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Comparison of serum iron, hemoglobin, ferritin and CRP levels in prostate cancer patients with a control group

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Abstract

Aim: The aim of the study was to investigate the differences between serum iron, ferritin, hemoglobin, and CRP levels between patients with new prostate cancer diagnosis and a control group.

Materials and Methods: This study was cross-sectional and prospectively recorded data from 323 patients with new prostate cancer (PCa) diagnosis and 346 healthy controls between April 2015 and June 2022. Parameters like age, PSA value, serum iron, ferritin and hemoglobin were compared between groups.

Results: The age distribution in groups was identified as 67.19±8.33 years in the PCa group and 62.11±8.16 years in the control group ($p<0.001$). The distribution of PSA (mean±SD) according to groups was determined as 8.40±41.80 (3.54-680) and 0.90±1.02 (0.13-2.94) ng/ml, respectively ($p<0.001$). The distribution of Fe levels in the groups was identified as 81.36±37.80 (21-283) and 90.96±31.23 (33-162) mcg/dL ($p= 0.014$). Hgb values were 14.06±1.56 (8.50-16.70) and 14.58±1.30 (8.98-17.20) g/dl ($p<0.001$). Ferritin values (median±IQR) were identified as 60.30±72.57 (3.6-546) and 54.60±64.04 (6.16-572) ml/ng, respectively ($p=0.427$).

Conclusion: It was identified that the iron and Hgb levels in serum of patients with new prostate cancer diagnosis were reduced compared to the control group. Low serum iron was identified to possibly be a risk factor for prostate cancer.

Introduction

Prostate cancer (PCa) is included in the top cancers with high morbidity and mortality rates most frequently diagnosed in men globally [1]. Autopsy studies estimate the frequency is about 15-25%. Apart from some risk factors like age and genetics, there is increasing evidence about some personal and environmental risk factors, though the definite reason for this disease is not known [2]. For example, men who migrate to America from Far East countries with lower PCa risk still reach the cancer frequency of men in the region they migrate to. Furthermore, cancer frequency may vary by up to 40 times for men living in different regions [3]. In spite of extraordinary developments in diagnosis and treatment processes, the frequency and mortality of the disease have not reduced. In fact, led by the region including our country, the frequency of this cancer is expected to increase around the world [4]. There is no recommendation or medication on hand to stop this increase or protect patients from this disease. Studies about identifying a marker that may be associated with cancer in the future in the serum or urine of patients continue. In relation to this topic, trace elements like iron (Fe) have attracted the attention of many researchers. Reporting about the relationship between some heavy metals especially with PCa has increased interest in this topic [5]. Iron plays roles in important physiological events like transporting oxygen to all living cells, energy production, DNA synthesis, cellular respiration, and as an enzyme building block. Additionally, hemoglobin (Hgb) comprises a building block, which is important for the transport of oxygen and carbon dioxide. A disruption related to iron may affect biological structures playing a role in the development and inhibition of cancer. Development of cancer is known to have a close relationship with an inflammatory environment and the presence of increasing oxidative compounds and DNA injury in this environment [6]. When the literature is examined, there are confusing results related to iron, and most studies have significant deficiencies. As a

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result, according to the best of our knowledge, there is no definite recommendation related to Fe in guidelines related to PCa. Studies continue about this topic. This study was planned to contribute to the literature and with the aim of illuminating problems related to this topic.

The aim of the study was to identify whether there were differences in iron, ferritin, hemoglobin and CRP levels in serum by comparing patients with new prostate cancer diagnosis with healthy peers.

Materials and Methods

Study design and patients

This study was conducted with the data of patients who applied to the urology clinic between April 2015 and June 2022 and were recorded prospectively and analyzed retrospectively. The study is a cross-sectional study. For the simplest in-group and between-group comparisons, the sample size needed was approximately n=220 at the alpha=0.05 level and the effect value determined for a statistical power of 0.95 (Sample size obtained using GPower 3.1 software). Therefore, data of 669 patients, 323 of whom were newly diagnosed with PCa and 346 of whom were in the control group, who applied to our clinic for other reasons in the same period, were recorded. All patients had serum obtained after 10-hours fasting in the morning on an empty stomach before invasive procedures.

Patients with accessible pathology report and laboratory values were included in the cancer group, while the control group had PSA <3 ng/dl as inclusion criteria. The study used exclusion criteria of patients with PSA above 4 ng/dl and no pathology outcomes, PSA value >3 ng/dl, presence of any infection, bone marrow disorder, radiotherapy history, any disorder related to Fe metabolism or receiving any preparate containing Fe, and blood transfusion within the last 12 months.

Demographic features like the age, body mass index (BMI), waist circumference, comorbid diseases, smoking and alcohol habits of patients along with serum Fe, ferritin, Hgb, PSA and C-reactive protein (CRP) levels were recorded.

The study was conducted in adherence to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (University Clinical Research Ethics Committee, Approval Number: 2022/288).

Statistical analysis

In order to apply the correct test method in hypothesis tests, it was first checked whether the data conformed to the normal distribution. As a result of the analysis, Kolmogorov-Smirnov test results were taken into account since the sample size was sufficient and it was determined that some data fit the normal distribution and some did not. Mann Whitney U, one of the non-parametric test methods, and Student's t test method, which is one of the parametric test methods, were used for hypothesis testing. Pearson test from parametric test methods and Spearman chi-square test from non-parametric test methods were used in correlation analysis. Kruskal Wallis Test was used to compare the values in different groups with each other. We used the Statistical Package for Social Sciences (version 20.0) software (IBM Corp., Armonk, NY) for the statistical assessment of the study data.

Results

Age (mean±SD) distribution according to groups was 67.19±8.33 years for the PCa group and 62.11±8.16 years for the control group (p<0.001). The BMI of groups was 27.18±3.99 for the PCa group and 27.73±3.84 for the control group (p=0.123). The PSA (median±IQR) distribution for the PCa and control groups was 8.40±41.80 (3.54-680) and 0.90±1.02 (0.13-2.94) ng/ml (p<0.001).

The distribution of Fe (mean±SD) levels according to group was identified as 81.36±37.80 (21-283) and 90.96±31.23 (33-162) mcg/dL (p= 0.014). Patients with prostate cancer were divided into ISUP grade groups and Fe levels were compared among themselves. Fe levels were 97.4±50.6 mcg/dL in group 1, 88.3±29.3 mcg/dL in group 2, 80.1±38.3 mcg/dL in group 3, 89.8±37.5 mcg/dL in group 4 and 82.2±21.7 mcg/dL in group 5. There was no statistical significance between the groups (p=980). For Hgb (mean±SD) values were 14.06±1.56 (8.50-16.70) and 14.58±1.30 (8.98-17.20) g/dl, respectively. For ferritin (median±IQR), values were identified as 60.30±72.57 (3.6-546) and 54.60±64.04 (6.16-572) ng/mL (p=0.427). Hgb and ferritin values were also compared between ISUP grade groups in patients with prostate cancer, no significant difference was observed between the groups (p=0.605, p=509) (Table 3). The CRP (median±IQR) distribution in the groups was identified as 0.25±0.41 (0.01-15.3) and 0.14±0.26 (0.01-3.78) mg/L (p=0.0123). There were no differences between the groups in terms of comorbid diseases like hypertension, heart disease and diabetes (p>0.05). When groups are compared in terms of smoking, 57.6% of the PCa patients (121/210) and 53.6% of the control group (149/278) smoked (p=0.376).

Table 1. Features of prostate cancer and control groups.

Groups	PCa	Control	p-value
Age[a]	67.19±8.33	62.11±8.16	<0.001*
BMI[a]	27.18±3.99	27.73±3.84	0.123
Waist circumference (cm)[a]	99.71±10.75	99.97±9.05	0.780
Smoking (n) %	(121/210) 57.6%	(149/278) 53.6%	0.376
Alcohol consumption (n) %	(51/203) 25.1%	(66/277) 23.8%	0.393

[a]: mean±SD, *: (p< 0.05). BMI, body mass index.

Table 2. Distribution of serum parameters in the groups.

Groups	PCa	Control	p-value
PSA[b] (ng/dL)	8.4 [41.8] (3.54-680)	0.90 [1.02] (0.3-2.94)	<0.001*
Iron[a] (mcg/dL)	81.36±37.80	90.96±31.23	0.014*
Ferritin[b] (ng/mL)	60.3 [72.57] (3.6-546)	54.6 [64.04] (6.1-572)	0.427
Hemoglobin[a] (g/dL)	14.06±1.56	14.58±1.30	<0.001*
Mg[a]	1.96±0.19	1.95±0.17	0.643
CRP[b]	0.25 [0.41] (0.01-15.3)	0.14 [0.26] (0.01-3.78)	0.0123*

[a]: mean±SD, [b]: median [IQR], *: (p< 0.05). CPR, C-reactive protein; PSA, prostate specific antigen.

Table 3. Comparison of serum parameters according to ISUP grade groups in prostate cancer patients.

ISUP Groups	Iron[a] (mcg/dL)	p-value	Ferritin[b] (ng/mL)	p-value	Hemoglobin[a] (g/dL)	p-value
1 (n=127)	97.4±50.6		76.0±70.6		14.08±1.4	
2 (n=56)	88.3±29.3		93.9±57.5		13.35±2.7	
3 (n=44)	80.1±38.3	0.980	70.8±71.4	0.605	13.71±1.4	0.509
4 (n=48)	89.8±37.5		101.7±117.5		14.76±1.9	
5 (n=48)	82.2±21.7		93.9±62.3		14.11±0.9	

[a]: mean±SD; [b]: median [IQR], *: (p< 0.05). ISUP, International Society of Urological Pathology.

When examined in terms of alcohol use, percentages were 25.1% (51/203) and 23.8% (66/277), respectively (p=0.393) (Tables 1 and 2).

Discussion

The results of this study identified that Fe and hemoglobin levels measured in serum in the PCa cancer group were significantly reduced compared to the control group, while ferritin indicating stored iron did not change. Additionally, CRP, an inflammatory parameter measured in serum, was observed to significantly increase. These results are consistent with the results of previous studies supporting the presence of an inflammatory environment in PCa patients. The reduction in serum Fe levels in PCa patients may be related to iron neutralizing the increasing oxidant compounds in the inflammatory environment or being a building material used by rapidly-proliferating cancer cells.

The number of studies supporting the correlation between prostate cancer with chronic infection and inflammation are increasing. The most important evidence for this topic comes from pathologic investigation of radical prostatectomy specimens. The close relationship of this tissue to the external environment may make it susceptible to invading pathogens. Sexual activity especially is an important risk factor [2]. The presence of pathogenic agents has even been shown in cancer tissue. A study about this topic by Radej et al. showed the presence of P. acne in cancer specimens [7]. In short, viruses and bacteria with oncogenic effects may reach prostate tissue through a variety of routes and cause chronic inflammation [8]. Immune system cells associated with release of several angiogenic factors and immunosuppressive cytokines are found in all human and rat cancers. In normal conditions, abundant lymphocyte and other immune system cells may increase even more in cancer tissue [9]. Frequent direct or indirect targeting of pro-inflammatory pathways by oncogenic genes supports this topic. For example, RAS activates the synthesis of the inflammatory cytokine IL-8. Other oncogenes c-myc and bcl-2 inhibit apoptosis [10]. In conclusion, an inflammatory environment may cause the occurrence of several proinflammatory cytokines and oxidative compounds causing oxidative stress. The oxidative environment may initiate DNA damage and carcinogenic processes and begin the development of PCa [11]. There are some cancers like gastric cancer, esophagus cancer, and hepatocellular cancer which are known to have close relationship with an inflammatory background [10]. The results of our study identified increased CRP elevation leading to consideration of an inflammatory environment in the PCa group. In short, there is increasing density of data showing a correlation between PCa with a chronic inflammatory environment [2,12].

In the body, iron participates in vital physiological processes in cells with inclusion in the structure of many agents like Hgb, myoglobin, cytochrome and enzymes. It is transported in the body by transferrin and stored as ferritin and hemosiderin. For healthy cell function, it is necessary to keep iron within a certain interval. In previous studies, excess Fe was reported to be effective in the development of CVD, cancer and some diseases [13]. The most important evidence about this topic comes from hereditary hematochromatosis (HH) cases. Excessive Fe accumulates in the liver, and is proposed to cause hepatocellular cancer development by oxidative process pathways [14]. However, not every HH case develops cancer, frequently it is necessary for cirrhosis to precede cancer development. In other words, if there is no cirrhosis, cancer development is very rare. In spite of the excess Fe in HH patients, it is not known why cancer is not observed in every case. Other factors apart from iron may be effective.

Just as it is associated with several diseases, excessive iron was associated with PCa. Excessive iron was proposed to be able to initiate carcinogenesis due to lipid peroxidation and/or DNA injury caused by the formation of oxidant compounds [15]. Karimi et al. investigated the trace element and heavy metal levels in tissue samples from PCa patients [16]. The authors proposed a correlation between iron increase and cancer that may be associated with the formation of reactive oxygen species (ROS) and DNA damage caused by this [17]. A study by Kaba et al. compared PCa patients and control group in terms of serum trace elements [18]. The results of this study found significantly reduced serum Fe in the cancer group compared to the control group [19]. Both studies associated the underlying pathology to the oxidant effects developing linked to excessive accumulation of iron in tissues.

In the literature, there are results that are fully opposite to this study. In one of these studies, Saleh et al. separated patients into three groups of prostate cancer, benign prostate hyperplasia and controls [20]. The groups were compared in terms of trace elements. In this study, the PCa group was reported to have increased iron compared to the other groups. The authors reported that this excessive iron may be associated with cancer due to DNA injury caused by oxidative stress. This study, just like our results, is incompatible with the results of other studies. The reason for this may be related to the patient features and disease stage. Additionally, it may be misleading to

reach a conclusion from this study without any information about parameters like Hgb, stored iron and transferrin. It is known that the body regulates iron hemostasis in a very tight fashion. In short, high iron is not always associated with cancer development. A study by Fischer et al. provides important information about this topic [15]. In this study, the correlation between low iron in the liver of rats with oxidative stress and nuclear factor-kappa B (NF-B) was investigated. The group receiving low iron had a moderate increase in oxidative stress observed compared to the high Fe group; however, no effect was shown on DNA double-strand breakage. In the group with high iron diet, NF-B activity, affected by oxidative stress and especially H_2O_2, did not change. This result is supported by the results of a study by Kuvibidila et al. The authors reported that increased iron stores were not associated with PCa [21]. Another carcinogenesis model investigated the effect of iron at different amounts in diet. In spite of a 16-fold increase in iron levels in the group fed with excessive iron compared to the control group, DNA injury did not occur. As a result of this study, it was reported that high doses of iron at impossible levels may be required to induce DNA injury with iron under in vivo conditions [22]. In conclusion, most ideas proposed related to excessive iron have not been proved. The body cannot be considered an in vitro environment, as there is a defense system of strong antioxidants fighting the effects of excessive iron and a DNA repair system.

In our study, patients after PCa diagnosis were compared with a control group in terms of serum iron, ferritin, Hgb and CRP. This study is considered important as parameters were measured in the early stage of disease, sex differences that may affect Fe levels were not present and many dimensions of iron were used (serum Fe, Hgb, stored form of ferritin). The results of the study found that Fe and Hgb reduced in the PCa group compared to the control group, while ferritin indicating stored iron did not change. The lack of difference in terms of ferritin between the groups shows the stored iron was similar in the groups. When prostate cancer patients were divided into ISUP grade groups according to their Gleason scores, it was seen that cancer grades did not have a significant effect on serum Fe, Hbg and ferritin values (Table 3). CRP increased in the cancer group. These results are consistent with previous studies supporting a close relationship between PCa with the inflammatory process. Iron participates in important biochemical processes like electron transport, ATP production, heme and DNA synthesis and is a building block for diverse enzymes, so it may be consumed as a building material in newly-forming cells or as an antioxidant.

The basis of the correlation between excessive iron and PCa reported in some studies in the literature may be affected by the methods used in the study and patient groups. It is not possible to say that the increase in iron levels causes PCa based on the available data, because iron is very tightly controlled in the body. A study about this topic investigated the effects of iron added to diet at different doses. Compared to those receiving high iron diet, the iron concentration in the liver of those receiving low and normal iron reduced. However, hematocrit values did not change. Additionally, excessive iron level did not affect DNA injury [15]. The lack of change in hematocrit values in the groups receiving low and high iron diets indicates that Fe stores did not change. As previously known, these results show that iron is tightly controlled within a certain interval. There is a need for stronger data to hold iron, playing a role in many biochemical processes like electron transport, ATP production, DNA synthesis and the immune system, responsible for cancer development. Contrarily, there are studies showing the benefits of iron. An experimental study by Bordini et al. reported that when iron was supplemented in cases with advanced PCa, there was an improvement in the efficacy of antiandrogens [23]. Though it is commonly accepted that free oxygen radicals play a role in injury in some diseases, there is no direct evidence showing that excessive iron causes these diseases. In conclusion, excess iron is not a significant source of concern for a healthy person, because the body has an important protective mechanism. Additionally, it should be remembered that most studies proposing a correlation between excessive iron and cancer are in vitro and experimental. Such an effect is not known in vivo. In a healthy body, excess iron received in diet is tightly controlled and a normal body has the capacity to store excess iron. As a result, freely-circulating iron is at negligible levels. Hence, there is little to no catalytic effect of iron [13]. Iron deficiency may be important in terms of the development or progression of cancer [24]. The basis of this relationship may be the reduction in antioxidant capacity on one hand, or the suppression of the immune system on the other. In our study, this situation may be the reason for the low iron levels in the PCa group. Additionally, cancer development may cause a reduction in iron stores or in the amount of metabolically available iron. This study has some limitations. Among these are the lack of information related to iron in prostate tissue in the cancer and control groups, the lack of oxidant and antioxidant levels and the results coming from a single center. However, in spite of the limitations of the study, we believe it is important due to patient data being prospectively collected, the high number of patients in the study, the investigation of parameters related to iron, the striking results, and additional information related to iron being added to the literature.

Conclusion

The identification of simple, measurable markers emerging in the early period in the serum of prostate cancer patients may be beneficial for the early diagnosis and prognosis of this disease. In our study, the Fe level measured in serum of patients receiving PCa diagnosis was identified to be reduced compared to the control group. Additionally, an increase in serum CRP level was identified in the cancer group and this result leads to consideration of an inflammatory environment in cancer patients. The reason for reduced iron may be its consumption as antioxidant in this inflammatory environment or its use for the construction of new cells. This is because iron plays a role in many vital cell functions like enzymes. Early detection of this reduction may be beneficial in terms of taking precautions to slow inflammation like beginning anti-inflammatory or antioxidant treatment and ceasing habits that may cause oxidative injury.

Ethical approval

The study was conducted in adherence to the Declaration of Helsinki. The study protocol was approved by the local ethics committee (University Clinical Research Ethics Committee, Approval Number: 2022/288).

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
2. Benli E, Yuce A, Cirakoglu A, et al. Comparison of Sexual Behavior and Inflammatory Parameters in Prostate Cancer Patients with Control Group: Prospective Controlled Study. Urol J. 2021;19:101-5.
3. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med. 2018;8:a030361.
4. Liu X, Yu C, Bi Y, Zhang ZJ. Trends and age-period-cohort effect on incidence and mortality of prostate cancer from 1990 to 2017 in China. Public Health. 2019;172:70-80.
5. Vinceti M, Venturelli M, Sighinolfi C, et al. Case-control study of toenail cadmium and prostate cancer risk in Italy. Sci Total Environ. 2007;373:77-81.
6. Demirci-Çekiç S, Özkan G, Avan AN, et al. Biomarkers of Oxidative Stress and Antioxidant Defense. J Pharm Biomed Anal. 2022;209:114477.
7. Radej S, Szewc M, Maciejewski R. Prostate Infiltration by Treg and Th17 Cells as an Immune Response to Propionibacterium acnes Infection in the Course of Benign Prostatic Hyperplasia and Prostate Cancer. Int J Mol Sci. 2022;23:8849.
8. Massari F, Mollica V, Di Nunno V, et al. The Human Microbiota and Prostate Cancer: Friend or Foe? Cancers (Basel). 2019;11:459.
9. Sfanos KS, Yegnasubramanian S, Nelson WG, De Marzo AM. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol. 2018;15:11-24.
10. Demaria S, Pikarsky E, Karin M, et al. Cancer and inflammation: promise for biologic therapy.J Immunother. 2010;33:335-51.
11. Thapa D, Ghosh R. Chronic inflammatory mediators enhance prostate cancer development and progression. Biochem Pharmacol. 2015;94:53-62.
12. Benli E, Cirakoglu A, Ayyıldız SN, Yüce A. Comparison of serum uric acid levels between prostate cancer patients and a control group. Cent European J Urol. 2018;71:242-7.
13. Reddy MB, Clark L. Iron, oxidative stress, and disease risk. Nutr Rev. 2004;62:120-4.
14. Kowdley KV, Brown KE, Ahn J, Sundaram V. ACG Clinical Guideline: Hereditary Hemochromatosis. Am J Gastroenterol. 2019;114:1202-18.
15. Fischer JG, Glauert HP, Yin T, et al. Moderate iron overload enhances lipid peroxidation in livers of rats, but does not affect NF-kappaB activation induced by the peroxisome proliferator, Wy-14,643. J Nutr. 2002;132:2525-31.
16. Karimi G, Shahar S, Homayouni N, et al. Association between trace element and heavy metal levels in hair and nail with prostate cancer. Asian Pac J Cancer Prev. 2012;13:4249-53.
17. Bae YJ, Yeon JY, Sung CJ, et al. Dietary intake and serum levels of iron in relation to oxidative stress in breast cancer patients. J Clin Biochem Nutr. 2009;45:355-60.
18. Kaba M, Pirincci N, Yuksel MB, et al. Serum levels of trace elements in patients with prostate cancer. Asian Pac J Cancer Prev. 2014;15:2625-9.
19. Kaba M, Pirinççi N, Yüksel MB, et al. Serum Levels of Trace Elements in Patients with Testicular Cancers. Int Braz J Urol. 2015;41:1101-7.
20. Saleh SAK, Adly HM, Abdelkhaliq AA, Nassir AM. Serum Levels of Selenium, Zinc, Copper, Manganese, and Iron in Prostate Cancer Patients. Curr Urol. 2020;14:44-9.
21. Kuvibidila S, Gauthier T, Warrier RP, Rayford W. Increased levels of serum transferrin receptor and serum transferrin receptor/log ferritin ratios in men with prostate cancer and the implications for body-iron stores. J Lab Clin Med. 2004;144:176-82.
22. Kang JO, Jones C, Brothwell B. Toxicity associated with iron overload found in hemochromatosis: possible mechanism in a rat model. Clin Lab Sci. 1998;11:350-4.
23. Bordini J, Morisi F, Elia AR, et al. Iron Induces Cell Death and Strengthens the Efficacy of Antiandrogen Therapy in Prostate Cancer Models. Clin Cancer Res. 2020;26:6387-98.
24. Basak T, Kanwar RK. Iron imbalance in cancer: Intersection of deficiency and overload. Cancer Med. 2022;11:3837-53.