

Comparison of serum uric acid levels between prostate cancer patients and a control group

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Citation: 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; 242-247.

Article history

Submitted: Dec. 10, 2017

Accepted: May 3, 2018

Published online: June 12, 2018

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Introduction The aim of this study is to investigate whether the uric acid levels, measured in the serum of patients with a new prostate cancer diagnosis, differ from those in the healthy subjects.

Material and methods The study included 117 patients who applied to our clinic due to a high prostate specific antigen (PSA) with prostate cancer diagnosis from 2013–2016 and 114 patients applying in the same period for other reasons. The serum uric acid levels and inflammatory markers like c-reactive protein (CRP) and neutrophil count were compared between the groups.

Results The age distribution of the patients in the prostate cancer and control group was 67.6 ± 9.4 and 62 ± 8.5 years, respectively. The uric acid levels were identified as 5.05 ± 1.14 and 6.04 ± 1.12 in the prostate cancer and control group, respectively. Additionally, inflammatory markers like CRP and neutrophil count were identified to be high in the prostate cancer group ($p < 0.05$).

Conclusions The uric acid levels measured in serum of patients with a prostate cancer diagnosis were reduced compared to the control group and inflammatory markers were found to be increased. Low serum uric acid levels and increased inflammatory markers were determined as risk factors for prostate cancer.

Key Words: c-reactive protein ↔ prostate cancer ↔ uric acid

INTRODUCTION

Prostate cancer (PCa) is the most common cancer among men globally and is among the leading causes of death. Although the cause is not fully known, age, genetic factors, diet, sexually-transmitted diseases and environmental factors are among the causes which are being focused on. Many recent studies have reported that the chronic inflammatory process plays an important role in the development of PCa. It is thought that many factors form the basis for the correlation between inflammation and cancer. For example, inflammatory compounds such as free oxygen radicals and cytokines released in this environment cause DNA damage and may affect the process of cancer development [1, 2]. The disrupted oxidant/antioxidant balance in favor of oxidants in this

process may contribute to this pathological process. As a result changing this balance in favor of antioxidants has been proposed to have a protective effect against cancer and many antioxidant compounds have been used with this aim [3]. In conclusion, there is a correlation, whether direct or indirect, between the inflammatory process and the process of cancer development. Pathologic studies of cancer specimens support this view through common observations of inflammatory cells [4].

Studies in recent times have reported that uric acid is a strong antioxidant compound and that it contributes to the antioxidant capacity of the body [5]. In an inflammatory process, the oxidant/antioxidant balance is disrupted in favor of the oxidants and this disruption is known to trigger the process of cancer development. As a result, administration of

external antioxidants might have a protective effect against cancer. Some studies on this topic have reported that uric acid has a protective effect against cancer by increasing the antioxidant capacity [6, 7]. As a marker of the antioxidant capacity of the body, uric acid may be beneficial in the diagnosis of the inflammatory process in the early period for a variety of diseases like cancer. Uric acid may be beneficial to identify this process in the early period. To the best of our knowledge to date, there is no study assessing the serum uric acid levels in patients with newly diagnosed PCa. This study was designed to determine serum uric acid levels in patients during biopsy for cancer diagnosis. According to our hypothesis, due to the increased oxidant compounds in cancer patients, there should be a reduction in serum uric acid levels, which is considered to be an antioxidant material.

The aim of this study was to investigate whether serum uric acid levels were different in patients with new PCa diagnosis compared to their healthy peers.

MATERIAL AND METHODS

This study was completed in the Urology clinic of Ordu University Education Research Hospital. The study received permission from the local ethics committee of Ordu University (No: 2016/78). Data belonging to 952 patients from April 2013 to April 2016 was accessed and retrospectively reviewed. Patients abiding by the study criteria were included. This included 117 patients applying due to a high prostate-specific antigen (PSA) with diagnosis of prostate cancer (Group 1) and 112 patients with normal PSA values applying in the same period for other reasons (control/Group 2); a total of 229 individuals were included into the study. Group 1 comprised of patients with a new diagnosis in stage T1c. Laboratory investigations of patients were completed on an empty stomach before invasive procedures.

For patients with a PSA value ≥ 4 ng/dl, possible reasons for PSA increase were excluded and increased PSA was confirmed by repeated measurements. After informing the patients about the biopsy, patients signed a written informed consent form. Under antibiotic prophylaxis, a 12-quadrant transrectal needle biopsy was performed.

Exclusion criteria for the study included known causes such as renal failure causing the possible hyperuricemia, lympho-myelo proliferative and hemolytic diseases, gout and advanced stage prostate cancers. The age, body mass index (BMI), waist circumference, additional diseases, cigarette and alcohol use in patients were recorded. Additionally serum uric acid levels, PSA value, c-reactive protein

(CRP), white blood cells (WBC), neutrophil (neu), neutrophil/lymphocyte ratio (neu/Lym), sedimentation rate, fibrinogen, lipid panel and pathology results of the biopsy were recorded.

Statistics

Parameters with normal distribution are given as mean \pm SD (standard deviation), while parameters with non-normal distribution are given as median \pm interquartile range (IQR). The Kolmogorov-Smirnov test was used to assess data with normal distribution, while the Shapiro-Wilk test was used to assess parameters with non-normal distribution. For comparison between groups the Student t test was used for parametric data analysis, while the Mann Whitney U test was used for nonparametric data. For correlation analysis the Pearson test was used for parametric data, while the Spearman correlation test was used for non-parametric data. All statistical analyses were completed with "SPSS for Windows Version 20.0" program. Data with p value < 0.05 were accepted as significant.

RESULTS

The age distribution in the groups was 67.6 ± 9.4 years for Group 1 (PCa) and 62 ± 8.5 years for Group 2 (control). There were differences between the groups in terms of age ($p < 0.001$). There were no differences between the groups in terms of additional diseases like hypertension, heart disease and diabetes ($p > 0.05$). The distribution of waist circumference in the groups was 99.7 ± 12.8 cm for Group 1 and 98.3 ± 12.2 cm for Group 2 ($p = 0.42$). The distribution of body mass index (BMI) between the groups was 27.7 ± 3.4 and 27.4 ± 4.1 respectively ($p = 0.63$) (Table 1).

The distribution of PSA in Group 1 and 2 was determined as 6.87 ± 7.27 and 0.91 ± 0.6 ng/dl, respectively ($p < 0.001$). The distribution of uric acid levels in the groups was 5.05 ± 1.14 mg/dl in Group 1 and 6.04 ± 1.12 mg/dl in Group 2. The serum uric acid levels were identified to be reduced in the prostate cancer group ($p < 0.001$). The distribution of CRP (mg/dl), an inflammatory marker, in the groups was 0.24 ± 0.37 and 0.18 ± 0.33 , respectively. CRP was identified to be increased in the prostate cancer group ($p = 0.039$). Similarly the distribution of WBC was 6.9 ± 1.1 and 6.5 ± 1.1 ($p = 0.04$), neutrophil count was 4.1 ± 1.2 and 3.7 ± 1.1 ($p = 0.04$), sedimentation rate was 16 ± 17 and 10 ± 6.7 ($p = 0.03$), fibrinogen levels were 321 ± 75 and 335 ± 44.7 ($p = 0.02$), and neu/lym ratio was 2.15 ± 1.1 and 2.08 ± 0.96 ($p = 0.02$) in the groups,

respectively (Table 2). There were no differences between the groups in terms of cholesterol, triglyceride, HDL and LDL levels (Table 3).

DISCUSSION

This study is the first to measure uric acid levels in serum of patients applying with a high PSA and receiving prostate cancer diagnosis after a biopsy. The results of the study found that uric acid levels measured in serum were reduced in the PCa group when compared to the control group. Additionally, there was an increase in inflammatory markers measured in the serum, indicating the presence of an inflammatory environment in patients with prostate cancer. These results show that the inflammatory process affects the development process of PCa. The reason for the reduction in uric acid levels measured in the serum of patients with prostate cancer is that uric acid is consumed during neutralization of increasing oxidant compounds in the inflammatory environment.

Prostate cancer is a disease commonly seen in men with advancing age. The definite cause of this disease is not fully known. Many studies in recent times have provided an increasing amount of evidence about a correlation between PCa and an inflammatory process. For example, macrophages related to many angiogenic factors and immunosuppressive cytokine secretion have been found in all human and rat cancers. Additionally oncogenic genes frequently target the pro-inflammatory pathways directly or indirectly, supporting this correlation. For example, oncogenic genes (RAS) activates synthesis of an inflammatory cytokine interleukin-8 (IL-8). Other oncogens such as c-myc and bcl-2 inhibit apoptosis [8]. A study by Cohen et al. showed the presence of microbial agents that might be related to chronic inflammation in a significant portion of prostate cancer specimens. The authors reported the inflammatory process might be an important trigger for PCa development [9]. In conclusion, the inflammatory environment causes the release of many pro-inflammatory cytokines and oxidative compounds causing oxidative stress. Oxidative stress is related to DNA damage and carcinogenic processes. A study on this topic reported that the inflammatory environment triggered the proliferation of prostate cancer cells [2, 3]. A previous study reported a close correlation between PCa and cholesterol and considered that this effect occurred due to oxidative stress. A study by Homma et al. showed that lipids triggered oxidative stress and carcinogenesis in prostate tissue. The authors reported that oxidative stress was the main cause for cancer development [10]. Miyake

Table 1. Properties of prostate cancer and control groups

Groups	Pca (prostate cancer) (n = 117)	Control (n = 114)	P-value
Age (years) (mean \pm SD – Standard Deviation)	67.6 \pm 9.4	62 \pm 8.5	<0.001*
BMI (Body Mass Index)	27.7 \pm 3.4	27.4 \pm 4.1	0.63
Waist circumference (cm)	99.7 \pm 12.8	98.3 \pm 12.2	0.42
Smoking habit (n) %	10.3%	8.8%	0.61
Alcohol consumption (n) %	35%	37%	0.95

*(p <0.05).

Table 2. Distribution of serum parameters of prostate cancer and control group patients

Groups	Group 1 (Pca) (mean \pm SD)	Group 2 (control) (mean \pm SD)	P-value
PSA (Prostate Specific Antigen) (ng/dl) ^a	6.87 \pm 7.27 ^a	0.91 \pm 0.6 ^a	<0.001*
Uric Acid	5.05 \pm 1.14	6.04 \pm 1.12	<0.001*
CRP (C-reactive protein) (mg/dl) ^a	0.24 \pm 0.37 ^a	0.18 \pm 0.33 ^a	0.039*
WBC (White Blood Cells)	6.9 \pm 1.1	6.5 \pm 1.4	0.041
Neu (Neutrophils)	4.1 \pm 1.2	3.7 \pm 1.1	0.043
Sedimentationa	16 \pm 17 ^a	10 \pm 6.7 ^a	0.031*
Fibrinogena	321 \pm 75 ^a	335 \pm 44.7 ^a	0.023
Neu/Lym (Lymphocytes) ratio	2.15 \pm 1.10 ^a	2.08 \pm 0.96 ^a	0.021*

^a median \pm IQR (Interquartile Range) used instead of mean \pm Sd, *p <0.05.

Table 3. Lipid distribution of groups

Groups	Group 1 (Pca) (mean \pm SD)	Group 2 (control) (mean \pm SD)	P-value
Cholesterol (mg/dl)	199.8 \pm 40.5	203 \pm 46.8	0.67
Triglyceride (mg/dl)	110 \pm 79 ^a	129.5 \pm 65.2 ^a	0.13
LDL (Low Density Lipoprotein) (mg/dl)	128.3 \pm 41.4 ^a	135.3 \pm 41 ^a	0.51
HDL (High Density Lipoprotein) (mg/dl)	42.7 \pm 9.7 ^a	43.4 \pm 9.7 ^a	0.071

^a median \pm IQR used instead of mean \pm Sd, *p <0.05).

et al. supported these results. Their study reported that oxidative stress played an important role in the process of prostate cancer development [11]. In short, chronic inflammation is a complicated and lively process involving many cells and mediators and appears to be an important initial mechanism for cancer development. This view is supported by the fact that some cancer cases developed, based

on a chronic inflammatory foundation. Examples may be given including gastric cancer based on chronic gastritis, esophageal cancer based on esophageal reflux, hepatocellular cancers based on cirrhosis and bladder and renal cancers based on urinary tract stones [8, 12, 13]. In the results of our study, the presence of an inflammatory environment in the PCa group was proven by the increased inflammatory marker levels like CRP, sedimentation rate, neutrophil count and neu/lym ratio.

As a result, the suppression of inflammation has been proposed by some authors to play a critical role in protection against cancer. Some studies on this topic have reported a protective effect of some non-steroidal anti-inflammatory (NSAID) medications on colon cancer [14]. Hahm et al. supported these results. The authors of this study showed that antioxidant medications suppressed the proliferation of PCa cells [15].

Uric acid is obtained by the oxidation of xanthine and hypoxanthine by the xanthine oxidoreductase (XOR) enzyme. This enzyme is the rate-limiting step for uric acid production. Studies have reported uric acid to be an antioxidant as strong as ascorbic acid. The excessive increase in the amount of oxidant compounds in an inflammatory process is known to destroy cell and DNA structure by lipid peroxidation. Antioxidant compounds remove the oxidant compounds and positively affect the cancer development process. Studies on this topic have shown a protective effect of uric acid against cancer [16]. Ames et al. first brought the protective effect against cancer to the agenda. The authors reported that uric acid played an important role in suppressing lipid peroxidation and free oxygen radicals formation. This study reported that uric acid was a strong antioxidant and had a protective effect against cancer [17]. Later studies reported a correlation between uric acid and many diseases with an inflammatory basis. Shiva et al. investigated patients with oral lichen planus, considered to be an inflammatory disease, in terms of antioxidant markers including uric acid. The study reported that uric acid was correlated with an antioxidant capacity and might be a beneficial marker for the use in diagnosis and following the progression of the disease [18]. Another study investigating the correlation between uric acid and coronary vascular disease reported that uric acid protected against oxidative inactivation of endothelial enzymes. The authors reported that uric acid was important in suppressing oxidative injury in the coronary microvascular system [19].

Another study by Linder et al. investigated the correlation between uric acid and colorectal cancer. The authors reported that in colorectal cancer pa-

tients, the XOR enzyme was reduced in tumor tissue compared to the control group. Additionally, this study reported a correlation between XOR enzyme expression and histologic cancer stage, progression and survival [20]. Another study investigated the correlation between lung cancer and XOR expression. This study found that low XOR expression had a close correlation with shortened survival and bad prognosis [21]. Though this study showed a correlation between uric acid and cancer prognosis, the cause of this effect is not fully understood. This effect is probably related to the antioxidant capacity of uric acid. A study by Dziaman et al. explained this topic. This study investigated the correlation between the antioxidant capacity and colon cancer. The study measured oxidative stress, oxidative DNA damage and antioxidant capacity (serum uric acid, Vit A, Vit E and Vit C). The authors reported that antioxidant capacity was correlated with uric acid and this situation was important for survival [22]. Additionally they proposed that this might be used as a predictor to assess the efficacy of cancer treatment. In another study, Taghizadeh et al. investigated the correlation between cancer-linked mortality and uric acid levels. The authors reported that high serum uric acid levels were correlated with low mortality risk linked to cancer [7]. Another study related to uric acid by Shi et al. reported that uric acid was important in stimulating the immune cells [23]. This effect of uric acid may be important for the protective effect against cancer. A reduction in the uric acid levels may be related to cancer, on one hand through the reduced antioxidant capacity or on the other hand by suppression of the immune system. In our study this situation may be another cause for the low uric acid levels in the prostate cancer group. Our results are in accordance with a previous study by Akinloye et al. In this study using uric acid as an antioxidant, the correlation between oxidant and antioxidant parameters and PSA level was investigated. The authors reported that oxidative stress was increased in the group with high PSA levels. This study also proposed that uric acid levels are reduced along with the antioxidants in the group with the high PSA values (increased PCa risk) [24].

Some studies have not shown a protective effect of uric acid and even proposed that it triggers the inflammatory process [25]. In a study on the correlation between uric acid and inflammation, inflammatory markers, IL-6, TNF- α (tumor necrosis factor alpha), and CRP were used. The authors reported a positive correlation between uric acid and these inflammatory markers [26, 27]. The protective effect of uric acid against cancer has not been shown

by all studies. One of these studies by Boffetta et al. monitored 16857 gout patients in the long term and investigated whether uric acid had a protective effect against cancer. Over the years of monitoring, the protective effect of uric acid against cancer was not observed in these patients [28]. Some studies have proposed that it triggers the development of cancer. A study by Kolonel et al. on this topic found a positive correlation between PCa and high uric acid levels. However, this study did not show a protective effect of uric acid against prostate cancer and at the same time the correlation with recurrence was not shown [16]. Another study by Sangkop et al. reported that uric acid initiated the pathway for prostate cancer progression. The authors proposed that the development of tolerance against factors inhibiting growth of cancer cells was important [29]. Another study by Fini et al. found that increased extracellular uric acid levels protected the cancer cells from oxidative compounds. Additionally they reported that uric acid was important for proliferation, migration and survival of tumor cells [30]. Hammarsten et al. proposed that high uric acid levels were a predictor of future development of PCa [31]. These results do not agree with the results of our study. The reason for this difference may be due to the different methods used as the standard in the studies.

As observed in the literature, there is confusion about uric acid. The use of different methods in the studies, cancer stage, sex, and measurement time of uric acid may be among the many reasons for this confusion. We believe that the cancer stage, when uric acid is measured, is very important. As it is known, due to the high rate of turnover of cancer cells in cancer patients' serum, uric acid levels may increase in relation to the tumor load. Also, additional diseases, medications or cancer itself may affect uric acid metabolism in cancer patients. We think that serum uric acid levels increase secondarily, during the cancer development process. As a result, in this study the increase in serum uric acid levels may be due to cancer itself, either directly or indirectly. To definitively establish the correlation between uric acid and cancer, we believe studies measuring uric acid in the period when cancer is newly diagnosed, or beforehand, are necessary. In our study, uric acid levels were examined in the period of a new diagnosis of cancer.

In our study, the serum uric acid levels and inflammatory parameters were compared between patients applying with a high PSA and PCa identified on biopsy and a control group. This study measured uric acid in a relatively early period of the disease and

we believe it is important, as it does not include any gender differences that may affect the uric acid levels (e.g., estrogen increases uric acid excretion). The study results identified that uric acid levels were reduced in the PCa group compared to the control group. Additionally inflammatory markers examined in the serum, like CRP, neutrophil and WBC, were increased in the PCa group. These results are in accordance with previous studies, supporting the close correlation between prostate cancer and the inflammatory process. The cause of the reduction in uric acid levels in the PCa group may be due to the increase in oxidant compounds in the inflammatory environment. Uric acid may be an antioxidant compound consumed during the removal of oxidant compounds from the environment. Another reason, as reported by Fini et al., is that, as uric acid is a material that protects cancer cells from oxidant compounds, the excessive oxidant compounds formed in the tumor microenvironment may consume it. However, we believe there is a need for multicenter, prospective studies on this topic including larger numbers of patients.

There are some limitations to this study. These include the low number of patients, the single center results and the retrospective nature of the study. However, despite these limitations, we believe that this study is important as it is the first study to measure uric acid levels in serum in PCa patients with a new diagnosis and the results are noteworthy.

CONCLUSIONS

For early diagnosis of prostate cancer, with known close correlation to the inflammatory process, the use of biomarkers showing the early inflammation process may be beneficial. In our study we identified that serum uric acid levels were reduced in patients with prostate cancer diagnosis when compared to the control group. This study also proved the presence of an inflammatory environment in cancer patients due to the increases in the inflammatory marker levels. These results show that serum uric acid levels are a marker that may be used for diagnosis and prevention of PCa. Early recognition of the reduction in serum uric acid levels may be beneficial in terms of precautions to slow down the inflammation such as starting an anti-inflammatory or antioxidant treatment and stopping habits which cause oxidative damage.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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