ORIGINAL ARTICLES

Aggressiveness of Inflammation in Histological Prostatitis – Correlation with Total and Free Prostate Specific Antigen Levels in Men with Biochemical Criteria for Prostate Biopsy

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Abstract

Background and Aims

Although prostatitis can contribute to the lack of prostate specific antigen (tPSA) specificity, there is disagreement concerning the effect of histological inflammation on free PSA (fPSA). We investigated the correlation between aggressiveness of histological inflammation and tPSA, fPSA and f/tPSA in patients without detectable prostate cancer (PC).

Methods

The study included 106 patients with tPSA <10 ng/mL, without clinical prostatitis and with biopsy negative for PC. The inflammation in prostate biopsies was scored for aggressiveness using the four-point scale reported by Irani. The patients were divided into two groups of less aggressive and more aggressive inflammation and compared by use of regression analysis.

Results

The median tPSA, fPSA and f/tPSA levels were 6.39 ng/mL, 1.1 ng/mL and 16% in the less aggressive inflammation group and 7.3 ng/mL, 0.79 ng/mL and l0.7% in the more aggressive inflammation group, respectively. There was no significant between-group difference in tPSA levels (P=0.16), however, statistically significant between-group differences were recorded in fPSA and f/tPSA levels (P<0.001 both). Spearman's analysis yielded a significant negative correlation of inflammation aggressiveness with fPSA (r=-0.34; P<0.001) and f/tPSA (r=-0.45; P<0.001). Free PSA and f/tPSA were lower in the group with more aggressive inflammation.

Conclusions

Histological inflammation has a high prevalence in cancer-free prostate biopsy specimens and exerts similar effects on fPSA and f/tPSA levels as PC. Our study suggests histological prostatitis to be an important cause of decreased fPSA and f/tPSA values; therefore, when it is identified, antibiotic or anti-inflammatory therapy should be introduced to reduce the percentage of men with a continuing indication for prostate biopsy.

Key Words

Prostate specific antigen, free prostate specific antigen, prostate inflammation, prostatitis, prostate biopsy, prostate cancer.

Introduction

Prostate-specific antigen (PSA) is the most useful serum marker for the early detection of prostate cancer (PC), but it is not cancer-specific and various benign pathological processes such as benign prostatic hyperplasia (BPH) or prostatitis also influence total serum PSA (tPSA) concentration.[1,2,3] In urological practice, patients classified in so called 'grey zone' (PSA <10 ng/mL) with a decreased free PSA (fPSA) and percent-free PSA (f/tPSA) levels, whose biopsies reveal no malignancy but only inflammation, are quite often seen. These patients pose a special problem for the early detection of PC, especially those with negative digital rectal examination (DRE) findings. Subclinical prostatitis is a very common histological finding on pathological examination of prostate biopsy and prostate surgery material. Although inflammation is known to potentially contribute to the lack of tPSA specificity, there is still disagreement concerning the effect of asymptomatic inflammation on fPSA and f/tPSA values.

In the present study, we evaluated the relationship between aggressiveness of asymptomatic, histological inflammation of the prostate and tPSA, fPSA and f/tPSA levels in patients free from PC or clinical signs of acute prostatitis, and with tPSA concentrations of up to 10 ng/mL.

Material and Methods

Our study included 106 consecutive patients with tPSA ≤10 ng/mL and eight-core prostate biopsy negative for PC and free from clinical signs of prostatitis. Serum PSA testing (tPSA, fPSA) (Immulite-DPC assay), DRE and transrectal ultrasound (TRUS)

Figure 1: Normal prostate epithelial tissue without inflammatory cell infiltrate (inflammation aggressiveness grade 0) (HE, x200)

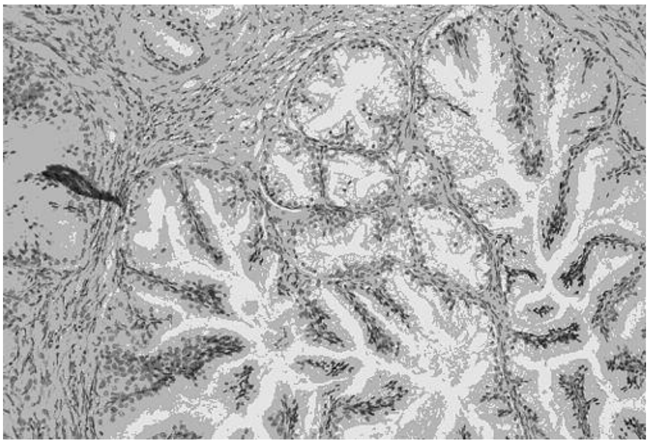


Figure 2: Stromal and periglandular mononuclear cell infiltrate without epithelium disruption (inflammation aggressiveness grade 1) (HE, x400)

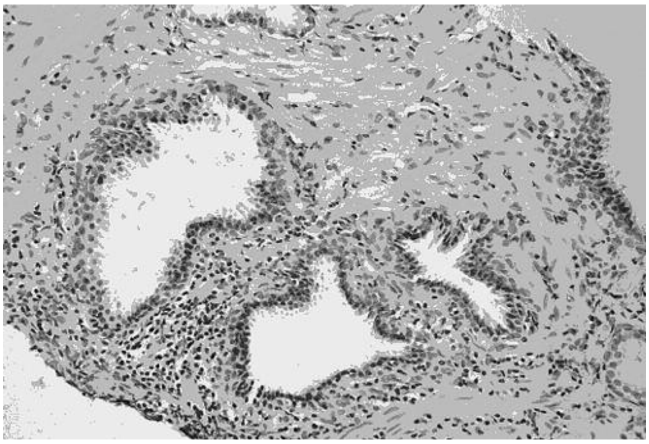


Figure 3: Mononuclear and polymorphonuclear cell infiltrate in stroma and partially in epithelium of glands and ducts (glandular epithelium disruption in less than 25% of the examined material) (inflammation aggressiveness grade 3) (HE, x400)

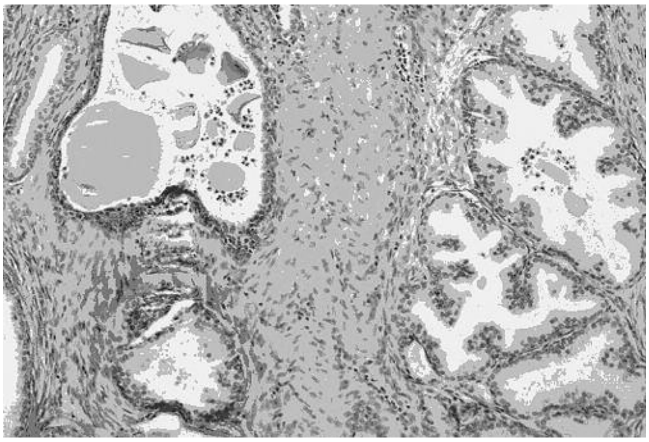
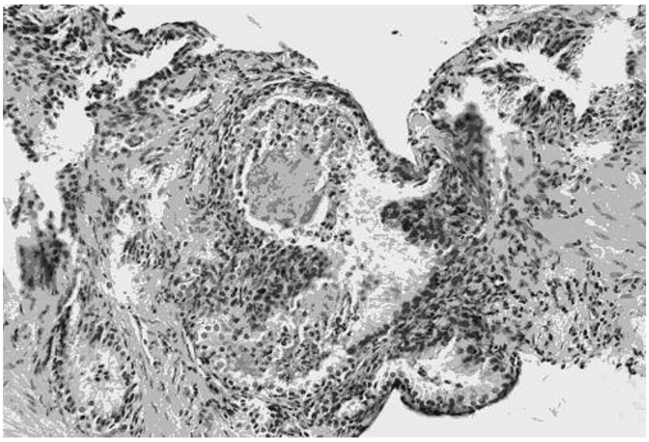


Figure 4: Aggressive polymorphonuclear cell infiltrate with extensive destruction of prostate epithelium and formation of microabscesses in lumina of glands or ducts (epithelium disruption in more than 25% of the examined material) (inflammation aggressiveness grade 4) (HE, x400)



(Siemens Sonoline SI-400) were performed prior to TRUS guided prostate biopsy. Patients with PC or premalignant lesions in definitive biopsy reports were excluded from the study. Patients were also excluded from the study if they had a documented history or clinical signs of prostatitis or urinary tract infection, serum PSA greater than l0 ng/mL and prostate volume measured by TRUS greater than 40 cm.[3]

The inflammation in prostate biopsies was scored for aggressiveness using a four-point scale described by Irani *et al*.[4] Each biopsy core of prostatic tissue (eight cores sampled from each patient) was scored for the aggressiveness of inflammation using the 4-point scale according to the degree of contact or disruption of prostatic glandular epithelium by inflammatory cell infiltrate, as follows: 0 – no contact between inflammatory cells and glandular epithelium (Figure 1); 1 – contact between inflammatory cell infiltrate and glandular epithelium (Figure 2); 2 – clear but limited, i.e. glandular epithelium disruption in less than 25% of the material, (Figure 3); and 3 – glandular epithelium disruption in more than 25% of the material (Figure 4).

Statistical analysis

Different patterns and types of histological inflammation with a range of inflammation aggressiveness grades were found in almost every set of prostate biopsies. Therefore, we used regression analysis to create a reduced classification for inflammation aggressiveness with two groups of patients for comparison. Descriptive statistics were used to describe patient clinical characteristics (patient age, prostate volume, tPSA, fPSA and f/tPSA values). Mann-Whitney nonparametric test was used on comparison of tPSA, fPSA and f/tPSA values between the two patient groups (level of significance: $P<0.05$). Correlations among clinical variables such as age, prostate volume, tPSA, fPSA, f/tPSA and inflammation aggressiveness factor scores were determined using Spearman's nonparametric correlation test (level of significance: $P<0.01$).

Results

Patients with prostate biopsy negative for PC and meeting the inclusion criteria were prospectively studied at our department between January 2005 and January 2006. Clinical characteristics of 106 study patients are shown in Table 1. The median age of study patients was 65 (range 47-83) years and median prostate volume 31.5 (range 16-40) cm^3. The median (range) levels of tPSA, fPSA and f/tPSA were 6.6 ng/mL (3.4-10), 0.9 ng/mL (0.14-3.1) and 13.45% (2.5-35%), respectively.

Table I: Clinical characteristics of study patients (N=106)

	Age (yrs)	Vp (cm^3)	tPSA (ng/mL)	fPSA (ng/mL)	f/tPSA (%)
Mean	65.44	31.56	6.95	1.01	14.71
Median	65	31.5	6.6	0,9	13.45
SD	6.89	7.27	1.95	0.54	6.74
Min.	47	16	3.4	0.14	2.5
Max.	83	40	10	3.1	35

Vp = prostate volume

After initial histological coding of each biopsy cylinder (eight cores *per* prostate biopsy) for inflammatory aggressiveness grade, we used regression factor analysis to create a reduced classification and form two groups of patients for comparison and statistical analysis: patients with less aggressive inflammation (n=59; 55.7%) and patients with more aggressive inflammation (n=47; 44.3%).

Characteristics and differences between the two inflammation aggressiveness groups according to age, prostate volume, tPSA, fPSA and f/tPSA values are shown in Table II.

Table II: Characteristics and differences between two patient groups according to age, prostate volume, tPSA, fPSA and f/tPSA levels (significance: P<0.05)

	Inflammation aggressiveness groups		P (Mann-Whitney)
	Less aggressive (n=59)	More aggressive (n=47)	
	Median (range)	Median (range)	
Age (yrs)	65 (47-83)	67 (53-81)	0.64
Vp	27 (16-40)	38 (16-40)	<0.001*
tPSA (ng/mL)	6.39 (3.4-10)	7.3 (4.1-10)	0.16
fPSA (ng/mL)	1.1 (0.28-3.1)	0.79 (0.14-2.9)	<0.001*
f/tPSA (%)	16 (5.8-35)	10.7 (2.5-29.6)	<0.001*

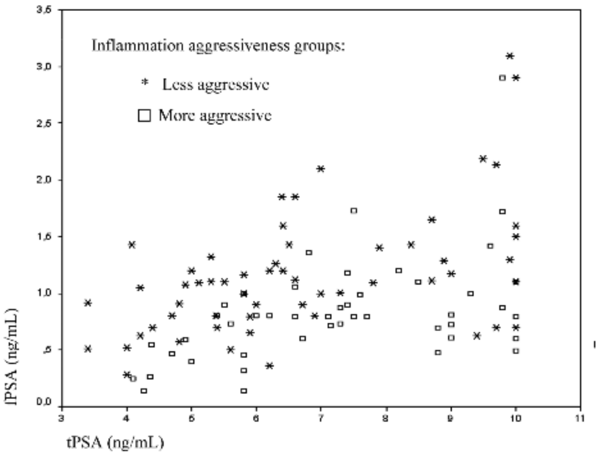
*statistically significant; Vp = prostate volume

The median (range) levels of tPSA, fPSA and f/tPSA were 6.39 ng/mL (3.4-10), 1.1 ng/mL (0.28-3.1) and 16% (5.8-35%) in the group with less aggressive inflammation and 7.3 ng/mL (4.1-10), 0.79 ng/mL (0.14-2.9) and 10.7% (2.5-29.6%) in the group with more aggressive inflammation, respectively. Statistically significant between-group differences were recorded in fPSA, f/tPSA and prostate volume (p<0.001 all), with decreased fPSA and f/tPSA levels found in patients with more aggressive subclinical inflammation of the prostate. Patient age and tPSA levels showed no statistically significant between-group differences according to inflammation aggressiveness (p=0.64 and p=0.16, respectively).

Figure 5 shows distribution of the two inflammation aggressiveness groups according to serum tPSA and fPSA levels. Although the scattergram shows some data overlapping, patients with more aggressive inflammation of the prostate tended to group around lower fPSA values and slightly higher tPSA values.

Relationship between the study characteristics was assessed by Spearman's nonparametric correlation test (Table III). There was a significant negative correlation between aggressiveness of inflammation and levels of fPSA (r=-0.34) and f/tPSA (r=-0.45) (P<0.001 both). Decreased levels of fPSA and f/tPSA were found in patients with more aggressive histological inflammation.

Figure 5: Scattergram of fPSA versus tPSA values in two groups of patients according to inflammation aggressiveness



There was a slight positive correlation between tPSA levels and grades of inflammation aggressiveness, but it did not reach statistical significance (r=12; P=0.23). Total PSA levels correlated positively with fPSA (r=0.4; P<0.001). As expected, there was no correlation between prostate volume and tPSA (r=0.12; P=0.22). On the other hand, prostate volume correlated significantly with age (r=0.29; P=0.003), fPSA (r=0.32; P=0.001) and f/tPSA (r=0.31; P=0.001). Interestingly, inflammatory aggressiveness tended to rise as the prostate volume increased (r=0.48; P<0.080).

Table III: Spearman's nonparametric correlation matrix showing relationships between quantitative characteristics and inflammation aggressiveness (significance: P<0.01)

r / P value	Age	tPSA	fPSA	f/tPSA	Vp	IAFS
Age	1	0.06	0.15	0.15	0.29	0.03
		0.54	0.13	0.13	0.003*	0.75
tPSA	0.06	1	0.4	-0.13	0.12	0.12
	0.54		<0.001*	0.17	0.22	0.23
fPSA	0.15	0.4	1	0.82	0.32	-0.34
	0.13	<0.001*		<0.001*	0.001*	<0.001*
f/tPSA	0.15	-0.13	0.82	1	0.31	-0.45
	0.13	0.17	<0.001*		0.001*	<0.001*
Vp	0.29	0.12	0.32	0.31	1	0.48
	0.003*	0.22	0.001*	0.001*		<0.001*
IAFS	0.03	0.12	-0.34	-0.45	0.48	1
	0.75	0.23	<0.001	<0.001*	<0.001*	

*statistically significant; Vp = prostate volume; IAFS = inflammation aggressiveness factor score

Discussion

On differential diagnosis of PC, patients with negative DRE findings and borderline serum tPSA levels (4-10 ng/mL) are the most controversial group; therefore, we included this particular subpopulation in our study. Prostate biopsy is usually performed to rule out PC in this group of patients, especially those with f/tPSA lower than 18%, which has been suggested as a useful diagnostic tool to differentiate between PC and benign prostatic diseases because it is lower in PC than in BPH.[5] However, when DRE is normal and serum PSA is between 4.1 and 10 ng/mL, 80% of biopsy specimens are reported as benign.[2] Different patterns of histological inflammation are frequently found in prostate biopsy reports negative for PC. Blumenfeld *et al.*[6] and Kohnen and Drach[7] report on a more than 90% rate of inflammation in prostatic biopsy specimens after transurethral resection of the prostate and open prostatectomy.

Recently, a number of studies have been published investigating the relationship between asymptomatic inflammatory prostatitis and elevated tPSA levels in patients without PC on the basis of morphological parameters, but very few analysed the effect of subclinical inflammation of the prostate on fPSA and f/tPSA levels. Most studies do confirm that prostatitis can increase tPSA levels, whereas major controversies exist about the effect of histological inflammation to fPSA levels. Some authors found no correlation between fPSA levels and subclinical inflammation,[8,9] whereas others found it to be significant.[10,11,12,13]

In our study, we tried to determine whether subclinical prostatic inflammation might influence serum fPSA and f/tPSA levels in men with clinically undetectable PC and with tPSA levels of up to 10 ng/mL.

In many recent studies on the issue, prostate volume was not considered on comparisons, although it has been shown to influence markedly serum tPSA and fPSA levels.[14] In our series there was no correlation between prostate volume and tPSA values as expected, because only patients with small prostates (<40 cm^3) were included in order to minimise the bias effect of prostatic adenoma on tPSA values. Meyer *et al.*[11] report on serum tPSA to have increased significantly only in patients with benign prostates larger than 40 cm^3, whereas we found positive correlation between prostate volume and fPSA level ($r=0.32$; $P=0.001$). Similar results have been reported by Kwak *et al.*[15]

It is well known that symptomatic prostatitis increases serum PSA levels.[16,17,18] In their study of negative prostate needle biopsies, Okada *et al.* found the degree of inflammation to correlate significantly with tPSA levels.[19] On the other hand, Brawer *et al.* report on elevated tPSA levels only in patients with clinically acute prostatitis, but not in patients with subclinical, chronic prostatitis,[16] which is consistent with our data on the relationship between subclinical prostatitis and tPSA levels. In our study, positive correlation was recorded between inflammation aggressiveness and tPSA, but it was not statistically significant, maybe because we only included patients with tPSA levels up to 10 ng/mL and free from clinical signs of acute prostatitis. Kwak *et al.* and Nickel *et al.* found no correlation between tPSA levels and type or extent of histological inflammation of the prostate either.[15,20] Opposite to our results, Ozden *et al.* found significant correlation between tPSA and asymptomatic inflammatory prostatitis with a high aggressiveness score in patients without clinical signs of prostatitis.[21] Hoekx *et al.* report on patients with elevated serum tPSA levels and no malignancy in their transrectal prostate biopsy to have a lower risk of biopsy missed PC in the presence of inflammation with a high aggressiveness score.[22]

Only a few studies examined the effect of histological inflammation on fPSA and f/tPSA levels in patients without clinically detectable PC. Most studies confirmed that more acute or more aggressive histological inflammation could cause a rise in tPSA, however, with major discrepancies in fPSA findings.

Our results are consistent with those reported by Jung *et al.* and Meyer *et al.*, who report reduced f/tPSA values in patients with PC and prostate inflammation compared to controls or BPH patients.[10,11] In our study, the group of patients with more aggressive inflammation of the prostate had significantly decreased fPSA and f/tPSA values as compared with the group of patients with less aggressive inflammation. However, our results differed from those reported by Ornstein *et al.*, where f/tPSA levels did not appear to alter with the presence or extent of subclinical inflammation.[8] Interestingly, Scattoni *et al.* report that a more acute subclinical histological prostatitis induced a high increase in the f/tPSA ratio, while chronic inactive prostatitis seemed to induce lower f/tPSA ratios in patients without PC.[13]

The molecular reasons for these inflammation-related changes in PSA forms have not yet been fully described. Irani *et al.* and Yaman *et al.* found serum PSA levels to correlate with aggressiveness, i.e. the grade of glandular epithelium disruption, but did not find any correlation between the extent of prostatic interstitial inflammatory cell infiltrate or type of inflammatory cells and serum PSA concentrations.[4,23] They assumed the inflammation to influence serum PSA concentrations by causing PSA leakage from the acini. An increased PSA concentration was only found in association with glandular epithelium disruption. Hasui *et al.* suggest that abnormal elevation of serum PSA levels is caused by leakage of PSA stored in the epithelial cells into the stromal tissue and blood circulation after epithelial cellular death.[18] An explanation for the decrease in fPSA levels due to the inflammation process has been proposed by Christensson *et al.* and Bjork et al.[24,25] They showed that α1-antichymotrypsin, which binds to fPSA molecule, is synthesised at a considerably greater rate in malignant cells than in benign tissue. In this way, more fPSA is complexed in tumour than in BPH, leading to a decrease in fPSA and an increase in tPSA, which is typical for PC. Similar intracellular changes can occur in prostatic inflammation because an increased production of α1-antichymotrypsin is a typical reaction to inflammation, thus more fPSA molecules being bound to α1-antichymotrypsin. This results in a decrease in fPSA and f/tPSA levels. Zackrisson et al., who measured serum values of fPSA, tPSA and their ratios in men with febrile urinary tract infection during one year follow up, have recently proposed an interesting explanation.[26] They demonstrated a relative decrease in fPSA and f/tPSA ratio in combination with sustained elevation of tPSA for up to six months after acute urinary tract infection.

To our knowledge, the present study is the first to explore the effect of histological prostatic inflammation on tPSA, fPSA and f/tPSA levels in patients within so called 'grey zone' (with tPSA levels up to 10 ng/mL) and without clinically detectable PC. Our results imply that a decreased level of serum fPSA and f/tPSA is not typical of cancer cells alone because these values are similarly affected by histologically more aggressive inflammation of the prostate. We think that all patients with abnormal PSA levels should undergo prostate biopsy because neither clinical examination nor PSA and its fractions permit reliable discrimination of PC and subclinical prostatitis, especially in the subgroup of patients with PSA levels up to 10 ng/mL. The question is when to perform repeat prostate biopsy. Long-term antibiotic or anti-inflammatory therapy seems to be a reasonable option in patients with considerable inflammatory infiltrate in biopsy reports negative for PC. We believe that pathologists should report on the extent and aggressiveness grade of histological inflammation, especially on initial prostate biopsies of small volume prostates, in order to help determine appropriate timing for repeat biopsy.

Conclusions

Because of the insufficient PC specificity of PSA, a considerable number of patients undergo unnecessary biopsies that result in a low rate of positive biopsy findings. Histological inflammation of the prostate is a common finding in almost every set of prostate biopsies performed in men free from PC or clinical signs of acute prostatitis. This subclinical inflammation can cause abnormal tPSA and fPSA levels. As seen from our results, a histologically more aggressive inflammation of the prostate was not characterised by elevated tPSA concentrations, but by significantly decreased fPSA values, a tendency similar to that in PC. In comparison with patients within the 'grey zone' (with PSA levels up to 10 ng/mL), whose prostate biopsies reveal no malignancy but only histological inflammation, this concept could help determine the need of antibiotic or anti-inflammatory therapy, thus reducing the percentage of men with a continuing indication for prostate biopsy.

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