Open Access
Journal of the Faculty of Medicine Baghdad
Print ISSN: 0041-9419, Online ISSN: 2410-8057
DOI: https://doi.org/10.32007/jfacmedbaghdad2476.
Research Article

Arrestin Beta-2 in Prostate Cancer and its Relationship with Trace Elements

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Received: Sept. 2024
Revised: Nov. 2025
Accepted: Dec. 2025
Published Online: Dec. 2025

Abstract

Background: Prostate cancer (PCa) is the most prevalent non-cutaneous malignancy and the second-leading cause of cancer-related mortality among males. Cancer is just one of the several disorders that may be linked to variations in trace element concentrations.

Objective: To evaluate serum arrestin β-2 as a prostate cancer tumor marker and its association with trace elements.

Methods: This case-control study was carried out at the Department of Biochemistry, College of Medicine, University of Baghdad and at the Urology department, Ghazi Al-Hariri Hospital for Surgical Specialties during the period from March 2022 to May 2023. In this case-control study 120 males were enrolled: Sixty men with newly diagnosed primary prostate cancer (PCa) and 60 healthy men as controls. Blood samples were tested for arrestin β-2 levels using an enzyme-linked immunosorbent assay (ELISA), and trace element levels, including Zinc, Copper, and Manganese, were measured using a flame atomic absorption spectrophotometer.

Results: Arrestin β-2 levels differed significantly between the control group and PCa patients. The serum copper level was significantly higher in the cases than in the controls. Zinc and manganese levels were significantly higher in the controls compared to the patients.

Conclusion: It can be concluded that high arrestin β-2 and Copper levels and low Zinc and Manganese levels may serve as potential biomarkers for patients with prostatic Adenocarcinoma.

Keywords: Arrestin Beta -2; Copper; Prostate cancer; Manganese; Zinc.

Introduction

As a major cause of mortality among men worldwide, prostate cancer (PCa) ranks second in cancer mortality, next to lung cancer (1). Almost always castration-resistant prostate cancer (CRPC) develops in patients with advanced PCa following excision of the prostate. Androgen-ablation therapy helps even though the disease may initially remit within two to three years (2). Arrestin β-2 is a key player in cancer progression as it acts as an adapter to direct different pathway signals and acts as a negative signaling regulator through G-protein-coupled receptors (GPCRs) (3).

Drug resistance in CRPC, non-small-cell lung cancer, bladder cancer, and breast cancer has been linked to arrestin β- 2 (4). By acting as scaffold proteins, β-arrestins have a role in various tumor processes, such as carcinogenesis, tumor development, angiogenesis, metabolism, invasion, metastasis, and treatment resistance (5). Much more evidence has been seen, as to the crucial roles played by β-arrestins to the progress and improvement of PCa. Previous studies have also demonstrated that β-arrestins have the potential to increase tumor growth, invasion, and migration in CRPC (6). Trace elements are essential micronutrients that the body has in minute quantities (7). They maintain physiological processes and are essential to the body's metabolism. Their importance to human health has long been recognized (8). Zinc (Zn) participates in signaling pathways, critical for processes such as cell-cycle regulation, immunological function, proliferation, differentiation, and apoptosis; it is both an enzyme and a component of many other enzymes (9).

As the prostate gland is the body's largest zinc reservoir and elevated zinc levels indicate a healthy prostate, low levels of one potential biomarker for prostate cancer is the presence of zinc in prostate tissues (10). Signal transduction, iron absorption, cellular energy metabolism, and reactive oxygen species (ROS) detoxification are just a few of the many vital bodily functions that involve copper (Cu), another vital mineral requirement (11). In many malignancies, such as cancers of the prostate, breast, kidney, and lungs, there is a correlation between low zinc levels and elevated copper levels (12).

Metalloenzymes like pyruvate decarboxylase and superoxide dismutase, which process cellular oxidative stress and produce energy, rely on

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manganese (Mn) as an essential component (13). Thus, it is reasonable to assume that reduced serum Mn concentrations would affect the antioxidant process, making certain organs more vulnerable to carcinogens. Several urological cancer patients demonstrated abnormally low Mn levels in the serum (13).

The study aimed to evaluate serum arrestin β- 2 as a prostate cancer tumor marker and its association with trace elements.

Patients and Methods

This case-control study was carried out from March 2022 to May 2023 at the Urology Department, Ghazi Al-Hariri Hospital for Surgical Specialties, and Baghdad Teaching Hospital by the Department of Biochemistry, College of Medicine, University of Baghdad. It involved 120 males in total, split evenly between two groups: Group 1 included 60 male patients recently diagnosed with primary prostate cancer (PCa) of varying stages and grades based on laboratory tests such as prostatic specific antigen (PSA), as well as clinical and ultrasound evaluations of the prostate. Group 2 included 60 males without a history or symptoms of prostate illness. The scientific and ethical committees of the Department of Biochemistry/ College of Medicine/ University of Baghdad approved the study, in addition to ethical approval obtained from Ghazi Al-Hariri Hospital for Surgical Specialties and Baghdad Teaching Hospital, Medical City Complex, Ministry of Health. Verbal Consent was obtained from each of the study participants.

Inclusion criteria

Patients with elevated PSA and hard nodules in the prostate were included in the group of males with PCa.

Exclusion criteria

Those who had prostatitis or had recently had urethral instrumentation were not eligible.

Serum samples were examined using ELISA to detect β -arrestin2 β-2, and flame atomic absorption spectrophotometer to evaluate serum Zn, Cu, and Mn

Statistical analysis

The data was analyzed using SPSS version 20. To determine whether differences between means are statistically significant, the T-test was employed with a p-value of 0.05 or less considered to be statistically significant within a 95% CI.

Results

Table (1) shows that the mean arrestin2 β-2 was noticeably greater in the patients compared to the controls (P<0.001). The S. Manganese and S. Zinc mean levels were significantly higher in the controls (0.017 ± 0.0045 µg/dl and 114.08 ± 20.851 µg/dl, respectively compared to the patients (0.008 ± 0.0013 µg/dl, and 69.05 ± 7.333 µg/dl, respectively) (P< 0.001). S. Copper mean levels were significantly higher in the patients (165. 72 ± 19.581 µg/dl) compared to the controls (114.05 ± 19.563 µg/dl) (P< 0.001), Table 1 and Figures 1 and 2.

One way to visually show the relationship between clinical specificity and sensitivity for each test cut-off is the receiver operator characteristic (ROC) curve. It shows that serum arrestin β-2 levels could distinguish between healthy and sick people. The optimal cutoff values for disease patient diagnosis, including specificity, sensitivity, and area under the curve (AUC) revealed a sensitivity of 90% and a specificity of 88%, are shown in Figure 3.

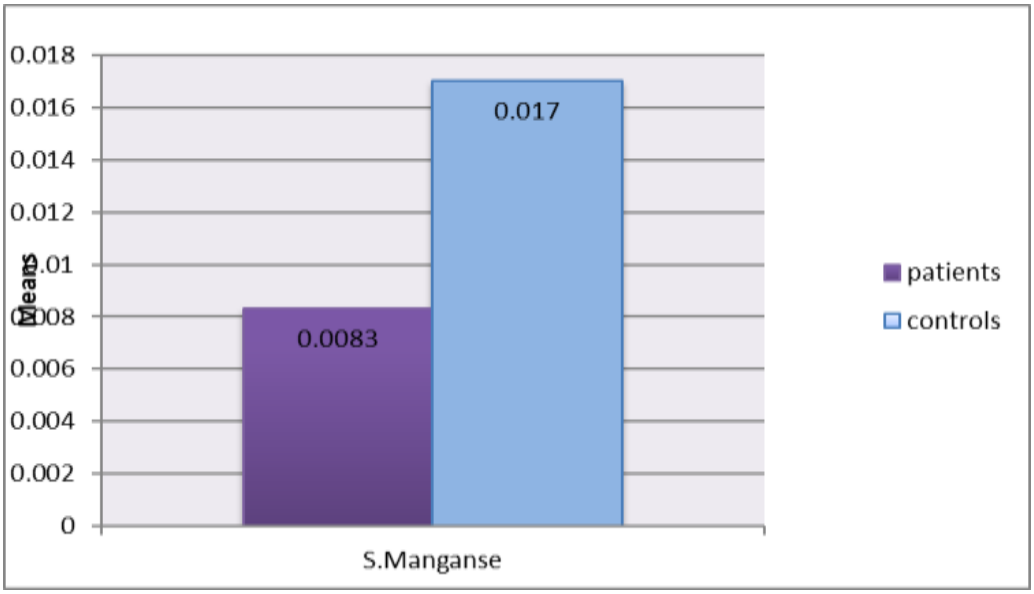

Figure (1): Mean serum manganese levels in the patients and controls.

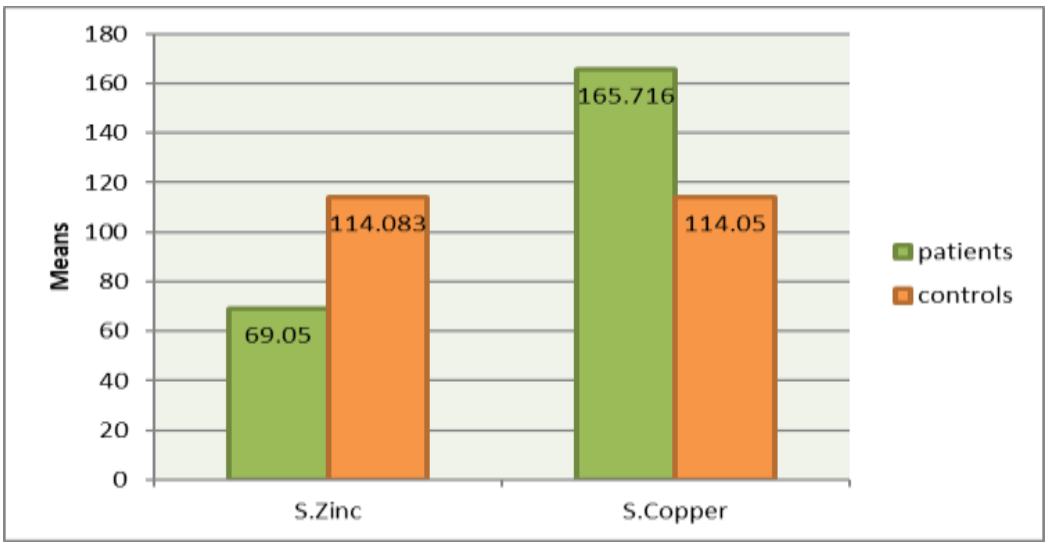

Figure (2): Mean serum zinc and copper levels in the patients and controls

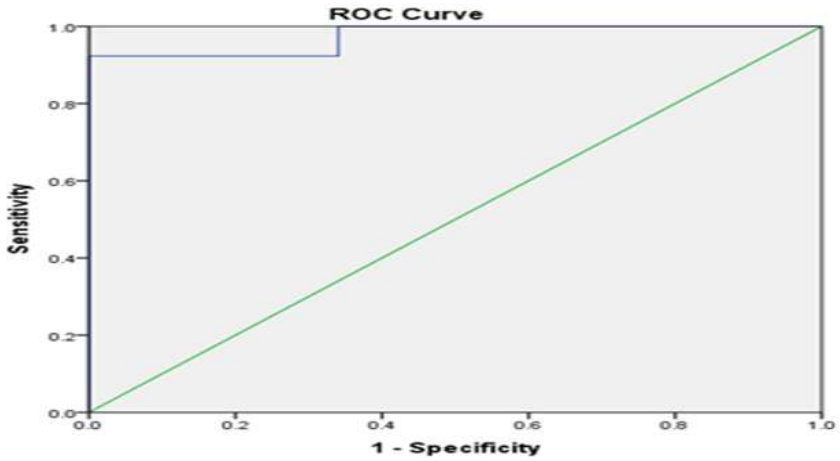

Figure (3): ROC curves for serum Arrestin β-2 in prostate cancer patients.

Table 1: Mean ± SD values of Arrestin β-2 in the study group

Parameters	Mean ± SD		Independent t-test - p-value
	Patients (n=60)	Controls (n=60)	
Arrestin β-2 (pg/ml)	973.5 ± 342.89	470.84	≤ 0.05
S. Manganese (0.010 - 0.025µg/dl)	0.008 ± 0.0013	0.017 ± 0.0045	< 0.001
S. Zinc (80 - 150 µg/dl)	69.05 ± 7.333	114.08 ± 20.851	< 0.001
S. Copper (80 - 150 µg/dl)	165.72 ± 19.581	114.05 ± 19.563	< 0.001

Discussion

The results of the current study demonstrated a significantly higher arrestin β-2 level in prostate cancer patients than controls, consistent with earlier studies. The study by Wu *et al* found that overexpressing the arrestin β isoform in prostate cancer cells enhances ERK-mediated mitogenic signaling and cell proliferation in response to β2-adrenergic receptor activation. It appears that the expression of arrestin β-2 enhances the proliferation of prostate cancer cells via its effects on β2-mitogenic kinase signaling, caused by adrenergic receptors, which involve signaling that is dependent on ERK1/2 and Src, and it also has effects on the AR and gene transcription that is dependent on the AR (14).

This theory is further supported by the fact that arrestin β- 2 seems to be participating in various malignancies, such as breast cancer, ovarian cancer, bladder carcinomas, and others (18,19).

Trace elements are involved in a wide variety of biological activities, whether it is as enzyme activators or inhibitors, binding site competitors, cell membrane permeability regulators, or some other methods [9]. The current findings were consistent with previous research which found that the PCa group had significantly lower mean serum of Zn and Mn, compared to the controls, while the PCa patients had significantly higher mean serum Cu levels (13, 17). However, Lim *et al*., found no significant changes in serum Cu concentration cases of prostate cancer cases compared to controls, in contrast to these study findings. Mn and Zn concentrations in the patients were significantly greater than in the controls .in their study (17).

Abdelmajid *et al* reported that serum Mn levels were high in prostate cancer patients probably because of changes in the interaction of the microelement equilibrium, such as the Zn/Fe ratio, in their population (17). Their findings corroborate our own that elevated Zn levels in the blood are shown to be linked to an elevated prostate cancer risk. They also corroborate the findings of other researchers who have postulated that an excess of Zn within the prostate itself could be crucial for the development of this malignancy (18). Contrarily, they found that PCa patients' serum copper (Cu) levels— were much greater than those of healthy individuals. This may be because intra-tumoral copper is known to be a factor that causes patients to have elevated Cu levels, which agrees with our result (19).

Limitation

The inability to include men who had received a recent diagnosis of prostate cancer because of the limited number of instances observed during the research period.

Conclusion

It can be concluded that high arrestin β-2 and Copper levels and low Zinc and Manganese levels may serve as potential biomarkers for patients with prostatic Adenocarcinoma.

Authors' declaration:

We confirm that all the Figures and Tables in the manuscript belong to the current study. Besides, the Figures and images, which do not belong to the current study, have been given permission for re-publication attached to the manuscript. Authors sign on ethical consideration's Approval-Ethical Clearance: The project was approved by the local ethical committee in (Ghazi Al-Hariri Hospital for surgical specialty and Baghdad Teaching Hospital) according to code number (253) on (10/9/2024).

Conflict of Interest: None.

Funding: This research was self-funded and no external entities were involved.

Data availability: Upon reasonable request, the corresponding author will make the data sets generated and/or analyzed during the current work available.

Authors' Contributions

Study conception (RHA, and MBI), Study design, and critical revision: (IHK, RHA, and MBI). Acquisition of data and analysis (RHA, and MBI), Drafting of the manuscript, and interpretation of data: IHK, RHA, and MBI).

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How to Cite this Article?
Kadhim IH, Ali RH, Ismaeel MB. Arrestin Beta-2 in Prostate Cancer and its Relationship with Trace Elements. J Fac Med Baghdad. 2025.
Available from:
https://iqjmc.uobaghdad.edu.iq/index.php/19JFacMedBaghdad36/article/view/2476

أريستين بيتا 2 كمؤشر محتمل للورم لتشخيص سرطان البروستات وارتباطه بالعناصر النادرة

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الخلاصة:
خلفية البحث: سرطان البروستات هو أكثر أنواع الأورام الخبيثة غير الجلدية انتشارا وثاني أكبر سبب للوفاة المرتبطة بالسرطان بين الذكور. السرطان هو واحد من العديد من الاضطرابات التي قد ترتبط باختلافات في تركيزات العناصر النزرة.
الأهداف: تقييم أريستين β-2 في المصل كعلامة ورم لسرطان البروستات وارتباطه بالعناصر النزرة
المنهجية: أجريت هذه الدراسة المقارنة في قسم الكيمياء الحيوية، كلية الطب، جامعة بغداد وفي قسم المسالك البولية، مستشفى غازي الحريري للتخصص الجراحي خلال الفترة من مارس 2022 إلى مايو 2023. وشملت 120 من الرجال: 60 مريضا تم تشخيصهم حديثا بسرطان البروستات الأولي، و 60 رجلا من الأصحاء كعينة ضابطة. وتضمنت التحقيقات قياسات مصل arrestin β-2 باستخدام اختبار الممتز المناعي المرتبط بالإنزيم (ELISA) وكذلك قياس العناصر النزرة بما في ذلك الزنك والنحاس والمنغنيز باستخدام مطياف الامتصاص الذري باللهب.
النتائج: أظهرت نتائج الدراسة الحالية أن مستويات arrestin β-2 تختلف بشكل كبير بين المجموعة الضابطة ومرضى سرطان البروستات. كما تبين أن مستوى النحاس كان أعلى في المرضى عند مقارنته بالمجموعة الضابطة مع وجود اختلاف إحصائي كبير، كما أظهرت أيضا أن مستويات الزنك والمنغنيز كانت أعلى في المجموعة االضابطة مقارنة بمجموعة المرضى مع وجود اختلاف إحصائي كبير.
الإستنتاج: يمكن استنتاج أن ارتفاع مستويات الأريستين β-2 والنحاس وانخفاض مستويات الزنك والمنغنيز قد تكون بمثابة مؤشرات حيوية محتملة للمرضى المصابين بسرطان البروستاتا الغدي.
الكلمات المفتاحية: أريستين بيتا 2, بسرطان البروستات, النحاس, الزنك, المنغنيز