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Evaluation of PSA, Prostatic Acid Phosphatase, Calcium and Magnesium in Case of Benign Prostatic Hyperplasia (BPH)

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Abstract

Benign prostatic hyperplasia **(**BPH) is the most common pathology of the prostate gland in men. Raised levels of PSA are seen in different pathological conditions involving the prostate. PAP levels are altered in inflammatory, infectious or abnormal growth of the prostate tissue. Serum calcium and magnesium levels were also found to be altered in prostate cancer and BPH. The present study was carried out to study the levels of PSA, Prostatic Acid Phosphatase (PAP), calcium, and magnesium in serum of patients with BPH and to evaluate the relationship between them as well.

Keywords: Benign prostatic hyperplasia **(**BPH); Prostatic Acid Phosphatase (PAP); Serum.

Introduction

Benign prostatic hyperplasia (BPH), also called benign enlargement of the prostate (BEP or BPE), is a noncancerous increase in size of the prostate, a common condition in men above 50 years. On histological evaluation, it shows hyperplasia of prostatic stromal and epithelial cells, resulting in the formation of large, fairly discrete nodules in the transition zone of the prostate.[1] BPH is an androgen-dependent process, the modifiable and non-modifiable risk factors for BPH include age, genetics, hormones, metabolic syndrome, obesity, diabetes, and chronic inflammation. Clinical manifestations of BPH are caused by extrinsic compression of the prostatic urethra leading to impaired voiding. Chronic inability to completely empty the bladder may cause bladder distension with hypertrophy and instability of the detrusor muscle.[2,3] Some patients with BPH present with hematuria. Because the severity of symptoms does not correlate with the degree of hyperplasia, and other conditions can cause similar symptoms, the clinical syndrome that often accompanies BPH has been described as lower urinary tract symptoms. PSA an important tumor marker that predicts the clinical progression and response to medical therapy in patients with BPH thus help in selecting the regimen for medical treatment.

Prostate specific antigen (PSA) is a 237-amino acid monomeric serine protease and 33 kilodalton glycoprotein produced in prostate epithelial cells

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and it is first identified by the Wang et al.[4] Its normal physiologic role is as a liquefying agent for seminal fluid; only a tiny amount leaks into the blood, therefore its normal serum level is usually very low. Elevated serum levels of PSA have been associated with prostate carcinoma. Men above 45 years are prone to BPH, a universal phenomenon which increases with age. It has shown considerable promise and has been acclaimed the best marker for prostate malignancy in recent years, although its plasma concentration also increases in BPH, but to a lesser extent. The reduced specificity of the two markers is further complicated by a number of pathological factors like prostatic infarct, acute bacterial prostatitis as well as acute urinary retention or digital rectal examination (DRE).[5,6]

Prostate specific antigen can exist in the serum in two forms:

Total PSA (tPSA) is a predominantly complexed to protease inhibitors bound/complexed (to serum protein) widely used tumour marker for the early detection and monitoring of patients with prostate cancer. One of the drawbacks of tPSA is the appreciable false-positive results. Manipulations of the prostate gland, benign conditions, such as BPH and clinical or subclinical prostatitis, have been reported to contribute to tPSA elevations.[7] These benign causes of elevated serum tPSA can create a diagnostic dilemma in prostate cancer detection programmes that use serum PSA only as a screening test.

Free PSA (fPSA) is not bound to these proteins. For unknown reasons, the percentage of fPSA (f/tPSA) is lower in serum from patients with prostate cancer than from patients with a normal prostate or benign disease. Preliminary examination suggests that a lower f/tPSA is more reliable and can reduce unnecessary biopsies in patients being evaluated for prostate cancer; elevated levels of fPSA are associated with benign prostatic hyperplasia (BPH). Measuring the different forms of PSA may help to discriminate between prostate cancer and benign diseases.[8]

Early detection and treatment in asymptomatic men may improve the mortality rate and the quality of life. Screening for markers such as prostate specific antigen (PSA) and prostate acid phosphatase (PAP) resulted in detection and treatment of the disease at an earlier stage. Men of 50 years of age or above without any family history of cancer and those at 40 years of age with family history must undergo digital rectal examination (DRE) and PSA levels should be checked annually as recommended by of American Urological Association (AUA) and Food and Drug Administration (FDA).

Prostatic acid phosphatase (PAP) is an enzyme produced by several types of tissue, including normal prostate tissue and it is secreted by prostate columnar epithelium secretory cells following puberty. PAP emerged as the world's first clinically useful tumor marker in the 1940s and 1950s. With the introduction of the PSA test in the 1980s, which performed significantly better than PAP in terms of screening and monitoring response to treatment, PAP fell into disfavor. Prostatic acid phosphatase (PAP), a sialoglycoprotein with a molecular weight of 100,000[9] has been used for early screening and detection of prostate carcinoma in high risk group [10,11], although its role in staging the carcinoma has been doubtful.[12,13] There are two forms of PAP, including the cellular form (cPAP, highly expressed in the prostate cells) and the secretory form (sPAP, expressed only in the prostate and is mostly released into seminal fluid),[14] with different isoelectric points and molecular weights.[15] Apart from different biomarker, trace elements such as Calcium (Ca) - magnesium (Mg) are essential to normal human homeostasis, results in a number of clinical complications including BPH. Suggested processes implicated in the progression of prostate disorders are from oxidative stress, to cellular senescence.[16,17]

One of the hypotheses suggests that a high intake of protein or calcium from dairy products may enhance the risk for prostate cancer hence calcium considered as the probable cause of prostate cancer and BPH. Conversely, high magnesium intake can reverse calcification damages and inflammation, if used intensely. As the physiology suggests an antagonistic effects of magnesium over calcium on our body and as a rule in general, the more rigid and inflexible our body structure, the less calcium and the more magnesium we need**.** There is reasonable evidence to suggest that calcium may play an important role in the development of prostate cancer," says Dr. Carmen Rodriguez, senior epidemiologist in the epidemiology and surveillance research department of the American Cancer Society (ACS). Several epidemiologic studies sustain the role of calcium in prostate cancer showed an increased risk for advanced or fatal prostate cancer among men whose diets are unusually high in calcium.[18] Both normal and cancerous prostate cells possess the calcium-sensing receptor, a G-protein coupled receptor that is activated by extracellular calcium[19] and also they express calcium-dependent channels that regulate

cell proliferation via the control of calcium entry into the cells.[20] Calcium and magnesium levels in the body are jointly regulated through a negative feedback system.[21] Magnesium (Mg) is an essential micronutrient for humans and plays many important roles in the function of over 300 enzymes and it is the second most abundant intracellular cation in the body.[22] At the extracellular level, an increase in Ca^{2+} or a decrease in extracellular Mg^{2+} further increased Ca^{2+} influx. The efflux control of Ca and Mg is regulated by a melastatin-like transient receptor potential (TRPM). These are a diverse group of voltage-independent $Ca^{2\pm}$ permeable cation channels present in mammalian cells. TRPM6/7 gene mutations have been demonstrated in hereditary hypomagnesaemia caused by Mg^{2+} reabsorption impairment.[23] Additionally, other studies have shown Mg^{2+} entry preference over Ca^{2+}. However, in the absence of Mg^{2+}, the channels are able to conduct Ca^{2+} currents, which ultimately increases in extracellular Ca^{2+} or a decrease in extracellular Mg^{2+} increases Ca^{2+} influx. Additionally, the subsequent increase in the Ca^{2+}/Mg^{2+} ratio and TRPM7 expression has been demonstrated in age-matched prostate cancer patients. Therefore, an increase in the serum Ca^{2+}/Mg^{2+} ratio will increase Ca^{2+} entry by the activation of TRPM7 channels, which eventually leads to increased cell proliferation and cancer formation.[24] High Ca/Mg ratio levels were associated with risk of prostate cancer. Mg levels were significantly lower among men with high-grade prostate cancer, particularly among men with high blood Ca levels. These findings suggest Mg interacts with Ca to affect prostate cancer risk. This provided evidence of the Ca/Mg hemostasis and its involvement in cell proliferation as well as prostate cancer development. The tight regulation of this channel has also been attributed to theTRMP7 gene and the Ca/Mg ratio has also been demonstrated in clinical studies of prostate cancer but not in case of BPH, so further studies are required.

Discussion

PSA is a serine protease enzyme produced by normal prostate cells and plays an important role in fertility. In men with prostate cancer there seems to be a lower proportion of fPSA and this has been expressed as a decrease in the f/t PSA ratio. The reasons for this are not fully understood. Studies in 1991 demonstrated that there is a higher proportion of PSA bound to Alpha-1-antichymotrypsin (ACT) in prostate cancer.[25,26] In human serum PAP is a secreted glycoprotein (100 kDa) enzyme is synthesized in the prostate gland's epithelial cells was widely studied as a surrogate marker for prostate cancer until the establishment of prostate-specific antigen (PSA) as the new standard.[27] PSA and PAP considered as potential biomarker and has a significantly higher correlation with the morphological characteristics of prostate cancer and can provide a more important in the diagnosis and prognosis than any other markers currently available.

Mg has an effect on a variety of cell membranes through a process involving Ca channels and ion transport mechanisms. Mg is therefore responsible for the maintenance of the trans-membrane gradients of sodium and potassium.[28] Ca reabsorption is truncated when Mg is adequately reabsorbed. It has been shown that Ca reabsorption is not altered in Mg deficiency; however, elevations of extracellular Mg results in a specific inhibition of Ca reabsorption within the loop of Henle.[29] The Ca/ Mg ratio play an important role in the initiation or progression of the disease remains doubtful and requires further studies.

Conclusion

PSA may be elevated more frequently than PAP in some patients with BPH, in combination, indicates either prostatitis or Prostate cancer and rules out BPH. The calcium level is also low in BPH patients which ultimately affect the Ca/Mg ratio.

References

1. Platz EA, Joshu CE, Mondul AM et al. Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men.J Urol. 2012 Aug;188(2):496–501.
2. McNeal J. Pathology of benign prostatic hyperplasia. Insight into etiology. Urol Clin North Am. 1990 Aug;17(3):477–86.
3. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. J Urol. 2011 May;185(5):1793–803.
4. Wang MC, Valenzuela LA, Murphy GP, et al. Purification of human prostate specific antigen. Invest Urol. 1979 Sep;17(2):159–63.
5. Collier DS, Pain JA. Acute and chronic retention of urine: relevance of raised serum prostatic acid phosphatase levels: A prospective study.

Urology. 1986 Jan;27(1):34–7.

6. Armittage TG, Cooper EH, Newling DWW, Robinson MRG, Appleyard I. The value of the measurement of serum prostatic specific antigen in patients with benign prostatic hyperplasia and untreated prostatic cancer. Br J Urol 1988;62:584–88.
7. Nadler RB, Humphrey PA, Smith DS et al. Effect of inflammation and BPH on elevated PSA levels. J Urol. 1995 Aug;154(2 Pt 1):407–13.
8. Christensson A, Bjork T, Nilsson O et al. Serum PSA complexed to alpha-1-antichymotrypsin as an indicator of prostate cancer.J Urol. 1993 Jul;150(1):100–5.
9. McCarthy RC, Jakubowsky HV. Markowitz H. Human prostatic acid phosphatase: Purification characterization and optimisation of condition of radioimmunoassay. Clin Chim Acta. 1983 Aug 31;132(3):287–99.
10. Cooper VF. The radioimmunochemical measurement of prostatic acid phosphatase: current state of the art. Urol Clin N Am 1980;7:653–56.
11. Vinko P. Konturri M. Lukkarinen O. Ervash J, Vinko R. Screening for carcinoma of the prostate, rectal examination and enzymatic and radioimmunologic measurements of serum acid phosphatase compared. Cancer 1985;56:173–79.
12. Whitesel JA, Donahue RE, Man: JH et al. Acid phosphatase: its influence on the management of carcinoma of the prostate. J Urol 1984;131:70–73.
13. Heller JE. Prostatic acid phosphatase: its current clinical status. J Urol. 1987 Jun;137(6):1091-103.
14. Lin MF, Lee MS, Zhou XW et al., Decreased expression of cellular prostatic acid phosphatase increases tumorigenicity of human prostate cancer cells. The Journal of Urology 2001;166(5):1943–50.
15. Quintero IB, Araujo CL, Pulkka AE et al. Prostatic acid phosphatase is not a prostate specific target. Cancer Research 2007;67(14)6549–54.
16. Begley L, Monteleon C, Shah RB, et al. CXCL12 overexpression and secretion by aging fibroblasts enhance human prostate epithelial proliferation in vitro. Aging Cell 2005;4:291–8. doi: 10.1111/j.1474-9726.2005.00173.x.
17. Bethel CR, Chaudhary J, Anway MD, et al. Gene expression changes are age-dependent and lobe-specific in the brown Norway rat model of prostatic hyperplasia. Prostate 2009 Jan;69(8):838–50. doi: 10.1002/pros.20935.
18. Tseng M, Breslow RA, Garubard BJ, et al. Dairy, calcium and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. Am J Clin Nutr. 2005 May;81(5):1147–54. [PubMed] [Google Scholar]
19. Sanders JL, Chattopadhyay N, Bai M, et al. Elevated extracellular calcium can prevent apoptosis via the calcium-sensing receptor. Biochem Biophys Res Commun. 1998 Aug 19;249(2):325–31. [PubMed] [Google Scholar]
20. Lallet-Daher H, Roudbaraki M, Bavencoffee A, et al. Intermediate-conductance $Ca^{2\pm}$ activated K^+ channels (IKca1) regulate human prostate cancer cell proliferation through a close control of calcium entry. Oncogene. 2009 Apr 16;28(15):1792–806.
21. Brown EM, MacLeod RJ. Extracellular calcium sensing and extracellular calcium signaling. Physiol Rev. 2001 Jan;81(1):239–297.
22. Iseri LT, French JH. Magnesium: Nature's physiologic calcium blocker. Am Heart J. 1984 Jul;108(1):188–93.
23. Chubanov V, Waldegger S, Mederos Y, et al. Disruption of TRPM6/TRPM7 complex formation by a mutation in the TRPM6 gene causes hypomagnesemia with secondary hypocalcemia. Proc Natl Acad Sci U S A. 2004 Mar 2;101(9):2894–9. doi: 10.1073/pnas.0305252101.
24. Flourakis M., Prevarskaya N. Insights into Ca^{2+} homeostasis of advanced prostate cancer cells. Biochim Biophys Acta. 2009 Jun;1793(6):1105–9.
25. Stenman U, Leinonen J, Alfthan H, et al. A complex between prostate specific antigen and alpha 1-antichymotrypsin is the major form of prostate specific antigen in serum of patients with prostate cancer: Assay of the complex improves clinical sensitivity for cancer. Cancer Res. 1991 Jan 1;51(1):222–6.
26. Lilja H, Christensson A, Dahlen U, et al. Prostate specific antigen in serum occurs predominantly in complex with alpha-1 antichymotrypsin. Clin Chem. 1991 Sep;37(9):1618–25.
27. Veeramani S, Yuan TC, Chen SJ, et al. Cellular prostatic acid phosphatase: A protein tyrosine phosphatase involved in androgen-independent proliferation of phosphatase. Endocr Relat Cancer. 2005 Dec;12(4):805–22.
28. Bara M, Guiet-Bara A, Durlach J. Regulation of sodium and potassium pathways by magnesium in cell membranes. Magnes Res. 1993 Jun;6(2):167–77.
29. Carney SL, Wong NL, Quamme GA, et al. Effect of magnesium deficiency on renal magnesium and calcium transport in the rat. J Clin Invest. 1980 Jan;65(1):180–8.