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Correlation of Serum Gamma Glutamyl Transferase and Prostate Specific Antigen Level in Patients with Prostate Disorders

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ABSTRACT

Objective: To correlate gamma-glutamyl transferase, prostate-specific antigen, and prostate-specific antigen density with ultrasound findings, including prostate-specific antigen volume and density, in patients with prostate disorders and to compare differences between Gamma-GT, prostate-specific antigen levels, and density based upon "American Urological Association" score questionnaire groups.

Study Design: Cross sectional study.

Place and Duration of Study: Combined Military Hospital Multan, Pakistan, from Nov 2019 to Dec 2021.

Methodology: We measured prostate indices, including prostate-specific antigen, prostate-specific antigen volume, prostate-specific antigen size, and prostate-specific antigen density, through biochemical measurements and ultrasound examination in a patient population [(n=336) and (age 45-90 years)] randomly after several exclusions that could have affected the results of gamma-glutamyl transferase in known prostate disorders.

Results: Gamma-glutamyl Gamma-glutamyl indices showed a low correlation with prostate-specific antigen levels (*p*-value= 0.170), ultrasound measures of the prostate gland (*p*-value=0.088), and derived indices incorporating prostate-specific antigen results (*p*-value=0.025). PSA showed moderate to higher correlation with Alkaline phosphatase (r=0.422, *p*<0.001), gamma glutamyl transferase (r=0.170, *p*=<0.001), PSA volume (r=0.513, *p*=<0.001), prostate gland size (r=0.520, *p*=<0.001) and PSA density (r=0.754, *p*=<0.001). Statistical analysis for various biochemical parameters and PSA measures between groups formulated based on prostate size and the AUA score system was not statistically significant.

Conclusion: Prostate derived ultrasound measures and PSA density showed a higher correlation with PSA. Gamma glutamyl transferase may not help depict prostate gland disease.

Keywords: Benign prostatic hyperplasia (BPH), Gamma glutamyl transferase, Prostate specific antigen, Prostate density, "American Urological Association" (AUA) score.

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INTRODUCTION

Prostate disorders are one of the most common disorders faced by almost all males with the aging process. The commonest disorders include Benign Prostatic Hyperplasia (BPH), a non-malignant enlargement usually prevailing among senior male citizens.[1] Currently, in the USA, guidelines suggest the use of PSA as a marker to measure prostate hyperplasia and malignancy.[2] In developing countries, the availability of advanced diagnostic tools is limited to tertiary care hospitals, and many challenges exist in providing diagnostic services to the larger population.[3] Daniyal et al. have also highlighted the importance of early diagnosis for prostate diseases in Pakistani setups. [4]

Considering the need for cost-effective and feasible investigations for prostate gland disease, the literature review highlights simple biomarkers. Earlier studies have highlighted the use of bone turnover markers for early screening of prostate cancers, albeit in a differential way.[5] Similarly, other researchers have highlighted the use of alkaline phosphatase as a prognostic marker in prostate cancer.[6] Furthermore, gamma-glutamyl transferase has been described as one of the components of the "secretome" of prostate secretions, which may also provide a similarly powerful surrogate biomarker for evaluating the degree of prostate disease. GGT is a membrane bound, cytoplasmic enzyme. The enzyme appears to perform its part in nourishing cancer and normal cells. It is required to metabolize glutathione and various gamma-glutamyl group-containing

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molecules as well. It is also recommended as an oxidative stress marker as it performs its part in glutathione re-synthesis by maximizing cysteine availability.[7] A recent multi-omics pipeline study by Drabovich *et al*. highlighted Gamma-Glutamyl Transferase as the component of prostate-specific secretome, thus highlighting its potential for possible use in prostate diseases.[8] A recent prospective study, "Kuopio Ischemic Heart Disease" (KIHD), recruited 2,390 men aged 42-61 years without a history of any malignancy at the outset. They were followed up for 24.6 years. The study depicted Gamma-Glutamyl Transferase as positively and independently associated with future prostate cancer risk over long-term follow-up.[9] However, there is available recent data that suggest GGT to be elevated with secondary malignancy after prostate cancer. Similarly, other factors, including hypertension and diseases associated with elevated oxidative stress, have been attributed to raising GGT in both males and females.[10]

Based upon differences in data in gamma-GT and a possible allowance of its use in peripheral setup as a biomarker for underlying malignancy, we developed a rationale for a study to evaluate the correlation of PSA, GGT, and ultrasonographic findings among men over 45 years old. As a secondary objective, we also evaluated the rise or otherwise of these biomarkers, PSA-defined indices, and ultrasound volumes with AUA symptom score and prostate size.

METHODOLOGY

The cross-sectional study was conducted at the Department of Chemical Pathology and Endocrinology, Combined Military Hospital Multan, Pakistan from November 2019 to January 2022, after the formal approval of the Institution Review Board.

Inclusion Criteria: Male subjects aged between 45 and 90 years reporting in urology OPD of the hospital with prostate disorders were included.

Exclusion Criteria: Subjects with a history of surgical treatments such as "Trans Urethral Resection of Prostate" TURP, radical prostatectomy, rectal biopsy, alcoholics, patients with urethral catheterization, patients who have undergone DRE, patients with any known malignancy, patients with suspected prostatitis and patients with known hepatobiliary disease and bone disease were excluded.

Subjects who volunteered for the study were briefed about the study type, data collection procedures, samples to be collected, analytical procedures, and intended use of data for research leading to publication. The candidate who volunteered after signing a "written consent" was sent to the radiology department for a transrectal ultrasound (TRUS). The radiologist was requested to report prostate volume for each patient during the TRUS examination. Prostate volume assessment was done using the ellipsoid formula: Volume=height X width X length X 0.52.

The sample size was estimated using the WHO sample size calculator.[11] Following the radiological evaluation for measuring prostate volume and size, these subjects underwent blood testing (5 ml) for serum PSA, GGT, and alkaline phosphatase. Serum PSA levels were analyzed by immunoassay on Cobas e 411 analyzer (Roche Diagnostics). Serum GGT and ALP were analyzed by automated chemistry analyzer Cobas c 501 (Roche Diagnostics).

Three groups were formulated per prostate sizes:Group-1- Prostate>49.99 g, Group-2: Prostate size=>24.99 to <50 g and G,roup-3: <25 g. Prostate disorders were evaluated as per the AUA symptoms score questionnaire as: Group-1 (Score: 0-7), Group-2 (Score 8-19), and group-3 (20-35) PSA density was measured using the formula as: PSA density =Serum PSA (ng/ml)/PSA volume (ml).[12-14]

Statistical Package for Social Sciences (SPSS) version 20.0 was used for the data analysis. Quantitative variables with normal distribution were expressed as Mean±SD and qualitative variables were expressed as frequency and percentages. Pearson's correlation was calculated between PSA and alkaline phosphatase, gamma-glutamyl transferase, prostate size, prostate volume, and prostate density. One-way ANOVA was compared for biochemical parameters, ultrasonographic findings, and PSA density with groups formulated according to prostate size. One-way ANOVA comparison was also done between groups based on participants' AUA symptoms score questionnaire replies. The p-value<0.05 was considered statistically significant.

RESULTS

Out of the total subjects recruited in our study (n=336), 158(47.02%) were in the age group of 45-60 years, 143(42.55%) were from the age group of 61-75 years, and 35(10.41%) were from the age group of 76-90 years. 131(38.9%) were diabetics, while 205(61.01%) were non-diabetic. 211(62.6%) were smokers, and the remaining 126(37.4%) were non-smokers. Gamma glutamyl indices lagged behind PSA levels, ultrasound

measures of the prostate gland, and derived indices incorporating PSA results and ultrasound data. As depicted in Table-I, PSA showed the highest correlation with gamma-glutamyl transferase, PSA volume, size, and density. Groups based on ultrasound-measured prostate size did not show statistically significant differences in PSA, GGT, ALP, PSA density, and PSA volume $p>0.05$ (Table-II).

Groups based on AUA symptom score also did not show much difference for Gamma Glutamyl Transferase and other ultrasound-derived calculated indices, ($p>0.05$) (Table-III).

the factual position that prostate-specific antigen remains the most central biomarker in the diagnosis of benign prostate hyperplasia. Prostate-related ultrasound measures, including PSA density, may be falsely raised in conditions where the prostate gland has been manipulated due to certain infections like prostatitis and occasional association with urinary tract infections (UTIs).[15,16] Provided these limitations, PSA-derived measures, especially once evaluated longitudinally, currently remain the best possible lens to visualize the benign and malignant progression of prostate disease.[17]

Table-I: Correlation Between Prostate Specific Antigen with Alkaline Phosphatase, Gamma-Glutamyl Transferase, Prostate Size, Prostate Volume and Prostate Density (n=336)

Parameter		Gamma Glutamyl Transferase (IU/L)	Alkaline phosphatase (IU/L)	Prostate Specific Antigen volume (ml)	Prostate gland size (g)	PSA density (PSA in ng/ml / Prostate volume in ml)
Prostate specific antigen (ng/ml)	Pearson Correlation	0.422**	0.170**	0.513**	0.520**	0.754**
		<0.001	0.002	<0.001	<0.001	<0.001
Alkaline phospatase (IU/L)	Pearson Correlation	1	0.125*	0.290**	0.291**	0.318**
			0.021	<0.001	<0.001	<0.001
Gamma glutamyl tranferase (IU/L)	Pearson Correlation	0.125*	1	0.088	0.088	0.123*
		0.021		0.108	0.109	0.025
PSA volume (ml)	Pearson Correlation	0.290**	0.088	1	.995**	0.079
		<0.001	0.108		<0.001	0.146
Prostate gland size (g)	Pearson Correlation	0.291**	0.088	0.995**	1	0.086
		<0.001	0.109	<0.001		0.116
PSA density (PSA in ng/ml / Prostate volume in ml)	Pearson Correlation	0.318**	0.123*	0.079	0.086	1
		<0.001	0.025	0.146	0.116	

PSA: Prostate specific antigen

Table-II: Comparison of Biochemical, Ultrasongraphic Findings and Prostate Specific Antigen Density Between Groups Formulated According to Prostate Size (n=336)

Parameters	Group-1 (n=31)	Group-2 (n=66)	Group-3 (n=239)	*p*-value
Gamma glutamyl tranferase (IU/L)	35.00±33.84	37.06±20.18	38.15±31.69	0.846
Alkaline phosphatase (IU/L)	129.71±25.17	118.74±35.91	126.00±35.61	0.162
Prostate specific antigen (ng/ml)	8.48±18.80	7.62±8.08	5.82±8.31	0.191
PSA volume (ml)	41.28±28.67	50.09±21.35	44.27±14.74	0.030
PSA density (PSA in ng/ml / Prostate volume in ml)	0.15±0.14	0.14±0.33	0.13±0.23	0.805

PSA: Prostate specific antigen

Table-III: Comparison Between Groups Based Upon American Urological Association (AUA) Symptom Index Score (n=336)

Parameters	Group-1 (n=184)	Group-2 (n=110)	Group-3 (n=42)	*p*-value
Gamma glutamyl tranferase (IU/L)	38.38±30.56	37.63±20.18	38.15±31.69	0.752
Alkaline phosphatase (IU/L)	127.15±37.37	123.85±34.21	126.62±25.16	0.733
Prostate specific antigen (ng/ml)	6.48±9.44	9.10±7.54	7.06±14.89	0.860
PSA volume (ml)	45.60±15.12	46.22±21.03	40.26±20.34	0.164
Prostate gland size (g)	45.30+30	46.12+21.47	40.04+20.01	0.164
PSA density (PSA in ng/ml / Prostate volume in ml)	0.14±0.27	0.11±0.09	0.15±0	0.624

PSA: Prostate specific antigen

DISCUSSION

Our research demonstrated that PSA density and ultrasound-driven prostate measures correlated well with PSA. These findings, though expected, highlight

Alkaline phosphatase is usually not secreted from the prostate, but any malignant transformation may be expected to raise bone and intestinal sources of alkaline phosphatase.[18] However, contrary to PSA, the

findings regarding alkaline phosphatase demonstrated a poor correlation with PSA and ultrasound-derived PSA calculations, including PSA density. Probable reasons include: Our data constituted sampling from participants who were not diagnosed to have any malignant prostate disease, so chances of finding a raised alkaline phosphatase were minimal. We believe that alkaline phosphatase may not have any role in detecting benign prostatic hyperplasia (BPH), and whenever there is a rise in alkaline phosphatase, emphasis must be placed on ruling out osteoblastic metastasis or reasons associated with other pathological disorders and liver disease.[19]

Though data related and highlighted in the introduction, a rise in Gamma Glutamyl Transferase can usually be secondary to some other organ involvement.[10] in subjects with prostate cancer still data is there which identifies Gamma Glutamyl Transferase to be part of pancreatic secretome and can be associated with benign and malignant prostate disease.[7-9] Our data suggests this marker to be mildly raised in subjects with higher prostate size but without reaching clinical significance. This aspect downsizes its utility as a possible biomarker in the identification of prostate disease, especially the benign variety. However, we feel that further evaluation of this biomarker may be considered for malignant disease of the prostate gland.

The study, though, has not shown a higher positive correlation between gamma glutamyl transferase with PSA and other PSA indices. Still, it helped us rule out community-level use of these biomarkers as they can yield more false negative cases in early disease and false positive results due to the generation of this enzyme from multiple other tissues. PSA and specific ultrasound-measured PSA indices over time can provide valuable data for early and timely screening of prostate disease. This pilot study must be explicitly replicated for various PSA-related measures at a community level to diagnose early disease and avoid false negative patient results.

LIMITATIONS OF STUDY

Our study has some limitations that must be highlighted for the appropriate interpretation of data. Firstly, our data set should have included cases of prostate cancers to allow us a real-time clinical comparison of alkaline phosphatase and gamma-glutamyl transferase among subjects with or without malignancy of the prostate gland. However, this was not made possible due to the rarity of prostate cancer cases in our setup. Secondly, the study data must only be extrapolated for our local region and cannot represent a generalized pattern.

CONCLUSION

Prostate derived ultrasound measures and PSA density showed a higher correlation with PSA. Gamma glutamyl transferase may not help depict prostate disease specifically.

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Authors Contribution

Following authors have made substantial contributions to the manuscript as under:

MAK & AH: Data acquisition, data analysis, drafting the manuscript, critical review, approval of the final version to be published.

MY & SBZR: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

WH & SH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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