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Arginase, a Possible Therapeutic Target in Prostate Cancer

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

With increasing populations, the prevalence of prostate cancer increases. In the future, a significant public health crisis can be recognized in the present incidence of prostate cancer. In order to counter this, markers should be established for the advanced diagnosis and treatment of the illness prognosis. The cells dominate our immune system and grow into a detectable tumour, causing cancer. At this stage in the body, several processes are dominated, governed and deregulated by the tumour. In most cases, immune response undertakes measures by limiting the availability of Arginine. In this context it is fascinating to examine how the levels of Arginine fluctuate with the severity of the disease and the levels of Arginase and NO. Substances and methods: In 25 beginning phases and 25 advanced stage of the prostate cancer patients and compared to 25 healthy controls, 5 ml of the blood were taken and tested for serum levels of Arginina, and nitric oxide. A substantial reduction in arginine ($p<0.001$) found was detected. In Arginase and levels a substantial increase ($p<0.001$) was detected. Conclusion: Increased Arginase levels are linked to the illness progression and the result lowers as Arginase uses most phases. Therefore, Arginase inhibition can be promising therapeutic target in prostate cancer.

Keywords: Arginase; therapeutic target; arginine; immunity; prostate cancer.

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1. INTRODUCTION

Prostate cancer is one of the common causes in the world death rate from cancer for men. India has previously a lower prevalence than Western nations of prostate cancer [1]. However, when urban development is growing, the rural population migrates to the urban region, which tends to modify their lifestyle as well as to increase disease awareness and make clinical practice simple to use [2]. In the future, a major public health concern can be considered in the existing incidence of prostate cancer. Late stage detection is correlated to the poor rate of success for prostate cancer treatment [3]. In contrast, early diagnosis can lower the development of the tumor to metastatic lesions and lower the mortality rate. Therefore, early detection and cancer diagnosis factors need to be developed [4]. The cells dominate our immune system and develop into a noticeable tumour, causing cancer. In this stage, the body maintains, regulates, and deregulates various mechanisms through the tumour and hence paralyses the immune system [1]. A robust immune system must be developed to fight cancer [5].

The paucity of a malignant tumour is typically successful in improving our immune function. The frontline guards faced by tumour cells perform as Arginine and NO. They are mediators for stimulation of cytokine and tumour activity mediated by macrophage [6]. Monocytes generate NO by activating inducible nitric oxide synthesis as a reaction to a microbial infection [7].

The production of NO is an enzyme used as a substrate material for inducing nitrogen oxide synthesis [8]. Arginase, a hydrolyzing enzyme that divides arginine into ornithine and urea, is another enzyme that employs Arginine as a substrate material. Penetration of immune response often limits the availability of arginine with an increase in the activity of arginase [9]. Arginase activity in breast cancer is said to rise and the Arginase activity in prostate cancer has thus been studied [10]. When Arginine's bioavailability for NO synthesis is in any way thrown into question, the ability to produce NOs is restricted by immunity [11].

2. MATERIALS AND METHODS

The study carried out in the Biochemistry department, B.J. Govt. Medical College and the general hospital of Sassoon, Pune, Germany includes 50 patients with prostate cancer of the ages (40 years - 80 years). In this investigation, both clinically and as pathologically demonstrated. They were classified into two categories: first (stage I+II) and advancement (stage III+IV), based on his pathological report and clinician consultations [12]. The tests included 25 normal, healthy people of the same age group. Details of the research have just been revealed before they were approved. Immediately after cancer diagnosis and before any treatment, 5 ml of the injectable quick blood samples from patients were collected. Samples were let to clot for 45 minutes at room temperature and then to centrifugation at 2,500 p.m. [13] in a conventional vacationer. During testing, the serum was refrigerated at -80oC. These serum samples were eventually investigated [14].

Exclusion Criteria

Patients with infectious or allergic diseases will also be excluded, such as diabetic, cardiovascled, renal, hepatic, automotive, and other systemic ailments.

A). The Sakaguchi Method investigated serum arginine levels [11].
B). Roman and Ray techniques (1970) measurement of serum marginase activity[15]: Design research- case-control study

3. STATISTICAL ANALYSIS

Applying SPSS version 21.0 as the average ±SD has also taken into account the inputs. Unpaired t-test was used to analyse the biomarker levels of the cases and controls. I was set at 95% with $p < 0.05$ for the data analysis.

Calculation of Sample Size

Sample size is based on sensitivity and prevalence

$$N = \frac{2[Z\alpha + Z\beta]\ 2\ p.q}{E2}$$

N= Specimen volume
p= Prevalence, q= 1-p
Power= 80%, Confidence interval= 95%
Absolute precision= 10%
Type I error Zα= 1.96, Type II error Zβ=0.84acceptable precision.

4. RESULTS

A) The serum arginine in the early stage and advanced prostate cancer values were detected

as a vital reduction (P<0.001) in comparison to controls. In the advanced stage a vital improvement was seen over the initial stage (P<0.001), which is still lower than tests.

B) In comparison with the controls in an initial group of patients with prostate cancer, there was a considerable rise (P<0.001) in serum arginase. Even though activity of arginase in patients with advanced stage of prostate cancer was diminished, it remained statistically high (P<0.001).

The chart in figure demonstrates the overall the association in the first stage of prostate cancer in patients with Serum Arginine levels and Serum Arginase activity. The graph illustrates that a negative association is there between serum quantity of arginine and serum movement of Arginase. Among the early stage, r=-0.931 in individuals with prostate cancer. The negative correlation confirms that Arginine is used to produce ornithines used for generating polyamins when serum arginase activity increases. This decreases the serum level of arginine and shows a negative correlation with serum activity in arginase.

The chart in Fig. 2 indicates a link in final grade CA prostate patients between serum arginine and serum arginase concussions. R = -0.865 in patients at advanced stage of CA prostate In advanced-stage patients, serum arginase activity decreases. The Arginine serum levels increase, demonstrating that the serum Arginine and Arginase always have negative correlations.

Table 1. Comparison of serum arginine, arginase. and serum no levels between controls, initial stage, and final stage prostate cancer patients

Variable	Stage	N	Mean ± Std. Deviation
Arginine (µmol/L)	Control	25	75.20 ± 13.35
	Initial	25	34.56 ± 8.50*
	Advanced	25	47.76 4.75*
Arginase(IU/L)	Control	25	2.83 ± 1.17
	Initial	25	9.28 ± 3.51*
	Advanced	25	1.93*

**P < 0.001*

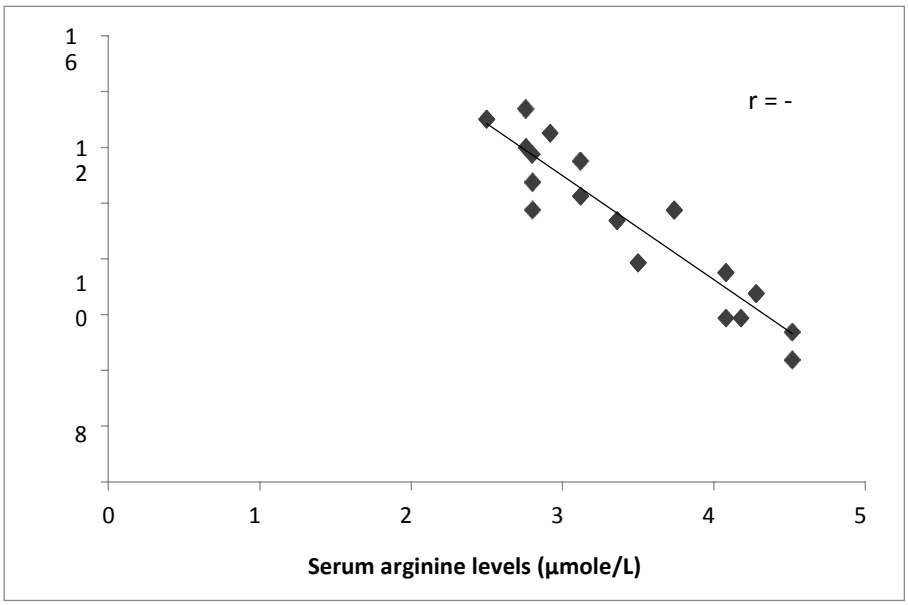

Fig. 1. Correlation between serum arginine levels and serum arginase activity in initial stage prostate cancer patients

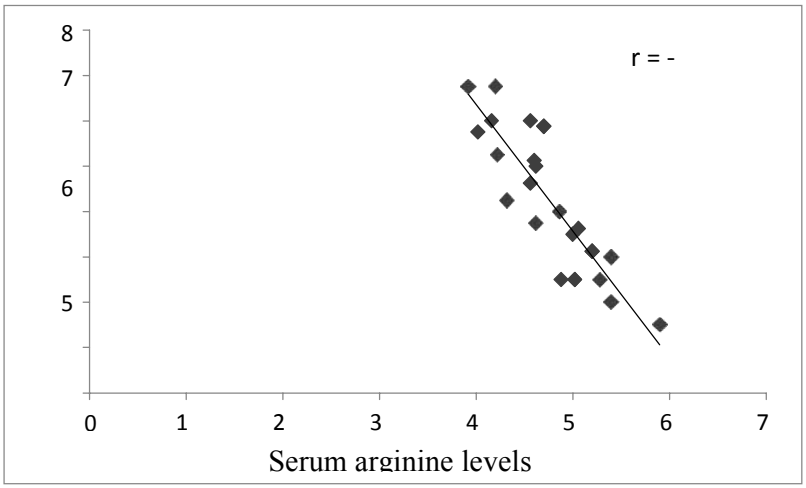

Fig. 2. Correlation between serum arginine levels and serum arginase activity in final stage prostate cancer patients

5. DISCUSSION

The immune system of the body prevents the normal cell from being mutated into a malignant tumor. The immune system provides tumour resistance. Arginine plays a major part in this process. Arginine's bioavailability is essential for macrophage activations via toll-like receivers. Decreased arginine levels in the initial and advanced stages in the current investigation (P<0.001,) were noticed in comparison with controls shown in Table 1. This reduction might encourage development of the tumour.

Recent work documents arginine metabolism anomalies in various tumour-bearing hosts and supports cancers depends on extracellular arginine to sustain the metabolic mechanisms necessary to begin and develop tumours. Increased levels of arginase tend to reduce the immune reaction significantly, as is done by Arginine Arginase, the investigation of the immunity-arginase link in prostate cancer. In the presence of tumor, the metabolism of the intestinal renal axis is shifted. The synthesis is decreased, even though the requirements for arginine are increased than normal in cancer individuals.

The significance of the Arginase pathway in the immune suppressive state is therefore at the earliest stage of prostate cancer patients. A study conducted by [16] and [11] demonstrated that both functionally active arginase I and II prostate cancer cell lines over regulated androgen receptors (AR). According to this [3], the level of Arginase in prostate cancer has considerably low between the common and benign prostate groups. There are also available data on reduced Arginase II in lines of androgen-insensitive prostate cancer cells [17]. These results indicate that in prostate cancer cells Arginase cannot play a significant role. Therefore, the participation of the Arginase pathway in the immune suppression is the early stage of prostate cancer patients. A research undertaken [6] and [11] showed that both functionally active lines for prostate cancer depend on the androgen receptors, Arginases I and II (AR). According to this [3], Arginase levels in prostate carcinogenicity were crucially low, with a contrast of common to benign prostates. There is also data available on minimal appearance of Arginase II in the androgen-insensitive prostate cancer cell lines [17]. These findings suggest that arginase could not play a major impact in prostate cancer cells. required for cancer cell proliferation in the advanced stage. Thus, arginase's immunosuppressive effect may have followed the proliferative role.

The cell proliferation is increased as the stage progresses. As polyamines stimulate growth, their cancer cell growth is enhanced. The blood arginase increased with a stage as demonstrated in Table 1 as reported in the current research.

There is a significantly adverse correlation, as determined from Fig. 1 and Fig. 2 between Arginine (r= 0.931) and Arginase (r = –0.865). This relationship between two parameters indicates that the levels of arginase rise with the

severe nature of the disease at the cost of arginine. That is why arginase levels are decreased and the level of arginase increased as the cancer spreads. These are low in arginine and high in arginase if compared to the control group. A negative correlation is therefore seen in both situations.

6. CONCLUSION

Arginase might include early phase prostate cancer, a hormonally sensitive proliferative stage, from the current evidence of prostate cancer. For polyamine production, it gives more and more supports. This causes tumour spread and leads to a progression of the immune system. A good indication for prostatic cancer detection at an early stage might be high arginase. The decrease in expression of the arginase is found when tumours are less differentiated and glandular development declines; this may lead to a decrease in serum activity of arginase in individuals with advanced prostatic cancer. Decreased Arginase levels can cause more aggressive prostate cancer at the late stage. Thus, it would be useful to prevent situations involving advanced-stage, metastatic diseases and inappropriate behaviour in individuals who have cancer. Numerous investigations have shown that the therapeutic target of arginina deficiency may be cancer [18]. This study implies that therapeutic methods in cancer therapy are useful to decrease enzyme activity and subsequently to lower polyamine formation. Therefore, arginase may be a superior target for enzyme inhibition.

7. LIMITATION

The study should be conducted with large sample size.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The institutional ethical committee approved the study of B J Medical College. Pune, Maharashtra, India, Ref no. is BJMC/IEC/Pharmac/00311052-52 Dt. 24/03/2011.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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