SEXUAL MEDICINE REVIEWS

REVIEW

Prostatic Calculi: Do They Matter?

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ABSTRACT

Introduction: Prostatic calculi (PC) are frequently detected at computed tomography or ultrasound in men attending the health center or the urology outpatient department. PC have attracted more attention from urologists, but the clinical significance of PC is unknown.

Aim: To review the available literature on the effects of PC on prostatic diseases and sexual function in men.

Methods: Relevant clinical trials were identified by searching the PubMed, Embase, and Cochrane Library databases. Results were classified, summarized, and analyzed.

Main Outcome Measures: Transabdominal and rectal ultrasonography; urodynamics analysis; International Prostate Symptom Score; pathologic examination of prostatic tissue; prostate-specific antigen; and expressed prostatic secretion.

Results: PC can not only prolong the duration of bothersome symptoms but also decrease the cure rate of antibacterial therapy in patients with chronic prostatitis. Patients with PC usually have more severe lower urinary tract symptoms (LUTS), and some studies reported that moderate to marked PC are a predisposing factor for moderate to severe LUTS. Studies also reported that the serum level prostate-specific antigen is not influenced by PC. In addition, the presence of PC is not associated with an increased risk of prostate cancer. However, the correlation between PC in the peripheral zone and prostate cancer is statistically significant. In addition, the association between PC and Gleason scores is controversial. Some novel studies suggested that PC might play an important role in sexual impairment in middle-age men or men with chronic pelvic pain syndrome or chronic prostatitis. Recently, PC were found to increase the incidence of severe LUTS, urinary retention, and hematospermia after transrectal ultrasound-guided prostate biopsy.

Conclusion: PC can aggravate LUTS, chronic prostatitis, and sexual dysfunction in men, but the association between PC and prostate cancer is still controversial. **Cao J-J, Huang W, Wu H-S, et al. Prostatic Calculi: Do They Matter? Sex Med Rev 2018;6:482–491**.

Key Words: Prostatic Calculi; Chronic Prostatitis; Benign Prostate Hyperplasia; Lower Urinary Tract Symptoms; Sexual Function

INTRODUCTION

Prostatic calculi (PC) are frequently detected incidentally at transabdominal ultrasonography, transabdominal rectal ultrasonography (TRUS), or computed tomography in health examination centers or outpatient urology departments. In general, they are neglected because they are usually asymptomatic. Recently, PC were reported to be found more commonly in patients with benign prostate hyperplasia (BPH), prostate cancer (PCa), or prostatitis.[1–3] In addition, some studies have investigated the effects of PC on prostate diseases and sexual function in men.

To our knowledge, no prior articles have provided an overview of the association between PC and prostate diseases and sexual function in men, and this is the first article systematically summarizing their relation. The aim of this article was to review the available literature on the effect of PC on prostate diseases and sexual function in men. These findings might help increase our knowledge of PC and motivate us to pay more attention to its potential effect in men.

METHODS

To perform a systematic review of the available literature on the effect of PC on prostate diseases and sexual function in men, a literature search was performed in May 2017 using the Embase, Cochrane Library, and PubMed databases. The terms *prostate,*

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calculus, calculi, stone, lithiasis, and *calcification* were searched with the following limits: humans, sex (male), and language (English). 3 authors (J.J.C., W.H., H.S.W.) separately reviewed the records to select the studies. Reference lists of the included studies also were checked manually to identify further studies. Only studies on the incidence and etiology of PC and their underlying associations with prostate diseases and male sexual function were included. The results were classified, summarized, and analyzed.

INCIDENCE OF PC

Whether PC are the direct byproduct of age is not clear, although aging has been positively associated with the presence of PC.[2,4,5] In a prior review of the etiology of PC published in 1985, Klimas et al[1] reported that PC were seldom seen in children, infrequent in men younger than 40 years, and common in middle-age or older men, which is consistent with the results of some recent studies.[2,6–8]

The prevalence of PC can be hard to determine because of the different definitions, imaging methods, and samples. In 1979, an autopsy study showed the incidence of PC was 70.1% in black men from Washington, DC and 29.1% in men from Ibadan, Nigeria and Accra, Ghana,[9] whereas Sondergaard et al[10] reported PC in 99% of 300 autopsy cases in 1987.

There is no knowledge of the incidence of PC in general screened populations and in patients with some prostate diseases. Therefore, we summarized the incidences of PC in articles published since 2000[2–4,6,8,11–24] (Table 1). Of the 19 studies listed in Table 1, 14 were form Asia (10 from Korea, 4 from China). It is noteworthy that the incidences of PC among studies are very different, with a range from 7.35% to 88.6%. Geramoutsos et al[23] reported an incidence of 7.35% in patients who attended their outpatient clinics; however, the imaging method used to detect PC was transabdominal ultrasonography but not TRUS, which was believed to be more accurate. TRUS combined with computed tomography or pathologic examination of the prostate appeared to yield a higher detection rate of PC. O'Neill et al[12] reported a PC rate as high as 86.8% in men with PCa who underwent radiotherapy using TRUS combined with computed tomography. In a study by Suh et al,[21] the pathologic examination of prostatic specimens obtained by prostatectomy or cystoprostatectomy yielded a PC incidence of 88.6%.

Table 1. Summary of the incidence of PC reported in different studies published since 2000

Study	Year	Country	Imaging methods	Subjects	Mean age (y)	Incidence
Lee et al[24]	2003	Korea	TRUS	Men without pca and prostatitis	61.9	40.7% (198/468)
Geramoutsos et al[23]	2004	Greece	TAUS	Men attending outpatient clinics	40.1	7.35% (101/1,374)
Shoskes et al[22]	2007	USA	TRUS	Men with CPPS after excluding PC < 3 mm in diameter	46.9	47% (22/47)
Suh et al[21]	2008	Korea	pathology	Men who underwent prostatectomy or cystoprostatectomy	61.5	88.6% (264/298)
Park et al[3]	2010	Korea	TRUS	Men with LUTS after excluding PC < 3 mm in diameter	67.2	41.8% (335/802)
Hwang et al[20]	2010	Korea	TRUS	Men who underwent TRUSB	68.4	43.6 (182/417)
Kim et al[6]	2011	Korea	TRUS	Healthy men	49.5	51.1 (799/1,563)
Zhao et al[18]	2012	China	TRUS	Men with CBP	37.6	38.7% (41/106)
Hong et al[19]	2012	Korea	TRUS	Men who received TRUS	56.7	41.5% (199/479)
Kim et al[8]	2013	Korea	TRUS	Men with BPH who underwent TRUS	68.7	71% (159/225)
Yang et al[17]	2013	Taiwan, China	TRUS	Men ≥40 y old who voluntarily underwent TRUS	54.6	60.8% (367/604)
Zhao et al[16]	2014	China	TAUS	Men with CP or CPPS	45.5	48.9% (175/358)
Kim et al[15]	2015	Korea	TRUS	Men who voluntarily underwent TRUS	NA	22.9% (79/346)
Smolski et al[14]	2015	UK	TRUS	Men who underwent TRUSB	67.5	42.3% (197/466)
Gu et al[2]	2015	China	TRUS	Men with serum PSA > 4 ng/ml	69.7	47.4% (325/685)
Kuei et al[13]	2016	Taiwan, China	TRUS	Men with LUTS	65.5	42.9% (48/112)
Park and Choo[11]	2016	Korea	TRUS	Men who underwent TRUS	58.2	76.6% (464/606)
Dell'Atti et al[4]	2016	Italy	TRUS	Men who underwent TRUSB	62.1	25.5 (168/664)
O'Neill et al[12]	2016	UK	TRUS, CT	Men with pca who underwent radiotherapy	NA	86.8% (210/242)

BPH = benign prostate hyperplasia; CBP = chronic bacterial prostatitis; CP = chronic prostatitis; CPPS = chronic pelvic pain syndrome; LUTS = lower urinary tract symptoms; NA = not available; PC = prostatic calculi; PCa = prostate cancer; PSA = prostate-specific antigen; TAUS = transabdominal ultrasonography; TRUS = transrectal ultrasonography; TRUSB = transrectal ultrasound-guided prostate biopsy; TURP = transurethral resection of prostate.

ETIOLOGY OF PC

Thomas[25] first proposed that the formation of PC was a result of calcification of the corpora amylacea. Then, various mechanisms emerged to explain the presence of calcification, such as the principle similar to the calcification of osteoids,[26] changes in citrate concentrations,[27] precipitation of normal components of prostatic fluid,[1] and so on.

According to the findings of concentric calcification layers within the small spheres of PC, Köseoğlu et al[7] suggested that urine obstruction and stasis within the prostate glands contribute to the calcification of the corpora amylacea and the precipitation of crystals, resulting in the formation of PC. Sutor and Wooley[28] and Torres Ramirez et al[29] suggested that urinary intraprostatic reflux might contribute to the formation of PC. In their studies, they used crystallography to study PC and discovered that many contained components found only in urine and not in prostatic secretions.

PC have been proposed to be more frequent in patients with BPH and prostatitis.[1–3] BPH and prostatitis are the most common benign prostate diseases, which affect most men. In addition, prostatitis appears to be closely related to BPH. Some investigators such as Nickel et al[30] and Lee and Park[31] found evidence of chronic inflammation in most BPH cases (up to 96% in the study by Lee and Park). Type A PC was believed to be a normal physiologic aging process without clinical significance.[23,32] However, Köseoğlu et al[7] found that PC appeared to be frequently accompanied by histologic inflammation. Some investigators stated that it was the chronic infection of the acini and the secretory duct of the prostate that led to the formation of PC.[26] Geramoutsos et al[23] observed that the presence of type B PC was closely correlated with prostatitis in their study, further confirming that prostate infection could be the underlying contributor to the formation of PC.

Kovi et al[9] proposed that dietary pattern was an important factor for the formation of PC. Studies have reported a correlation between a higher body mass index and larger prostate volume (PV)[33–35] and greater frequency of prostatic inflammation.[34,35] Moreover, these studies reported a positive correlation between metabolic disorders and the size of PC.[34,35] Alkaptonuria, a rare metabolic disorder, was reported to be associated with the presence of large PC.[36] Sridhar et al[36] suggested that the formation of PC in patients with alkaptonuria was secondary to the accumulation of homogentisic acid in the prostate, which precipitates the formation of calculi crystals. Cases of pediatric patients with hypercalciuria, increased urinary calcium-to-creatinine ratios, and PC also have been reported.[37] Engelhardt et al[38] found that increased levels of uric acid might be a predictor for PC. Therefore, there are reasons to believe that metabolic disorders could be contributing factors in the formation of PC, although certain mechanisms should be studied further.

Other factors, including penetration of spermatozoa into prostatic glands, desquamation of prostatic epithelium, and treatment modalities, have been proposed as associated mechanisms.[39,40] Currently, there are mainly 2 controversial hypothetical mechanisms on the formation of PC. One theory is that PC are formed by precipitation of substances within prostatic secretions and calcification of the corpora amylacea under inflammatory conditions.[8,20,25,40] Another theory is that urinary intraprostatic reflux contributes to the formation of PC.[28,29] These 2 theories are reasonable and should be studied further and confirmed or refuted.

CLASSIFICATION OF PC

Because of the diverse sizes and distributions of PC and different imaging methods, the classification of PC is not unified or standardized. Classifications among articles vary. Sometimes, PC are simply classified as large or small.[41]

According to x-ray findings, Vilches et al[42] classified PC into type I (lobular) and type II (larger, multifaceted). This classification corresponds well to another classification of calculi (types A and B) detected by ultrasound. Type A PC present as discrete small reflections at ultrasound and type B PC present as a large mass of multireflection.[43] Kim et al[8] classified the coexistence of types A and B as type M.

Some investigators have classified PC as mild and moderate or marked using ultrasound.[4,17,21] They have defined moderate or marked PC as multiple ($\geq$3) hyperechoic foci with a significant area ($\geq$3 mm in largest diameter) and a coarse shadow detected in 2 dimensions and mild as 1 focus or multiple small foci without a coarse shadow. Recently, a novel study proposed the definition "calculi burden" as a classification of PC.[11] Those investigators defined calculi burden as the sum of transverse diameters (millimeters) of all visible calculi within the prostate measured by TRUS.

PC, BPH, AND PROSTATITIS

It is widely accepted that PC are associated with BPH and prostatitis. However, the positive and negative interactions and causal relations between them are unclear. Trinchieri et al[44] concluded that PC are common in patients with chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) and connected with more severe urinary symptoms. Geramoutsos et al[23] proposed that prostatitis was correlated with the size but not with the number or localization of PC after comparing the incidence, morphology, and clinical presentation of PC.

In a study by Shoskes et al[22] (including 47 men with CP or CPPS), men with PC were less likely to have pelvic floor tenderness (50% vs 85%; $P = .03$), more likely to have bacteria in the prostatic fluid ($P = .05$), more likely to have a higher median white blood cell count (3.5 vs 0 white blood cells per high-power field; $P = .058$), longer symptom duration, and smaller PV. These findings are in line with those reported by Zhao et al,[16] except their patients with PC were more likely to have positive pelvic floor tenderness.[16]

Significant associations have been found between PC and the severity of prostate inflammation and urinary symptoms ($P < .02$ for each) in patients with obstructive BPH.[38] However, opposite conclusions have been reported by some investigators. In patients with BPH, Kim et al[45] noted no connections between grades of prostate inflammation and each type of PC. By detecting voided bladder-3 specimen, Park et al[3] found no statistical difference ($P = .094$) in the incidence of prostatitis between PC and no-PC groups of patients with lower urinary tract symptoms (LUTS). Similarly, Kim et al[8] observed that PC were not related to prostatic inflammation and had no effect on BPH.

These contrasting findings could be due to the different subjects in their studies (patients with CP or CPPS, LUTS, or BPH), different imaging methods, and limited samples; therefore, further studies should be conducted.

Interestingly, some novel studies have investigated the influence of PC on the efficacy of antibiotic therapy in patients with chronic bacterial prostatitis (CBP). Kim et al[46] observed more severe symptoms of prostatitis and lower response to treatment in patients with type B PC than those without this subtype. Zhao et al[18] noted that men without PC presented a higher rate of continued microbiological eradication and a lower relapse rate ($P < .01$ for each) than those with PC at the end of study, whereas microbiological eradication rates were not significantly different between groups at the end of treatment. Shoskes et al[5] reported a similar result. They studied anti−nano-bacterial therapy in men with recalcitrant CPPS refractory to multiple prior conventional therapies who had detectable PC. Significant improvements in symptoms were observed after 3 months in their study; moreover, in 62.5% of patients (10 of 16), PC shrank or resolved in 50% after treatment (Table 2).

Mazzoli[49] isolated potential biofilm-producing bacteria from patients with CBP to evaluate the ability of bacteria to produce in vitro biofilms and to characterize intraprostatic bacteria and prostatic calcifications. For the first time, Mazzoli proposed that bacterial strains could produce biofilms in patients with CBP and contribute to high antibiotic resistance. In addition, prostatic calcifications were associated with biofilms.

It seems patients with CP or CPPS are more likely to have PC and that PC are associated with greater intraprostatic inflammation. PC in patients with CP or CPPS can not only aggravate the severity but also prolong the duration of symptoms. The noticeable low cure rate of CBP in patients with PC should be attributed to relapse after antibiotic therapy, which proves that prolonging the antibiotic treatment is necessary in patients with CBP and PC.

ASSOCIATION BETWEEN PC AND LUTS

With the exception of BPH, factors such as prostatitis, obesity, and type 2 diabetes have been proposed to contribute to LUTS.[50] Recently, a great deal of attention has been paid to the effect of PC on LUTS. However, the clinical significance of PC in patients with LUTS remains unclear and controversial.

Bock et al[51] noted that no specific symptoms were clearly connected with calcification in their study conducted in 1989. In addition, no significant associations between PC and LUTS have been observed in some investigations.[3,8,48] In the study by Park et al,[3] including 802 subjects with LUTS, higher overall International Prostatic Symptom Scores (IPSSs; $P = .013$) and lower maximum flow rates (Qmax; $P = .003$) were observed in the group with PC than in the group without PC. However, further multivariate analysis showed PC were not the risk factor for severe LUTS. In addition, differences in age and PV were found to be the predisposing factors of PC. They hypothesized that men with PC have more severe LUTS not only because of PC but also because of age and other factors.

Contrary to these studies, some investigators considered that large PC are an independent risk factor for moderate to severe LUTS.[6,17] Kim et al[6] reported that old age (>50 years), obesity (body mass index > 25 kg/m^2), and large calculi (type B) were significant associated factors for an IPSS higher than 8. Moreover, their study presented a 1.784-fold increase in risk of the likelihood of the IPSS being higher than 8 in a large calculi group compared with groups with no and small calculi. A more detailed study was performed by Yang et al.[17] Significantly higher age-adjusted IPSS, quality-of-life score, storage score, and voiding score and more Qmax lower than 15 mL/second were observed in the PC group compared with the non-PC group in this study. Moreover, moderate to marked PC was found to be an independent risk factor for moderate to severe LUTS by further multivariate analysis.

Kuei et al[13] reported that PC could have a negative effect on á-blocker treatment for BPH-induced LUTS. Notably, the locations of PC also could have an impact on LUTS. A study evaluating the effect of periurethral PC on LUTS was performed by Cha et al.[47] After following 223 men with LUTS, they found that voiding, storage, and total IPSS but not quality-of-life score, Qmax, and postvoid residue, were significantly higher in the group with periurethral PC than in the group without periurethral PC. Furthermore, after treatment with doxazosin 4 mg gastrointestinal therapeutic system, a significant improvement of these factors, except postvoid residue, was found in the group without periurethral PC. This study indicated that the periurethral PC might not only aggravate LUTS but also decrease the efficacy of α-blockers.

In 2016, Park and Choo[11] first used calculi burden as an indicator to evaluate the connection between PC and LUTS. They proposed that the presence of PC was not an independent predisposing factor of moderate or severe LUTS, whereas PC burden was significantly associated with storage symptoms in men with PC. Unfortunately, 2 important LUTS parameters, Qmax and postvoid residue, were not investigated in this study (Table 2).

Table 2. Studies investigating the association among PC, prostatitis, and LUTS

Study	Year	Country	Imaging methods	Subjects (N)	Groups (%)	Parameters	Conclusions
Geramoutsos et al[23]	2004	Greece	TAUS, TRUS	Men with PC (101)	type A (71.3), type B (28.7)	Symptom inventory, EPS, VB3, WBC count	Type B calculi were more often associated with CP or CPPS
Shoskes et al[5]	2005	USA	TRUS	Men with recalcitrant CPPS (16)	PC (100)	EPS, nano-bacterial antigen, CPSI, size of PC	Significant improvement in symptoms were observed after anti—nano-bacteria therapy; pc were smaller or resolved in 50% after treatment
Shoskes et al[22]	2007	USA	TRUS	Men with CPPS (47)	PC (47), NPC (53)	CPSI, EPS, PV	Greater inflammation, bacterial colonization, and symptom duration in PC group
Cha et al[47]	2008	Korea	TRUS	Men with LUTS (223)	Pu-PC (36.3), NPu-PC (63.7)	IPSS, Qmax, PVR, QOL	Pu-PC might aggravate LUTS and decrease the effect of α-blockers
Trinchieri et al[44]	2010	Italy	TRUS	Men with CP (399)	PC (88), NPC (22)	CPSI, PV, Qmax, PVR	PC are common in patients with CP or CPPS and are associated with higher scores for CPSI domains of urinary symptoms
Park et al[3]	2010	Korea	TRUS	Men with LUTS (802)	PC (41.8), NPC (58.2)	IPSS, EPS, PV, VB3	PC are not an independent predictive factor of severe LUTS, no statistically difference in incidence of prostatitis was found between PC and NPC groups in patients with LUTS
Zhao et al[18]	2012	China	TRUS	Men with CBP (101)	PC (38.6), NPC (61.4)	EPS, UC, CPSI, SGA, MER	There was a noticeable decrease in cure rate of patients with CBP and PC because of relapse after antimicrobial therapy
Kim et al[48]	2010	Korea	TRUS	Men with BPH (121)	PC (59.5), NPC (40.5)	Uroflowmetry, IPSS, QOL, PSA, PVR, PV	Presence of PC was not shown to influence urinary symptoms, uroflowmetry, residual urine, and serum PSA
Kim et al[6]	2011	Korea	TRUS	Healthy men (1,575)	Type A (39.3), type B (11.8), NPC (51.1)	IPSS	Presence of large PC was a significant associated factor of moderate LUTS, whereas there was no statistical difference in IPSS between NPC and type A groups
Yang et al[17]	2013	China	TRUS	Men $\geq$40 y old (604)	Mm-PC (42.7), Mi-PC (18.0), NPC (39.3)	IPSS, Qmax, PV, QOL	Moderate or marked PC status was an independent risk factor for moderate to severe LUTS
Kim et al[8]	2013	Korea	TRUS	Men underwent TURP for BPH (225)	PC (71), NPC (29)	Pathology, IPSS, PSA, PV	PC were not related to prostatic inflammation and had no effect on BPH
Zhao et al[16]	2014	China	TAUS	Men with CP or CPPS (358)	PC (48.9), NPC (51.1)	CPSI, EPS	Patients with PC: more likely to have higher WBC counts or positive bacteria cultures in EPS, longer symptom duration
Kim et al[46]	2014	Korea	TRUS	Men with prostatitis (482)	type A (36.5), type B (15.1), NPC (48.3)	CPSI	More severe symptoms of prostatitis and lower response of treatment in patients with type B PC than in those without this subtype

(continued)

Table 2. Continued

Study	Year	Country	Imaging methods	Subjects (N)	Groups (%)	Parameters	Conclusions
Kuei et al[13]	2016	Taiwan, China	TRUS	Men >40 y old with IPPS > 8 (112)	PC (42.9), NPC (57.1)	IPSS, Qmax, PVR	PC are unfavorable predictors of successful α-blocker treatment for BPH-induced LUTS
Park and Choo[11]	2016	Korea	TRUS	Men with LUTS (606)	PC (76.6), NPC (23.4)	Transverse diameters of PC, IPSS, QOL	Presence of PC was not a significant factor predicting moderate to severe LUTS, but an increased calculi burden might be associated with aggravating storage symptoms
Engelhardt et al[38]	2016	Austria	TRUS, radiography	Men who underwent TURP for BPH (96)	PC (32.3), NPC (67.7)	Pathology, IPSS, CPSI	Significant correlations were found between PC and severity of inflammation and urinary symptoms

BPH = benign prostate hyperplasia; CBP = chronic bacterial prostatitis; CP = chronic prostatitis; CPPS = chronic pelvic pain syndrome; CPSI = National Institutes of Health Chronic Prostatitis Symptom Index score; EPS = expressed prostatic secretion; IPSS = International Prostate Symptom Score; LUTS = lower urinary tract symptoms; MER = microbiological eradication rate; Mm-PC = moderate/marked prostatic calculi; Mi-PC = mild prostatic calculi; NPC = no prostatic calculi; NPu-PC = no periurethral prostatic calculi; PC = prostatic calculi; PSA = prostate-specific antigen; Pu-PC = periurethral prostatic calculi; PV = prostate volume; PVR = postvoiding residual urine; Qmax = maximum flow rates; QOL = quality of life; SGA = Subjective Global Assessment; TAUS = transabdominal ultrasonography; TRUS = transrectal ultrasonography; TURP = transurethral resection of prostate; type A = discrete, multiple small prostatic calculi; type B = large mass or multiple, coarser prostatic calculi; UC = urine culture; VB3 = urine sample after prostatic massage; WBC = white blood cell.

PC, PROSTATE-SPECIFIC ANTIGEN, AND PCA

The effects of PC on serum prostate-specific antigen (PSA) and PCa have not been well established. Some investigators have reported a positive relation between histologic prostatic inflammation and increased serum PSA[52,53] and stated that PSA increases are related to the degree of disruption of the normal prostatic architecture by inflammatory cells.[53] Therefore, being similar to prostatitis, PC also might affect the serum level of PSA.

Lee et al[24] were the first to investigate the relation between PC and serum PSA in men with clinically undetectable PCa or prostatitis. They found no association between PC and serum PSA, which is in line with findings documented by other studies.[4,14,48] Furthermore, their multivariate analysis indicated that age and PV were associated with increased PSA.[24]

2 reasons can be proposed to explain these findings. On the one hand, these findings indicate that factors increasing serum PSA can be multiple, such as age and PV, but that inflammation is not the only factor. On the other hand, the presence of PC does not always accompany prostatic inflammation.[54]

Chung et al[55] observed that patients with PCa were more likely to have been diagnosed with kidney calculi, bladder calculi, or unspecified calculi except for ureter calculi. Is there a connection between PC and PCa?

Griffiths et al[56] proposed a 63% correlation between PC and PCa at TRUS. Hwang et al[20] found that Gleason scores in patients with PCa were statistically higher in those with PC than in those without PC ($P = .023$). However, further analysis showed the presence of PC was not a risk factor for PCa. Contrary to these studies, Woods et al[57] noted that prostatic microcalcifications were less commonly associated with PCa than with benign pathology.

In a blinded study of 476 men undergoing TRUS and prostate biopsy, Smolski et al[14] found that peripheral zone calcification appeared to be strongly associated with PCa, whereas interface calcification was not associated with any particular prostatic pathology. Dell'Atti et al[4] also observed that the correlation between PCa and the presence of PC in the peripheral zone was statistically significant ($P < .001$). However, Gleason scores in their study were not statistically associated with PC, which was contrary to result of Hwang et al[20] (Table 3).

EFFECTS OF PC ON SEXUAL FUNCTION

A significant association has been reported between CP or CPPS and sexual dysfunctions, such as erectile dysfunction (ED), decreased sexual desire, and premature ejaculation.[58,59] However, studies exploring connections between PC and sexual function remain limited. Recently, some investigators have explored this problem.[16,41]

A study composed of 358 patients with CP or CPPS used the 15-item International Index of Erectile Function (IIEF-15) and the 5-item Premature Ejaculation Diagnostic Tool to evaluate

Table 3. Connections between PC and PCa

Study	Year	Country	Imaging methods	Subjects (N)	Groups (%)	Parameters	Conclusion
Hwang et al[20]	2010	Korea	TRUS	Men who underwent TRUSB (417)	PC (43.6), NPC (56.4)	Pathology, PSA, gss, PV	Presence of PC was not a risk factor for pca, but PC were more common in patients with pca and were associated with a higher GS
Smolski et al[14]	2015	England	TRUS	Men who underwent TRUSB (476)	IZ PC (42.3), TZ PC (9.0), PZ PC (6.8), NPC (41.9)	Pathology, PSA, PV	IZ PC are common and not associated with any particular pathology; PZ PC appears to be strongly associated with PCa
Dell'Atti[40]	2016	Italy	TRUS	Men who underwent TRUSB (664)	TZ PC (12.8), PZ PC (5.1), CZ PC (7.4), NPC (74.7)	Pathology, PSA, gss	Correlation between pca and presence of PZ PC was statistically significant, but gss were not statistically associated with PC

CZ = central zone; GSs = Gleason scores; IZ = interface zone; NPC = no prostatic calculi; PC = prostatic calculi; PCa = prostate cancer; PSA = prostate-specific antigen; PV = prostate volume; PZ = peripheral zone; TRUSB = transrectal ultrasound-guided prostate biopsy; TZ = transitional zone.

male sexual function.[16] Lower scores for the IIEF-15 total, erectile function domain, and intercourse satisfaction domain ($P < .001$ for each) were observed in patients with PC,[16] whereas premature ejaculation and IIEF orgasmic function, sexual desire, and overall satisfaction domain scores were not statistically significant between groups with and without PC.[16] Similarly, Kim et al[41] found that men with large PC were more likely to manifest ED ($P < .001$) and that there was a 2.126-fold increase in the risk of ED in the group with PC vs the group without PC or with small PC. However, other factors evaluating male sexual function were not applied in their study.

Some investigators have found that ejaculatory pain is a common compliant in patients with CP or CPPS.[60] As mentioned earlier, the presence of PC is closely associated with CP or CPPS. Therefore, the presence of PC very likely also has a negative impact on men's ejaculatory dysfunction or aggravates ejaculatory discomfort in patients with CP or CPPS. However, no studies have investigated the associations between PC and men's ejaculatory function.

The findings in these 2 studies suggested that PC might play an important role in the decline of sexual function in middle-age men or men with CP or CPPS. Nevertheless, the relevant data are limited and more high-quality studies are needed.

EFFECTS OF PC ON MEN WHO UNDERWENT TRUS-GUIDED PROSTATE BIOPSY

Rare reports have described the influence of PC on TRUS-guided prostate biopsy (TRUSB) in middle-age and older men with PSA levels higher than normal. Gu et al[2] were the first to propose that PC could aggravate discomfort symptoms after TRUSB in patients with higher serum levels of PSA.

Dell'Atti[40] evaluated the association between PC and hematospermia in men who underwent TRUSB and its impact on their sexual function. In their study, 212 patients were divided into 2 groups: patients with moderate or marked PC (group A) and patients with absent or sparse PC (group B). They observed that the complication of hematospermia was statistically different between groups (65.1% in group A and 39.7% in group B; $P <$ .001). Further multivariate analysis showed PC was a significant predictor of hematospermia.

These 2 studies, to some extent, alert urologists to be aware that, after biopsy, patients with PC could be at higher risk of experiencing more discomfort symptoms.

TREATMENT OF PC

Because most PC are asymptomatic and produce no complications, treatment is rarely recommended and follow-up can be considered.[1,61] When patients with PC have acute prostatitis or CP and severe symptoms, antibiotics are a valid therapeutic option.[5,11,18,49,62] Surgical removal of large PC is alternative when large PC protrude into the urethra or bladder and cause obvious LUTS.[3,63,64] However, Klimas et al[1] stated transurethral removal of PC could offer relief but could not guarantee the removal of all calculi or avoid the relapse of PC. They suggested transurethral removal for younger patients was a good choice to preserve sexual function, but that prostatectomy can be used for older patients. According to the chemical components of PC, we also can draw lessons from calcium phosphate kidney stone treatments, such as potassium citrate or sodium thiosulfate, to deal with PC,[11] but to our knowledge, no studies have been conducted to validate the efficacy of this therapeutic method.

CONCLUSION

The association between PC and prostatitis is controversial; however, most studies have reported that patients with CP or CPPS are more likely to have PC. In addition, PC could not only prolong the duration of symptoms but also decrease the cure rate of antibacterial therapy in patients with CBP, which suggests prolonging antibiotic treatment is necessary in patients with CBP and PC. Although LUTS were more severe in patients with PC, PC were not an independent predictive factor of severe LUTS. Nevertheless, some studies paradoxically reported that moderate or marked PC was an independent risk factor of moderate to severe LUTS. The serum level of PSA was found to be not influenced by PC. In addition, the presence of PC was not associated with an increased risk of PCa. However, the correlation between PC in the peripheral zone and PCa was statistically significant. In addition, the association between PC and Gleason scores was controversial. Some novel studies found that PC could play an important role in sexual impairment in middle-age men or men with CP or CPPS. Recently, it has been reported that PC can increase the incidence of severe LUTS, urinary retention, and hematospermia after TRUSB. These findings expand our knowledge of PC and might motivate us to pay more attention to its adverse impact in LUTS, CP, and ED, and more studies with more details should be carried out to make clinicians fully understand these easily overlooked calculi.

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