Review Article

The influence of prostatic calculi on lower urinary tract symptoms and sexual dysfunction: a narrative review

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Abstract: Prostatic calculi (PC) are commonly found in patients who present for urologic consultation. However, the effect of PC on urinary symptoms remains controversial. In this study, we searched the Embase and PubMed databases for literature related to the following keywords: "prostatic calculi", "prostatic stone", "prostatic lithiasis" and "prostatic calcification", along with the limits, "lower urinary tract symptoms", "sexual dysfunction", "erectile dysfunction", "erectile function", and "premature ejaculation". According to the literature, there are various subtypes of PC based on X-ray or ultrasound findings, including type I/II, type A/B, and endogenous PC/extrinsic PC. Furthermore, the formation of PC remains unclear, and more importantly, the ability of PC to cause lower urinary tract symptoms (LUTS) and sexual dysfunction (SD) is worth exploring. We retrospectively reviewed all available literature and found that most studies agreed that PC are associated with LUTS. The factors which may play an important role in the pathogenesis of LUTS include the size and location of PC, induced inflammation, and the blood flow of the prostate. Similarly, SD was also examined in the patients with PC, and psychological factors cannot be ignored in this regard. However, more in-depth study of the molecular mechanisms, including prospective, controlled, longitudinal, and large- sample studies, are needed in the future.

Keywords: Prostatic calculi (PC); lower urinary tract symptoms; sexual dysfunction

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Introduction

In the past, prostatic calculi (PC) had received only minor attention. However, with the advent of transrectal ultrasound (TRUS) and computerized tomography (CT), they have garnered greater focus from both patients and urologists. The earliest description of PC was reported by Donatus in 1586 (1). At present, the definition and classification of PC has not been standardized. The terms "prostatic calculi", "prostatic calcification", and "prostatic stones" are variably used to describe hyper-echoic calcium deposits in the prostate (2). In clinical practice, most patients with PC present in health examination centers or urology clinics. PC are usually asymptomatic, but are commonly found in patients with benign prostate hyperplasia, chronic pelvic pain syndrome, prostatitis, or prostate radiotherapy (3,4). The incidence of PC varies widely from 7% to 70% across different studies, and about 51.65% of men among the healthy Han Chinese population suffer from PC (3,5,6). Experts have classified PC into different types and categories. Vilches *et al.* classified PC into type I (a lobular

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surface composed of small spheres) and type II (a larger, multifaceted surface) using an energy dispersive type X-ray micro-analyzer (7). Also, Harada *et al.* divided PC into type A (discrete small reflection) and type B (large multi-reflective mass) by TRUS (8). According to crystallography analysis, PC are often also classified into endogenous PC and extrinsic PC. Endogenous PC are primarily formed by prostatic secretions, while extrinsic PC result from urinary reflux and are often larger than endogenous PC (3,9,10).

Lower urinary tract symptoms (LUTS) and sexual dysfunction (SD) have been brought into focus during PC research. LUTS are a syndrome of storage or voiding problems, and affect approximately 50–70% of men over the age of 50. Furthermore, the medical expenses brought on by the high prevalence rate of LUTS present a huge burden to both patients and society (11-13). Notably, there are numerous studies reporting on the pathophysiological mechanism of LUTS; however, a unified perspective is still lacking. Coincidentally, SD, a multi-factorial disease that is not only caused by an organic disorder or disease, may also exist in patients with PC, with premature ejaculation and erectile dysfunction (ED) representing the two most common types of SD in men (14,15).

PC might play an important role in the pathogenesis of LUTS and SD. To our knowledge, although numerous articles have provided an overview of the association between PC and LUTS, they have not verified the relationship between LUTS and the inflammatory response, the size and location of PC, or prostate blood flow. Furthermore, few authors have investigated the association between PC and SD. The aim of this paper was thus to review the available literature in order to summarize the relationship between PC and LUTS, and between PC and SD, and to expound the relevant mechanisms. We present the following article in accordance with the NARRATIVE REVIEW reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1046).

Methods

In order to detect the impact of PC on LUTS and SD, we obtained all relevant articles by comprehensively searching the PubMed and EMBASE databases from 1979 to 2020 using the keywords, “prostatic calculus”, “prostatic calculi”, “prostatic stone”, “prostatic lithiasis”, and “prostatic calcification”, along with the limits, “lower urinary tract symptoms”, “sexual dysfunction”, “erectile dysfunction”, “erectile function”, and “premature ejaculation”. We screened 58 articles. The language of the articles was primarily limited to English. We mainly focused on the publications and iconic articles from the past 10 years, and summarized the relevant information from these and other related articles.

Formation of PC

The results of the reviewed studies suggested that type I PC may be caused by the obstruction of prostatic secretions around benign prostatic hyperplasia or occlusion caused by chronic inflammation (1), and that type II PC may be associated with urinary reflux, which leads to the formation of PC via changing local ion and *pondus hydrogenii* (2,9). Other studies have analyzed the chemical composition of PC and consistently reported that calcium phosphate stones were the main components of PC (16). However, there does exist an inconsistency, as calcium phosphate is not a component of prostate secretion. Köseoğlu *et al.* found that PC contained many ingredients that were found only in urine and not in prostate secretions (17). Consequently, they hypothesized that urine obstruction and stasis in the prostate glands contribute to the formation of PC by promoting calcification of the corpora amylacea and the precipitation of crystals (17). Tang *et al.* reported that age and the anteroposterior diameter of the prostate were stronger risk factors for PC than other factors, with bilirubin level being the only protective factor found in the study after adjustment for other factors (5). Moreover, metabolic disorders could contribute to the formation of PC, and serum uric acid might participate in the formation of PC (18-21). Moreover, Qian *et al.* speculated that patients with PC often seek medical consultation due to psychological or emotional reasons, and thus experience a decreased frequency of sexual activity with increasing depression, which ultimately leads to the excretion of prostatic secretions that are involved in the formation of PC (22).

PC and LUTS

In recent decades, LUTS with PC has garnered increasing attention from authors, however, the effect of PC on LUTS remains controversial. Some studies reported that PC were not a predictive factor of severe LUTS, and independent of prostatic inflammation (23,24). Park *et al.* enrolled 802 patients with LUTS into their study using multivariate

analysis, and the International Prostatic Symptoms Score (IPSS) exhibited no statistical differences. Meanwhile, the differences in age and prostate volume were significant, and thus they believed that patients with PC might have developed LUTS not only from PC but also because of age and other factors (24). Kim *et al.* believed that inflammation of the prostate aggravated LUTS, but the degree of inflammation had nothing to do with the type of PC, and PC had no clinical significance, however, this study exhibited an important limitation: they only selected benign prostatic hyperplasia patients with severe symptoms requiring surgical treatment (23). Similarly, another study showed that the presence of PC was not a predictor of moderate/severe LUTS, but the increased calculi burden, which the researchers defined as the sum of the transverse diameters of all visible calculi within the prostate, might be associated with aggravating urinary storage symptoms, a possible explanation for this is that PC may cause prostatic inflammation (25). As can be seen, there are a variety views concerning the relationship between PC and LUTS. The inflammatory response, the size and location of PC, and prostate blood flow should be considered. The key disputes are listed in *Table 1*.

Chronic prostatitis (CP) is one of the most common diseases in men, with an incidence of 2.2–9.7% (35). Chronic pelvic pain syndrome (CPPS) is among the most common types of prostatitis, and often occurs with forms of LUTS, although the pathogenesis is presently unknown (36), many factors were considered to be involved. The presence of PC is closely related to CP/CPPS, and PC associated with chronic prostate inflammation may be accompanied by chronic pelvic pain. Some studies reported that PC can frequently be found in patients with CPPS (26,34,37). Soric *et al.* reported that the IPSS questionnaire and National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) questionnaire scores were higher in the group with PC compared to the group without PC, and significantly lower maximum urinary flow occurred in the group with PC (34). Fei *et al.* proposed that PC plays a key role in CPPS. They suggested that PC may lead to local prostate tissue injury and inflammation, and that PC could itself be the source of infection that harbors microorganisms (37). Notably, inflammation of prostate tissue and drug resistance caused by PC may also lead to the occurrence of LUTS (31,38-40). Shoskes *et al.* suggested that PC could contribute to the obstruction of intraprostatic ducts and the production of bacterial biofilm, and ultimately lead to chronic inflammation of prostate (38). Moreover, Han *et al.* explained that inflammation of the periurethral area could maximize induction of LUTS due to inflammation-induced periurethral fibrosis, and that calcification of the urethra can also give rise to urethral stiffness (31,41,42). According to these points, PC can not only generate LUTS but also prolong the duration of bothersome symptoms (32).

Large or marked PC is a significant risk factor for severe LUTS (16,26,28,30,43). Sun *et al.* enrolled 79 prostatitis patients over 50 years of age, and the composition of PC in patients with LUTS was detected by quantitative real-time polymerase chain reaction, Western blotting, and immunofluorescence. Their conclusion suggested that large PC were related to LUTS, and that calcium oxalate (the main component of PC) leads to the occurrence of large PC (16). The results of Geramoutsos *et al.* are consistent with those of Sun et al; that is, the small PC observed in elderly men were normal, but large PC were associated with chronic prostate inflammation and LUTS (26). Other studies have also reported this phenomenon (10,44).

PC can be distributed throughout the entire prostate gland, but are more frequently observed in the transition zone than in other zones (45). Han *et al.* divided the location of peri-urethral calcification (PUC) into three areas (proximal, mid, and distal), and found that the mid-PUC group had worse urinary symptoms than the control group, implying that the mid-PUC area could be a potential risk factor of LUTS (33). Cha *et al.* also indicated that PC in the periurethral prostate transit zone may aggravate LUTS (27). For this reason, the urethra tends to straighten to reduce its resistance by reducing the prostatic urethral angle during the voiding phase. If the prostatic urethral angle remains at a fixed tone due to limited urethral movement induced by mid-periurethral calcification fibrosis by PC, LUTS may result (46-48).

Moreover, PC may change prostatic blood flow, and alteration of prostatic blood flow or vascular resistance has an impact on LUTS (34,49). Wu *et al.* performed a prospective analysis involving 133 elderly male patients with clinically diagnosed benign prostatic hyperplasia. They concluded that the alteration of prostatic blood flow was related to the occurrence of LUTS (49). In theory, LUTS caused by hypoxia or congestion at the bottom of the bladder may be characterized by alteration of the blood flow of bilateral neurovascular bundles, and chronic hypoxic-ischemic changes may increase the contraction of prostate

Table 1 The relationship between PC and LUTS

Authors (year)	Measures	Design	Parameters	Subjects	Criteria	Main findings
Geramoutsos *et al.* (26) (in 2004)	transabdominal ultrasound, TRUS	Case-case study	Symptom inventory, EPS, VB3, WBC count	Type A (n=72); type B (n=29)	Young adults (21–50 years) whose prostatic lithiasis were defined by ultrasound imaging	Larger prostatic calculi may be related to LUTS; small prostatic calculi is a normal ultrasonographic finding
Cha *et al.* (27) (in 2008)	TRUS	Prospective cohort study	IPSS, QoL, Qmax, PVR	PC (n=81); no PC (n=142)	The patients who first visit and after treatment with an alpha-blocker in BPH	PC might aggravate LUTS
Park *et al.* (24) (in 2010)	TRUS	Retrospective cohort study	IPSS, EPS, PV, VB3	PC (n=335); no PC (n=467)	The patients who completed transrectal ultrasonography, voided bladder-3 specimen and IPSS	PC are not an independent predictive factor of severe LUTS; but old age and large PV are independent predisposing factors for PC
Kim *et al.* (28) (in 2011)	TRUS	Retrospective cohort study	IPSS	Type A (n=615); type B (n=184); no PC (n=764)	Healthy Korean men aged 40–59 years visited the health promotion center for a routine check-up	Large PC are associated with moderate LUTS; there was no statistical difference between the no calculi group and small calculi group
Hong *et al.* (29) (in 2012)	TRUS	Retrospective cohort study	PSA, prostate volume, IPSS, QoL, the PC rate	healthy men at the Health Promotion Center (n=268); patients with LUTS at the Urology Outpatients Department (n=211)	The patients who underwent transrectal ultrasonography at the Health Promotion Center and the Urology Outpatients Department	PC can aggravate LUTS but does not result in differences according to the number, size, or appearance of the calculi
Kim *et al.* (23) (in 2013)	TRUS	Retrospective cohort study	IPSS, PSA, PV	types A (n=66), B (n=44), M (n=77) and N (n=38);	The patients who underwent transurethral resection of the prostate for BPH	PC had no significant association with LUTS
Yang *et al.* (30) (in 2013)	TRUS	Prospective cohort study	IPSS, Qmax, PV, QoL, storage score, voiding score	Mild PC (n=258); moderate/marked PC (n=109); no PC (n=237)	The patients aged 40 years or older who voluntarily underwent transrectal prostate ultrasound and fulfilled IPSS	PC had negative impact on LUTS; moderate/marked PC were an independent risk factor for moderate to severe LUTS
Han *et al.* (31) (in 2015)	TRUS	Retrospective cohort study	IPSS, Qmax, PV, the storage symptom score	No PC (n=270); small PC (n=246); large PC (n=514)	Patients with complete data and without comorbidities affecting voiding function	PUC is associated with Qmax and urinary symptoms
Kuei *et al.* (32) (in 2016)	TRUS	Prospective cohort study	IPSS, Qmax, PVR	PC (n=48); No PC (n=64)	Patients over 40 years old with IPSS ≥8	PC are adverse to alpha-blocker treatment for BPH-induced LUTS

Table 1 (*continued*)

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Authors (year)	Measures	Design	Parameters	Subjects	Criteria	Main findings
Han *et al.* (33) (in 2017)	TRUS	Case-case study	OABSS, IPSS, voiding symptoms, storage symptoms	Proximal-PUC (n=35); mid-PUC (n=63); distal-PUC (n=19)	First-vist patients with total prostate volume <30 mL and without comorbidities affecting voiding function	Mid-PUC could be a potential causal factor of LUTS, and the midportion of the prostatic urethra might play a pivotal role in the process of micturition
Park *et al.* (25) (in 2017)	TRUS	Retrospective cohort study	IPSS, QoL	No PC (n=142); PC (n=464)	The patiens who new incom? Urological outpatients presenting with LUTS and examined for health check-up at the Health Promotion Center	The presence of PC were not a significant factor predicting moderate/severe LUTS; however, an increased calculi burden may be associated with aggravating storage symptoms
Soric *et al.* (34) (in 2017)	TRUS	Prospective cohort study	IPSS, NIH-CPSI, PSA, cytokines interleukin, Qmax	No PC (n=35); PC (n=35)	The patiens, 21–49 years old, with prostate size up to 40 mL in volume with LUTS	PC may affect the severity of LUTS and the symptoms of chronic prostatitis
Sun *et al.* (16) (in 2018)	Not mentioned	Prospective cohort study	The mRNA and protein levels of clusterin, BMI, PV, PSA, IPSS	No PC (n=32); PC (n=47)	47 patients prostatitis and BPH patients with stones and 32 patients prostatitis and BPH patients without stones	Large PC were associated with LUTS; calcium oxalate leads to large PC

BPH, benign prostate hyperplasia; BMI, body mass index; EPS, expressed prostatic secretion; IPSS, International Prostate Symptom Score; LUTS, lower urinary tract symptoms; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; OABSS, overactive bladder symptom score; PC, prostatic calculi; PSA, prostate-specific antigen; PUC, periurethral calcification; PV, prostate volume; PVR, postvoiding residual urine; Qmax, maximum flow rates; QoL, quality of life; TRUS, transrectal ultrasound; VB3, urine sample after prostatic massage; WBC, white blood cell.

Table 2 The relationship between PC and SD

Authors (year)	Measures	Design	Parameters	Subjects	Criteria	Main findings
Zhao *et al.* (52) (in 2014)	Transabdominal ultrasonography	Prospective cohort study	CPSI, IIEF-15, 5-item Premature Ejaculation Diagnostic Tool scales	PC (n=175); no PC (n=183)	Patients were diagnosedwith CP/CPPS according to the NIH criteria	PC were significantly associated with the presence of ED in CP/CPPS men
Cho *et al.* (53) (in 2016)	TRUS	Prospective cohort study	IPSS, IIEF-5, PSA, BMI, PV	Group A (n=267, no or small PC); group B (n=79, large PC)	Patients who underwent TRUS for a routine check-up prostate with aged 40 years or older were enrolled, and the prostatic calcification grading and prostate volume were checked by TRUS	Large PC and old age may worsen ED
Fei *et al.* (37) (in 2017)	TRUS	Prospective cohort study	NIH-CPSI, IPSS, IIEF-5, white blood cell counts	PC (n=121); no PC (n=151)	Young males with CP/CPPS	The study did not reveal the association of ED of patients with and without calcifications

BMI, body mass index; CP/CPPS, chronic prostatitis/chronic pelvic pain syndrome; CPSI, chronic prostatitis symptom index; ED, erectile dysfunction; IIEF-15/5, international index of Erectile Function-15/5 items; IPSS, International Prostate Symptom Score; NIH, the National Institutes of Health; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; PC, prostatic calculi; PV, prostate volume; PSA, prostate-specific antigen; SD, sexual dysfunction; TRUS, transrectal ultrasonography.

smooth muscle, both of which can cause LUTS (50,51).

In summary, most studies agree that PC may affect LUTS. However, due to the lack of criteria for the definition and classification of PC, the above studies failed to uniformly define and classify PC, and thus, selection bias might have affected their results.

PC and SD

SD is an important component of the clinical phenotype in patients with PC. Studies exploring relationship between PC and SD are scarce, but a diverse set of related viewpoints have emerged (as shown in *Table 2*). PC might play a vital role in the decline of sexual function, even influence semen quality (54). Cho *et al.* found that middle-aged men with large PC appeared to be more likely to develop ED (53). Zhao *et al.* discovered a significant relationship between PC and ED in a prospective study of 358 patients with CP/CPPS. They observed higher white blood cell counts or positive bacteria cultures in their prostatic fluid, longer symptom durations, and lower total scores of the International Index of Erectile Function (IIEF)-15 ($P<0.001$) were demonstrated in patients with PC. Furthermore, logistic regression analyses revealed that PC was significantly associated with self-assessed ED (52). As is often assumed, PC could cause chronic inflammation, which might affect ED by influencing smooth muscle relaxation and prostatic micro-vascularization, impairing cytokines, and enzymes, and impacting the surrounding neurovascular bundle, thus making it difficult for penile tissue to engorge and maintain erection (55-57). Another result published by Fei *et al.* showed that patients without PC, whose sexual function was assessed by the IIEF-5 questionnaire, responded better to medication, although they failed to verify the relationship between PC and ED (37). However, Qian *et al.* offered different perspectives. They proposed that psychological factors might play a key role in the pathogenesis of ED in CP/CPPS patients, and the psychological burden could occur in patients with prostatic calcification. In addition, the frequency of sexual activity may decline due to increasing depression, leading to decreased excretion of prostatic secretions (22). Neural factors should also be mentioned; an association between the presence of multiple stones of the prostatic urethra and ejaculation was reported in a case of spinal dysraphism (58). Generally, PC may have a certain effect on sexual function, but due to the lack of relevant research, the relationship between PC and sexual function is uncertain.

Discussion

As mentioned above, PC have been found in many patients with LUTS or SD. The formation of PC is unclear and multifactorial. While some studies assert that PC are not significantly associated with LUTS or SD, the majority of studies indicate that the inflammatory response, the size and location of PC, and the blood flow of the prostate are likely the key factors causing LUTS and SD. Owing to the chronic irritation to the surrounding tissue in PC, chronic inflammation-induced prostate fibrosis aggravates LUTS and promotes the formation of new stones. Large or marked PC are found to be significantly correlated with LUTS, and the fixation of prostatic urethral angle due to PC-induced mid-periurethral calcification fibrosis is shown to be involved in LUTS. In addition, hypoxia is discovered to possibly increase prostatic smooth muscle contraction, ultimately resulting in LUTS. As for SD, chronic inflammation may affect smooth muscle relaxation, prostatic micro-vascularization, cytokines, enzymes, and blood flow of the penis, thereby leading to ED. Importantly, psychological factors cannot be ignored. Patients may experience decreased libido due to worrying about PC, which may lead to the occurrence of ED and further accelerate the formation of PC.

However, the above studies exhibit the following limitations. Firstly, due to the variety of classifications and definitions of PC, they do not define and classify PC consistently. Secondly, the different inclusion criteria used might have led to differences in the samples studied; for example, if the selected samples are elderly patients who require surgery due to benign prostatic hyperplasia, patients with mild LUTS or asymptomatic patients may be ignored. Thirdly, some studies were retrospective studies and contained a small sample size, and thus methodological deficiencies of included studies should be considered as a major limitation of this review. In addition, most of the articles were based on clinical data, which might have led to selection and information biases, with the study's conclusion also lacking the support of basic research. Thus, more in-depth studies of the molecular mechanisms are needed.

For future research, the following aspects require further attention. (I) The development of consistent criteria for defining and classifying PC is crucial. This includes the same instruments being used to measure and obtain a unified diameter of each category. (II) Multicenter, large-sample, prospective, controlled, and longitudinal studies should be carried out. For instance, prospective cohort studies should be conducted to determine whether PC are risk factors for LUTS, and intervention studies that remove PC of patients with LUTS should be performed to validate whether this is effective. (III) The relationship between PC and LUTS/SD should be examined using pathological studies to evaluate the clinical significance and explore the molecular mechanisms. Finally, (IV) the influence of psychological factors, such as anxiety disorder caused by PC, requires further elucidation by experiments.

Conclusions

Through a literature review, the relationship between PC and LUTS/SD was summarized. The results in this review indicate that most studies agree that PC may be a risk factor for LUTS and SD. We also expounded the relevant mechanisms by reviewing the available literature, and determined that PC may aggravate LUTS and SD. The size and location of PC, inflammation, changes in prostatic blood flow, and psychological factors should be fully considered, and action could be taken to treat LUTS and SD in order to reduce the incidence of PC.

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Footnote

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