Prostatic Acid Phosphatase Discriminates Between Chronic Pelvic Pain Syndrome and Lower Urinary Tract Symptoms in Elderly Men

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Abstract

Lower urinary tract symptoms (LUTS) which result from the constriction of the urethra by the enlarged prostate gland, often coexists with chronic pelvic pain syndrome (CPPS), especially in elderly men. The symptoms of both prostatic disorders overlap in some domains. This makes the discrimination between these two debilitating illnesses difficult, especially considering the fact that validated clinical questionnaires are often used in their assessment as other diagnostic methods are cumbersome. The potential of prostatic acid phosphatase (PAP) in discriminating between LUTS and CPPS in cases of uncertainty in the clinical diagnosis of the disorders was evaluated. Ninety seven adult males were divided into three groups consisting of those found to have LUTS, those with CPPS, and those without any diseases of prostatic origin. Serum PAP levels were measured in all subjects and comparisons made between the groups. Our results show that PAP effectively discriminates between LUTS and CPPS in elderly men. Further studies are required to replicate and possibly corroborate this finding.

Keywords: chronic pelvic pain, lower urinary tract symptoms, prostatic acid phosphatase

Introduction

Prostatitis is a debilitating inflammation of the prostate gland. The term prostatitis is often used to refer to several conditions of prostate inflammation with distinct characteristics (Collins *et al.*, 2000). In an effort to formalize the diagnostic criteria for prostatitis, the National Institutes of Health (NIH) defined four distinct categories of prostatitis – three of which are symptomatic and one of which is asymptomatic (Kreiger *et al.*, 1999).

The NIH classification is shown in Table 1. Category I prostatitis or acute bacterial prostatitis results from acute bacterial infection, usually caused by *Escherichia coli* or other gram negative bacteria. Affected men often are very ill, with signs of systemic infection and significant pelvic pain. Category II prostatitis, also known as chronic bacterial prostatitis results from persistent bacterial infection despite antimicrobial treatment. Men with this disease have constant or chronic pain but no sign of systemic infection. Category III prostatitis or chronic non-bacterial prostatitis/chronic pelvic pain syndrome is the most common form of prostatitis. Affected men suffer episodic to constant bouts of pain in the pelvis, perineum and/or external genitalia. Expressed prostatic secretion (EPS) from such affected men are used to divide them into two sub groups – NIH Group IIIa if the EPS has inflammatory cells and NIH Group IIIb if the EPS is devoid of leukocytes. Category IV prostatitis, known as asymptomatic prostatitis, is a histological diagnosis of prostatic inflammation that is made on histological examination of the prostate tissue of a man with no symptoms of prostatitis (Palapattu *et al.*, 2004).

Types I and II prostatitis account for 5% to 10% of cases of prostatitis, while Type III prostatitis accounts for more than 90% of cases (de la Rossette *et al.*, 1993).

The oldest 'gold standard' test for prostatitis is the four glass test, or the bacteria localization test proposed by Meares and Stamey (1968). This quantitative culture technique involves an initial stream urine sample, a mid stream urine sample, a sample of EPS obtained after prostatic massage, and a post prostatic massage urine sample. Because of the cumbersome nature of this test, it is popularly known but rarely used. Collins *et al.* (2000) described it as the text book method of diagnosis. To simplify the test, Nickel (1997) proposed a two glass test, involving the culture and microscopic examination of urine obtained only before and after prostatic massage. Domingue and Hellstrom (1998) pointed out that the microbiologic diagnosis of chronic bacterial and chronic non-bacterial prostatitis are particularly challenging.

However, for NIH Group III prostatitis, which account for more than 90% of cases (and where our interest lies), Litwin *et al.* (1999) have developed the NIH chronic prostatitis symptom index (NIH-CPSI), a psychometrically validated questionnaire for the identification of men with chronic pelvic pain syndrome. However, like other clinical questionnaires, the NIH-CPSI is not used for confirmative diagnosis.

Lower urinary tract symptoms (LUTS) are the clinical manifestations of an enlarged prostate constricting the urethra. They are evaluated clinically using the American Urological Association's (AUA's) symptom index (Barry *et al.*, 1992). It is possible for chronic prostatitis and LUTS to coexist (Bedalov *et al.*, 1999) especially in elderly men. Their symptoms overlap and both reduce the quality of life of the sufferers. This makes the discriminatory capacity of the NIH-CPSI among elderly men questionable, and accurate diagnosis in that age range difficult (Collins *et al.*, 1999).

Prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) are secretions of the prostate that are used as biochemical markers

of prostate pathologies, the former being more elevated in prostate carcinoma than in other prostatic diseases (Jespen and Bruskewitz, 2000). This is understandable since the disruption of prostatic architecture due to a disorder, would invariably lead to prostatic secretions leaking into the blood stream. Potts (2000) reported elevated PSA in men with prostatitis and suggested that screening for prostatitis should be done in men with elevated PSA. Tchetgen and Oesterling (1997) also reported that prostatitis can increase PSA levels, leading to unnecessary biopsies.

Bearing in mind that the discovery of biochemical markers that can effectively differentiate between chronic pelvic pain syndrome (CPPS) and LUTS would enhance diagnosis, and remove the effect of the confounding overlap of the symptoms of CPPS and LUTS, this study evaluated the differences in the PAP levels of men with CPPS, men with LUTS and apparently healthy men without any symptoms.

Materials and Methods

The AUA index was used to assess the level of LUTS in adult males aged 40 and above and resident in Nsukka, as described elsewhere (Ezeanyika *et al.*, 2006a). Men with moderate to severe obstruction of the urethra (moderate to severe enlargement of the prostate) were invited to participate in the study as the LUTS group. The NIH-CPSI was also administered to the same population of men. Men with a pain score of four or more on a 0-21 scale were identified as having significant CPPS. These men were also approached to participate in the study as the CPPS group. Men who had an AUA index score of 0-2, and a pain score of zero were also invited to form the control group.

From the men that accepted to be part of the study, those who had apparent symptoms of ill-health, or reported having sex or prostatic massage two days prior to sampling, and those on any form of prescription drugs or alternative medicine, were excluded. Those who had a pain score of one or more were excluded from the LUTS group, while those who had an AUA index score of three or more were excluded from the CPPS group.

Firm each of the included participants; 4ml of blood was collected by venipuncture using disposable syringes. The blood samples were then transferred into sterile sample containers and allowed to clot before being spun in a centrifuge for five minutes at 2,000g to separate cells from sera. The quantities of PAP in the sera were then determined using the method of Fishman and Lerner (1953).

Since the questionnaires used required the respondents to indicate their age range, not absolute age, we represented their relative ages by the means of the age ranges, whereby 40-49 is reported as 45 years, 50-59 as 55 years and 60+ as 65 years.

A total of 97 subjects participated in the study. Those in the CPPS group were 24 in number (mean relative age 55 ± 8.8 years), LUTS group had 30 men (mean relative age 60 ± 6.8 years) and 43 men (mean relative age 57.1 ± 8 years) were in the control group.

PAP values were calculated and the differences between means separated using one way ANOVA. Where necessary, multiple comparisons were done to see the effect of certain factors. All data analyses were done using the statistical software package SPSS for windows version 11.0 (SPSS Inc., Chicago IL).

Results and Discussion

There was no significant ($p>0.05$) difference in the means of the relative age of the three groups. However, multiple comparisons showed that this was true only if the control group was compared to the LUTS or CPPS groups (Table 2). The mean relative age for those with LUTS was significantly ($p<0.05$) different from the CPPS group.

The mean PAP values, as expected, increased with age, irrespective of the group to which each respondent belonged. The mean difference of the PAP values for those aged 40-49 and 60+, but not 50-59 years were seen to be significant ($p<0.05$) (Table 2). Any disruption of the prostatic architecture would result in prostatic secretions finding their way into the blood stream. As one ages, the chances of these events occurring increases. We have discussed this significant increase in the mean PAP values with age elsewhere (Ezeanyika *et al.*, 2006b).

Subjects with LUTS had the highest level of PAP irrespective of age, while those of the CPPS group and the control group had about the same values. The difference in the mean values for those with LUTS was independently significantly ($p<0.05$) different compared to those with CPPS. There was no significant ($p>0.05$) difference in the mean PAP values for those with CPPS and the control group. This suggests that PAP discriminates between subjects with LUTS and those with CPPS and normal subject, but not between those with CPPS and normal subjects (Table 2). This holds a lot of promise in the clinical diagnosis of these disorders.

Within the age range 40-49 years, PAP was seen to be highest in those with LUTS and lowest in those in the control group. However, the apparent difference was not significant ($p>0.05$). A similar trend was noticed within the age range 50-59 years. Within the age range 60+ years, those with LUTS still had the highest level of PAP, but were followed by the control group, while the CPPS group had the least value (Table 2). The difference in the PAP means of the age range (60+ years) differed significantly ($p<0.05$) with that of those aged 40-49 with CPPS.

These findings suggest that PAP distinguishes between subjects with CPPS and those with LUTS especially in elderly men. This is particularly interesting since the chances of both diseases co-occuring are higher in elderly men. Benign prostate hyperplasia, which results in LUTS, is an age-related neoplastic condition affecting largely elderly men (Eaton, 2003) while prostatitis is the third most common diagnosis in men older than 50 years (Collins *et al.*, 1998; Mehik *et al.*, 2000; Nickel *et al.*, 2001).

Table 1: NIH Classification of Prostatitis

NIH Category	Name	Symptomatic	Acute/ Chronic	Bacteria in EPS	Leukocyte in EPS
I	Acute bacterial prostatitis	Yes	Acute	Yes	Yes
II	Chronic bacterial prostatitis	Yes	Chronic	Yes	Yes
III	Chronic non-baterial prostatitis/chronic pelvic pain syndrome				
IIIa	Inflammatory	Yes	Chronic	No	Yes
IIIb	Non-Inflammatory	Yes	Chronic	No	No
IV	Asymptomatic prostatitis	No	-	No	No

Table 2: Summary of Results

Age range	Mean PAP Concentration ± Standard Deviation			
	CPPS Group	Control Group	LUTS Group	Total Irrespective of Group
40-49 years	1.7 ± 0.7^{d}	1.4 ± 1.1	2.4 ± 1.5	1.7 ± 1.0^{e}
	n = 9	n = 10	n = 3	n = 22
50-59 years	2.3 ± 1.6	1.6 ± 1.0	2.8 ± 2.3	2.2 ± 1.6
	n = 6	n = 14	n = 9	n = 29
60+ years	1.9 ± 1.2^{e}	2.5 ± 1.4	3.3 ± 2.2^{de}	2.7 ± 1.8^{c}
	n = 9	n = 19	n = 18	n = 6
Total Irrespective of Age	1.9 ± 1.1^{a}	2.0 ± 1.3^{b}	3.1 ± 2.1^{ab}	2.3 ± 1.6
	n = 24	n = 43	n = 30	n = 97

Values with the same superscript (both in a row and in a column) are significant ($p<0.05$)

We are not aware of any other study assessing the role of PAP in resolving the confounding issues in CPPS and LUTS in men.

Our data show that PAP can be used to discriminate between elderly men with CPPS and those with LUTS. However, it is limited by the number of our subjects. This calls for a cautious interpretation of the data and for further studies.

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