Testosterone status is not associated with bladder cancer parameters in adult male patients: results of a prospective controlled study

Alper Kafkasli, Ozgur Yazici, Utku Can, Erdinç Dinçer, Oktay Akca and Onder Canguven

ABSTRACT

Purpose: This controlled study assessed whether there was a correlation between serum total testosterone levels and bladder cancer (BCa) in terms of tumor grade and stage as objective measures in adult men.

Materials and method: Our prospectively-designed study included 257 patients who were diagnosed with primary BCa and its surgery between January 2017 and January 2020. Hundred and forty patients who had surgery in the same period with TUR for prostate or endoscopic ureteral stone treatment were included in the study as a control group. All patients in the study and control groups were male. The age range of the patients was between 34 and 90 years old. In order to examine groups, fasting blood glucose, lipid profile, albumin, total testosterone, and vitamin D levels of all patients included in the study.

Results: The relationship between tumor aggression and total testosterone level was investigated with a multinomial logistic regression model, where the control group was accepted as a reference, following adjustment for potential confounding variables, including age and serum albumin levels. Testosterone level was not found to be associated with any of the categories that determine tumor aggressiveness ($p > 0.05$).

Conclusion: In the present study, there was no correlation between any categories that determine tumor aggressiveness of BCa and total testosterone levels in adult men. It is obvious that our findings should be supported and further investigations are needed.

Introduction

Bladder cancer (BCa) is the second most common cancer in urology and the seventh most common cancer in the male population [1]. The worldwide incidence rate of BCa is 9–22/100,000 person/years for men and women, respectively [1]. Urothelial cell carcinomas that originate from transitional epithelium are responsible for >90% of BCa cases [2]. According to the invasion depth, BCa are mainly classified into two categories as muscle invasive BCa (MIBCa) and non-MIBCa [3]. MIBCa is a far more dangerous disease than non-MIBCa, with a higher likelihood of metastasis which can lead to serious complications and eventually death [3].

According to the guidelines, common risk factors for BCa include tobacco smoking, occupational exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, family history which seems to have little impact, exposure to ionizing radiation and schistosomiasis [4–6]. A gender-specific difference in BCa incidence was noted worldwide in favor of females [7]. BCa is commonly a disease of the elderly and the population overall is aging [8]. Additionally, BCa in men tends to be diagnosed about three to four times more often than in women, even calibrating for lifestyle and environmental factors, suggesting that androgens are responsible or have some kind of correlation with BCa [5]. Moreover, BCa is observed more frequently in postmenopausal women than in premenopausal women and BCa in women has a more aggressive course than in men, suggesting that estrogen is protective for BCa [9,10]. In support of the latter, earlier both basic [11,12] and clinical [13] studies showed some evidence of correlations between BCa and testosterone status [8,14].

The literature reveals many gaps in the knowledge. Firstly, although previous studies evaluated the androgen receptors of BCa patients in basic sciences, it
might not reflect the clinical conditions [13]. Secondly, previous research employed 5-alpha reductase inhibitor [14], we do not know pre-treatment testosterone levels but we are not aware of studies that employed both of these. Therefore, this controlled study assessed whether there was a relationship between serum total testosterone levels and BCa in terms of tumor grade and stage as objective measures.

Materials and methods

The study was approved by the Institutional Review Board of a training and research hospital (Approval No: 202051416912). Our prospectively-designed study included 257 patients who were diagnosed with primary BCa and had transurethral resection (TUR) of BCa between January 2017 and January 2020. As a control group, 140 patients who had surgery in the same period with TUR of the prostate or endoscopic ureteral stone treatment were included in the study. All study participants in the study and control groups were male. Blood samples were taken between 07:00 and 9:00 h after fasting overnight to measure fasting blood glucose, lipid profile, albumin, total testosterone, and vitamin D levels of all patients included in the study. The measurements were made in accordance with the standards set by the international guidelines.

Any person in the study groups who received any kind of hormonotherapy previously, who had chronic diseases such as chronic kidney and heart diseases, uncontrolled diabetes mellitus, cerebrovascular event history and those with history of any malignancy were excluded from the study. Patients with body mass index of >35 and who had primary incomplete TUR-BCa were also excluded from the study. The pathological stages of patients with primary BCa were determined and their biochemical values were evaluated among themselves according to the disease stage. Again, the data for patients separated according to pathological stages were compared with the data of the individuals in the control group according to age. Patients were categorized into three groups based on serum total testosterone levels: low (<230 ng/dl), intermediate (230–350 ng/dl) and normal (>350 ng/dl) [15].

This study was conducted in accordance with all recognized international standards, including the principles of the Helsinki Declaration, and written, signed informed consent was obtained from patients for the use of each patient's information.

Statistical analyses of the values were carried out using SPSS (Statistical Package for Social Sciences) 22.0 statistical software package. The distribution of the variables was measured with the Kolmogorov–Smirnov test. The distribution of selected characteristics for the three testosterone groups was compared using the Chi-square test for categorical variables. Mann–Whitney U-test and Kruskal–Wallis test were performed to examine continuous variables. \( p < 0.05 \) was considered statistically significant. The data are also represented as box-and-whisker plots.

Results

Patients' distribution, age and characteristics according to serum total testosterone levels are shown in Table 1. The age range of the patients was 34 - 90 years old. Accordingly, the average age of patients with low testosterone levels was found to be significantly higher compared to the intermediate and normal groups \( (p = .014) \). There was no significant difference

| Characteristics                        | All     | Low     | Intermediate | Normal   | \( p \) |
|----------------------------------------|---------|---------|--------------|----------|--------|
| Total number of patients               | 257     | 40      | 99           | 118      |        |
| Age at diagnosis (years)               | 65 (34–90) | 69 (34–90) | 65 (38–86) | 63 (39–84) | 0.014  |
| Tumor grade, n(%)                      |            |         |              |          | 0.741  |
| Low                                    | 122 (47.5) | 20 (50) | 44 (44.4) | 58 (49.2) |        |
| High                                   | 135 (52.5) | 20 (50) | 55 (55.6) | 60 (50.8) |        |
| Tumor stage, n (%)                     |            |         |              |          | 0.303  |
| Ta                                     | 152 (59.1) | 25 (62.5) | 57 (57.6) | 70 (59.3) |        |
| T1                                     | 60 (23.3)  | 11 (27.5) | 19 (19.2) | 30 (25.4) |        |
| T2                                     | 45 (17.5)  | 4 (10)   | 23 (23.2) | 18 (15.3) |        |
| Concurrent CIS, n (%)                  |            |         |              |          | 0.071  |
| Yes                                    | 6 (2.3)   | 0 (0)   | 5 (5.1)    | 1 (0.8)  |        |
| No                                     | 251 (97.7) | 257 (100)| 94 (94.9) | 117 (99.2)|        |
| Tumor size, n(%)                       |            |         |              |          | 0.186  |
| < 3 cm                                 | 64 (24.9)  | 14 (35)  | 20 (20.2) | 30 (25.4) |        |
| \( \geq 3 \) cm                        | 193 (75.1) | 26 (65)  | 79 (79.8) | 88 (74.6) |        |

Serum total testosterone levels were classified as normal (\( \geq 350 \) ng/dl), intermediate (230–350 ng/dl) or low (<230 ng/dl). Data are presented as median (range) for continuous variables, and number of patients (%) for categorical variables.
between the groups in terms of tumor grade, stage and size (p > .05). There were no significant differences between the study and control groups in terms of age and serum albumin levels. Total testosterone level was investigated with a multinomial logistic regression model, where the control group was accepted as a reference, following adjustment for potential confounding variables, including age and serum albumin levels. Total testosterone level was not found to be associated with any of the categories that determine tumor aggressiveness (p > 0.05).

### Discussion

In this study, we demonstrated that there is no relationship between total testosterone level and tumor aggression before and after adjustment for potential confounding variables, including age and serum albumin levels.

Most BCa are superficial and can be completely resected by endoscopic instruments. The most bothering problem in BCa is that it recurs very often and progresses to the muscle-invasive state [16]. Although there are different local agents used to stop progression, unfortunately they are not really effective in the majority of cases [17]. In terms of relapse, BCa is the cancer type with the highest cost per patient during the period from diagnosis to death because it requires at least follow-up throughout life [18,19]. This is why reducing BCa incidence, recurrence and mortality appears to be an urgent requirement for both human health and economic reasons.

The fact that the incidence and prognosis of BCa varies depending on gender and androgen receptor was demonstrated in bladder epithelium [20] and has led scientists [12,21] to investigate whether androgen hormones have an effect on the development and prognosis of BCa because androgen hormone may affect growth, differentiation and maintenance of bladder epithelium [14]. Research about human and animal urothelial epithelium has shown a relationship between the androgen hormone receptor and BCa development [21]. In a laboratory study of rats, it was found that testosterone has an enhancing effect on the development of BCa in females, and estrogen and antiandrogens in males offer a preventive effect on the formation of BCa [22].

Data in the clinical setting are still very limited unlike preclinical studies. Few studies have evaluated the effect of androgen hormone on BCa patients [23–25]. Clinical research found a relationship between androgen-deprivation therapy (ADT) with decreased incidence, recurrence and progression of BCa [23,24]. Chen et al. proposed that finasteride could diminish the risk of BCa and inhibit cancer cell growth [25]. In a study, it was stated that taking ADT due to prostate cancer may have a protective effect on BCa development [26]. In another study, it was reported that taking ADT due to prostate cancer showed a relapse-reducing effect on concomitant BCa [27]. On the other hand, some other clinical research could not verify an unequivocal relationship between androgen receptor expression and BCa development and progression [18,28].

In addition, there are some studies that obtained the opposite results [29,30]. For example, a study showed reduced androgen receptor detection in high-grade and high-stage disease [29]. Another study also reported that there is a significantly lower expression of androgen receptors in high-grade and MIBC compared with low-grade BCa and NMIBC, respectively [30]. All these studies show that data that will allow us to reach a consensus about the role of androgen hormone on BCa are not available. Some studies say that androgen has positive effects on BCa, while other studies say the opposite. In fact, our study is compatible with these contrasting results in the literature, because all analyses we completed on the size, stage, and degree of the tumor according to blood testosterone level show that
Testosterone has no effect on BCa. Indeed, the guidelines do not include any hormones in the etiology of BCa. In an environment of confusion created by studies that declare opposite results are correct, the fact that no correlation between testosterone and BCa could be detected in this clinical study makes it an important study in the literature as it argues that there is no significant relationship between testosterone and BCa.

The present study has some limitations. A limitation of this study is that our control group does not consist entirely of healthy individuals and the study includes low number of patients. Despite its practical value, another limitation as the lack of free testosterone and sex hormone-binding globulin levels examined in our study. We believe that future studies should be designed taking these shortcomings into account.

Conclusions

In the present study, we showed that there is no correlation between any categories that determine tumor aggressiveness of BCa and total testosterone levels in adult men. Considering the studies in literature and the results of this article, it does not seem possible to say that there is a relationship between the blood testosterone level and BCa at least at present. It is obvious that our findings should be supported and further investigations are needed.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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