



# Does PSA reduction after antibiotic therapy permits postpone prostate biopsy in asymptomatic men with PSA levels between 4 and 10ng/mL?

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## ABSTRACT

**Purpose:** We investigated the effect of antibiotics on PSA in asymptomatic patients with mild PSA elevation.

**Materials and Methods:** We prospectively evaluated, in a non-randomized design, 106 asymptomatic patients with PSA of 4-10ng/mL, with a negative digital rectal examination and with no urinary tract infection evidence for 2 years. Patients were divided into two groups: those treated with antibiotics for 3 weeks (G1) and those who were not treated (G2). PSA was taken six weeks after and prostate biopsy was performed in all patients.

**Results:** PCa was diagnosed in 25 of 106 patients (23.6%): 16 (25.0%) in G1 and 9 (21.4%) in G2 ( $p>0.05$ ). PSA normalization was experienced in 24.5%. In G1, PSA returned to  $<4\text{ng/mL}$  in 15 (23.4%) patients compared to 11 (26%) patients in G2. In the patients with a positive biopsy, no significant variation was noted in PSA, fPSA, %fPSA and DPSA after antibiotic treatment. A significantly lower cancer detection rate was noted with decreased PSA, fPSA, and DPSA after antibiotic use. A PSA reduction rate of  $\geq 10\%$  occurred in 58.5%, and this was similar in both G1 and G2 groups. The sensibility, specificity and accuracy of PSA reduction of  $\geq 10\%$  were 31%, 23% and 25%, respectively.

**Conclusion:** Empirical antibiotic therapy in asymptomatic male patients is not related to PSA reduction. The greater than 10% PSA reduction after antibiotic in this population cannot postpone prostate biopsy.

## ARTICLE INFO

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## INTRODUCTION

Prostate cancer (PCa) is a frequent cancer that can be cured if early diagnosed (1). However, diagnosis and treatment of localized disease remains a challenge for urologists. Prostate Specific Antigen (PSA) has become an important tool in PCa screening (2, 3) and men with serum PSA greater than 4ng/mL are at higher risk of PCa. These patients are usually referred for a prostate biopsy

(BxP). However, increased PSA levels are also associated with conditions other than cancer (3), such as benign prostatic hyperplasia (BPH) and prostatitis (4, 5).

Chronic abacterial prostatitis is a common diagnosis in men of all ages, with widespread demographics, and it is a common reason for yearly visits to the doctor in the United States (3). Only a few studies have linked prostatitis to an increase in serum PSA (6-9). Subclinical inflammation of the

prostate could elevate serum PSA in asymptomatic patients, confounding the use of PSA values to indicate BxP (10). In the majority of cases, prostatitis is an incidental pathological finding that has no clinical relevance. There has been investigation into ways to decrease the misleading diagnosis resulting from inflammation. Repeat PSA measurements after a period of observation in asymptomatic men can help to avoid unnecessary BxP (10-12).

It has been suggested that antibiotic therapy (AT) can also avoid BxP in many patients with prostate inflammation, in the PSA grey zone (4.0 to 10.0ng/mL) (6, 13, 14). Currently, the indications of re-BxP in patients with a negative initial biopsy are few; therefore, the first BxP must be precise. In an effort to improve the reliability of PSA reduction as an indicator, and consequently avoid unnecessary prostate biopsy, we conducted a prospective, controlled, non-randomized study to evaluate the effect of AT on PSA levels in patients who have an initially mild PSA elevation (4.0-10ng/mL).

## MATERIAL AND METHODS

A prospective, controlled, non-randomized trial was carried out, with 106 asymptomatic men with total PSA (tPSA) levels between 4.0 and 10.0ng/mL, who underwent routine evaluation from April 2007 to October 2011. The criteria for inclusion in the trial were digital rectal examination (DRE) with no suspicion of malignancy and no history of urologic instrumentation, use of antibiotics, and urinary infection or sexually transmitted disease in the previous 12 months. Patients with diseases like diabetes or alcoholism, those describing the use of illegal drugs, those undergoing treatment for bladder outlet obstruction and patients with previous BxP (positive and negative) were excluded, as were those participants who did not use the AT correctly or who did not carry out the follow-up correctly. After institutional review board (ethical committee) approval, all study participants provided informed written consent before enrolment.

After the initial consultation, the serum levels of total PSA (tPSA) and free PSA (fPSA) were determined. The body mass index (BMI), free PSA

fraction (%fPSA), and PSA density (DPSA) were calculated for all patients.

The participants were divided into two groups (Figure-1) according to their decision regarding the use of antibiotics. This decision was made after the authors explained about the lack of evidence for this treatment. Group I patients received antibiotics, while Group II patients chose not to use AT. In Group I, 64 men used ciprofloxacin 500mg twice a day for a period of three weeks. Then, three weeks after the end of AT, the serum PSA, DPSA, and fPSA were again determined (Figure-1). The results of these patients were compared with those of 42 participants with PSA between 4.0 and 10.0ng/mL whose exams were repeated after 6 weeks, without antibiotics, at the participant's discretion. PSA was considered to be normalized after treatment when the values returned to lower than 4ng/dL. All of the participants underwent BxP 2-4 weeks after the second PSA determination. Based on the pre- ( $PSA_{pre}$ ) and post-treatment ( $PSA_{post}$ ) PSA values, the variation ( $PSA_{var}$ ) was calculated:  $PSA_{var} = PSA_{post} - PSA_{pre}$ . Thus, the variation rate ( $PSA_{var}$ ) can be calculated with  $\Delta PSA = (PSA_{var} / PSA_{pre}) \cdot 100\%$ . The BxP was ultrasound-guided and a minimum of 12 cores were sampled with determination of prostate volume in cubic centimetres (cc). For those participants whose biopsy did not show PCa, PSA was determined after 6 months as in routine practice.

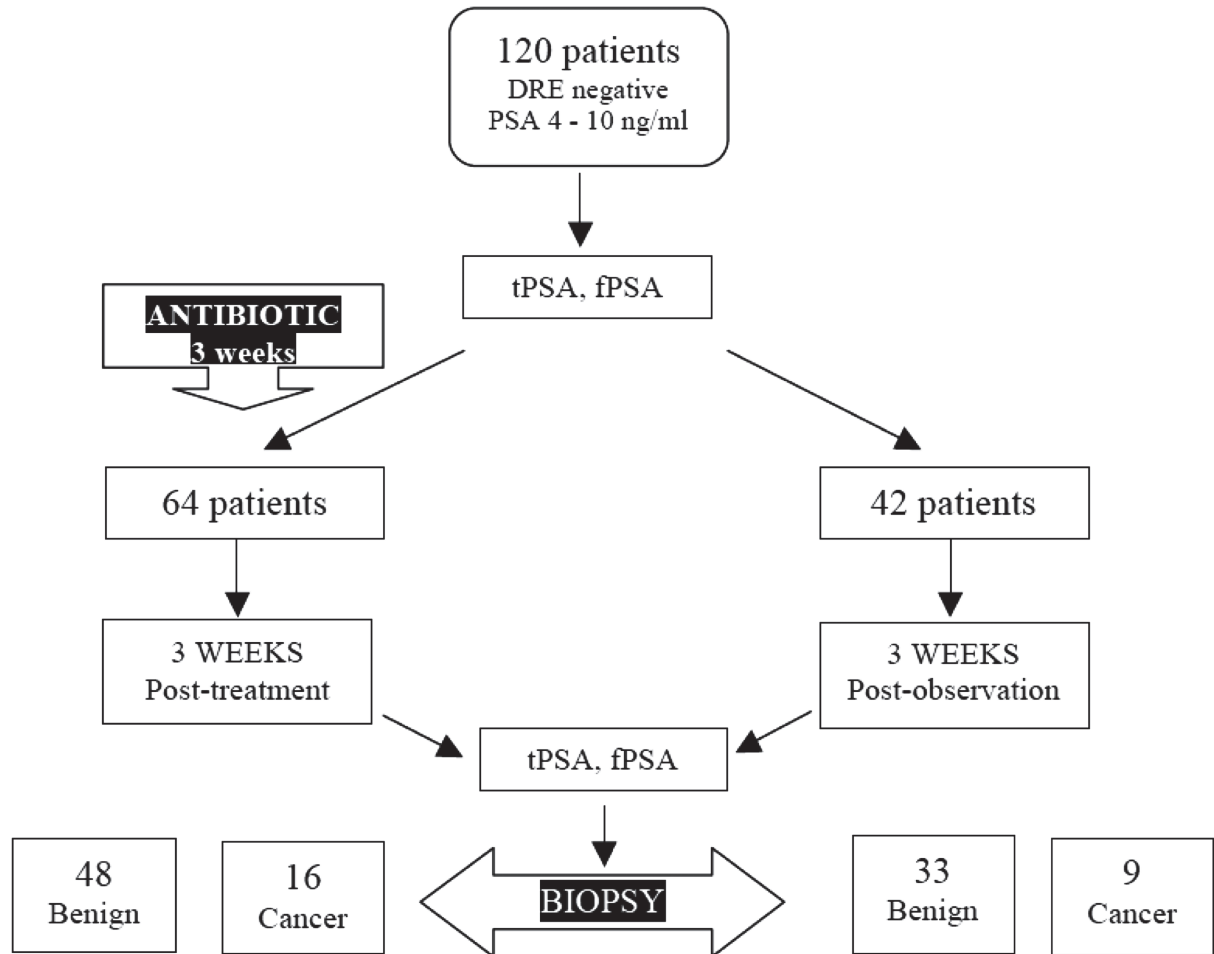
## Statistical analysis

The data obtained were analysed by testing the difference between two proportions for incidence of PCa in each group, and evaluation of the decrease in PSA levels. The other data were evaluated using the Student t test, citing the critical t for a significance level of 0.05.

## RESULTS

The age of the participants ranged from 47 to 78 years, with a mean age of 66.1 years and median age of 61.8 years. The mean age of G1 was 61.8 years and of G2 was 62.6 years ( $p=0.60$ ). The prostate volume was  $51.1 \pm 23.8$  gr in G1 and  $53.9 \pm 19.2$  gr in G2 ( $p=0.52$ ). These values are sho-

Figure 1 - Study design and data organogram. DRE: digital rectal examination; tPSA: PSA total; fPSA: PSA free.



wn in Table-1. The diagnosis of PCa was confirmed in 25 of the 106 participants (23.6%); in 9 out of 42 participants in G2 (21.4%) and in 16 out of 64 in G1 (25%) ( $z=0.42$ ;  $p>0.05$ ).

There was a more than 10% PSA decrease in 72 out of 106 patients (67.9%); this rate was 65.6% and 71% in Groups 1 and 2, respectively ( $z=-0.63$ ;  $p>0.05$ ). Of the 42 participants from G1 in which the PSA decreased after AT, 6 (14.3%) had a positive and 36 (85.7%) a negative biopsy. In G2, 30 participants had a PSA reduction, with 4 (13.3%) with a positive and 26 (86.7%) a negative biopsy. After the use of AT, the PSA level decreased to  $<4\text{ng/mL}$  in 26 participants (24.5%); in 15 (23.4%) of those who used

AT, and in 11 (26%) from G2 ( $z=-0.032$ ;  $p>0.05$ ). The percentage of participants who had a value below  $2.5\text{ng/mL}$  in the second PSA was 9.4% for G1, and 7.1% for G2 ( $z=0.40$ ;  $p>0.05$ ). The initial and final values for PSA, fPSA, %fPSA and DPSA decreased significantly in both groups (Table-2).

The mean total PSA in G1 was  $6.82\pm 1.66$  and  $5.29\pm 1.8\text{ng/mL}$  before and after treatment, respectively ( $p<0.001$ ); this represents a  $\text{PSA}_{\text{var}}$  of  $-1.53\pm 1.93\text{ng/mL}$ . In G2, the mean PSA before and after antibiotics was  $6.76\pm 1.68$  and  $5.38\pm 2.16\text{ng/mL}$ , respectively, with a  $\text{PSA}_{\text{var}}$  of  $-1.38\pm 1.87$  ( $p<0.001$ ). The  $\Delta\text{PSA}$  in G1 was 25.56, and in G2 was 28.7 ( $p=0.429$ ). The differences between G1

**Table 1 - Comparison of initial values of the variables between groups.**

	Group I	Group II	p
	With ATB Mean±SD	Without ATB Mean±SD	
Age (years)	61.81±7.83	62.57±6.37	0.6
BMI (Kg/m <sup>2</sup> )	27.86±3.51	29.66±8.09	0.02
Volume (cc)	51.15±23.87	53.97±19.28	0.527
PSA <sub>pre</sub>	6.82±1.66	6.76±1.68	0.429
PSA <sub>post</sub>	5.29±1.8	5.38±2.16	0.409
fPSA <sub>pre</sub>	1.25±0.47	1.31±0.40	0.233
fPSA <sub>post</sub>	1.03±0.44	1.06±0.48	0.383
DPSA <sub>pre</sub>	0.15±0.05	0.14±0.06	0.261
DPSA <sub>post</sub>	0.11±0.06	0.11±0.07	0.369

Values expressed in mean ± standard variation. Student t test

**Table 2 - Comparison of initial and final PSA values between groups.**

Group I				Group II		
	Pre-ATB	Post-ATB	p	PSA initial	PSA final	p
tPSA	6.82±1.66	5.29±1.8	<0.001	6.76±1.68	5.38±2.16	<0.0001
fPSA	1.25±0.47	1.03±0.44	0.0002	1.31±0.4	1.06±0.48	0.0003
%fPSA	18.26±5.08	20.13±6.35	0.0017	19.91±5.56	21.08±6.95	0.072
DPSA	0.15±0.05	0.11±0.06	<0.0001	0.14±0.04	0.11±0.07	0.0003

Values expressed in mean±standard variation. Student t test

and G2 are shown in Table-2, according to the initial and final fPSA and DPSA. There was no statistical difference between these values.

In relation to DPSA, for G1, the initial mean was 0.15±0.05ng/mL/gr of prostate, which decreased to 0.11±0.06ng/mL/gr ( $p<0.0001$ ). In G2, these figures were 0.14±0.04ng/mL/gr and 0.11±0.07ng/mL/gr, respectively ( $p=0.0003$ ). Therefore, there was no statistical difference. These same comparisons, analysing the cases with and without PCa, are shown in Table-3. In the participants diagnosed with PCa, there was no statistical difference in relation to variation in PSA, fPSA, %fPSA or DPSA. However, in the participants with negative BxP, there was a significant reduction in PSA, fPSA and DPSA, but not in %fPSA.

The sensitivity to a decrease greater than 10% in PSA after the use of AT to a diagnosis of prostate cancer was 31%, with a specificity of 23%; the positive predictive value (PPV) was 12% and the negative predictive value (NPV) was 23%. The accuracy of the method was 25%. Regarding to the possibility of reducing unnecessary BxP after AT, it should be emphasized that none of the 25 participants with PCa had a final PSA below 4ng/mL.

## DISCUSSION

The present study analysed the effect of AT on PSA (tPSA, fPSA, %fPSA and DPSA) and investigated whether a relevant PSA reduction induced

**Table 3 - Comparison of PSA values between patients with and without prostate cancer.**

Benign				Prostate Cancer		
	PSA initial	PSA final	p	PSA initial	PSA final	p
tPSA	6.85±1.72	4.96±1.98	0.001	6.63±1.49	6.52±1.19	0.2
fPSA	1.35±0.44	1.06±0.47	0.001	1.02±0.37	0.97±0.40	0.077
%fPSA	19.96±5.05	22.20±5.89	0.124	15.52±4.75	15.01±5.69	0.641
PSAD	0.14±0.06	0.10±0.06	<0.00001	0.15±0.02	0.15±0.07	0.61

Values expressed in mean±standard variation. Student t test

by AT could be related to a decreased cancer detection rate at biopsy. PSA is tumour-associated but not tumour-specific. Physiological conditions other than cancer can cause an increase in serum PSA levels that lead to potentially unnecessary biopsy procedures, increasing inconvenience for the patient, and causing over-diagnosis, over-treatment and elevated medical costs (15).

Prostate cancer is determined in only 34% of biopsies performed on the basis of PSA elevation (1), and in 20–30% in patients with normal DRE and PSA values of between 4 and 10ng/mL. Therefore, there is a high level of unnecessary biopsies, particularly in this group (16, 17). The literature demonstrates a relationship between acute and chronic inflammation with elevated PSA, but there have been recent studies that suggest the effects and benefits of chronic prostatitis treatment on PSA (18–21). In our study, PCa was diagnosed more frequently in patients treated with AT (25% versus 21.4%,  $p>0.05$ ), but without statistical relevance. Antibiotics certainly did not cause changes in PSA in these men with PCa. Scardino (22) suggested that the changes in PSA with AT were similar to the random variations found in healthy men. Also, Potts (23) demonstrated no significant differences in bacterial cultures before or after AT between PSA responders and non-responders.

Okada (24) and Schatteman (25) concluded that subclinical inflammation could cause PSA elevation, and emphasized the fact that nearly half of all clinically asymptomatic men with elevated PSA levels have laboratory signs of prostatitis. They suggest that the use of antibiotics would result in a decrease in PSA levels in almost 50% of patients, thereby avoiding BxP. This approach,

however, requires careful follow-up, especially for patients whose PSA levels fail to decrease to within the normal range (26, 27). Kaygisiz (1) and Del Rosso (19) suggested that AT should be administered for 3 weeks, regardless of the presence of inflammation when PSA levels are in the grey zone, before making a decision regarding whether or not to carry out a biopsy.

On the other hand, Serretta et al. (28) found no cancer present if PSA levels decreased to below 4ng/mL, or more than 70%, and postulated that biopsy can be postponed, with only a small risk of failing to detect cancer. In multivariate analysis with other clinical variables, the PSA reduction rate was a significant independent predictor of biopsy results. Although this was not a randomized trial, it was prospective, assessing asymptomatic males without a clinical indication of prostatitis; the study demonstrated that a large reduction in PSA following antibiotics may help to avoid biopsy in selected patients in whom the PSA elevation is probably due to inflammation/infection.

Our data show that those patients who received AT and those who did not had the same rate of normalization of PSA (<4ng/mL). Prostatic Specific Antigen normalization occurred in 24.5% of individuals. In the AT group, PSA returned to normal levels in 23.4% of patients, compared with 26% patients in the non-treatment group. The reason for this is still unclear, although PSA normalization does not rule out PCa diagnosis, and biopsy must still be considered. Magri et al. (29), showed that the presence of BPH may prevent the reduction of PSA induced by combination pharmacological therapy, and suggest that care must be taken in the adoption of PSA as a marker of

therapeutic efficacy in the presence of confounding factors like BPH. According to these authors, PSA should be used as a significant component of a strategy that integrates multiple diagnostic approaches.

Our results are different from those reported by other authors. Hochreiter et al. (11) showed a PSA reduction in 63% of patients following AT, with PSA returning to normal values in 9% of cases, thus avoiding prostate biopsy. After AT, Potts et al. (23) documented PSA normalization in 42% of patients, and Brett et al. (30) found the same in 41% of patients. These studies did not perform BxP in all patients to exclude the diagnosis of PCa after treatment. Our study demonstrated a PSA normalization after antibiotics in only 23.4% of patients. However, our study performed biopsy in all patients (treated and not-treated), comparing the PCa incidence between groups. It is therefore more significant in terms of prostate biopsy decision. However, the entry of participants was not random, but based on the decision made by each participant; this may represent a selection bias. Moreover, the shared decision with the patient is one of the commonalities in international guidelines.

Approximately 10-15% of men will have a PSA level  $>4\text{ng/mL}$  in any given round of screening. However, the level will return to normal in the subsequent test in 26-37%, and will become normal with the next testing in 40-55%. Heldwein et al. (31) showed that PSA levels tend to fall when repeated after 45 days, regardless of AT. Once normalized, 65-83% of men have normal PSA levels for several years without therapy (32). If PSA levels do not fall, the probability of finding cancer is higher than if levels decrease. This occurs because PCa is more likely to occur in men with sustained PSA elevation than in those with a randomly variable PSA that is temporarily elevated (24).

Our study shows a lower, but not significant, cancer detection rate in patients with decreased PSA, fPSA and DPSA after antibiotic therapy, demonstrating a correlation between PSA normalization and prostatitis or negative biopsy. A PSA reduction rate of 10% occurred in 58.5% of patients; however, it was lower in patients who received antibiotics than in those who received no treatment (65.6% versus 71%), but there was

not significant difference ( $p>0.05$ ). The sensitivity, specificity and accuracy of a PSA reduction rate of 10% were 31%, 23% and 25%, respectively. This level is therefore not recommended as a cut-off point for clinical decision-making. Serreta et al. (28) showed a significantly lower cancer detection rate in patients with decreased PSA after antibiotic therapy, demonstrating a correlation between PSA reduction and negative biopsy, with an odds ratio varying from 1.2 to 3.9 for reduction percentages of between 10 and 90%. They suggested that a PSA reduction rate of 50% can be adopted and 11% of biopsies avoided until a further PSA increase occurs. Dirim et al. (33) reported that the f/t PSA ratio appears to be more suggestive of PCa than PSA in these cases. It should be emphasized, however, that a long follow-up time is needed to determine whether any of these men will have prostate cancer in the near future, and wider studies are required to identify the optimal PSA reduction level at which biopsy can be postponed.

The influence of prostatitis on PSA concentrations remains a controversial issue (34). Ozen et al. (35) claimed that BPH and prostatitis appear to be more frequent causes of PSA elevation. Scardino (22) recommended that asymptomatic men presenting with a modestly elevated PSA level ( $<10\text{ng/mL}$ ) and a normal digital rectal examination could be reassured and then the PSA level could be repeated once or twice; if the levels remained elevated, this would be an indication of the need to perform a biopsy. Stopiglia et al. (36), in a prospective randomized and double-blind trial with placebo, demonstrated that PSA reduction occurred after antibiotic and placebo application, and suggested that a decrease in PSA does not indicate the absence of PCa. Recently, Faydaci et al. (37) demonstrated that AT given to patients with PSA levels higher than the threshold value has not led to a significant change in prostate needle biopsy decisions, and suggested that BxP should be considered without the use of AT in patients with high PSA values if a suspicion of prostatitis does not exist. The literature does not support the evidence that antibiotics alter PSA levels except in the presence of bacterial prostatitis, which is an uncommon condition. We should wait for a second PSA assessment before prostate biopsy in asymp-

tomatic male patients once the PSA will spontaneously reduce in a quarter of cases; and that antibiotic use has no role in this clinic scenario (36).

There are several implications in the use of empiric AT for patients with elevated PSA levels. Scardino (22) emphasized some disadvantages of this approach, such as cost, toxicity, and the fact that it can cause complications of infection. Moreover, a decrease in PSA after AT does not absolutely exclude the presence of PCa, even if the PSA decreases to very low levels. In addition, there is concern that the indiscriminate use of empiric antibiotics could lead to the development of resistant bacterial species and thereby expose the patient to more resistant and aggressive sepsis, should a biopsy eventually be performed (38-40).

## CONCLUSIONS

Empirical antibiotic therapy in asymptomatic male patients is not related to PSA reduction and that PSA reduction after antibiotic cannot postpone prostate biopsy. Based in our findings, only PSA normalization can postpone prostate biopsy. Additionally, it is not possible to define a safe rate reduction and further studies stratifying the relative values of reduction and cancer risk are needed.

## CONFLICT OF INTEREST

None declared.

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