Journal of Chemical Health Risks

www.jchr.org

JCHR (2024) 14(6), 198-205 | ISSN:2251-6727

Serum Levels of Zinc and Copper and Cu/Zn Ratio in Algerian Prostate Cancer Patients

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(Received: 16 September 2024 Revised: 11 October 2024 Accepted: 04 November 2024)

KEYWORDS

Copper

Zinc

Cu/Zn ratio

Prostate-cancer

Algerian - population

ABSTRACT:

Introduction: Trace elements play a crucial role in the proper functioning of the body's metabolic processes. Among them, copper (Cu) and zinc (Zn) are particularly important in maintaining physiological and pathological balance. Their involvement in various health conditions, including prostate cancer, is increasingly recognised. Prostate cancer, the second most common cancer in men worldwide, is also the fifth most common male cancer in Algeria. Understanding the variations in levels of these trace elements in prostate cancer patients could offer important insights into their potential role in the pathology and diagnosis of this disease.

Objectives: In the present study, Serum levels of zinc (Zn) and copper (Cu) of Algerian patients, diagnosed with prostate cancer. The Cu/ Zn ratio was calculated to explore a possible correlation between these elements and cancer prostate in the study groups.

Methods: In the present study, serum levels of copper (Cu) and zinc (Zn) were measured in 35 patients recently diagnosed with prostate cancer and 40 healthy volunteers using polarography.

Results: Serum Zn level of prostate cancer patients were significantly decreased compared to control groups. The level of serum Cu e were significantly higher in prostate cancer patients than in controls. Consequently, the Cu/Zn ratio was significantly higher in prostate cancer patients that for control groups.

Conclusions: The study conducted on prostate cancer patients in western Algeria provide compelling insights into the correlation between trace elements and cancer progression. Specifically, the results indicate significant alterations in the serum levels of copper (Cu) and zinc (Zn) among these patients. Elevated levels of copper and reduced levels of zinc were consistently observed, resulting in a markedly increased Cu/Zn ratio when compared to healthy control subjects. The elevated Cu/Zn ratio observed in this study presents a promising avenue for cancer diagnostics. This ratio could serve as a significant biomarker to assess the risk of prostate cancer in the western Algerian population.

1. Introduction

Prostate cancer (PCa) is the fourth most common cancer and the second most common malignancy among men worldwide. In 2022, there were 1,467,854 new cases of prostate cancer reported across the globe, with an estimated 397,430 (7.3%) deaths related to these diagnoses. This underscores the significance of PCa as a major public health concern. In Algeria, the incidence of prostate cancer is notably high, with rates suggesting that around 12% of all male cancers are attributed to PCa. Last year alone, over 3,500 new cases of this disease were identified, further emphasizing the need for research in this area [1]. Recent studies have drawn attention to the significant impact of diet, lifestyle and genetic background may have on development as well as progression until death ensues from prostate carcinoma (PCa). Among the various biological factors, metal ions

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JCHR (2024) 14(6), 198-205 | ISSN:2251-6727

play crucial roles in cellular processes. Essential cofactors like iron, zinc, copper, and magnesium are vital for numerous biological functions, including energy production, DNA synthesis, enzyme regulation, and immune system support [2-5].

Copper (Cu) is an essential trace element that plays a crucial role at all stages of tumor development, as it affects important processes such as epithelial-mesenchymal transition (EMT), which in turn is crucial for cancer cell migration and invasion. By inducing EMT, copper ensures that tumor cells will be able to move more freely and invade surrounding tissues. Moreover, Cu has a tremendous effect on micro-environment formation at the tumor site; it promotes angiogenesis (growth of new blood vessels for supplying developing tumors) besides helping with metastasis [7-10]. Cu also takes part in oxidative stresses connected with tumorigenesis: it initiates biological harm through generation of superoxides as well as other reactive oxygen species. The compound helps reduce activation levels for hydrogen peroxide which is an agent for oxidative stress while increasing them for hydroxyl radicals. These reactive species can damage DNA, proteins and lipids, which can promote cancer progression [11].

Zinc (Zn), another essential trace element, is renowned for its antitumor properties [12]. It serves as a cofactor for numerous proteins and enzymes involved in DNA repair, thereby maintaining genome integrity and stability [13, 14]. In particular, zinc is a key cofactor for copper/zinc superoxide dismutase (SOD), a key enzyme with strong antioxidant properties. By promoting the activity of SOD, zinc helps neutralize superoxide radicals, thereby reducing the formation of oxidative damage in cells. This ability to reduce oxidative stress is considered a key mechanism by which zinc exerts its antitumor effects and protects cells from genetic mutations and carcinogenesis [15].

Maintaining an appropriate balance between copper and zinc is important, as an excess of one can lead to a deficiency of the other [16-18]. An imbalance in the concentrations of these trace elements, with low zinc and high copper, can lead to increased oxidative stress and impair the antioxidant activity of various enzymes, thereby compromising cellular defense against oxidative damage [17]. Moreover, the copper-zinc (Cu/Zn) ratio is often considered a more reliable prognostic indicator of overall health status, carcinogenesis, and cancer progression than analysing the concentrations of individual minerals alone [19-21]. This ratio may reflect physiological and metabolic imbalances that affect disease susceptibility and response to treatment.

In this context, we propose to conduct the first case-control study of its kind in Algeria, aiming to measure and compare serum copper and zinc levels in healthy volunteers (controls) and prostate cancer patients. The outcomes of this study could provide valuable insights into the role of trace elements in the pathophysiology of prostate cancer and potentially inform future diagnostic and therapeutic strategies.

2. Methods

Study Design and Blood Sample Collection

This cross-sectional study was conducted on 35 newly diagnosed PCa patients (mean age 69.5 ± 3.8 years) registered at Tidjani Damerdji University Hospital Center in Tlemcen (Algeria) and 40 healthy volunteer (mean age 64.9 ± 3.5 years), with no report of cancer or any other systematic diseases. All participant groups had similar socio-economic status. PCa patients were newly diagnosed, and the blood samples were collected before any intervention. Venous blood samples were collected in the morning from PCa patients as well as healthy controls. Collected blood samples were left at the ambient temperature for 30 minutes to coagulate, next centrifuged at 3000 rpm for five minutes, and then serums were separated by sampler. The obtained serum was aliquoted and stored at −70°C until use. Participation in this study was voluntary, with all participants providing written informed consent. Each participant was given detailed information about the study's objectives and procedures to ensure full understanding. This study was approved by the scientific council of the faculty as well as by the ethics and deontology committee of the University of Tlemcen, in accordance with the principles set out in the Declaration of Helsinki.

Determination of Serum Zinc and Copper Concentrations

Serum zinc and copper levels were assessed using a polarographic analyser (Metrohm 797 Computrance, Switzerland) following our earlier researchs [22, 23]. Prior to analysis, 500 µL of serum was mineralised in a 6:2 (v/v) mixture of nitric acid (HNO3, 65%) and

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JCHR (2024) 14(6), 198-205 | ISSN:2251-6727

hydrogen peroxide (H_2O_2, 30%) using a TOPWAVE microwave digester (Analytik Jena, Germany). All the chemicals and standards used in the analysis were of analytical quality.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics version 25 software (IBM Corporation, USA). The concentrations of trace elements (copper and zinc) were expressed in micrograms per milliliter (µg/mL). Descriptive statistics were calculated, with mean concentrations reported as mean ± standard deviation (SD). To compare the trace element concentrations between prostate cancer patients and healthy volunteers, Student's t-test was employed. A p-value of less than 0.05 was considered statistically significant, indicating a meaningful difference between the groups. This approach allowed for the assessment of potential correlations between trace element levels and prostate cancer status, providing insights into the role of these elements in the disease.

3. Results

In this study, serum levels of copper (Cu), zinc (Zn), and the Cu/Zn ratio were measured in two groups: 40 healthy controls and 35 prostate cancer (PCa) patients from the west of Algeria. The mean values of Cu, Zn, and the Cu/Zn ratio for both groups are summarized in Table 1
The results revealed significant differences between the two groups:

• Copper levels: Serum Cu levels were significantly higher in PCa patients (1.63 ± 0.25 µg/mL) compared to healthy controls (1.03 ± 0.21 µg/mL), with a p-value of less than 0.001. This indicates a potential relationship between elevated Cu levels and prostate cancer progression.

• Zinc levels: In contrast, serum Zn levels were significantly lower in PCa patients (0.65 ± 0.12 µg/mL) than in the control group (0.84 ± 0.13 µg/mL), suggesting that lower Zn concentrations may be associated with the disease.

• Cu/Zn ratio: The Cu/Zn ratio was also significantly higher in the PCa group compared to controls ($p < 0.001$), further supporting the notion of an imbalance in trace elements associated with prostate cancer.

These findings highlight the potential importance of copper and zinc levels in the context of prostate cancer and suggest that alterations in these trace elements may play a role in the disease's pathophysiology. The results prompt further investigation into the mechanisms underlying these changes and their potential utility as biomarkers for prostate cancer progression.

Table 1. Concentration of Cu, Zn and their ratio in serums collected from cases and controls groups.

Element	**Controls** (n = 40)		**Cases** (n= 35)		***p*-value**
	Mean ± SD	Median	Mean ± SD	Median	
Cu (µg/mL)	1.03 ± 0.21	1.01	1.63 ± 0.25	1.58	< 0.001
Zn (µg/mL)	0.84 ± 0.13	0.81	0.65 ± 0.12	0.64	< 0.05
Cu/Zn	1.23	1.25	2.51	2.47	< 0.001

4. Discussion

Essential elements are fundamental to the proper functioning of the human body, playing critical roles that include protection against various diseases such as cancer. Among these essential elements, zinc and copper are particularly important, as they regulate numerous biological processes that can influence the onset and development of cancer.

Prostate cancer, a prevalent health issue worldwide, represents a significant challenge, as it is not only common among men but also has potential life-threatening consequences. Understanding the mechanisms through which zinc and copper affect

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prostate cancer risk is essential in shaping strategies for prevention, diagnosis, and treatment. Evidence suggests that maintaining appropriate levels of these trace elements may help mitigate the risk of developing prostate cancer.

In this study, the association between zinc and copper levels and prostate cancer risks were investigated. To our knowledge, this is the first ever study to examine the association between serum Cu and Zn levels among Algerian prostate cancer patients.

Zinc is an essential trace element for every living organism. More than 300 enzymes and transcription factors require zinc as a functional component. Therefore, zinc deficiency affects several vital biological processes, in particular those linked to the regulation of oxidative stress and DNA repair. In the absence of sufficient quantities of Zn, the activity of antioxidant enzymes such as superoxide dismutase (SOD), which depends on zinc for its functioning, decreases, leading to an accumulation of free radicals and oxidative damage. This damage can affect not only DNA, but also proteins and lipids, contributing to cellular ageing and various pathologies, including cancer. In addition, zinc plays a key role in stabilising the structures of proteins and transcription complexes such as p53, NF-κB and AP-1. In cases of zinc deficiency, p53's ability to bind DNA is impaired, compromising its protective function against tumor development [24-28].

In men, the prostate is particularly vulnerable to zinc deficiency, as it requires high levels of this mineral to function properly [29]. Indeed, prostate epithelial cells absorb zinc at levels up to 10 times higher than other cell types in the body. What is particularly remarkable is that zinc levels in these cells fall significantly when the cells develop a cancerous phenotype [30, 31]. These observations suggest a potential link between zinc levels and prostate cancer prevention. In the present study, we identified a significant difference in serum zinc concentrations between the patient and control groups, with patients exhibiting lower zinc levels compared to the controls ($p < 0.05$ (Table 1)). This finding is in concurrence with some previous studies that have shown the relationship of Zn deficiency and cancer prostate [32-37]. A plausible explanation for this observation could be zinc's crucial role in cell metabolism. Tumor cells, known for their highly malignant metabolic activity, may consume zinc at a faster rate than normal cells, leading to decreased serum levels in patients.

Copper is another essential trace element for the human body and has a variety of physiological functions. It affects the activity of many enzymes (copper/zinc superoxide dismutase (Cu/Zn-SOD), ceruloplasmin, cytochrome oxidase, tyrosinase, dopamine hydroxylase, and lysine oxidase) as a cofactor and variant component. These enzymes are essential for cellular respiration, free radical defense, melanin synthesis, connective tissue formation, and iron metabolism. Copper, as a prooxidant, promotes the harmful effects of free radicals, while as an antioxidant, it can eliminate free radicals and neutralize their potential harmful effects. Several reports in the literature describe a positive correlation between copper levels in serum, blood, plasma, and tissues and the incidence of malignant tumors [38-41]. Previous studies have shown that patients diagnosed with prostate cancer have elevated copper levels in whole blood, serum, and saliva as compared to controls [42-44]. Our study found significantly increased serum copper levels in PCa patients compared to controls, consistent with previous literature that reports similar findings in various cancers. Studies have shown that the elevated serum copper levels in cancer patients are a result of increased production of copper-containing ceruloplasmin. This is triggered by the cancer inflammatory response or decreased catabolism of serum ceruloplasmin [45]. Zn is known as a Cu antagonist, which can be reflected in the hypozincaemia and hypercupraemia observed in malignant transformation. Due to the direct interaction between the intestinal absorption of Zn and Cu, Cu can displace the binding of Zn to metallothionein, as Cu has a high affinity for this protein [46]. This mechanism could explain the decrease in serum zinc concentration associated with the increase in serum copper concentration observed in the present study.

The copper/zinc (Cu/Zn) ratio has emerged as a potential indicator for diagnosing and prognosing various diseases, including cancer [47-50]. An imbalance in copper and zinc levels in the body can lead to excessive production of free radicals or ROS (reactive oxygen species), leading to the development of tumors [51]. Free radicals are known to damage DNA, and as mitochondrial DNA is particularly sensitive to oxidative damage, abnormal levels of copper and zinc may be associated with mitochondrial DNA mutations in cancer

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JCHR (2024) 14(6), 198-205 | ISSN:2251-6727

cells [52]. In general, an increase in copper combined with a decrease in zinc results in a higher copper-to-zinc ratio. An elevation in this ratio is common in various types of cancer. It has been suggested that a copper/zinc ratio close to 1:1 will optimize the function of many important enzymes while higher values reflect increased inflammation and oxidative stress [53,54]. Our findings showed a significantly higher Cu/Zn ratio in PCa patients compared to healthy controls, suggesting that this ratio may serve as an effective biomarker for diagnosing prostate cancer. Elevated copper/zinc ratios often reflect metabolic imbalances associated with cancer. As a result, this ratio could help identify patients at risk and assess disease progression. By integrating the copper/zinc ratio as a biomarker, it would be possible to better target clinical interventions and optimise prostate cancer treatment, offering promising prospects for the personalised management of this disease.

Conclusion

The study conducted on prostate cancer patients in western Algeria provides compelling insights into the correlation between trace elements and cancer progression. Specifically, the results indicate significant alterations in serum levels of copper (Cu) and zinc (Zn) among these patients. Elevated levels of copper and reduced levels of zinc were consistently observed, resulting in a markedly increased Cu/Zn ratio compared to healthy control subjects. The findings highlight that the elevated Cu levels may contribute to tumorigenic processes, such as promoting angiogenesis and cellular proliferation, while the decreased Zn levels could impair essential protective mechanisms, including antioxidant defenses and DNA repair. This imbalance between copper and zinc not only underscores the intricate role these trace elements play in prostate cancer biology but also suggests that monitoring these levels could be vital for understanding disease progression. The elevated Cu/Zn ratio observed in this study presents a promising avenue for cancer diagnostics. This ratio could serve as a significant biomarker to assess the risk of prostate cancer in the western Algerian population, potentially guiding clinical decisions and enabling targeted interventions. By integrating the Cu/Zn ratio into routine assessments, healthcare providers may improve early detection and risk stratification for prostate cancer, ultimately enhancing patient outcomes.

Acknowledgements We are grateful to the patients and healthy volunteers who participated in this study.

Funding This work was supported by the General Direction of Scientific Research and Technological Development (DGRSDT), as part of the socio-economic research project entitled “Implication of micronutrients in the development of certain pathologies in western Algeria” (Project No. 12/Univ-Tlemcen/DGRSDT, 2019, Algeria).

Declarations

Ethics Approval: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the scientific council of the faculty as well as the ethics and deontology committee of the University of Tlemcen, Algeria.

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

Competing Interests: The authors declare no competing interests.

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