

Association between PSA Levels and Biomarkers of Subclinical Systemic Inflammation in Middle-Aged Healthy Men from the General Population

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Key Words

CRP • Fibrinogen • PSA • Prostate cancer • Systemic inflammation

Abstract

Introduction: This study was aimed to determine the association between PSA levels and biomarkers of subclinical systemic inflammation based on data from 119 middle-aged healthy men from the general population. **Materials and Methods:** Serum levels of PSA and biomarkers of systemic inflammation (CRP and fibrinogen) were measured. Demographic data were also collected. Subjects were divided into two groups according to PSA levels; < 2 ng/ml and ≥ 2 ng/ml. **Results:** The mean (SD) age of men was 55 ± 4.0 years. We found a positive significant correlation between PSA and fibrinogen levels ($r = 0.20$, $p = 0.04$), and between CRP and fibrinogen levels ($r = 0.60$, $p = 0.01$). On the other hand, no significant correlation between PSA and CRP levels was found. Men with PSA values ≥ 2 ng/ml had significantly higher levels of fibrinogen as compared to those with PSA < 2 ng/ml (2.9 ng/ml vs. 2.4 ng/ml, $p = 0.01$). In a multivariate regression analysis model adjusted for the age of subjects, BMI, marital status, smoking, snuff, and alcohol intake with serum levels of PSA as a dependent variable, serum level of

fibrinogen predicted higher PSA-values (odds ratio = 3.30, 95% CI = 1.05–10.20, $p = 0.042$). **Conclusions:** The present results indicate that serum fibrinogen is a biomarker of subclinical systemic inflammation associated with PSA elevation among middle-aged healthy men from the general population.

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Introduction

Prostate-specific antigen (PSA) is the most widely used biomarker of prostatic diseases. High PSA levels can result from different common prostatic conditions such as prostate cancer (PCa), benign prostatic hyperplasia, acute and chronic prostatitis, and prostatic manipulation (prostate biopsy, transurethral interventions).

Normally, men with PSA levels ≥ 3 ng/ml are subjected to invasive investigations, including prostate biopsy. PCa is usually detected in about 30% of the initial biopsies [1]. The remaining 70% of men with no cancer cells detected in the biopsies usually undergo a strict follow-up program, including regular evaluation of PSA

levels. In clinical practice, urologists are often confronted with the question of whether to do any further evaluation related to PSA elevation in this group of men. Should PSA elevation be interpreted as a warning sign for the presence of missed cancer cells, and thus necessitate a repeat biopsy? Or could it be caused by other co-existing subclinical conditions, and a repeat biopsy can therefore be omitted?

Recent evidence has led investigators to focus on the possible role of systemic inflammation as a potential underlying cause of PSA elevation in this group of men. Yet, only one study has addressed the issue of the possible association between biomarkers of subclinical systemic inflammation and PSA levels in men without clinical signs of prostatic diseases. The authors observed that fibrinogen is a biomarker of subclinical systemic inflammation associated with PSA elevation [2]. However, no information about the upper limit of age of the study subjects was given. Moreover, some of the included men were on regular medications and data regarding co-morbid conditions was missing. Therefore, we conducted this study to determine the association between biomarkers of subclinical systemic inflammation and PSA levels in a group of middle-aged healthy men from the general population.

Materials and Methods

This study was based on 119 middle-aged healthy men from the general population between January, 2006 and January, 2011. An invitation letter was sent to 1,601 men aged 40 to 60 years old in the southern part of Sweden asking them to participate in a study about male sexual function and subclinical cardiovascular diseases. Enclosed in the envelope were 2 questionnaires regarding their general medical health and sexual function. Men who were interested in taking part of the study were asked to sign a written informed consent and submit it to the Department of Cardiology, Malmö University Hospital along with the completed questionnaires. A medical doctor then examined the completed questionnaires, and men who were found eligible were scheduled for an interview and thorough medical examination.

Exclusion criteria were past or present history of medical diseases including psychological diseases, or prescription of regular medications during the last 6 months prior to inclusion. Men outside the range of 40–60 years of age were not included.

Demographic data such as age, marital status, and lifestyle behaviours (such as smoking, snuff, and alcohol drinking) were collected through questionnaires. Meanwhile, medical examinations were conducted and each participant's body mass index (BMI) was measured. The consistency of the prostate was assessed thorough digital rectal examination by one experienced urologist. Unfortunately, we were not able to perform transrectal ultrasound examination to estimate the prostate size, and were unable to use

Table 1. Descriptive statistics of the study population

Variables	Mean (\pm SD) or N (%)	Range
Age (years)	55 (\pm 4.0)	46–60
BMI (kg/m ²)	27 (\pm 3.0)	20–38
Marital status		
Married	94 (80%)	–
Single	24 (20%)	–
Smoking		
Never	61 (52%)	–
Past/current	57 (48%)	–
Snuff		
Never	100 (85%)	–
Past/current	18 (15%)	–
Alcohol intake		
0–50 ml/week	41 (34%)	–
60–100 ml/week	15 (13%)	–
> 100 ml/week	63 (53%)	–
Biomarkers		
PSA (ng/ml)	1.4 (\pm 1.0)	0.20–6.0
CRP (mg/l)	2.0 (\pm 3.0)	0.20–16
Fibrinogen (g/l)	2.5 (\pm 0.7)	1.4–7.0

N = 119; BMI= body mass index; PSA = prostate-specific antigen; CRP= C-reactive protein.

this variable in statistical analyses. Finally, each man was asked to deliver a blood sample for analysis of PSA and biomarkers of subclinical systemic inflammation (C-reactive protein and fibrinogen). The samples were drawn between 07:00 and 10:00 am.

A few men included in the analyses had missing data on one or more of these variables: PSA (11 men), CRP (11 men), or fibrinogen (6 men). The main outcome measures were the association between PSA levels and biomarkers of subclinical systemic inflammation as assessed by CRP and fibrinogen levels.

Statistical Analysis

Statistical analyses were done using SPSS software, version 16 (SPSS, Inc; Chicago, IL). The correlations between PSA levels and biomarkers of subclinical systemic inflammation (CRP and fibrinogen) were performed using Pearson's rank coefficient correlation test. Since the number of men with PSA levels \geq 3 ng/ml was only 7, we decided to divide the subjects into two arbitrary groups according to the level of PSA: < 2.0 ng/ml and \geq 2.0 ng/ml in order to increase the statistical power of the analysis. Moreover, PSA values less than 2.0 ng/ml is considering the minimum threshold value of the so called "grey zone" in detection of PCa. In addition, routine prostate biopsy was recommended for highly suspicious digital rectal examination findings in subjects with PSA levels less than 2.0 ng/ml [3]. The age of subjects, BMI, and biomarkers of subclinical systemic inflammation were compared between groups using the Mann-Whitney U test. Thereafter, the independence of association between PSA and fibrinogen levels as independent variable adjusted for the age of subjects (< 50, \geq 50 years), BMI (continuous), smoking (never, past/current), snuff (never, past/current), alcohol intake (0–50 ml/week, 60–100 ml/week, > 100ml/week), and marital status (married, single) was tested. P-values below 0.05 were considered statistically significant.

Table 2. Correlation coefficients (r) between PSA levels and age of subjects, BMI, and biomarkers of systemic inflammation (CRP and fibrinogen) based on data from 119 middle-aged healthy men from the general population.

Variables	PSA (ng/ml)		Age (years)		CRP (mg/l)		Fibrinogen (g/l)	
	r	p	r	p	r	p	r	p
PSA (ng/ml)	–	–	0.030	0.01*	0.10	0.30	0.20	0.04*
Age (years)	0.03	0.01*	–	–	0.08	0.40	0.15	0.10
CRP (mg/l)	0.10	0.30	0.08	0.40	–	–	0.60	0.01*
Fibrinogen (g/l)	0.20	0.04*	0.15	0.10	0.60	0.01*	–	–

PSA = Prostate-specific antigen; CRP = C - reactive protein. Analysis was done using Pearson's rank coefficient correlation. * indicating statistically significant correlation. p < 0.05 are considered statistically significant.

Table 3. Comparison of age of subjects, BMI, marital status, smoking, snuff, alcohol intake, and biomarkers of systemic inflammation in consider PSA in 119 middle-aged healthy men from the general population.

Variables	PSA	
	< 2 ng/ml	≥ 2 ng/ml
N	85	23
Age (years)	54 (± 4.0)*	57 (± 3.0)*
MBI (kg/m ²)	27 (± 4.0)	26 (± 3.0)
Marital status		
Married	67 (89%)	17 (77%)
Single	18 (21%)	5.0 (23%)
Smoking		
Never	45 (54%)	12 (52%)
Past/current	39 (46%)	11 (48%)
Snuff		
Never	70 (82%)	22 (96%)
Past/current	15 (18%)	1.0 (4.0%)
Alcohol intake		
0–50 ml/week	28 (33%)	11 (48%)
60–100 ml/week	9.0 (11%)	3.0 (13%)
> 100 ml/week	48 (56%)	9.0 (39%)
Biomarkers		
PSA (ng/ml)	0.9 (± 0.48)	3.0 (± 1.2)
CRP (mg/l)	1.8 (± 3.0)	2.4 (± 3.0)
Fibrinogen (g/l)	2.4 (± 0.6)**	2.9 (± 0.9)**

N = Number; Values are mean (±SD) or number (%). BMI = body mass index; PSA= prostate-specific antigen; CRP= C - reactive protein. Values with matching superscript signs differ statistically from each other. Statistical analyses were done using the Mann-Whitney U test. P-values below 0.05 are considered statistically significant.

Results

The questionnaire return rate was 16% (255/1,601). Of the 255 returned questionnaires, 108 were excluded (mainly due to prevalent cardiovascular disease such as hypertension). Of the remaining 147 men, 28 (19%) were

further excluded, one with pathological echocardiogram, one with abnormal urological findings, 11 that did not want to continue, and 15 that were excluded due to other causes, resulting in 119 middle-aged healthy men with full medical examinations who were included in this study.

Descriptive statistics of the study population are summarized in table 1. We found a positive significant correlation between PSA and fibrinogen levels (r = 0.20, p = 0.40), and between CRP and fibrinogen levels (r = 0.60, p = 0.01). On the other hand, no significant correlation was found between PSA and CRP levels (table 2). Men with PSA values ≥ 2 had significantly higher levels of fibrinogen as compared to those with PSA < 2 ng/ml (2.9 vs. 2.4 ng/ml, p = 0.01), and they were slightly older (57 vs. 54 years, p = 0.004) (table 3).

In a multivariate regression analysis model adjusted for age, BMI, marital status, smoking, snuff, and alcohol intake with PSA levels as a dependent variable, serum levels of fibrinogen independently predicted higher values of PSA (odds ratio = 3.30, 95% CI = 1.05–10.20, p = 0.04) (data not shown).

Discussion

In a group of 119 middle-aged healthy men from the general population, we found a positive significant correlation between PSA and fibrinogen levels. Thus, men with higher PSA had significantly higher fibrinogen as compared to those with lower values of PSA. In a multivariate regression analysis model adjusted for potential confounders, fibrinogen was still a predictor for men with higher PSA. Our results are in accordance with previous reports [2] indicating that biomarkers of subclinical systemic inflammations are associated with PSA elevation.

Systemic inflammation can be reflected by an array of biomarkers including serum levels of fibrinogen, CRP, neutrophils, lymphocytes, and platelets. These are generally non-specific biomarkers that are used in clinical practice to detect acute inflammation as well as to determine the appropriate treatment response. Researchers have investigated the possible association between some of these biomarkers and PSA levels. Of these biomarkers, fibrinogen and CRP have attracted the most attention.

A constantly increasing body of evidence supports a prominent role for fibrinogen and its degradation products in regulating the inflammatory response in several target tissues [4]. Moreover, patients with malignant tumors were presented with significantly higher levels of fibrinogen as compared to patients with benign tumors and healthy individuals [5–7]. Regarding men with PCa, Toriola et al. [8] reported a non significant association between fibrinogen levels and PCa- risk among Finnish men aged ≥ 42 years; however the relationship between fibrinogen and PSA levels was not examined in this study. Recently, McDonald et al. [2] observed a positive significant association between PSA and fibrinogen levels in healthy men without prostatic disease, aged > 40 years. In accordance, we found a positive significant association between PSA and fibrinogen levels in a group of middle-aged healthy men from the general population, indicating that subclinical systemic inflammation could explain the elevated PSA in this group of men.

CRP levels have been suggested to be an indicator of intraprostatic inflammation in men with symptomatic benign prostatic hyperplasia [9]. Regarding men with PCa, a positive significant correlation between CRP and PSA levels was found [10, 11]. Moreover, men with metastatic PCa had significantly higher levels of CRP as compared to those with non-metastatic disease [12]. Furthermore, Trautner et al. [13] found that elevated CRP levels were associated with a higher probability of tumor recurrence and poor prognosis. On the other hand, inconsistent results were found regarding the relationship between CRP and PSA among men from the general population. In this line, St Sauver et al. [14] conducted a study on a random sample of community-dwelling men, aged 40–79 years, and reported no significant association between CRP and PSA levels. In a retrospective epidemiological analysis on 302 men from the general population undergoing PSA screening, aged > 35 years, CRP levels were strongly associated with PSA elevation [15]. In our study, we were not able to find a significant association between CRP and PSA in middle-aged healthy men from the general population.

Our study has some shortcomings. Although the men invited were randomly chosen from the general population, the participation rate in this study was only 16%, and one could question whether this group of men was representative for the general population of middle-aged Swedish men. Since no information was available for the men who chose not to reply to on the questionnaires, the characteristics of this group could not be compared to that of the included group of men. However, we believe that the results are still valid and support the notion that there is a relationship between biomarkers of subclinical systemic inflammation and PSA elevation in this group of men.

Our work has some implications, at least, for our understanding of the biological mechanisms behind elevated PSA levels. Thus, it supports a significant contribution of subclinical systemic inflammation to serum PSA elevation. The nature of our study, however, did not allow us to make a recommendation that biomarkers of subclinical system inflammation could be used routinely in the PSA-based PCa work up. Large case-control follow-up studies are needed to examine the clinical utility/cut-off values of these biomarkers in the era of PCa detection. Such studies will probably help us to determine the source of PSA elevation. If it is found that elevated PSA levels are caused by subclinical systemic inflammation in cases with previous negative biopsies for PCa, then such men could escape undergoing unnecessary repeated prostate biopsies.

In conclusion, the present results indicate that serum fibrinogen is a biomarker of subclinical systemic inflammation associated with PSA elevation among middle-aged healthy men from the general population.

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