A Study of Age-Specific Reference Range for Serum Prostate Specific Antigen in South Indian Men

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ABSTRACT

BACKGROUND

Prostate specific antigen (PSA) is the widely used tumour marker for screening and diagnosis of prostate cancer. PSA levels are known to be influenced by many factors like race, ethnicity, environmental factors, advancing age etc. The present study was designed to determine the age specific reference range for serum PSA among healthy south Indian male volunteers and compare age-specific serum PSA levels in south Indian men with that reported from different regions of India.

METHODS

A total of 500 adult men who attended Master Health Check-Up programme in a tertiary care hospital in Chennai, India, were included in the study. 39 men were excluded from the study and 461 men who satisfied the inclusion criteria were assayed for PSA levels using eCLIA method.

RESULTS

The mean ± SD of serum PSA levels in different age groups in our study was found to be 0.68 ± 0.42 ng/mL in those less than 40 yrs.; 0.77 ± 0.46 ng/mL in 40-50 yrs.; 0.99 ± 0.75 ng/mL in 50-60 yrs.; 1.33 ± 1.06 ng/mL in 60-70 yrs.; and 1.36 ± 1.09 ng/mL in more than 70 yrs.

CONCLUSIONS

Our study showed lower age-specific serum PSA ranges for healthy south Indian men when compared to different regions in India. The study has also confirmed that serum PSA levels increased as age increases. It is necessary to establish separate age specific reference ranges of serum PSA for Indian men.

KEYWORDS

Prostate Specific Antigen (PSA), Prostate Cancer, Age-Specific Reference Range

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BACKGROUND

Prostate-specific antigen (PSA), a 33-kDa protein, homologous with the protease kallikrein family is widely used as a marker for prostatic carcinoma, a common malignancy in men and is considered to be the most valuable marker in screening and diagnosis of prostate cancer. PSA is an androgen regulated serine protease produced by prostate ductal and acinar epithelium.[1] It is organ-specific and can be detected in patients with normal prostate, benign prostatic hyperplasia, in both primary and metastatic prostatic cancer[2] after rectal examination and in prostate infection (prostatitis). PSA has a plasma half-life of about 3 days and its main function is to help liquidize semen. Levels of PSA increase with age, which is mainly due to increase in the volume of prostate, hence there is a need for age-adjusted reference ranges to diagnose prostate cancer.[3] Plasma PSA concentrations greater than 10 ng/mL are strongly suggestive of carcinoma, although carcinoma may be present even if values fall within the reference range. A PSA >20 ng/mL is suggestive of prostatic carcinoma that has spread beyond the prostate gland.[3]

Globally the 95th percentile value of serum PSA (4.0ng/mL) is not always accurate for all ages.[4] It has been suggested that age specific cut-off values for PSA are better than the currently used single cut-off of 4.0 ng/mL.[5] Several studies conducted worldwide and in India have reported that the serum PSA level varies with different geographical areas, age and ethnicity.[6,7] This study is to establish age –specific reference range of serum PSA in healthy South Indian male volunteers and compare age-specific serum PSA level in south Indian men with that reported in different regions of India. The definition of reference interval is based on that of reference individual: "an individual selected for comparison using a defined criteria". The interpretation of values obtained from an individual must be clearly defined. We must specify their age and gender and whether they should be healthy or have a certain disease. The definition of reference individual also covers the cases in which the individual under clinical investigation is her or her own reference- termed subject based reference values.[8]

METHODS

The study was conducted at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, after obtaining Institutional Ethics Committee Clearance. This observational study included 500 healthy male volunteers in the age group of more than 18 yrs. to 90 yrs. Men having urological complaints, who had undergone surgery of prostate gland or history of prostate disease, on chemotherapy or radiotherapy or anti-androgen drugs and having pus cells in urine analysis were excluded from the study.

Out of 500 volunteers, only 461 participants satisfied the inclusion and exclusion criteria. The study participants were divided into five groups. Group A- less than 40 yrs. (n=99), Group B-40-50 yrs. (n=111), Group C-50-60 yrs. (n=89), Group D-60-70 yrs. (n=95), Group E-more than 70 yrs. (n=67). After obtaining informed consent blood samples were collected from all the participants. The serum samples were analysed using electro- chemiluminescence method with cobas 6000 integrated analyser (e601) after passing internal quality control on daily basis. Urine analysis was done using dipstick method and read in semi- automated urine analyser (Laura M). The prostate enlargement was ruled out using ultrasound pelvis.

Statistical Analysis

The SPSS software was used for statistical analysis. Mean, median, SEM and 95th percentile confidence intervals-low & high were calculated for all groups. p Value of <0.05 was considered significant.

RESULTS

Age in Years	Less than 40 yrs. (A)	40-50 yrs. (B)	50-60 yrs. (C)	60-70 yrs. (D)	More than 70 yrs. (E)	Total
N	99	111	89	95	67	461
PSA (ng/mL) Mean ± SD	0.68 ± 0.42	0.77 ± 0.46	0.99 ± 0.75	1.33 ± 1.06	1.36 ± 1.09	0.99 ± 0.82
Median	0.6	0.7	0.8	1.1	1.04	0.77
SEM	0.04	0.04	0.08	0.11	0.13	0.04
95% CI-Low	0.06	0.68	0.84	1.12	1.10	0.91
95% CI-High	0.77	0.85	1.15	1.55	1.62	1.06
p Value		A vs. B 0.17	A vs. C 0.001**	A vs. D <0.001**	A vs. E <0.001**	
PSA values (min-max)	0.02-2.5	0.1-2.8	0.1-3.8	0.01-5.1	0.02-5.7	0.01-5.7

Table 1. Age Specific Serum Prostate Specific Antigen (PSA) Levels in Healthy Male Volunteers

(SEM-Standard Error of Mean, CI- Confidence Interval, *Significant, **Highly significant)

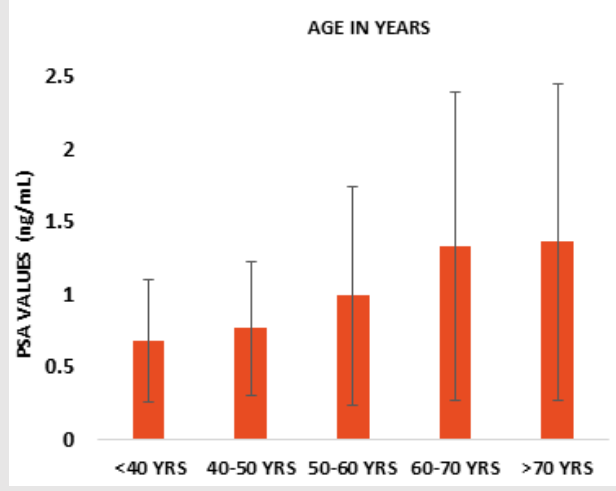

Figure 1. Age Specific Serum Prostate Specific Antigen (PSA) Levels in Healthy Male Volunteers

The serum PSA levels of 461 healthy male volunteers as per age group from <40 yrs. to >70 yrs. are shown in Table 1. The range of serum PSA values in healthy male volunteers was 0.01-5.70 ng/mL. The mean serum PSA values was 0.68 ± 0.42 ng/mL in those younger than 40 yrs.; 0.77 ± 0.46 ng/ml in 40-50 yrs.; 0.99 ± 0.75 ng/mL in 50-60 yrs.; 33 ± 1.06 ng/mL in 60-70 yrs.; 1.36 ± 1.09 ng/mL in more than

70 yrs. age group. Age-wise distribution of serum PSA in the entire study group is shown in Fig. 1 There was a progressive increase in mean and 95% CI values with advancing age from below 40 yrs. to above 70 yrs. age group. The p value was statistically highly significant when PSA levels of <40 yrs. of age was compared with other four groups (p value <0.001).

DISCUSSION

PSA is considered to be the widely used tumour marker in the screening and follow-up of patients with prostate cancer. The PSA is bound in the plasma to either α1-antichymotrypsin or α 2-macroglobulin. The concentration of bound or complexed PSA is higher in prostate carcinoma, whereas that of free PSA (fPSA) is higher in BPH. The ratio of free to total PSA (tPSA) is lower in men with prostatic carcinoma.[3] The total PSA assay has low specificity for prostate cancer detection. Hence to improve the diagnostic efficiency of serum PSA measurements several approaches, such as those employing PSA density, PSA velocity, age-specific reference ranges and fPSA: tPSA ratio have been introduced. Since serum PSA measurement plays a crucial role in the screening and management of prostate cancer it has become essential to establish age specific reference ranges to improve the diagnostic efficacy.

The study conducted in Asian men have shown lower PSA level than men in other races (African & American).[9] This may be due to lower levels of androgen in Asian men but there have not been any studies investigating the cause. Lower rates of prostate cancer in Nepal when compared to India and Pakistan have reported by Pradhananga et al.[10] In the present study the serum PSA level of 1.06 ng/mL was found to be the 95th percentile in healthy male volunteers. This was found to be lower than healthy Haryana men (1.17 ng/mL), Gujarati men and south Indian men (1.51 ng/mL) as reported by Aditi Gupta et al.[11]

Age acts as one of the key risk factors for the prostate disease because with the increase in age, susceptibility towards the disease also increases.[7] Oesterling et al[12] have reported that the serum PSA concentration directly correlated with patient age rather than to rely on a single reference range for men of all age groups i.e. for a healthy 60 yr. old man with no evidence of prostate cancer, the serum PSA concentration increased by approximately 3.2 per cent per year (0.04 ng/mL). The study conducted on healthy multi-ethnic Asian population (Malay, Chinese and Indian men) by Lim et al[13] support the concept that the baseline PSA level varies between different ethnicities across all age groups. Therefore, for Indian population also it becomes essential to determine age specific PSA values.

A study done on serum PSA levels in a community-based population of Gujarat reported that age specific PSA ranges were on the lower side and the prostate specific antigen density were on the higher side.[14] This study also concluded that 89.17 per cent had a PSA of <4 ng/mL, 8.9 per cent had a PSA between 4-10 ng/mL, while 1.8 per cent had a PSA more than 10 ng/mL.[14] Agnihotri et al[15] in his study on 4702 patients for defining the cut-off value of PSA for biopsy in symptomatic Indian men concluded that 70.9 per cent had PSA values of <4 ng/mL and 29.1 per cent had PSA values of >4 ng/mL.

In our study, the normal upper limit of serum PSA level in healthy male volunteers was 1.06 ng/mL which was considerably lower than the international standard reference range of 4.0 ng/mL. The mean PSA level of healthy men was 0.99 ng/mL which was lower than that of healthy Haryana, Gujarati and south Indian men (1.4 ng/mL). The men were distributed into five age groups (<40 yrs to >70 yrs. of age) to see the upper limit of normal range (95th percentile) across different age groups which increased from 0.77 ng/mL to 1.62 ng/mL.

CONCLUSIONS

Our study showed lower age-specific serum PSA ranges for healthy south Indian men when compared to different regions in India. The study has also confirmed that serum PSA levels increased as age increases. It is necessary to establish separate age specific reference ranges of serum PSA for Indian men.

Limitations

The limitation of this study is that prostate biopsy was not done as the participants were apparently healthy male volunteers who opted for this test as a part of their regular health check-up.

REFERENCES

[1] Balk SP, Ko YJ, Bubley GJ. Biology of prostate-specific antigen. J Clin Oncol 2003;21(2):383-391.
[2] Placer J, Morote. Usefulness of prostatic specific antigen (PSA) for diagnosis and staging of patients with prostate cancer. Arch Esp Urol 2011;64(8):659-680.
[3] Crook MA. Metabolic effects of tumour. Chap- 24. In: Crook MA, ed. Clinical biochemistry and metabolic medicine. 8th edn. CRC Press 2012:343-344.
[4] Loeb S, Nadler RB, Roehl KA, et al. Risk of prostate cancer for young men with a prostate-specific antigen less than their age specific median. J Urol 2007;177(5):1745-1748.
[5] Senior K. Age specific PSA screening better. Lancet Oncol 2007;8(5):378.
[6] Malati T, Kumari GR. Racial and ethnic variation of PSA in global population: age specific reference intervals for serum prostate specific antigen in healthy south Indian males. Indian J Clin Biochem 2004;19(1):132-137.
[7] Shah S, Jha B, Khanal MP. Effects of aging and ethnicity on serum free prostate specific antigen. Asian Pac J Cancer Prev 2011;12(10):2509-2512.
[8] Burtis CA, Ashwood ER, Bruns DE. Establishment of reference value. In: Tietz textbook of clinical chemistry

and molecular diagnostics. 5th edn. Elsevier Health Sciences 2012: p. 96.
[9] Morgan TO, Jacobsen SJ, McCarthy WF, et al. Age specific reference ranges for serum prostate specific antigen in black men. N Engl J Med 1996;335:304-310.
[10] Pradhananga KK, Baral M, Shrestha BM. Multi-institution hospital based cancer incidence data for Nepal: an initial report. Asian Pac J Cancer Prev 2009;10(2):259-262.
[11] Gupta A, Gupta D, Raizada A, et al. A hospital based study on reference range of serum prostate specific antigen levels. Indian J Med Res 2014;140(4):507-512.
[12] Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men. Establishment of age-specific reference ranges. JAMA 1993;270(7):860-864.
[13] Lim J, Bhoo-Pathy N, Sothilingam S, et al. Ethnicity is an independent determinant of age-specific PSA level: findings from a multi-ethnic Asian setting. PLoS One 2014;9(8):e104917.
[14] Ganpule AP, Desai MR, Manohar T, et al. Age-specific prostate specific antigen and prostate specific antigen density values in a community-based Indian population. Indian J Urol 2007;23(2):122-125.
[15] Agnihotri S, Mittal RD, Kapoor R, et al. Raising cut-off value of prostate specific antigen (PSA) for biopsy in symptomatic men in India to reduce unnecessary biopsy. Indian J Med Res 2014;139(6):851-856.