Serum Prostate-Specific Antigen Levels in Middle Eastern Men with Subclinical Prostatitis

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Key Words

Prostatitis · Benign prostate disease · Prostate cancer · Prostate-specific antigen · Middle Eastern men

Abstract

Objective: To investigate the influence of subclinical or histologically diagnosed prostatitis on serum prostate-specific antigen (PSA) in patients investigated for prostatic disease in Kuwait. **Materials and Methods:** Serum PSA was assayed in patients investigated for prostatic disease in Mubarak Al-Kabeer Hospital, Kuwait, between December 2002 and December 2004. These included patients undergoing transrectal ultrasound with needle biopsy of the prostate gland and those who were treated with transurethral resection of the prostate or retropubic prostatectomy. The tissue was evaluated for prostatitis as well as the underlying disease, and the type and severity of prostatitis were compared with levels of serum PSA. **Results:** Of the 331 tissue specimens, 18 (5.4%) did not show prostatitis, while 233 (70.4%) with benign prostate and 80 (24.2%) with malignant prostate disease showed prostatitis. Of 270 men with known serum PSA levels, 198 and 72 had benign and malignant prostate disease, respectively. Of the 198, 77 (41%) with benign prostate disease and prostatitis and of the 72, 52 (76%) with malignant prostate disease and prostatitis had serum PSA levels >10 ng/ml. **Conclusion:** The data showed that although raised serum PSA is

more commonly associated with prostate cancer, subclinical prostatitis is a significant source of high serum PSA in over 40% of men in Kuwait. That local factors may obscure the usefulness of serum PSA as a screening tool suggests the need for a locally applicable paradigm to identify prostate cancer.

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Introduction

Prostate cancer is increasingly being diagnosed in Kuwait. Although it ranks fourth of all malignancies in Kuwaiti men, its incidence during the past decade has increased threefold, from 4.3 per 10⁵ population in 1994 to 12.8 per 10⁵ population in 2003 [1, 2]. Worldwide, assay of serum prostate-specific antigen (PSA) is currently the accepted first-line investigation in the diagnosis of prostate cancer [3–5]. Sensitivity and specificity have been confirmed in many studies, and clinical utility is strengthened by other diagnostic modalities, such as digital rectal examination (DRE) and transrectal ultrasound (TRUS) [6, 7]. Because serum PSA increases in nonmalignant conditions such as benign prostate hyperplasia (BPH), following needle core biopsy or transurethral resection of the prostate (TURP), and in symptomatic or acute clinical prostatitis, a cutoff level of serum PSA has been defined

below which the probability of prostate cancer is low. The customary cutoff level, based on studies in the USA and Europe, is 4 ng/ml. Similarly, the level of serum PSA above which the diagnosis of prostate cancer has been considered most probable is 10 ng/ml [5]. The current paradigm in the diagnosis of prostate cancer, therefore, is to subject men with serum PSA levels between 4 ng/ml and 10 ng/ml to DRE and TRUS to determine the size, texture, and presence of masses in the prostate gland. TRUS-guided needle biopsy is added to ensure correct tissue diagnosis in such subjects [6]. The above regimen has proved satisfactory, especially in developed countries where adequate facilities are available to ensure the protocol.

The effect of subclinical prostatitis or histologic prostatitis on serum PSA levels has recently been discussed. In particular, high serum PSA levels have been reported in men with BPH, but no accompanying clinical prostatitis [8, 9]. Subclinical or histologic prostatitis is a common finding in prostate specimens especially in association with BPH [10]. We have observed this in Middle Eastern men and reported a high prevalence of active chronic prostatitis associated with high levels of serum PSA [11]. We found levels of serum total PSA over 10 ng/ml and often exceeding 50 ng/ml in at least 30% of men with benign prostate disease but no clinical prostatitis in our institution [9, 11]. Others have commented on similar, often empiric findings and advocated a thorough study of serum PSA levels in benign prostate diseases [12–14]. Such studies should provide appropriate guidelines for the use of serum PSA in the diagnosis of prostate cancer in different communities.

In this study, we have carried out a prospective investigation of the relationship between serum PSA levels and histologic prostatitis in subjects without clinical prostatitis. In addition, we have examined the influence of co-existing features such as the presence of calcification (as determined by TRUS and confirmed by histology) and the presence of fibromuscular reparative nodules in the prostate gland on serum PSA levels. These are morphological features that may be associated with chronic inflammation in the prostate. The effect on serum PSA of coexistent diabetes mellitus, a systemic disease that predisposes to deep-seated infections, was also assessed.

Materials and Methods

All men (of Middle Eastern origin) investigated for BPH or symptoms of urinary obstruction in Mubarak Al-Kabeer Hospital (Kuwait) between December 2002 and December 2004 were included in the study. These included patients at our hospital for

whom full clinical data including serum PSA were available as well as patients referred to our institution for TRUS and needle biopsy. The main exclusion criteria in this study were a clinical diagnosis of prostatitis, the presence of an indwelling urethral catheter and a history of previous biopsy or urological procedure. Informed consent was obtained from the subjects, and the study was approved by the Ethics Committee of the institution.

A standard protocol was used for the collection of clinical data, which included information on the presence and duration of diabetes mellitus and measurement of residual urine at initial presentation. Blood was collected at initial presentation and used for total PSA assay by one clinical pathologist (O.A.M.) using a chemiluminescent assay (Immulite 2000, DPC, Los Angeles, Calif., USA). The percentage of free PSA was determined for patients found to have PSA levels between 4 and 10 ng/ml. DRE was performed by experienced urologists (E.O.K., A.Y., K.A.A.), who also performed TURP or retropubic prostatectomy as required for management of the patients. TRUS of the prostate was performed by one radiologist (M.A.S.) using a GE Logic 500 scanner (GE Medical Systems, Wisc., USA) followed by needle biopsy using 18-gauge needles driven by a spring-loaded biopsy gun (Bard, USA) on those with an abnormal DRE or serum PSA above 4 ng/ml or both. A minimum of sextant biopsies was performed for each patient. When DRE revealed an enlarged or irregular and firm prostate gland, an abnormality was detected on TRUS, or the percentage of free PSA was below 12.5%, additional biopsies were obtained up to a maximum of 12. Prostate volume was determined as well.

Serum PSA was determined 3 months after treatment of the presenting urological disorder. Patients with PSA >4 ng/ml and no previous diagnosis of prostate cancer had repeat TRUS and prostate biopsy. Those found to have prostate cancer were managed according to the local protocol and excluded from the study.

All tissue was fixed in a 4% solution of formaldehyde, processed routinely into paraffin blocks and sections stained with hematoxylin and eosin were examined microscopically by one pathologist (J.T.A.). Parameters determined by microscopy included the presence of prostate inflammation, which was classified into: (1) active chronic prostatitis (periglandular inflammatory infiltrate consisting predominantly of chronic inflammatory cells, but with some disruption of glandular epithelium as well as neutrophilic and macrophage infiltrate) and (2) chronic inactive prostatitis (periglandular fibrosis with surrounding chronic inflammatory infiltrate and/or lymphoid aggregate replacing a completely destroyed gland) (fig. 1, 2), as reported previously [9, 14, 15]. The severity of prostatitis was also graded semiquantitatively [9]. The presence and extent of fibromuscular 'reparative' nodules, as well as calcific deposits were noted. Reparative nodules are circumscribed areas of stromal repair following destruction of prostate acini.

The relationship between serum PSA levels and prostatitis, reparative nodules, intraprostatic calcification as well as diabetes mellitus in the subjects was analyzed.

Statistical Analysis

Simple descriptive statistical methods were employed for analysis of the data, and the χ^2 test was used to determine statistical significance of variables. A *p* value <0.05 was considered significant.

Fig. 1. Photomicrograph showing active chronic prostatitis. The prostate gland acinus is surrounded by predominantly chronic inflammatory cells with some neutrophils, and there is infiltration of the epithelial layer by neutrophils (arrows). The lumen of the gland is also shown (L). HE. $\times 400$.

Fig. 2. Photomicrograph showing chronic inactive prostatitis. There is fibrosis around the gland (F), in addition to a heavy chronic inflammatory infiltrate. There are no neutrophils in the epithelial layer (arrows). The lumen is shown (L). HE. $\times 400$.

Results

A total of 331 patients aged between 43 and 90 years were seen during the study period. These included 270 patients in our hospital with complete data including serum PSA. Microscopic examination on all 331 tissue specimens including 192 needle biopsies, 131 TURPs and 8 retropubic prostatectomy specimens enabled categorization of tissues into benign (246) and malignant (85). The presence and severity of active chronic and chronic inactive prostatitis in the specimens are summarized in table 1. Of the 177 active chronic prostatitis cases, 150 (85%) were benign while 27 (15%) were malignant. Thus, active chronic prostatitis was found proportionately more often in benign biopsies ($p < 0.001$, table 1).

Relationships between both forms of chronic prostatitis and serum PSA levels in 270 of these patients with known serum PSA levels are given in table 2. A prominent feature of this table is that 77 (41%) of the patients with benign disease and microscopic evidence of prostatitis had serum PSA levels in excess of 10 ng/ml, and 31 (17%) had serum PSA levels above 20 ng/ml. However, among those with malignant prostate tissue, 51 (76%) had serum PSA levels >10 ng/ml and of these, 38 (57%) had serum PSA levels above 20 ng/ml. Follow-up of the 59 patients (table 2) with benign biopsies and serum PSA levels <4 ng/ml showed that only 1 patient (0.8%) had a persistent serum PSA el-

Table 1. Findings of prostatitis in benign and malignant tissues of 331 patients

Microscopic diagnosis	Grade	Benign (n = 246)	Malignant (n = 85)	Total (n = 331)
No prostatitis	–	13 (5%)	5 (6%)	18
Chronic inactive prostatitis	1	58	35	93
	2	25	18	43
	3	0	0	0
Subtotal ¹		83 (34%)	53 (62%)	136
Active chronic prostatitis	1	87	19	106
	2	53	7	60
	3	10	1	11
Subtotal ¹		150 (61%)	27 (32%)	177
Grand total		246	85	331

¹ Number and type of prostatitis in benign vs. malignant tissue ($p < 0.001$).

evation above 12 ng/ml after 3 months. Repeat TRUS and biopsy of the prostate of this patient revealed a focus of low-grade carcinoma. There was no significant correlation between the severity of both active chronic and inactive chronic prostatitis and serum PSA levels in either benign prostatic disease or prostate cancer.

Table 2. Correlation of PSA with prostatitis in 270 patients

Disease	Type of prostatitis	Serum PSA, ng/ml				Total
		<4	4–10	10–20	>20	
Benign prostate tissue (n = 198)	no prostatitis	3	5	2	2	12
	chronic inactive	24	16	19	13	72
	active chronic	35	34	27	18	114
	total prostatitis	59 (32)	50 (27)	46 (25)	31 (16)	186
Malignant prostate tissue (n = 72)	no prostatitis	1	0	2	2	5
	chronic inactive	3	8	6	27	44
	active chronic	1	4	7	11	23
	total prostatitis	4 (6)	12 (18)	13 (19)	38 (57)	67

Figures in parentheses indicate percentages.

Correlations between inactive chronic prostatitis and active chronic prostatitis with ancillary features to evaluate any relationship between these findings and inflammation in the prostate gland are shown in table 3. These findings include: diabetes mellitus determined in 143 patients and calcific deposits and reparative fibromuscular nodules as observed in the 331 biopsies. Active chronic prostatitis correlated significantly with diabetes mellitus ($p = 0.014$) and the presence of reparative fibromuscular nodules in tissue sections ($p = 0.001$) but not with calcification in tissue ($p = 0.514$).

Table 4 correlates serum PSA levels with the same three parameters. It shows no significant correlation between diabetes mellitus or intraprostate calcification and serum PSA levels. Reparative nodules correlated significantly with serum PSA levels above 4 ng/ml ($p = 0.031$), but not above 10 ng/ml ($p = 0.164$).

Discussion

In standard urologic practice, serum PSA levels in excess of 10 ng/ml are considered indicative of prostate cancer and values above 20 ng/ml would be considered diagnostic. Yet in the present study, as many as 77/186, or approximately 41% of patients with microscopic features of prostatitis (both chronic inactive and active chronic) had serum PSA in excess of 10 ng/ml. Of these, 31 patients (17%) with benign prostate gland had serum PSA levels above 20 ng/ml, levels generally considered diagnostic for prostate cancer. This confirms our earlier finding [9] and further emphasizes the high number of false-positive results in our population, relying solely on serum PSA val-

Table 3. Coincidence of chronic prostatitis with three clinical and morphologic findings

	Parameter	Prostatitis		Total	p value
		inactive	active		
Diabetes mellitus (n = 143)	present	11	31	42	0.014
	absent	50	51	101	
Intraprostatic calcification (n = 331)	present	26	33	59	0.514
	absent	110	144	254	
Reparative nodules (n = 331)	present	13	47	60	0.001
	absent	123	130	253	

ues for the diagnosis of prostate cancer, even with the higher cutoff level of 20 ng/ml.

Our findings are in accord with those of Simardi et al. [16]. Similar results have been reported by Yaman et al. [17], who related the PSA elevation to the extent of inflammation within the prostate tissue. In view of these findings, some advocate repeat biopsies in men with high PSA levels and inflammatory changes in the prostate tissue, stressing the importance of lowering PSA levels by appropriate treatment to avoid overdiagnosis of cancer [18]. Antibiotic treatment has been recommended before repeat biopsy [11, 19]. We have observed a rapid and dramatic fall in serum PSA levels following antibiotic treatment in those patients with very high serum PSA in the absence of prostate cancer.

We had previously reported our experience with repeat biopsies of the prostate gland following treatment of prostatitis [11]. Where PSA level failed to normalize after treatment (e.g. TURP for patients with BPH or antibiotics

Table 4. Correlation of serum PSA with clinical and morphologic findings

	Parameter	Serum PSA, ng/ml				Total
		<4	4–10	10–20	>20	
Diabetes mellitus (n = 143)	present	15	11	9	7	42
	absent	29	22	20	30	101
		p = 0.263 ¹		p = 0.144 ²		
Intraprostatic calcification (n = 270)	present	14	17	12	17	60
	absent	53	50	51	56	210
		p = 0.454 ¹		p = 0.416 ²		
Reparative nodules (n = 270)	present	19	11	14	9	53
	absent	48	56	49	64	217
		p = 0.031 ¹		p = 0.164 ²		

¹ p value for PSA <4 vs. >4 ng/ml.
² p value for PSA <10 vs. >10 ng/ml.

such as amikacin, ciprofloxacin, norfloxacin or septrin in appropriate doses where prostate biopsy showed inflammation), the subsequent rate of detection of prostate cancer was low [11]. In the present study, we have confirmed this observation and noted the impact of subclinical (microscopically detected) prostatitis on serum PSA levels. In all our patients but 1 with benign prostate disease, subclinical prostatitis and a PSA level above 4 ng/ml at initial examination, the PSA level returned to normal following treatment. Previous studies explained the high levels of PSA found in patients with inflammatory disorders of the prostate by the 'leak phenomenon' [14, 20, 21].

The prevalence of diabetes mellitus in the Kuwaiti population is reported to be 15% [22]. Of the 143 patients in this study with full clinical data, diabetes was present in 42 (29.4%), which is double the general rate. In diabetics, active chronic prostatitis was significantly more prevalent than inactive chronic prostatitis ($p = 0.014$), but this difference was not reflected in the level of serum PSA (table 4). This indicates diabetes may predispose to more active inflammatory changes in the prostate gland, but is not a determinant of serum PSA levels. Intraprostatic calcification was present in only 61/331 (18%) cases, with no significant relationship with either active or inactive chronic prostatitis. Similarly, there was no association between calcific deposits and serum PSA levels. Calcific deposits are commonly located either within intact glands (calcified corpora amylacea) or in hyalinized stroma. In both situations, there is no association with active glandular destruction. There was no relationship between calcification and diabetes mellitus in this study. Repara-

tive fibromuscular nodules are considered repair tissue following destruction of prostatic acini. In this study, these nodules were more commonly associated with active chronic prostatitis compared to inactive ($p < 0.001$) and showed a significant relationship only with moderate elevation of serum PSA. This may be due to glandular destruction.

Conclusion

This study has confirmed the prevalence of subclinical or microscopic prostatitis in Kuwaiti (Middle Eastern) men, as well as the relation of subclinical prostatitis to high levels of serum PSA in the absence of cancer. The findings indicate the need to establish the local prevalence of subclinical prostatitis to determine relevant cut-off levels of serum PSA in order to rationally screen disparate communities. The study also shows that neither diabetes mellitus nor intraprostatic calcification has any significant relation to the serum PSA level.

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