Prostate-Specific Antigen and its Derivatives in Spinal Cord Injured Patients; A Case-Control Study

Spinal Kord Yaralanmalı Hastalarda, Prostat-Spesifik Antijen ve Türevleri: Bir Vaka-Kontrol Çalışması

Spinal Kord Yaralanması ve Prostat Spesifik Antijen / Spinal Cord Injury and Prostate Specific Antigen

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Çalışma Amerikan Üroloji Derneği'nin 2011 yıllık kongresinde poster olarak sunulmuştur. (Mayıs 2011, WashingtonDC, ABD)

Özet

Amaç: Motor-komplet spinal kord yaralanmasının (SKY) prostat hacmi (Vp), total prostat spesifik antijen (PSA), serbest PSA (sPSA), serbest/total PSA oranı (s/tPSA) ve PSA dansitesi (PSAD) üzerine etkilerini araştırmak. Gereç ve Yöntem: Yirmi-beş SKY hastası ve 32 yaş-uyumlu kontrol analize dahil edildi. Vp transrektal ultrason yardımı ile hesaplandı, PSA, sPSA, FSH, LH ve total ve serbest testosteron seviyeleri ölçüldü ve s/tPSA ve PSAD değerleri hesaplandı. Bulgular: Ortalama hasta yaşı 44.26±6.9yıl idi. SKY grubunda ortalama Vp, kontrol grubuna göre anlamlı derecede düşük iken (19.30±6.88mL ve 26.96±8.79mL, p=0.001), her iki grubun serum PSA, FSH, LH, total ve serbest testosteron düzeyleri benzerdi (p>0.05). SKY grubunda sPSA ve s/tPSA oranı kontrole göre düşük (sırasıyla 0.16±0.096 ve 0.28±0.18, p<0.001; 0.20±0.18 ve 0.28±0.13, p=0.002), PSAD ise daha yüksek olarak saptandı (0.056±0.027, 0.043±0.035; p=0.014). Tartışma: Sonuçlarımıza göre SKY kontrollere göre hipofizer-gonadal akstan ve serum testosterondan bağımsız olarak daha düşük Vp, sPSA ve s/tPSA değerlerine neden olmaktadır. sPSA ve PSAD ile ilgili sonuçlarımızın desteklenmesi gereklidir.

Anahtar Kelimeler

Spinal Kord; Prostat; Prostat-Spesifik Antijen

Abstract

Aim: To evaluate the effects of motor-complete spinal cord injury (SCI) on prostate volume (Vp), total prostate specific antigen (PSA), free PSA (fPSA), free-total PSA ratio (f/tPSA) and PSA density (PSAD). Material and Method: 25 SCI patients and 32 age--matched outpatient able--bodied controls were included in the analysis. Vp was measured on transrectal ultrasound, PSA, fPSA, FSH, LH and total and free testosterone levels were obtained and f/tPSA and PSAD were calculated for all patients. Results: Mean patient age was 44.26±6.9 years. Mean Vp of the SCI group was significantly lower than controls (19.30±6.88 vs 26.96±8.79, p=0.001) while mean serum PSA, FSH, LH, total and free testosterone of the two groups were similar (p>0.05). Mean fPSA and f/tPSA were significantly lower (0.16±0.096 vs 0.28±0.18, p<0.001 and 0.20±0.18 vs 0.28±0.13, p=0.002, respectively) and PSAD was higher (0.056±0.027 vs 0.043±0.035, p=0.014) than those of the controls. Discussion: According to our findings, motor-complete SCI causes lower Vp, fPSA and f/tPSA than the controls, independent from pituitary-gonadal axis and serum testosterone without any significant impact on serum PSA. Our results regarding fPSA and PSAD need further confirmation.

Keywords

Spinal Cord; Prostate; Prostate-Specific Antigen

DOI: 10.4328/JCAM.1108 Received: 21.05.2012 Accepted: 10.07.2012 Printed: 01.11.2013 J Clin Anal Med 2013;4(6): 484-487
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Introduction

The effects of spinal cord injury (SCI) on male genital anatomy and function have been of interest during the last two decades which mainly involve fertility and sexual problems. As a result of improvements and refinements in surgery, urology and rehabilitation, a remarkable increase in the life expectancy of SCI patients has been achieved and SCI patients became vulnerable to the same risks of becoming an "aging male" as the able-bodied population. Erectile dysfunction, infertility and voiding problems, benign prostatic hyperplasia (BPH) and prostate cancer (CaP) are among the common urologic diagnoses observed in this patient population [1].

Despite few studies reporting lower incidences of CaP in the SCI patients, others report respectable CaP rates and even more frequent high stage disease than able-bodied CaP patients [2-5]. Today PSA is still the most frequently used tool in CaP diagnosis. Although there are numerous reports about the effects of SCI on PSA levels, the results are controversial and a conclusion is yet to be achieved [1,6-12]. Nevertheless, it seems logical to assume that the use of PSA in SCI patients may be different in some aspects, as numerous factors that can affect PSA levels are involved, i.e. urinary infections, intermittent or indwelling catheters, and possible changes in volume as well as the function of the prostate. Likewise there are also studies regarding Vp in SCI patients with various results, and a consensus is yet to be achieved [1,6,10-13].

F/t PSA and PSAD are the two PSA derivatives used in conjunct with total serum PSA, in order to increase the sensitivity and specifity of serum PSA when serum PSA is in so called "gray zone". To our knowledge, there are no data in the literature regarding fPSA, f/tPSA and PSAD levels in SCI patients. Therefore, we compared fPSA in order to evaluate the altered PSA kinetics in SCI patients as well as f/tPSA and PSAD in order to get a primary idea about the changes in PSA derivatives.

Effects of motor-complete SCI on PSA, fPSA, f/tPSA, PSAD and Vp were evaluated in this study, in comparison with able-bodied controls.

Material and Method

Male complete-motor SCI patients from a Rehabilitation Center and age matched able-bodied controls from outpatient urology unit of our institution were included in the study over a period of five months. Control group was formed among the patients applying with any urological complaints other than erectile dysfunction, infertility or lower urinary tract symptoms. Inclusion criteria were SCI for at least 18 months for the SCI group, and at least 30 years of age for all. Patients with acute urinary infections, diabetes mellitus, known neurological disorders, CaP and history of androgen or anti-androgen treatments and prostatic surgery were excluded. Informed consent was obtained from all of the patients and the study was carried out in accordance with the Helsinki Declaration (1975,1983).

A detailed medical history was obtained including the time from SCI onset, medications used, past surgeries and co-morbid medical situations. A digital rectal examination was performed evaluating the size and morphology of the prostate. Laboratory tests included urine-analysis, serum PSA, fPSA, total testosterone (T), FSH and LH (Beckman Coulter DXI, Brea CA, USA), free testosterone (fT) (BIO-TEK 987, Ankara, Turkey). Vp was calculated by transrectal ultrasound (TRUS) with 6.5MHz biplanar probe (Hitachi.EUB-420, Hitachi Medical Systems, Tokyo, Japan), using ellipsoid formula (0.52xwidthxlengthxdepth). PSAD and f/tPSA were calculated by dividing serum PSA to Vp, and dividing fPSA by PSA, respectively. Level and severity of the SCI was determined by spinal MRI and scoring of the lesion according to the American Spinal Injury Association (ASIA) classification. ASIA A and B lesions were accepted to be complete motor lesions. Twenty-five patients who had a motor-complete SCI and 32 controls were included in the analytical phase of the study.

Statistical calculations were made using the software SPSS13 for Windows (SPSS Inc. Chicago, Il., USA). Normality of data distribution was tested with Shapiro-Wilk test. Continous variables were compared using Student's t test and Mann-Whitney U tests, while multiple comparisons were made using Kruskal-Wallis test. Categorical data were analyzed with chi-square test. P values lower than 0.05 were accepted to be significant.

Table 1. Characteristics of SCI patients and able-bodied controls.

	SCI (n=25)	Control (n=32)	p
Age (Years)	44.88±7.48	43.78±6.94	0.55*
Vp (ml)	19.30±6.88	26.96±8.79	0.001*
PSA (ng/ml)	1.05±0.56	1.09±0.73	0.816†
fPSA (ng/ml)	0.16±0.096	0.28±0.18	<0.001†
f/tPSA	0.20±0.18	0.28±0.13	0.002†
PSAD	0.056±0.027	0.043±0.035	0.014†
T (ng/ml)	3.78±1.35	3.87±1.43	0.981†
fT (pg/ml)	9.27±4.26	9.30±3.74	0.917†
FSH (mIU/ml)	7.6±5.9	6.59±4.35	0.994†
LH (mIU/ml)	4.59±3.50	4.47±2.27	0.541†

* Independent samples T-test, †Mann-Whitney U Test
Vp: Prostate volume, fPSA: Free PSA, f/tPSA: free to total PSA, PSAD: PSA density, T: Testosterone, fT: free testoeterone

Table 2. The relation between bladder management of SCI patients and PSA, fPSA levels.

n=25	RV (n=7)	ICC (n=9)	IC (n=9)	p*
PSA (ng/ml)	1.15±0.52	0.84±0.40	1.19±0.70	0.458
fPSA (ng/ml)	0.21±0.14	0.14±0.072	0.13±0.06	0.291

* Kruskal Wallis test
RV: Reflex voiding, ICC: Intermittent clean catheterization, IC: Indwelling Catheter

Results

Records of 25 SCI and 32 control patients were analyzed. Mean age of all patients was 44.26±6.9 (31-60) years, and the mean age of the two groups were similar (p=0.55) (Table1). Median time from the onset of SCI was 42 (18-396) months. Of the SCI patients, 2 had cervical, 14 had thoracic and 9 had lumbar spinal lesions. As bladder management, 7 patients were able to void with triggered reflex voiding, while 9 patients were on clean intermittent catheterization and 9 used indwelling catheters due to nursing needs.

Mean prostate volume of the patients with SCI was significantly lower than that of controls (p=0.001). Serum PSA of SCI patients was not significantly different from the controls, while their fPSA was significantly lower (p>0.05, p<0.001) (Table1). T, fT, FSH and LH values of the two groups were similar. Two

PSA derivatives, f/tPSA and PSAD of the two groups were compared; f/t PSA ratio of the SCI group was lower than the controls (p=0.002) while the PSAD was significantly higher (p=0.014). Clean intermittent catheterization and use of indwelling catheters had no effect on serum PSA and fPSA within the SCI group (Table2).

Among the SCI group, the level of the spinal cord lesion did not affect Vp, Vt, VS and any of the blood tests (p>0.05 for all).

Discussion

The effects of complete motor SCI on male reproductive system has been studied in various aspects in the literature, scoping mainly on structural and functional changes in the prostate, testis, seminal vesicles and penis. However, to our knowledge there is no study in the literature on patients with motor-complete spinal lesions only. Patients with only motor -complete SCI were included in our study regardless of the level of the lesion, as not only it was shown that the severity of the paralysis is related to the magnitude of the effect of SCI on Vp and PSA serum levels, but also completeness of the lesion is an independent factor affecting PSA and Vp in SCI patients [10-12].

Data regarding the levels and use of PSA for CaP diagnosis in SCI patients is debateful. There are studies reporting lower, similar and higher levels of PSA serum levels in SCI patients when compared to able-bodied controls, in which the diversity of the results may be due to factors like differences in patient age, time from SCI onset, lesion severity, bladder management used, etc. [1,6-12]. In our study, PSA of patients with complete motor SCI was not significantly different from the controls. This finding is consistent with tendency in the literature, as in majority of the studies, serum PSA of SCI patients were found to be similar with the controls, although differences in seminal PSA levels were defined [1,4,8,9,11]. In the largest series presented which consisted of 366 SCI patients and 371 age-matched controls, Pramudji et al [4] failed to demonstrate differences in PSA levels between SCI patients and controls and also in the age-stratified sub-groups. Similarly, Pannek et al [1] could not demonstrate a significant difference between PSA levels of 100 SCI patients and 575 non injured men. In a more recent study however, Bartoletti et al [12] showed lower PSA levels in SCI cohort of their study including 113 SCI and 109 controls, and they claimed that age at SCI onset and completeness of the spinal lesion are two independent factors which significantly affect PSA and prostate volume in SCI patients. Although the lower PSA levels in SCI patients is rationalized with the early age at onset of SCI in their patient population, the mean age at onset given for the entire cohort was not far from the one given by former study of Pannek et al (46.6 vs 39.9 yrs) who did not find a significant difference between PSA levels of SCI patients and controls. Therefore, a consensus regarding the effects of SCI on PSA is yet to be achieved, although no significant interactions were demonstrated in the majority of the studies.

The effects of SCI on Vp are investigated in various studies in the literature. The need for somatic and/or autonomic innervation together with androgenic stimulation for the growth, function and maintenance of the prostate was demonstrated in animal models [14-18]. Pelvic plexus denervation caused an overall decrease in cell height, unilateral sympathectomy caused unilateral atrophy and decreased DNA and protein content, and lysis of efferent autonomic nerves to prostate caused loss of tissue configuration and vanishing of entire epithelium, all of which suggest a role for the nervous system in prostate morphology and function [15,16,18]. Demonstration of prostatic involution stimulated by Botox in both rat and human prostates further supports the role of nervous system in prostatic growth [17,19]. Studies on prostates of human SCI patients, however, reported conflicting results. Tendency in the literature is towards a lower Vp in SCI patients, although a few studies reporting similar Vp's with controls are also present. In our study, mean Vp of the SCI patients was significantly lower than controls (19 vs 27ml), in accordance with the majority of the studies. Pannek et al [1] reported a numerical but not significant difference in Vp's of SCI patients and controls, and Shim et al [11] reported similar Vp of SCI patients and controls in Korean men. One possible reason for this result may be that their SCI population was heterogeneous regarding the completeness of the lesion (41% complete, 59% incomplete for the former). It was shown in rats that unilateral denervation affects ipsilateral portion of the prostate, hence bilateral denervation would have a larger, global impact on gland volume [15,16]. Similarly, in humans, Frisbie et al [10] reported lower Vp's in severely paralyzed patients when compared to less severely paralyzed patients and able-bodied controls. Moreover, Bartoletti et al showed in a multivariate analysis that, completeness of the lesion is an independent factor for Vp in SCI patients [12]. Other studies report lower Vp in SCI patients with different characteristics (Age, origin etc) [10,12,13]. Our SCI cohort being consisted entirely of patients with complete motor SCI's was probably an important factor for demonstration of almost 35% reduction in Vp of SCI patients with a strong statistical significance. To our knowledge, our study is the first one to investigate fPSA, f/tPSA and PSAD in SCI population. Although PSA of the SCI patients were similar with controls in our study, their mean Vp which is a major determinant of serum PSA, was significantly lower. In order to correct PSA levels for Vp, PSAD values were calculated. Mean PSAD of SCI patients was significantly higher than the controls, which indicated a higher amount of serum PSA per gram of prostate tissue. This was an interesting result which was supported by the previous findings of Alexandrino et al [9], who concluded that SCI affected seminal PSA levels negatively, without changing PSA serum levels; which can be explained by the simultaneous secretory dysfunction and structural deterioration of the prostate, of which, former decreasing seminal PSA levels, and latter increasing the PSA leak into the circulation.

Conclusions

Motor-complete SCI causes lower prostate volume, lower serum free PSA and free-to-total PSA ratios when compared to controls. On the other hand, serum total PSA is not affected, although amount of PSA secreted by ml of prostate tissue increased. These findings suggest that production, secretion and forms of PSA in circulation may be altered by SCI, and use of PSA in SCI patients in the exact same way as it is used in able-bodied population may have to be questioned in larger prospective studies including higher number of patients.

Competing interests

The authors declare that they have no competing interests.

References

1. Pannek J, Berges RR, Cubick G, Meindl R, Senge T. Prostate size and PSA serum levels in male patients with spinal cord injury. Urology 2003; 62(5): 845-48.
2. Federman Q, Tannenbaum M, Verecczkey Z. Reduced incidence risk of prostatic carcinoma in patients with spinal cord injury. Am J Paraplegia 1993; 16(Suppl):280-2.
3. Frisbie JH. Cancer of the prostate in myelopathy patients: lower risk with higher level of paralysis. J Spinal Cord Med 2001;24(2):92-4.
4. Pramudji CK, Mutchnik SE, DeConcini D, Boone TB. Prostate cancer screening with prostate specific antigen in spinal cord injured men. J Urol 2002;167(3):1303-5.
5. Scott PA Sr, Perkash I, Mode D, Wolfe VA, Terris MK. Prostate cancer diagnosed in spinal cord-injured patients is more commonly advanced stage than in able-bodied patients. Urology. 2004;63(3):509-12.
6. Benaim EA, Montoya JD, Saboorian MH, Litwiller S, Roehborn CG. Characterizationof prostate size, PSA and endocrine profiles in patients with spinal cord injuries. Prostate cancer and prostatic dis 1998;1(5)5:250-5.
7. Lynne CM, Aballa TC, Wang TJ, Rittenhouse HG, Ferrell SM, Brackett NL. Serum and semen prostate specific antigen concentrations are different in young spinal cord injured men compared to normal controls. J Urol 1999;162(1):89-91.
8. Konety BR, Nguyen TT, Brenes G, Lewis N, Saul M, Nelson JB et al. Evaluation of the effect of spinal cord injury on serum PSA levels. Urology 2000;56(1):82-6
9. Alexandrino AP, Rodrigues MA, Matsuo T. Evaluation of serum and seminal levels of prostate specific antigen in men with spinal cord injury. J Urol 2004;171(6 Pt 1):2230-2.
10. Frisbie JH, Kumar S, Aguilera EJ, Yalla S. Prostate atrophy and spinal cord lesions. Spinal Cord 2006;44(1):24-7.
11. Shim HB, Kim YD, Jung Ty, Lee JK, Ku JH. Prostate-specific antigen and prostate volume in Korean men with spinal cord injury: a case-control study. Spinal Cord 2008;46(1):11-5.
12. Bartoletti R, Gavazzi A, Tommaso C, Mondaini N, Morelli A, Popolo GD et al. Prostate growth and prevalence of prostatic diseases in early onset spinal cord injuries. Eur Urol 2009;56(1) :142-50.
13. Hvarness H, Jakobsen H, Biering-Sorensen F. Men with spinal cord injury have smaller prostate than men without. Scand J Urol Nephrol 2007;41(2):120-3.
14. Vaalasti A, Alho AM, Tainio H, Hervonen A. The effect of sympathetic denervation with 6-hydroxydopamine on the ventral prostate of the rat. Acta Histochem 1986;79(1):49-54.
15. Martinez-Pineiro L, Dahiya R, Nunes LL, Tanagho EA, Schmidt RA. Pelvic plexus denervation in rats causes morphologic and functional changes of the prostate. J Urol 1993;150(1):215-18.
16. McVary KT, Razzaq A, Lee C, Venegas MF, Rademaker A, McKenna KE. Growth of the rat prostate is facilitated by the autonomic nervous system. Biol Reprod 1994;51(1):99-107.
17. Doggweiler R, Zermann DH, Ishigooka M, Schmidt RA. Botox-induced prostatic involution. Prostate 1998;37(1):44-50.
18. Diaz R, Garcia LI, Locia J, Silva M, Rodriguez S, Perez CA et al. Histological modifications of the rat prostate following transection of somatic and autonomic nerves. An Acad Bras Cienc 2010;82(2):397-404.
19. Thomas CA, Chuang YC, Giannantoni A, Chancellor MB. Botulinum A toxin for the treatment of benign prostatic hyperplasia/lower urinary tract symptoms. Curr Urol Rep 2006;7(4):266-71