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ORIGINAL PAPER

Association between large prostate calculi and prostate cancer

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Summary ***Objective: We investigated the relationship between large prostate calculi and prostate cancer (PCa) risk.***
Materials and methods: The medical records of 340 patients who received a prostate biopsy at our institution between January 2015 and August 2016 were reviewed retrospectively. Of the patients, 82 had large prostatic calculi visualised by transrectal ultrasonography and 88 did not or had scarce prostatic calculi. We divided these patients into two groups: patients with large prostatic calculi (group 1) and patients without prostatic calculi (group 2). These groups were compared according to age, total prostate specific antigen (PSA) level, prostate volume, and final pathological diagnosis.
Results: The mean age of all patients was 61.4 ± 6.2 years, the mean total PSA was 12.3 ± 17.4 ng/mL, the mean prostate volume was 41.7 ± 17.6 mL, and the overall cancer detection rate was 31.5%. The cancer detection rates were 41.3% and 22.6% in groups 1 and 2, respectively (p = 0.018). No significant differences in mean age, mean total PSA, or mean prostate volume were observed between the groups.
Conclusions: In the present study, large prostatic calculi were associated with PCa. However, more study is needed to examine the relationship between large prostatic calculi and PCa in more detail. The effects of particularly large prostate calculi in the development of PCa will be a necessary focus of future research.

KEY WORDS: Prostatic calculi; Prostate cancer; Ultrasound; Risk factors.

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INTRODUCTION

Prostatic calculi are presumed to form by precipitation of prostatic secretions and desquamated acinar cells under inflammatory conditions (1). However, the clinical significance of prostatic calculi for evolution of cancer is unknown, immunological and inflammatory reactions may contribute to the carcinogenic process (2). Histopathological and molecular biology studies have shown that inflammation of the prostate gland may contribute to the development of *prostate cancer* (PCa) (3). Inflammation may affect the development of PCa in patients with prostate calculi compared to patients without prostate calculi (4). Two kinds of calculi exist in the prostate. Type 1 are discrete, multiple small echoes and are usually diffusely distributed throughout the gland, whereas type 2 calculi are larger, multifaceted, and situated mainly in the prostatic ducts (5, 6). Larger prostate calculi are reportedly related to clinical prostatitis (5).
Transrectal ultrasonography (TRUS)-guided prostate biopsy remains the gold-standard method for diagnosing PCa, and prostatic calculi are frequently diagnosed by TRUS (1, 7). Although prostatic calculi are commonly seen in TRUS-guided prostate biopsy, the relationship between PCa and prostatic calculi is unclear. In the present study, we investigated the relationship between large prostate calculi and PCa risk.

MATERIALS AND METHODS

The medical records of 340 patients who received a prostate biopsy at our institution between January 2015 and August 2016 were reviewed retrospectively. Indications for prostatic biopsy included an abnormal digital rectal examination and/or an elevated serum *prostate specific antigen* (PSA) concentration (≥ 4.0 ng/mL). After informed consent was obtained from patients, all biopsies were taken transrectally with ultrasonographic guidance using a 25 cm, 18 gauge, side-notch cutting (Tru-cut) needle. The biopsy was obtained from patients in the lateral decubitus position with periprostatic nerve blockage. Prostatic calculi and prostate volume were measured by TRUS. Prostate volume was calculated using the prostate ellipse formula (0.52 × length × width × height). We defined large prostatic calculi as multiple (≥ 3) or large (≥ 3 mm largest diameter) hyperechoic zones.
In the present study, among 340 patients, we included only patients who have large prostate calculi or have not prostate calculi. We excluded patients who have fewer than three prostatic calculi or < 3 mm prostatic calculi (67 cases). We also excluded patients who have chronic diseases (diabetes, hyperlipidemia, hypertension, cardiovascular disease) (49 cases), malignancy (9 cases), psychiatric disorders (9 cases), acute infections (8 cases), a history of urinary tract surgery (15 cases), a prior diagnosis of Pca (11 cases) and a history of irradiation (2 cases). A total number of 170 patients were enrolled in this study.
Patients were divided into two groups, group 1 included 82 patients with large prostatic calculi visualised by TRUS, whereas group 2 included 88 patients without

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prostatic calculi. These groups were compared according to age, total PSA level, prostate volume, and final pathological results. We identified the PCa detection rates and Gleason scores of the two groups. We also compared the patients according to their final pathological diagnosis.

Statistical Analysis

The conformity of variables to a normal distribution was assessed with the Kolmogorov-Smirnov test. Descriptive statistics for variables with a normal distribution and categorical variables are shown as means ± standard deviations and percentages, respectively. Student's t test and the chi-square test were used for intergroup analyses of continuous variables. More than two independent averages were compared using analysis of variance and the Kruskal-Wallis test. Data were analysed using SPSS ver. 22.0 (*SPSS Inc., Chicago, IL, USA*), and a p-value < 0.05 was considered significant.

Results

A total of 170 patients participated in this study.

The mean age of all patients was 61.4 ± 6.2 years, the mean total PSA was 12.3 ± 17.4 ng/mL, the mean prostate volume was 41.7 ± 17.6 mL, and the overall cancer detection rate was 30%. The clinical and demographic characteristics of the study patients are listed in Table 1.

According to the final pathological diagnosis, in group 1, 18 patients (21.9%) had prostatitis, 31 patients (37.8%) had benign pathology, 33 patients (40.2%) had PCa; in group 2, 34 patients (38.6%) had prostatitis, 36 patients (40.9%) had benign pathology and 18 patients (20.5%) had PCa (Table 2). The Gleason score was 6 in 23 (69.7%), 7 in three (9.1%) and ≥ 8 in seven (21.2%) patients in group 1 who were diagnosed with PCa; it was 6 in 16 (88.9), 7 in one (5.6%) and ≥ 8 in one (5.6%) patients who were diagnosed with PCa in group 2 (Table 2).

The cancer detection rates were 40.2% and 20.5% in groups 1 and 2, respectively (p = 0.018). No differences in mean age, mean total PSA, or mean prostate volume were observed in group 1 compared to group 2.

The comparisons of the patients according to their final pathological diagnosis, is summarized in Table 3.

Table 1.
Clinical and biological characteristics of all patients (n = 170).

Variables	Mean (SD)
Age (years)	61.4 (± 6.2)
PSA (ng/mL)	12.3 (± 17.4)
Prostate volume (ml)	41.7 (± 17.6)
Pathology (n, %)	
Prostatitis	52 (30.6)
BPH	67 (39.4)
PCa	51 (30.0)
Gleason score (n, %)	
6	39 (76.4)
7	4 (7.6)
≥ 8	8 (15.6)

PSA: prostate specific antigen, BPH: benign prostatic hyperplasia, PCa: prostate cancer

Table 2.
Clinical variables for patients with and without prostatic calculi.

Variables	Group 1 (n = 82) (with calculi)	Group 2 (n = 88) (without calculi)	P value
Age (years)	60.5 (± 8.1)	61.8 (± 7.2)	0.946
PSA (ng/mL)	12.8 (± 15.1)	11.3 (± 7.8)	0.439
Prostate volume (ml)	42.5 (± 10.7)	39.2 (± 18.5)	0.345
Pathology (n, %)			
Prostatitis	18 (21.9)	34 (38.6)	0.438
BPH	31 (37.8)	36 (40.9)	0.790
Pca	33 (40.2)	18 (20.5)	0.018
Gleason score (n, %)			
6	23 (69.7)	16 (88.9)	0.289
7	3 (9.1)	1 (5.6)	0.302
≥ 8	7 (21.2)	1 (5.6)	0.041

PSA: prostate specific antigen, BPH: benign prostatic hyperplasia, PCa: prostate cancer

Table 3.
Comparisons of patients according to the final pathologic diagnosis.

Variables	Prostatitis (n = 52)	BPH (n = 67)	PCa (n = 51)	P value
Age (years)	58.8 (± 7.3)	60.2 (± 6.6)	65.2 (± 7.2)	0.686
PSA (ng/mL)	8.7 (± 9.1)	7.9 (± 8.5)	21.7 (± 12.3)	< 0.01
Prostate volume (ml)	40.2 (± 9.4)	43.6 (± 11.2)	40.7 (± 8.1)	0.867
Large prostate calculi (n, %)	18 (34.6)	31 (46.2)	33 (64.7)	< 0.01
Absent prostate calculi (n, %)	34 (65.3)	36 (53.7)	18 (35.2)	< 0.01

PSA: prostate specific antigen, BPH: benign prostatic hyperplasia, PCa: prostate cancer

Discussion

Prostatic calculi are generally detected while performing TRUS (8). Prostate calculi occur during the aging process and may not produce any symptoms (9). The definition of prostatic calculi has not been well described in the literature, so the incidence of prostatic calculi may differ by definition; it is about 30% in histological studies and increases to 71% in radiological-histological correlational studies. Prostatic calculi exist in about 99% of autopsy specimens (10). In our study, large prostate calculi were found in 48.2% of participants.

A limited number of studies are available on the correlation between PCa and calculi (4, 8, 11, 12). *Griffiths et al.* analysed the ultrasound images of 221 patients with diagnosed PCa and observed a 63% association between PCa and prostatic calculi (11). *Hwang et al.* reviewed the medical records of 417 patients who underwent a TRUS-guided prostate biopsy and reported that prostatic calculi were found more often in patients diagnosed with PCa (4). They also reported that prostatic calculi are correlated with a higher Gleason score when PCa is proven.

In another study, *Smolski et al.* found that 78.1% of peripheral zone calculi were associated with PCa (8). This percentage was higher than in our study. We did not assess the prostate zones separately. A specific zone assessment of the prostate may be more useful for detect-

ing PCa. Contrary to the aforementioned studies, *Woods et al.* analysed the histological material of 266 radical prostatectomy and 10 cystoprostatectomy cases and suggested that prostatic microcalculi were less commonly associated with PCa (12). In our study we observed that PCa was more common in patients with large prostatic calculi, and, similar to *Hwang et al.*, we found that prostatic calculi were correlated with high-grade PCa.

Chronic inflammation damages the prostate cells and promotes proliferation, so PCa can develop from the damaged cells. Mutations in prostate cells also contribute to the development of PCa. Although the relationship between inflammation and PCa remains unclear, anti-inflammatory drugs (e.g., aspirin) potentially reduce the incidence of PCa and PCa-specific mortality (13).

A meta-analysis of 11 studies revealed a 60% increased risk of PCa in patients with prostatitis (14). Contrary to the aforementioned studies, the *Reduction* by *Dutasteride of Prostate Cancer Events* trial reported that patients with inflammation in an initial negative biopsy had a lower risk of PCa than those who received a repeat prostate biopsy. Inflammation can elevate PSA levels, and these patients are selected more often for repeat prostate biopsy; thus, these patients have a lower risk of being diagnosed with PCa (15). In our study, patients with large prostatic calculi tended to have higher PSA levels than patients who had no prostatic calculi, but this difference was not significant. The *Prostate Cancer Prevention Trial* (PCPT) found that PCa, in particular high-grade PCa, was more common in patients with chronic inflammation (16). In the present study, we observed that PCa was more common in patients with large prostatic calculi. Although our study had a small sample size, we achieved similar results to those reported in the PCPT trial.

Conclusions

Prostate calculi are a common finding on ultrasonographic evaluation of the prostate, but their role in the development of PCa is not fully understood. In the present study, large prostatic calculi were associated with PCa. However, more work is needed to examine the relationship between large prostatic calculi and PCa in more detail. The effects of particularly large prostate calculi in the development of PCa will be a focus of further research.

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