ORIGINAL PAPER

Assesment of anogenital distance as a marker in diagnosis of prostate cancer

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Summary
Objectives: Anogenital distance (AGD), the distance from the sexual organs to the anus, is a sexually dimorphic feature in mammals. In this study, we investigated the relationship between anogenital distance and prostate cancer (PCa).
Methods: 52 patients diagnosed with PCa and 60 patients with benign prostate hyperplasia as a control group were included in the study. AGDAP (cephalad insertion of the penis to the center of the anus) and AGDAS (posterior base (first fold) of the scrotum to the center of the anus) measurements of patients were done and noted before biopsy.
Results: The mean ages of 52 patients diagnosed with PCa and 60 patients with benign prostatic hyperplasia (BPH) were 67.70 ± 7.74 and 67.03 ± 7.89, respectively. There was no statistically significant difference in terms of age and serum testosterone levels of the patients diagnosed with prostate cancer or BPH (p > 0.05). Mean PSA values of patients diagnosed with prostate cancer wto be statistically higher than patients with BPH (p = 0.000). The mean AGDAP measurements of patients diagnosed with prostate cancer were statistically higher than those diagnosed with BPH (p = 0.000) and there was no significant difference in AGDAS measurements.(p = 0.823; p > 0.05).
Conclusions: Androgen exposure is thought to play a role in the development PCa. Also AGD may be an indicator of prenatal androgen activity. In our study, we found a direct correlation between AGDAP and PCa. In order to reach a definitive conclusion, randomized controlled trials with larger sample number are needed.

KEY WORDS: *Anogenital distance; Prostate cancer; Benign prostate hyperplasia; Androgens.*

Submitted 12 June 2019; Accepted 26 July 2019

INTRODUCTION

Anogenital distance (AGD), the distance from the sexual organs to the anus, is a sexually dimorphic feature in mammals (1). The researchers used AGD as a measure of genital development and androgen status to measure reproductive toxicity in both experimental animals and humans. AGD is androgen dependent and males have longer AGD measures than females (2-4).
Studies showed that AGD is determined in utero and persists during adulthood (5). However, it has been shown that in rats AGD shows a plasticity that can be mediated by local androgen/estrogen effect (6). In animals, it has been shown that anogenital distance can change with the effect of fetal androgens. Exposure to chemicals, such as dioxins that exhibit antiandrogenic activity results in shorter AGD distances in rat models (7). Further exposure to prenatal androgen causes longer AGD development. Therefore, AGD may be an indicator of prenatal androgen activity (8). In human models studies have shown that, exposures to endocrine disruptors, such as dichlorodiphenyltrichloroethane metabolites, phthalates, dioxins and bisphenol A have been related with shorter AGD (9-12). Additionally, it was founded that children who had cryptorchidism orhypospadias have shorter AGD (13). Men with prostate cancer also have shorter AGD compared to a control group (14).
In this study, we investigated the relationship between anogenital distance and prostate cancer.

MATERIALS AND METHODS

The study was conducted in accordance with the Helsinki Declaration. All participants gave informed consent for participation. The study was approved by the ethics committee of *Fatih Sultan Mehmet Training and Research Hospital*. Patients diagnosed with prostate cancer with transrectal prostate biopsy due to PSA elevation (PSA > 2.5 ng/dl) in the urology clinic of *Fatih Sultan Mehmet Training and Research Hospital* were included in the study. The control group consisted of patients with lower urinary tract complaints who were diagnosed with benign prostate hyperplasia with transrectal prostate biopsy due to PSA elevation (PSA > 2.5 ng/dl). *Body mass index* (BMI) was calculated as weight in kilograms divided by squared height in meters. Two AGD variants; AGDAP, (from the center of the anus to the cephalad insertion of the penis) and AGDAS, (from the center of the anus to the posterior base of the scrotum) were evaluated (15-16). A digital caliper was used for measuring AGD variants in lithotomy position with his thighs at a 45° angle to the examination table. AGDAP and AGDAS was measured by two separate physicians and each AGD variant was measured three times. The average was calculated. Adjustment was made for body mass index instead of weight and height.

RESULTS

A total of 112 patients with age ranging 47-86 years of age were included in the study between April 2018 and

May 2019. The mean age of 52 patients diagnosed with prostate cancer was 67.70 ± 7.74; The mean age of 60 patients with *benign prostate hyperplasia* (BPH) was 67.03 ± 7.89. There was no statistically significant difference in terms of age of the patients diagnosed with prostate cancer or BPH (p > 0.05). Mean PSA values of patients diagnosed with prostate cancer were found to be statistically higher than patients with BPH (p = 0.000) and there was no statistical difference in terms of serum testosterone levels (p > 0.05). The mean AGDAP measurements of patients diagnosed with prostate cancer was statistically higher than those diagnosed with BPH (p = 0.000) whereas there was no significant difference in AGDAS measurements.(p = 0.823; p > 0.05) (Table 1). There was a statistically significant difference between patients with prostate cancer and BPH in terms of BMI averages (p = 0.043; p < 0.05). Adjusted AGDAP values obtained by dividing the AGDAP by BMI values were significantly higher in the prostate cancer group than in the BPH group (p = 0.007). On the other hand there was no statistically significant difference in adjusted AGDAS (AGDAS/BMI) values (p > 0.05).

Statistical analysis

While evaluating the findings obtained in the study, IBM SPSS Statistics 25 program was used for statistical analysis.The fit of the parameters to normal distribution was evaluated by ShapiroWilks test. In addition to descriptive statistical methods (mean, standard deviation), Student's t-test was used for comparison of quantitative data between two groups of parameters that were normally distributed. Significance was determined as p < 0.05.

DISCUSSION

We investigated the relationship between AGD, which is a biological marker of prenatal androgen exposure, and PCa. Anogenital distance is a sexually dimorphic feature, which is longer in males than in females (17). Androgens are necessary for normal development of prostate (18, 19). In a study by *Castano et al.*, men with prostate cancer showed shorter AGD compared to control group (14). *Maldonado et al.* found that patients with longer AGDAS had higher cancer severity (20). *Boyle et al.* reported that prostate cancer patients were more

exposed to prenatal androgens and their findings are consistent with hypothesis suggesting a relationship between testosterone levels and severity of PCa (21). Studies reported that there was a relationship between AGDAS and testosterone levels in both men and women (22, 23). A longer AGDAS is an indicator of more androgenic prenatal hormonal environment. Therefore, it may affect the proliferation of Leydig cells, which will cause higher androgen levels in adulthood (24). For this reason, having a longer AGDAS may increase the possibility that testosterone will be higher in adulthood, resulting in a greater risk of developing a more severe prostate cancer. On the other hand a review (25) reported that, there is no obvious indication that endogenous testosterone is positively correlated with prostate cancer and because of that it does not directly correlate with the aggression of the prostate cancer. There are also additional reports that prostate cancer development is independent of endogenous testosterone levels (26). Data obtained from the current literature indicate that *testosterone replacement therapy* (TRT) can be given with the condition that close follow-up is applied to symptomatic hypogonadal patients who underwent radical prostatectomy, brachytherapy or external radiotherapy because of prostate cancer (27).

In our study there was no statistical significant difference between groups in terms of serum testosterone levels (p > 0.05). Also there was no significant difference between groups in terms of AGDAS measurements (p = 0.823; p > 0.05) and adjusted AGDAS (AGDAS/BMI) values. (p > 0.05). In our study, AGDAP measurements were significantly higher in the prostate cancer group. Also according to adjusted AGDAP (AGDAP/BMI) values obtained by dividing AGDAP by BMI, it was found to be statistically higher in PCa group compared to BPH group (p = 0.007).

However, it is difficult to establish a relationship between testosterone and PCa because it is difficult to predict the current testosterone levels of an individual in clinical practice. Firstly the methods used to measure testosterone are variable. Secondly testosterone levels in an individual can be variable at any time of the day. Therefore singular measures are not a good indicator of normal testosterone levels. *Porcaro et al.* (28) reported that PCa was significantly associated with serum total testosterone. Another study from Spain reported that longer AGD was associated with lower risk of PCa (14).

Hsieh et al. showed that shorter AGDAS measurements is associated with genital anomalies (cryptorchidism or hypospadias) in men and established a link between normal genital development and AGD in humans (29).

Furthermore, in many studies, AGDAP measurements have been found to be associated with prenatal exposure and prostate cancer to endocrine disruptors (30-34, 14).

AGDAS measurements were associated with semen quality and other reproductive hormones (15, 22 to 23).

Table 1.
Comparison of patients diagnosed with prostate cancer and BPH.

	Prostate Ca (n = 52) Mean ± SD	BPH (n = 60) Mean ± SD	P
Age (years)	67.70 ± 7.74	67.03 ± 7.89	0.498
PSA (ng/mL)	13.78 ± 10.44	8.22 ± 3.23	0.000**
Testosterone (ng/mL)	4.06 ± 117	4.37 ± 1.77	0.292
BMI (kg/m^2)	28.23 ± 3.0	27.05 ± 3.04	0.043*
AGD$_{AP}$ (cm)	13.9 ± 1.31	12.58 ± 1.73	0.000**
AGD$_{AS}$ (cm)	4.91 ± 1.20	4.96 ± 0.89	0.823
Adjusted AGD$_{AP}$ (AGD$_{AP}$/BMI)	0.49 ± 0.07	0.46 ± 0.04	0.007*
Adjusted AGD$_{AS}$ (AGD$_{AS}$/BMI)	0.17 ± 0.04	0.18 ± 0.03	0.312
Independent Student t test	*p<0.05 **p<0.001		

As can be seen, many studies have been conducted in different areas related to anogenital distance and there are no clear results yet. Therefore, it is not true to hold only androgens responsible for the development of prostate cancer. Further experimental studies are needed for relationship between AGD (AGDAP and AGDAS) and fetal androgen exposure.

Limitations of the study
The main limitation of our study was that although the patients with PSA values of 2.5 ng/dL and above were taken in both groups and histologically differentiated as benign prostatic hyperplasia and prostate cancer by transrectal biopsy, the mean PSA value of the control group was statistically lower than the prostate cancer group. Choosing patients with similar PSA values and prostate volumes in both groups could be better in terms of excluding androgen exposure and AGD relationship. Additionally, the methods used to measure testosterone are variable. Testosterone levels in an individual can be variable at any time of the day.Therefore, singular estimates are not a good indicator of normal testosterone levels. So, it is difficult to state anything definite about testosterone levels.

CONCLUSIONS
There is a scarce number of studies in the literature about the relationship between anogenital distance and prostate cancer. Androgen exposure is thought to play a role in the development of PCa, but recent studies demonstrated that there is no relationship between androgens and prostate cancer. On the other hand there are different conclusions about relationship between AGD and prostate cancer. In our study, we found a direct correlation between AGDAP and prostate cancer. In order to reach a definitive conclusion, randomized controlled trials with larger sample number are needed.

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