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LETTER TO THE EDITOR

Prostate Disease

The prevalence and risk factors of prostatic calcification: an analysis of 68 705 subjects

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Dear Editor,

Prostatic calcification is a common condition observed by the urology community. The earliest description was proposed by Donatus in 1586, followed by Pohl in 1737.[1] In clinical practice, an overwhelming majority of prostatic calcification cases are discovered incidentally. This issue has attracted considerable interests, albeit its clinical significance continues to stir discussion and debate. Patients with prostatic calcification often seek medical consultation owing to psychological or emotional reasons, thereby incurring a significant burden.

The incidence of prostatic calcification varies across different groups. In addition, multiple literatures have concentrated on the impact of prostatic calcification on urological diseases and disorders. For instance, studies have reported an association between prostatic calcification and lower urinary tract symptoms (LUTS) or chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).[2] In this study, we performed a retrospective study in subjects who underwent a comprehensive medical checkup at the West Hospital of China between December 2014 and December 2015. During this period, 70 546 consecutive male subjects underwent a transabdominal ultrasonography examination for screening. All clinical and laboratory assessments were performed on the same day for each subject. Of the 70 546 subjects, 864 who had a history of surgery of the prostate were excluded. We also excluded 977 subjects aged <18 or >79 years. Prostatic calcification was diagnosed using transabdominal ultrasonography. We defined prostatic calcification as any hyperechoic foci located in the prostate, regardless of its size or location. To investigate the association between risk factors and prostatic calcification in a dose-dependent manner, factors were stratified. Logistic regression analysis was used to analyze the association between risk factors and prostatic calcification. Multivariate analysis was performed using all the variables that were found to be significantly associated with the prostatic calcification in the univariate analyses.

The prevalence of prostatic calcification among different ages is shown in **Supplementary Figure 1**. Overall, the prevalence shows an upward trend with increasing age, that is, 9.0%, 32.3%, and 66.7% for ages 18–29, 50–59, and 70–79 years, respectively. Most of the subjects (n = 54 836, 78.1%) had no demonstrable prostatic calcification, whereas the remaining 13 869 (20.1%) subjects had prostatic calcification. The baseline characteristics of the study sample are shown in **Supplementary Table 1**. Overall, the patients with prostatic calcification showed significant differences from the patients without prostatic calcification in terms of most of the variables, except drinking score, and aspartate aminotransferase and creatinine levels. To identify the factors related to prostatic calcification, we examined all the 37 variables using a univariate analysis. In the multivariate analysis (variables with $P < 0.05$ were included, **Table 1**), age (odds ratio [OR] = 1.029, $P < 0.001$), anterior-posterior diameter (OR = 2.197, $P < 0.001$), smoking score (OR = 1.013, $P = 0.02$), alkaline phosphatase level (OR = 1.002, $P < 0.001$), triglyceride level (OR = 1.047, $P = 0.016$), and high-density lipoprotein-cholesterol (HDL) level (OR = 1.177, $P = 0.003$) remained as independent risk factors of prostatic calcification. Hip circumference (OR = 0.99, $P = 0.008$), albumin/globulin (A/G; OR = 0.576, $P = 0.004$), direct bilirubin level (OR = 0.985, $P = 0.008$), and cystatin c level (OR = 0.741, $P < 0.001$) appeared to be protective factors of prostatic calcification.

Furthermore, we investigated the robustness of our findings by stratifying the independent factors in **Table 2.** In an all-patient analysis group, age and anterior-posterior diameter were stronger risk factors of prostatic calcification than the other factors. The likelihood of having prostatic calcification was also related to

Table 1: Multivariate regression analysis for the association of prostatic calcification with risk factors

	OR	*95% CI*	*P*
Age (year)	1.029	1.026–1.031	<0.001
Anterior-posterior diameter (cm)	2.197	2.031–2.377	<0.001
Smoking score	1.013	1.002–1.024	0.02
Hip circumference (cm)	0.990	0.983–0.998	0.008
Alkaline phosphatase (IU l^{-1})	1.002	1.001–1.003	<0.001
Triglycerides (mg dl^{-1})	1.047	1.009–1.086	0.016
HDL cholesterol (mg dl^{-1})	1.177	1.058–1.311	0.003
A/G	0.576	0.397–0.834	0.004
Direct bilirubin	0.985	0.974–0.996	0.008
Cystatin c	0.741	0.630–0.871	<0.001

HDL: high-density lipoprotein-cholesterol; A/G: albumin/globulin; CI: confidence interval; OR: odds ratio

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Table 2: Univariate and multivariable analyses of the risk factors for prostatic calcification by stratifying

	Univariate model			*Multivariable model*		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*
Age (year)						
18–29	1 (reference)			1 (reference)		
30–39	1.712	1.575–1.861	<0.001	1.522	1.392–1.663	<0.001*
40–49	2.650	2.447–2.868	<0.001	2.234	2.032–2.456	<0.001*
50–59	3.631	3.347–3.938	<0.001	2.698	2.406–3.025	<0.001*
60–69	5.006	4.559–5.496	<0.001	3.399	2.866–4.030	<0.001*
70–79	6.043	5.439–6.713	<0.001	4.249	3.301–5.469	<0.001*
Anterior-posterior diameter (cm)						
≤3	1 (reference)			1 (reference)		
3.1–3.5	2.159	2.071–2.251	<0.001	1.724	1.649-1.803	<0.001*
3.6–4.0	3.211	2.966–3.477	<0.001	1.932	1.769-2.110	<0.001*
≥4.1	3.649	3.176–4.192	<0.001	1.741	1.497-2.025	<0.001*
Smoking score						
0	1 (reference)			1 (reference)		
1	1.550	1.363–1.762	<0.001	1.009	0.882–1.154	0.898
2	0.855	0.810–0.903	<0.001	1.001	0.944–1.060	0.992
3	0.826	0.775–0.881	<0.001	1.030	0.961–1.104	0.408
4	1.184	1.119–1.253	<0.001	1.105	1.038–1.176	0.002*
5	1.593	1.498–1.694	<0.001	1.051	0.980–1.127	0.164
Hip circumference (cm)						
≤90	1 (reference)			1 (reference)		
91–100	0.971	0.914–1.031	0.334	-	-	-
101–110	0.908	0.847–0.972	0.006	0.962	0.827–1.118	0.610
≥111	0.763	0.595–0.978	0.033	0.910	0.567–1.460	0.695
A/G						
<1.5	1 (reference)			1 (reference)		
1.5–2.2	0.799	0.760–0.839	<0.001	1.038	0.963–1.119	0.326
>2.2	0.649	0.595–0.708	<0.001	0.826	0.631–1.080	0.163
Cystatin c (mg l^{-1})						
<0.75	1 (reference)			1 (reference)		
0.75–1.1	1.230	1.139–1.328	<0.001	1.022	0.942–1.108	0.603
>1.1	1.939	1.761–2.136	<0.001	1.184	1.008–1.390	0.04*
Triglycerides (mg dl^{-1})						
<1.7	1 (reference)			1 (reference)		
1.7–2.26	1.024	0.974–1.077	0.347	-	-	-
>2.26	1.099	1.050–1.150	<0.001	1.154	1.077–1.236	<0.001*
HDL cholesterol (mg dl^{-1})						
<1.4	1 (reference)			1 (reference)		
1.4–2	1.027	0.987–1.068	0.194	-	-	-
>2	1.349	1.242–1.466	<0.001	1.238	1.089–1.408	0.001*
Direct bilirubin (μmol l^{-1})						
<3.5	1 (reference)			1 (reference)		
3.5–7	0.967	0.927–1.010	0.128	-	-	-
>7	0.830	0.774–0.891	<0.001	0.760	0.646v0.893	0.001*
Alkaline phosphatase (IU l^{-1})						
≤75	1 (reference)			1 (reference)		
76–100	1.028	0.987–1.069	0.183	-	-	-
101–125	1.096	1.030–1.166	0.004	1.064	0.996–1.137	0.065
≥126	1.229	1.085–1.392	0.001	1.162	1.017–1.327	0.027*

The first level of candidate factors is used as the control for logistic regression. *P<0.05. A/G: albumin/globulin; HDL: high-density lipoprotein-cholesterol; OR: odds ratio; CI: confidence interval

the >2 mg dl^{-1} HDL cholesterol level group, with a 1.238-fold increase in risk from that of the control group (95% CI: 1.089–1.408, P = 0.001). Triglyceride and alkaline phosphatase levels showed a similar relative risk ratio for prostatic calcification, with ORs of 1.15 and 1.16, respectively. Direct bilirubin levels of >7 μmol l^{-1} showed significantly protective effects on prostatic calcification (OR = 0.760; 95% CI: 0.646–0.893; P = 0.001).

Prostatic calcification often drives patients to call for consultation because of psychological burden or related symptoms. For its clinical significance, one study documented that small prostatic

calcification occurred physiologically during the aging process.[3] On the contrary, Han *et al*.[4] demonstrated that prostatic calcification is closely associated with reduced urinary flow rate and LUTS severity. The results of Smolski and Turo[5] study denoted that peripheral zone prostatic calcification tended to be strongly associated with prostate cancer. Given that prostatic calcification is not a single entity and may be subcategorized into two types, we define prostatic calcification as any hyperechoic foci located in the prostate, regardless of its size or location. The literature has shown that age and prostate size are widely accepted risk factors of prostatic calcification.[6,7] Our study reinforces this idea. In our cohort, age was the most important risk factor of prostatic calcification. This is not counterintuitive because the precipitation of substances and calcification of the corpora amylacea under inflammatory conditions have been postulated in most of previous studies.[8] As a result, prostatic calcification develops as a matter of course during aging and as part of the benign prostate hyperplasia/chronic inflammation process.[4] Prostate size is another independent risk factor of prostatic calcification; however, prostatic volume is estimated only using the anterior-posterior diameter at the transabdominal ultrasonography because of study method limitations.

Apart from age and prostate size, our findings provide valuable insight into other factors associated with prostatic calcification. Bilirubin level is the only protective factor found in our study after adjustment for other factors. Although data on the effect of bilirubin level in prostatic calcification are lacking, a relationship between bilirubin levels and calcification has been reported in the field of cardiovascular diseases.[9] Studies showed that the serum bilirubin level was inversely associated with coronary artery calcification or negatively correlated with the coronary artery calcium score.[10] In addition, the result of the multivariate analysis in our series indicated that the risk factors associated with vascular calcification (e.g., extent of smoking, triglyceride and cystatin c levels) are also independent predictors of prostatic calcification. On this basis, it is reasonable to assume that some prostatic calcification may be derived from small vessels in the prostate, which is markedly different from the inflammation process. Projecting this assumption more aggressively but without histological evidence, prostatic calcification may be a manifestation of a calcific environment throughout the blood vessels.

AUTHOR CONTRIBUTIONS

ZT and XMW performed the data collection and drafted the manuscript. QW and LNW designed this research and revised the manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

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Supplementary information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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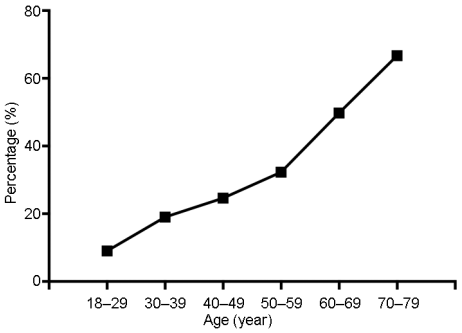

Supplementary Figure 1: The prevalence of prostatic calcification among different ages.

Supplementary Table 1: Clinical characteristics of participants

	Total (n=68 705)	*Pcal (n=13 869)*	*No Pcal (n=54 836)*	*P*
Age (years)	43.8±12.4	48.6±12.6	42.6±12.1	<0.001*
Height (cm)	168.6±5.8	167.6±5.9	168.8±5.8	<0.001*
Weight (kg)	70.2±9.6	69.8±9.3	70.3±9.6	<0.001*
Body mass index (kg m^{-2})	24.7±3.0	24.8±2.9	24.7±3.0	<0.001*
Waist circumference (cm)	84.8±8.1	85.4±7.9	84.7±8.2	<0.001*
Hip circumference (cm)	95.9±5.4	95.7±5.3	95.9±5.4	<0.001*
Smoking score	2 (0, 3)	2 (0, 4)	2 (0, 3)	<0.001*
Drinking score	2 (0, 2)	2 (0, 2)	2 (0, 2)	0.353
Anterior-posterior diameter (cm)	3 (3.0, 3.1)	3 (3.0, 3.3)	3 (3.0, 3.1)	<0.001*
Diabetes mellitus, *n* (%)	8214 (12.0)	2265 (16.3)	5949 (10.8)	<0.001*
Hypertension, *n* (%)	23014 (33.5)	5474 (39.5)	17540 (32.0)	<0.001*
Metabolic syndrome, *n* (%)	6865 (10.0)	1611 (11.6)	5254 (9.6)	<0.001*
Systolic blood pressure (mmHg)	122.2±15.3	124.4±16.5	121.6±14.9	<0.001*
Diastolic blood pressure (mmHg)	77.6±10.1	78.2±10.3	77.5±10.1	<0.001*
Direct bilirubin (μmol l^{-1})	4.3 (3.4, 5.6)	4.3 (3.3, 5.5)	4.4 (3.4, 5.6)	<0.001*
Total bilirubin (μmol l^{-1})	14.3 (11.3, 18.3)	14.3 (11.3, 18.2)	14.3 (11.2, 18.3)	<0.001*
AST (IU l^{-1})	25 (21, 31)	25 (21, 31)	25 (21, 31)	0.53
ALT (IU l^{-1})	28 (20, 41)	27 (20, 40)	28 (20, 41)	<0.001*
AST/ALT	0.9 (0.7, 1.1)	0.9 (0.7, 1.2)	0.7 (0.9, 1.1)	<0.001*
GGT (IU l^{-1})	27 (18, 46)	28 (19, 47)	27 (18, 46)	<0.001*
α-HBDH (IU l^{-1})	140.3±27.2	141.0±27.6	140.1±27.0	<0.001*
Lactate dehydrogenase (IU l^{-1})	180.4±34.1	181.2±34.5	180.2±34.0	<0.001*
Albumin (g l^{-1})	47.9±2.7	47.4±2.7	48.0±2.7	<0.001*
Globulin (g l^{-1})	27.7±3.7	27.9±3.7	27.7±3.7	<0.001*
Serum total protein (g l^{-1})	75.6±4.2	75.3±4.1	75.7±4.2	<0.001*
A/G	1.7 (1.6, 1.9)	1.6 (1.7, 1.9)	1.7 (1.6, 1.9)	<0.001*
Cholesterol (mg dl^{-1})	4.9±0.9	4.9±0.9	5.0±0.9	<0.001*
Triglycerides (mg dl^{-1})	1.5 (1.1, 2.2)	1.5 (1.1, 2.2)	1.5 (1.1, 2.1)	<0.001*
HDL cholesterol (mg dl^{-1})	1.4±0.4	1.4±0.4	1.3±0.3	<0.001*
LDL cholesterol (mg dl^{-1})	2.8±0.7	2.8±0.7	2.8±0.7	<0.001*
Fasting glucose (mg dl^{-1})	5.4±1.2	5.6±1.3	5.4±1.2	<0.001*
Creatinine (mg dl^{-1})	83.3±12.6	83.2±13.1	83.3±12.5	0.426
Creatine kinase (IU l^{-1})	107 (84, 139)	106 (83, 139)	107 (84, 139)	<0.001*
Urea (mmol l^{-1})	5.2±1.3	5.2±1.3	5.1±1.2	<0.001*
Cystatin c (mg l^{-1})	0.9±0.1	0.9±0.1	0.9±0.1	<0.001*
Alkaline phosphatase (IU l^{-1})	78.1±19.6	78.8±20	78.0±19.5	<0.001*
Uric acid (umol l^{-1})	390.9±77.9	385.9±77.2	392.2±78.0	<0.001*

Data are number, percentage, or mean±s.d. Smoking score, drinking score, anterior-posterior diameter, serum bilirubin, ASL, ALT, GGT, A/G, triglyceride and creatine kinase are expressed as median and interquartile range, due to skewed distribution. Selected characteristics of all participants at baseline were compared using the Chi-square test for categorical variables and Student's *t*-test for continuous variables. *$P<0.001$. GTP: gamma-glutamyl transpeptidase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDLC: low-density lipoprotein-cholesterol; HDLC: high-density lipoprotein-cholesterol; α-HBDH: α-hydroxybutyrate dehydrogenase; s.d.: standard deviation