Gleason score was 3+3 in 67% (4/6), 4+4 in 17% (1/6). In case of positivity for prostatic cancer, PSA was

Table 1.

Patients characteristics at visit 1 and visit 2.

	Visit 1	Visit 2	P (< 0.005)
Age (mean, years)	64.56	-	-
PSA (mean, ng/ml)	6.84	4.65	< 0.0001
PSA F/T (mean, %)	16.8	19.68	< 0.0036
Prostate volume (mean, ml)	48.34	-	-
PSA D	0.16	-	-

Table 2.

*Patient's characteristics according to the PSA value after trial *.*

	Patients with PSA lowered under 4 ng/ml (n. 24)	Patients withwith PSA lowered still over 4 ng/ml (n. 17)	Patientswith PSA augmentation (n. 9)
Mean age (years)	63.4	65.29	66.2
Mean PSA variation (ng/ml)	2.91	2.71	0.70
Mean prostatic volume (ml)	46.62	53.17	43.7
Number positive biopsies	-	1	5
Number negative biopsies	-	16	4

** Not statistically significant differences were found.*

Table 3.

Patient's characteristics according to the prostatic biopsies results.

	Biopsy positive for cancer	Biopsy negative for cancer	Biopsy not performed
Number of patients	6	20	24
Mean PSA (ng/ml)	6.48	6.19	2.89
Mean PSA D	0.14	0.17	0.16
Mean PSA F/T (%)	13.8	20.35	20.75
Mean PSA variation (ng/ml)	0.664*	2.43**	2.91

** Mean value calculated on 5 cases with PSA progression; in one case, PSA total has been lowered by trial (0.5 ng/ml)*

*** All variation were negative.*

in elevation in 5 cases out of 6. Only in one positive case, despite the total PSA reduction of 0.5 ng/ml (from 9 ng/ml to 8,5 ng/ml), we have diagnosed an adenocarcinoma. This could mean that in 16 case of 17 (94%) who underwent TRUSbx for PSA not sufficiently reduced, TRUSbx could not be performed based on the finding of PSA reduction after the trial with curcuma extract.
The mean of reduction was 2,94 ng/ml (range 0.26-16.2 ng/ml). The 44.5% (4/9) of patients in whom PSA increased despite the extract intake had a neoplastic biopsy outcome, but in 2/9 biopsy findings was a PIN hg. Thus, the 67% of these (6/9) with a PSA elevation after the trial, had a non benign biopsy result.
In Table 2 and Table 3 we reported mean PSA values according to results after trial and biopsies findings (negative or positive for neoplasm). All subjects included in the evaluation tolerated treatments with Curcuma extract. No major complications were registered in case of ultrasound guided prostate biopsy.

Discussion

A raised PSA is one of the most common indications for referral to an urologist. However, before a PSA test is undertaken, it is important that a frank and honest discussion should be had with the patient about the pros and cons of this blood test (3). In effect, PSA measurement has marked a new era in the diagnosis of prostate cancer (4). This antigen, produced almost exclusively by the epithelial cells of the prostate, is not a cancer specific but an organ-specific marker (5). Therefore, its serum levels may increase in non malignant conditions such as benign prostate hypertrophy, prostatic infection or inflammation, and prostate cancer (1). The histological architecture of the prostate is disturbed in both prostate cancer and prostatitis, causing greater PSA leakage from the lumen of the prostatic glands into the circulation, increasing PSA levels (6). Because elevated serum PSA is associated with prostate cancer and is used in screening programs for prostate cancer, patients with benign causes for elevation of serum PSA present a challenge, especially when clinical evaluation and DRE are unremarkable. Twenty-five percent of men with PSA levels from 4 to 10 ng/ml have a biopsy-proven prostate cancer, but 75% undergo unnecessary prostate biopsies, potentially leading to anxiety, discomfort and significant additional health care cost (7). In men with an increasing PSA without clinical evidence of infection, a common rational is to treat a subclinical prostate infection, in order to reduce the PSA value, avoiding unnecessary prostate biopsies (8). Several years ago, already, *Scardino* criticized the unjustified use of antibiotics in a group of patients with a PSA elevation and no symptoms due to an UTI. He emphasized the various inherent disadvantages associated with this approach, such as costs, toxicity, and the promotion of resistant bacterial species development that would have exposed the biopsied patient to more resistant and aggressive sepsis (9). Also in 2014, *Fandella et al.*, showed no advantages due to an empiric antibiotic therapy (full dose fluoroquinolone for 20 days) to reduce PSA values and avoid unnecessary biopsy in patients with PSA levels between 4-10 ng/mL and no signs or symptoms of infections. They concluded that empiric use doesn't seem to be of clinical benefit in absence of a clinical or laboratory evidence of infection and it might paradoxically be harmful. In their opinion, the repetition of a PSA test before scheduling a biopsy remains the only acceptable approach (10). However, over the years, we have witnessed the presentation of various therapeutic approaches aimed at the intervention on the increase of PSA before resorting to a biopsy. Even the current increased recourse to *multiparametric Magnetic Resonance Imaging* (mpMRI) presents some aspects of accuracy and costs that make it impracticable in a first level of investigation (11-12). *Bozzini et al.* recently reported their multicentric observational experience with *beclomethasone dipropionate* (BDP) rectal suppositories in case of nonbacterial prostatitis. The eighty-four percent of the patients enrolled underwent a 20-day course of therapy with BDP suppositories and *Serenoa Repens* (*Saw palmetto*, dose of 320 mg per day).
Results showed an effect on symptoms related to prostatitis, but not on PSA levels. Authors declared that, as expected, PSA levels remained stable since it is not a specific parameter for lower urinary tract inflammation (13). But, we know from the literature that inflammation of the prostate is an histological finding in almost every set of prostate biopsies, even when there are no signs of clinical prostatitis. As observed in our study population, this subclinical inflammation can cause PSA elevation. Furthermore, not the extent of inflammation is of importance, but the disruption of epithelial integrity caused by the inflammatory infiltrate. When confronted with a patient with an elevated PSA level whose prostate biopsies reveal no malignancy but only inflammation, this concept can help in determining the need for quick repeat biopsies (14). Instead, a PSA assessment is more and more frequently prescribed also by general practitioners before being sent to the specialist. Hence, the increasing interest in and use of *complementary and alternative therapies* (CAM), especially nutraceuticals (15).
In Italy, 50% of the medications used for benign prostatic hyperplasia are phytotherapies, and in Germany and other European countries, phytotherapies are first-line treatment for mild to-moderate *benign prostatic hyperplasia* (BPH)/LUTS (16). The best-studied CAM therapies for prostate disease include dietary modification, the aforementioned *Serenoa repens* (*Saw palmetto*), *Pygeum africanum*, phytosterols, rye pollen extract and others, and vitamins and minerals, such as vitamin E and selenium (17-20). These products may be utilized alone or in association with antibiotics (21, 22) or anti-inflammatory drugs (23) exploiting in particular the rational of Serenoa's anti-inflammatory action (24). Nevertheless, many of the studies are small, short, not randomized, and/or not placebo controlled and they are not focused on the effects on the PSA. We have focused our study on curcuma for the growing attention that literature is addressing to this substance, given its proven effects on PSA (25-26) and the interest of research on the possible use in the treatment of symptomatic prostatitis (27).
In particular, we wanted to evaluate the possibility of obtaining an effect on PSA in just a few weeks so as to reduce the patient's stress and reassure him about the

need to deal with a diagnosis of cancer (28). The results obtained allowed us to verify how curcuma extract is able to lower PSA. Among the biopsies performed, we observed that the positive ones show a PSA increasing or however a less marked reduction compared to patients with negative biopsy. As regards the analysis of the data, taking into account the number of biopsies carried out in patients treated with curcuma extract, it can of course be said that the treatment with this curcuma extract has greatly reduced the number of biopsies to be performed, with 26 biopsies performed respect the 50 that would have been made on the basis of the value of the initial PSA, with a reduction of biopsy performed of 48%.

We are certainly not able to state that the reduction of PSA after intake of curcuma extract, in case of PSA > 4 ng/ml and negative DRE, can be used as "*ex adiuvantibus criterion*" for not perform unnecessary biopsy. However, considering the verified statistical power of the results obtained in our cohort, it is undeniable that this curcuma extract is able to lower the value of PSA.

In particular, when PSA raise after trial, biopsy results are not benign in 67% of cases. We recognize that our study suffer from several limitations. First. The lack of a control group. In order to define the role of curcuma extract in reducing unnecessary biopsy, we should make a comparison with a placebo control group. Second, to confirm our preliminary real life experience, concerning the rapid and significant reduction of PSA, this curcuma extract must be employed in a more sized patient's sample. Third. Not all 50 patients enrolled were biopsied.

It should be recognized that the execution of the biopsy with a reduced PSA, after rising, would have been outside the current indications (2).

Conclusions

PSA rising is one of the most common indications for urological evaluation. Because elevated serum PSA is associated with prostate cancer and is used in screening programs, patients with benign causes for elevation of serum PSA present a challenge, especially when clinical evaluation and DRE are unremarkable. Use of curcuma extract is able to lower the value of PSA. We are not able to state that the reduction of PSA after trial may exclude a prostate cancer. We need further studies to evaluate that. It is desirable that the use of nutraceutical products in the treatment of prostatic pathology is correctly evaluated in appropriate studies so that, in particular, the use of curcuma does not remain a non-evidence-based practice.

Authors' contributions

All Authors participated in the design and conduct of the study. All Authors reviewed and approved the final version of the manuscript.

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