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SERUM URIC ACID - PHOSPHATE RATIO AS A DIFFERENTIAL DIAGNOSTIC MARKER OF PROSTATE DISORDERS

SUDHA K, RESHMA K* AND AKSHATHA L N

Department of Biochemistry, Kasturba Medical College, Mangalore, Manipal University Manipal ,India

ABSTRACT

Prostate cancer (PC), benign prostatic hyperplasia (BPH) and prostatitis are the most common disorders of the prostate gland. Prostate specific antigen (PSA), the marker of prostate cancer has shown reasonable sensitivity but has limited specificity for distinguishing PC from BPH.This study attempts to evaluate the use of uric acid phosphate ratio as a tool in differential diagnosis of prostate disorders. PSA, uric acid and phosphate were estimated in serum of 75 patients with prostate disorders .PSA levels were significantly high in PC compared to other disorders. Phosphate levels were significantly lower in prostatitis patients, and an apparent increase in uric acid levels in BPH patients. Serum uric acid phosphate ratio was markedly high in prostatitis followed by BPH patients and least in PC establishing the role of the ratio in the differential diagnosis of prostate disorders.

KEY WORDS: Prostate cancer, Prostatitis, Benign prostatic hyperplasia, Uric acid/phosphate ratio

RESHMA K
Associate Professor Department of Biochemistry, Kasturba Medical College, Mangalore, Manipal University Manipal ,India

INTRODUCTION

Prostate cancer is one of the most common malignancies in old aged men in India.The second most important prostate disorder of the prostate includes benign prostatic hyperplasia (BPH) where accumulation of dihydrotestosterone with aging leads to enlargement of prostate[1].Bacterial prostatitis both acute and chronic are characterized by inflammation due to urogenic infections of prostate gland[2].Whether there is an association between the development of BPH and PC is controversial [3].Prostate specific antigen (PSA) is the most common serum marker of prostate cancer. PSA has shown reasonable sensitivity for detection of incipient cancer and can predict response to treatment but in the critical diagnostic range of 4-10ng/ml it has limited specificityfor distinguishing PC from BPH[4]. A mounting body of evidence suggests that increased production of reactive oxygen species(ROS) is linked to inflammatory diseases, aging processes and to etiopathogenesis of age related diseases like PC and BPH [5].Association of uric acid an extracellular antioxidant with inflammation is an established fact. Hyperuricemia in cancer patients is thought to result from increased nucleic acid turnover in rapidly proliferating tissue [6]. The complexity of acute and chronic inflammatory process may either lead to prostate hyperplasia and / or prostate cancer. Prostate cells are activated by chemokines and trigger processes like angiogenesis, cellular growth and extravasation as well as neoplasia[7]. Experimental and clinical data implicate calcium as the risk factor in development of prostate cancer[8], Serum levels of calcium correlated with PSA which supported the hypothesis that hypercalcemia may stimulate prostate cancer[9], however data on relation between phosphate ions and PC or BPH is sparse. Hence, the present study aims at evaluating uric acid and phosphate in the serum of patients with prostatic disorders and then exploring the possibility of using the ratio in differential diagnosis.

MATERIALS AND METHODS

75 patients with prostate disorders aged between 40-60 years and with serum PSA levels greater than10 ng/ml were considered for the study.25 patients had prostate cancer, 25 had benign prostatic hyperplasia and 25 had prostatitis. The study was approved by Institutional ethics committee and informed consent was taken from all the subjects. Prostate cancer was confirmed by biopsy report. Patients with acute urinary tract infection, smokers, alcoholics and diabetics were excluded from the study. Fasting blood sample was collected in plain vacutainer and serum was used for estimations. Prostate specific antigen was estimated by ECLIA in Cobas e 411[10]. Serum uric acid was estimated by uricase -peroxidase method and phosphate was estimated by ammonium phosphomolybdate end point method spectrophotometrically[11].Statistical analysis was done using ANOVA to compare the data between the three diseases. Correlation study was done by Kruskalwalis test[12].

RESULTS

The present study clearly indicates that prostate cancer is more prevalent in men who are in age group of more than 65 years. Followed by BPH which is more common in men above 55 years of age .Prostatitis is found to be highly prevalent in younger age group. PSA levels were significantly higher in serum of men with prostate cancer ($p<0.000$) compared to BPH and prostatitis. Post hoc test revealed that the difference was more significant between prostate cancer and BPH($p<0.002$) and slightly less significant between PC and prostatitis ($p<0.01$). Serum phosphate level was significantly lower in prostatitis compared to the other two groups ($p<0.008$). The difference was much more significant between BPH and prostatitis ($p<0.006$).There was an apparent increase in serum uric acid in BPH than prostatitis and PC. Though the mean uric acid showed considerable variations across the groups, post hoc test did not show any significance

between the groups. Uric acid phosphate ratio was also markedly high in prostatitis, followed by BPH and cancer. However, the values were statistically insignificant. (Table 1) There was a positive correlation between PSA and age in all the three prostate disorders which was statistically significant in BPH (r =0. 344, $p < 0.05$) (Table 2). There was a negative correlation between PSA and uric acid phosphate ratio in all the three disorders (r=-0.619), though it was statistically significant only for PC. (Table 3)

Table 1
Comparisons of PSA , Uric acid, Phosphate and Uric acid/Phosphate ratio in PC, Prostatitis and BPH (Mean ±SD)

	Prostate cancer (n=25)	BPH (n=25)	Prostatitis (n=25)
AGE	73.62±9.34	67.70±8.28	61.28±15.67
PSA(ng/mL)	118.27±77.7***	9.42±6.98[a]	14.22±7.38[c]
URIC ACID (UA) (mg/dL)	6.6±3.83	13.18±9.27	9.44±3.84
PHOSPHATE(P) (mg/dL)	4.4±1.49	4.82±1.54[b]	3.25±0.93*
UA/P	1.64±0.79	2.7±1.68	3.02±1.34

***p<0.000 significantly different from BPH &Prostatitis*
**p=0.008 statistically different from BPH &PC*
a; p=0.002, c ; p<0.01significantly different from PC
b ;p=0.006significantly different from Prostatitis

Table 2
Correlation of PSA with Age in prostate disorders

	r	p
Prostatitis	-0.327	0.326
BPH	0.530	0.05*
Prostate Cancer	0.569	0.05*

**Statistically significant*

Table 3
Correlation of PSA with uric acid phosphate ratio in prostate disorders

	r	p
Prostatitis	-0.173	0.612
BPH	-0.113	0.53
Prostate Cancer	-0.619	0.05*

**Statistically significant*

DISCUSSION

PSA an androgen regulated protease produced by prostate epithelial cell and prostate cancer cells increase in prostatitis, BPH,prostate cancer, acute urinary retention and renal failure[13].Though PSA had a limited capacity in distinguishing prostate cancer and BPH due to considerable overlap,in the present study PSA level were significantly higher in cancer patients compared to BPH and prostatitis. However PSA level has low specificity as BPH and prostatitis could not be differentiated further in this study. PSA level were higher in prostatitis compared to BPH. Earlier studies on PSA indicate that in the critical diagnostic range of 4 to 20 ng per ml PSA had limited capacity for distinguishing early prostate cancer and BPH. In cancer and inflammatory disorders, oxidative stress, an

innate key event characterized by supra physiological reactive oxygen species has been identified as one of the hall mark of disease progression[14].One of the studies showed that various inflammatory processes and cell biological cascades are involved in the etiopathogenesis of either Prostatitis, BPH or prostate cancer[15].. In the present study uric acid level were markedly high in BPH compared to the other two groups clearly suggesting the role of uric acid as a novel growth factor .Supporting our findings Hammarstemet.al [16]also observed hyperuricemia in patients with BPH, underlining the hypothesis of an association of hyperuricemia in development of BPH. In one of the earlier studies patients with prostate cancer and chronic prostatitis presented with decreased antioxidant capacity[5].Lopez Lauret.al [18] also did not support the theory of protective role of uric acid against PC occurrence. Further hypouricemia in cancer patient is thought to reflect increased renal secretion as a result of tubular damage or tumour related humoral factor[19].However, Hammarsten et al [20]considered hyperuricemia as a risk factor in development of prostate cancer. Low uric acid level in prostate cancer and prostatitis observed in the present study is well supported by an earlier study which shows significantly low uric acid and depletion of antioxidant in prostate cancer patients with high PSA level [21], although it is not in agreement with one of the earlier studies[22] In the present study patients with prostatitis have significantly lower inorganic phosphate level in serum compared to patients with prostate cancer and BPH. Hypophosphatemia stimulate active vitamin D_3 production which has anti tumour effect in prostate[23],phosphate level was slightly lowered in patients with prostate cancer compared to that of BPH. Supporting the above data a case study showing hypophosphatemia and hyper phosphaturia in a 65 year old man with prostate cancer has been reported[24].Prostate cancer induced oncogenic hypophosphatemicosteomalacia. Calcitriol slows the rate of PSA secretion into serum providing indirect evidence for a protective influence of high vitamin D_3 on prostate cancer[23]. Thus it can be argued that low serum phosphate level in prostatitis is advantageous in preventing development of cancer. Hypophosphatemia stimulates activation of vitamin D_3 and increases circulating calcitriol[25]. In this study uric acid phosphate ratio was markedly high in BPH compared to prostate cancer. Mean U/P ratio in BPH was double that of PC indicating the fact that the ratio can be used as a marker that can differentiate between BPH and prostate cancer,The ratio higher in prostatitis compared to BPH also suggests the importance of U/P ratio in differential diagnosis of prostate disorder.

CONCLUSION

PSA had low specificity and additional biomarker was needed to differentiate between prostate cancer and BPH. In this article we evaluated a novel approach to find a diagnostic marker for prostate disorders. The study supports the utility of UA/P ratio as a diagnostic marker for BPH and offers an alternative sensitive unique marker in differentiating BPH and PC.

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