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**ORIGINAL ARTICLE**

Prostate Disease

# Redundant prepuce increases the odds of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

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**Some published evidence has revealed that the dendritic cells can interact with pathogens that exist in the inner foreskin. This information provides a new vision that pathogens could play a role through the redundant prepuce; numerous studies have failed to find pathogens in prostates of patients who had chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). However, no studies have reported an association between foreskin length and CP/CPPS. Hence, we conducted a retrospective case-control study of clinical data from 322 CP/CPPS patients (case group) and 341 nonCP/CPPS patients (control group). Demographic characteristics, lifestyle factors, and foreskin lengths were collected and analyzed. Multivariate logistic regression was adopted to calculate the odds of foreskin length for CP/CPPS. According to the multivariate logistic regression results, when the foreskin length covered up more than half of the glans penis, the odds for CP/CPPS were higher with an increased foreskin (odds ratio (OR): 1.66, 95% confidence interval (CI): 1.04–2.66). In comparison, when the glans penis was completely covered by the foreskin, the OR value increased to 1.86 (95% CI, 1.2–2.88). The study results showed an association between foreskin length and the odds of CP/CPPS. When the foreskin length covered up more than half of the glans penis, there were greater odds for CP/CPPS. This possible mechanism might result from interaction between pathogens and DCs in the inner foreskin, consequently activating T-cells to mediate allergic inflammation in the prostate and producing the autoimmunizations causing CP/CPPS.**

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**Keywords:** case control study; chronic pelvic pain syndrome; chronic prostatitis, prepuce

## INTRODUCTION

Type III (chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)) is the most common type of CP. It mainly manifests as a long-term repeated pelvic pain or discomfort which lasts for more than 3 months; it may be accompanied by varying degrees of urinary symptoms and sexual dysfunction. This condition exerts serious consequences on a patient quality-of-life. However, CP/CPPS pathogenesis is still unclear and its etiology is complicated.[1,2] A combination of pathogen infections and immune abnormalities reportedly involved in this process.[3] Some nonbacterial pathogens have been reported to associate with nonbacterial CP, mainly manifested as chronic inflammations.[4,5]

The antigen-presenting function of dendritic cells (DCs) in the inner foreskin has been considered as the prominent disease mechanism, as it can change the inner foreskin cytokine secretions and increase HIV susceptibility.[6] Results from a large multicenter clinical trial in Africa indicated that circumcision could lower the probability of human immunodeficiency virus (HIV) infection by 60%.[7] Circumcision also was reported to lower human papillomavirus (HPV)[8,9] and herpes simplex virus 2 (HSV-2) infection rates.[10] These clinical study rates showed that pathogens may play a role in CP/CPPS. If DCs located in the inner foreskin can present the antigens of foreign pathogens, the redundant foreskin may be a pathogenic pathway to cause CP/CPPS. However, previous study results alone are not sufficient enough to support this view. In order to affirm this hypothesis, we performed a retrospective case-control study to identify associations between foreskin length and the odds of CP/CPPS among the Chinese population.

## MATERIALS AND METHODS

### *Study population*

Data were retrospectively collected and analyzed from 322 patients with CP/CPPS hospitalized at the Outpatient Department of Urology, Shanghai First People's Hospital between April 2012 and June 2013. There were 341 age-matching (1:1) non-CP/CPPS subjects enrolled into the control group. The diagnostic criteria of CP/CPPS were based on the United States (US) National Institutes of Health (NIH) criteria[11] including NIH CP Symptom Index (NIH-CPSI), expressed prostatic secretions (EPS), and preprostatic/postprostatic massage urine.[12]

### *Selection criteria for cases and controls*

Patients with confirmed CP/CPPS as well as symptoms of discomfort in the pelvic and perineal zones lasting for at least 3 months were enrolled into the case group. Other inclusion criteria included negative EPS bacterial culture, pre-/post-prostatic massage urine, and presence of EPS leukocytosis. In order to increase NIH-CPSI accuracy in evaluating CP-CPPS, the study excluded patients with a history of prostate cancer, inguinal hernia, urethritis, benign prostatic hyperplasia, and circumcision.

In the control group, selected patients arrived for the physical examination at the outpatient department. Patients with long-term

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pelvic and perineal symptoms, abnormal EPS results, and pre- and post-prostatic massage urine, and circumcisions were excluded.

Before commencing this study, approval from the Ethics Review Committee of Shanghai First Peopleai Hospital was granted. Written informed consent was then obtained from all patients.

***Data collection***

Examiners who had received uniform training individually communicated with the volunteers and cases. The following study participant lifestyle factors and demographic characteristics were collected: condom use, frequency of sexual activity, number of previous sexual partners, age of first sexual intercourse, and history of sexually transmitted infections (STIs).

***Measurement of foreskin length***

Before the CP/CPPS diagnosis, the foreskin length of enrolled patients was measured according to the following described manner. Subjects lay supinely in an inspection room (constant temperature: 25°C); the penis was lifted up at a 90° angle with the body. The foreskin spontaneously covered the glans penis, and the ratio of the distance from the distal foreskin to coronal sulcus and the distance from the coronal sulcus to the urethral orifice were both measured under the flaccid penis and without external force to retract or stretch the foreskin. As per coverage degrees of the glans penis, foreskin length was classified into four levels: level I – complete glans penis exposure, with foreskin not exceeding the coronal sulcus; level II – majority glans penis exposure, with foreskin within the middle point between the glans penis and coronal sulcus; level III – minority exposure of glans penis, with the foreskin exceeding the middle point between the glans penis and coronal sulcus; and level IV – complete coverage of the glans penis by the foreskin (**Figure 1**).

***Statistical analysis***

Statistical analysis was performed using SPSS software (IBM SPSS version 19.0, SPSS lnc., Chicago, IL, USA). The following data were analyzed using univariate logistic regression analysis: body mass index (BMI); marital status (single, married, or divorced); educational level (high school and below, college, or postgraduate and above); annual income (US$ 0–8000, US$ 8000–16 000, US$ 16 000–32 000, or US$ >32 000); smoking habit (0, 1–5 years, 6–10 years, or >10 years); alcohol consumption (0–5 years, 6–10 years, or >10 years); age of first sexual intercourse (none, 15–20 years old, 21–25 years old, or >25 years old); number of previous sexual partners (none, 1, 2–5, or >5); history of STIs; condom use (never, sometimes, most of the time, or every time); frequency of sexual intercourse (almost never; 1–3 times per week, or >3 times per week). The odds ratio (OR) and 95% confidence interval (CI) were calculated by univariate logistic regression analysis. Multivariate logistic regression analysis was adopted for relationships between different foreskin length classification and CP/CPPS, considering clinically-related possibilities and previous univariate analyses of age, marital status, income, STIs, and sexual intercourse frequency as adjustment variables.

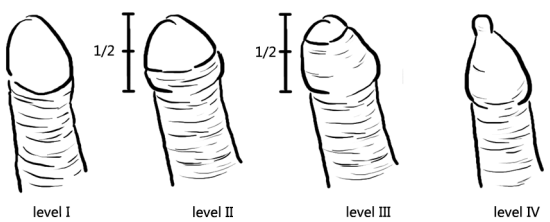


**Figure 1:** Classification of foreskin length. Level I: the glans penis is completely exposed, with the foreskin not exceeding the coronal sulcus; level II: majority of the glans penis is exposed, with the foreskin within the middle point between the glans penis and coronal sulcus; level III: minority of the glans penis is exposed, with the foreskin exceeding the middle point between the glans penis and coronal sulcus; level IV: the glans penis is completely covered up by the foreskin.

## RESULTS

Demographic characteristics and lifestyle factors are shown in **Tables 1** and **2**. As compared with the control group, the odds of CP/CPPS was about 50% higher for those who almost never had sexual activity than patients with regular sexual activity (OR = 1.5; 95% CI, 1.03–2.05). Note BMI, marital status, annual income, history of smoking and alcohol consumption, age of first sexual intercourse, number of previous sexual partners, condom use, and STIs showed no differences between the case and control groups.

**Table 3** demonstrates the results of multivariate logistic regression analyses. The odds of CP/CPPS increased along with the foreskin length. In classification 1, the odds of CP/CPPS was about 57% higher for those with foreskin length exceeding the coronal sulcus (level II and III) than patients with foreskin length within the coronal sulcus (level I) (95% CI, 1.02–2.4); in comparison, the odds of CP/CPPS for those with glans penises completely covered by the foreskins (level IV) increased about 86% (95% CI, 1.2–2.88). In classification 2, the difference in the odds of CP/CPPS between level I and II patients was not significant (95% CI, 0.87–2.42). The odds of CP/CPPS in level

**Table 1: Demographic and baseline characteristics**

| *Demographic characteristics* | *Control group (N=341), n (%)* | *Case group (N=322), n (%)* | *OR (95% CI)* |
|---|---|---|---|
| Age (year) | | | |
| 16–25 | 67 (19.6) | 58 (18.0) | 1.0 |
| 26–35 | 130 (38.1) | 125 (38.8) | 1.1 (0.72–1.71) |
| 36–45 | 103 (30.2) | 100 (31.1) | 1.1 (0.72–1.75) |
| 46–55 | 41 (12.0) | 39 (12.1) | 1.1 (0.63–1.93) |
| BMI | | | |
| <20 | 44 (12.9) | 30 (9.3) | 1.0 |
| 20–25 | 216 (63.3) | 209 (64.9) | 1.4 (0.86–2.34) |
| 26–30 | 79 (23.2) | 77 (23.9) | 1.4 (0.82–2.50) |
| >30 | 2 (0.6) | 6 (1.9) | 4.4 (0.83–23.29) |
| Marital status | | | |
| Unmarried | 102 (29.9) | 96 (29.8) | 1.0 |
| Married | 231 (67.7) | 224 (69.6) | 1.0 (0.74–1.44) |
| Divorced | 8 (2.3) | 2 (0.6) | 0.3 (0.06–1.28) |
| Education level | | | |
| High school and below | 214 (62.8) | 198 (61.5) | 1.0 |
| College | 120 (35.2) | 118 (36.6) | 1.1 (0.77–1.46) |
| Postgraduate and above | 7 (2.1) | 6 (1.9) | 0.9 (0.31–2.80) |
| Annual income, US$ | | | |
| <8000 | 65 (19.1) | 58 (18) | 1.0 |
| 8000–16 000 | 141 (41.3) | 124 (38.5) | 1.0 (0.64–1.51) |
| 16 000–32 000 | 111 (32.6) | 120 (37.3) | 1.2 (0.78–1.88) |
| >32 000 | 24 (7.0) | 20 (6.2) | 0.9 (0.47–1.86) |

BMI: body mass index; OR: odds ratio; CI: confidence interval

III patients was about 66% higher than that seen in the level I patients (95% CI, 1.04–2.66), and the odds in level IV patients was about 86% higher than that seen in the level I patients (95% CI, 1.2–2.88).

**Table 2: Lifestyle factors in men with CP/CPPS and controls**

| *Lifestyle factors* | *Control group (N=341), n (%)* | *Case group (N=322), n (%)* | *OR (95% CI)* |
|---|---|---|---|
| Cigarette smoking (year) | | | |
| <5 | 30 (8.8) | 22 (6.8) | 1.0 |
| 5–10 | 49 (14.4) | 46 (14.3) | 1.3 (0.65–2.53) |
| >10 | 70 (20.5) | 74 (23.0) | 1.4 (0.76–2.73) |
| Never | 192 (56.3) | 180 (55.9) | 1.3 (0.71–2.30) |
| Alcohol drinking (year) | | | |
| <5 | 303 (88.9) | 284 (88.2) | 1.0 |
| 5–10 | 19 (5.6) | 12 (3.7) | 0.7 (0.32–1.41) |
| >10 | 19 (5.6) | 26 (8.1) | 1.5 (0.79–2.70) |
| Age of first sexual intercourse | | | |
| 15–20 | 90 (26.4) | 96 (29.8) | 1.0 |
| 21–25 | 196 (57.5) | 160 (49.7) | 0.8 (0.54–1.09) |
| >25 | 32 (9.4) | 40 (12.4) | 1.2 (0.68–2.02) |
| Never | 23 (6.7) | 26 (8.1) | 1.1 (0.56–1.99) |
| Number of sex partners | | | |
| 1 | 186 (54.5) | 167 (51.9) | 1.0 |
| 2–5 | 112 (32.8) | 105 (32.6) | 1.0 (0.74–1.47) |
| >5 | 20 (5.9) | 24 (7.5) | 1.3 (0.71–2.51) |
| None | 23 (6.7) | 26 (8.1) | 1.3 (0.69–2.29) |
| Sexually transmitted diseases | | | |
| No | 301 (88.3) | 288 (89.4) | 1.0 |
| Yes | 40 (11.7) | 34 (10.6) | 0.9 (0.55–1.44) |
| Condom use | | | |
| Never | 72 (21.1) | 70 (21.7) | 1.0 |
| Sometimes | 86 (25.2) | 82 (25.5) | 1.0 (0.63–1.53) |
| Most of the time | 91 (26.7) | 82 (25.5) | 0.9 (0.59–1.45) |
| Every time | 92 (27.0) | 88 (27.3) | 1.0 (0.63–1.53) |
| Frequency of sexual intercourse (times per week) | | | |
| 1–3 | 218 (63.9) | 188 (58.4) | 1.0 |
| >3 | 37 (10.9) | 26 (8.1) | 0.8 (0.48–1.40) |
| <1 | 86 (25.2) | 108 (33.5) | 1.5 (1.03–2.05) |

OR: odds ratio; CI: confidence interval; CP: chronic prostatitis; CPPS: chronic pelvic pain syndrome

**Table 3: OR for CP/CPPS with respect to foreskin length**

| *Classification of foreskin length* | *Control group n (%)* | *Case group n (%)* | *OR (95% CI)* |
|---|---|---|---|
| Classification 1 | | | |
| Level I[a] | 78 (22.9) | 48 (14.9) | 1.0 (Reference) |
| Level II+level III | 146 (58.8) | 140 (43.5) | 1.57 (1.02–2.4) |
| Level IV | 117 (34.3) | 134 (41.6) | 1.86 (1.2–2.88) |
| Classification 2 | | | |
| Level I | 78 (22.9) | 48 (14.9) | 1.0 (reference) |
| Level II | 62 (18.2) | 56 (17.4) | 1.45 (0.87–2.42) |
| Level III | 84 (24.6) | 84 (26.1) | 1.66 (1.04–2.66) |
| Level IV | 117 (34.3) | 134 (41.6) | 1.86 (1.2–2.88) |

[a]Level I: the glans penis is completely exposed, with the foreskin not exceeding the coronal sulcus; Level II: majority of the glans penis is exposed, with the foreskin within the middle point between the glans penis and coronal sulcus; Level III: minority of the glans penis is exposed, with the foreskin exceeding the middle point between the glans penis and coronal sulcus; Level IV: the glans penis is completely covered up by the foreskin; OR: odds ratio; CI: confidence interval; CP: chronic prostatitis; CPPS: chronic pelvic pain syndrome

## DISCUSSION

This study results showed that a redundant prepuce may impact the incidence of CP/CPPS. The odds of CP/CPPS were higher for patients with longer foreskin.

In the past decade, many hypotheses have been proposed in relation to the etiology of CP/CPPS, including neurologically-rooted increases in pain sensitivity, autoimmunity, persistent inflammation, and psychological stress. In our findings, the relationship between foreskin length and CP/CPPS showed some interesting results. It appears there is no interaction between the foreskin and prostate because of their different anatomic locations. One theory for disease development reflects developmental or genetic risk of CP/CPPS; hence, more studies should be performed to research the genetic relevance between foreskin and the prostate.

The redundant prepuce made the glans penis more sensitive, which may contribute to the pain score of the NIH-CPSI. When the foreskin length reached level IV, the turbulent flow of urine will increase the pressure of lower urinary tract, causing the onset of voiding problems associated with the NIH-CPSI. In summary, men with a redundant prepuce could be more symptomatic.

We proposed a new theory explaining cellular and molecular relationship mechanisms between foreskin length and CP/CPPS. Specifically, we believe the interaction between pathogens and DCs in the inner foreskin activated the T-cells to mediate allergic inflammation in the prostate and produce the autoimmunizations causing CP/CPPS occurrence.

Ever since the discovery that circumcision could reduce 60% of HIV infection risk,[6] other studies showed that circumcision could reduce HPV,[8,9] HSV-2,[10] and some anaerobe bacterial infections.[13] Even though, the etiology of these pathogen infections is still under investigation, growing evidence has supported the involvement of DCs in the inner foreskin that presented pathogen antigens to T cells[7,14-16] but not the previously thought retrograde movement of the pathogens into the urethra.

Numerous studies have failed to find any specific link between infection and CP/CPPS. However, our findings may be able to provide a new bridge between infection and CP/CPPS, specifically through the foreskin.

In CP/CPPS, the bacterial culture of EPS and both pre- and post-prostatic massage urine is negative. In addition, the definitive association between isolation of an infective agent and its prostatic origin is limited by various factors.[4] This association may indicate that CP/CPPS incidence does not result from retrograde movement of the pathogens into the prostate through the urethra. The study results (**Table 3**) showed that the higher odds of CP/CPPS was observed when foreskin length exceeded level II (level III: OR 1.66, 95% CI 1.04–2.66; level IV: OR 1.86, 95% CI 1.20–2.88). At level III, the glans penis was partially covered up by the foreskin: there was some distance from the foreskin to urethral orifice. Although the chance was not great for pathogens bred inside the foreskin to retrograde travel into the urethra, it still increased the odds of CP/CPSS incidence by 66%. This indicates that the antigen-presenting pathogen by abundant DCs residing in the foreskin may be the most probable reason to cause CP/CPPS. Thus, the longer the foreskin, the more likely antigens presented to the T-cells cause CP/CPPS. Meanwhile, the level II foreskin length might not increase the odds of CP/CPPS (95% CI, 0.87–2.42), which indicated that pathogen content in the foreskin was one of the factors in CP/CPPS. Hence, insufficient pathogen levels might not cause CP/CPPS.

CP/CPPS has also been reported to be an autoimmune disease.[17,18] Published evidence has shown that CD4 + T-cells are more active in immunoreaction with self-produced proteins such as prostatic acid phosphatase (PAP) and prostatic specific acid phosphatase from prostate.[19]

Meanwhile, some cytokines such as interleukin (IL)-2,[20] IL-6,[21] IL-8,[22] IL-10,[20] transforming growth factor alpha,[23] and monocyte chemotactic protein-1[24] also have changed in the presence of CP/CPPS. Speculation for this outcome may result from antigen-presenting pathogens to CD4 + T-cells by DCs that resided in foreskin,[25] which then circulated through the blood, and activated T-cells. This generated immunoreactions with prostate-producing proteins to cause inflammatory responses in CP/CPPS. However, these specific mechanisms require further research.

In the current study, CP/CPPS patients did not report higher STI rates as compared to patients without CP/CPPS. Recently, many studies have demonstrated the relationship between STIs and prostate cancer.[26] Theories from those studies argued that the STIs occurred due to prostatitis.[27,28] However, some studies have provided contradictory results, concluding that circumcision before first sexual intercourse could lower the prostate cancer incidence by 15%.[29] The same study also reported an association of prostatitis with prostate cancer. Therefore, some nonspecific pathogens might also play more important roles in CP/CPPS.

Some limitations exist in this study. First, STI data were acquired through self-reporting rather than laboratory tests. Some patients might not know that they were infected; otherwise, they may have considered themselves infected without seeing a doctor. Second, some researchers might question the foreskin length classification used in this study. The classification of foreskin length by proportion, but not actual length, may exclude the individual differences in body size. Reasons for setting the boundary line at half the distance from coronal sulcus to urethral orifice are to employ a method that can observe the impact of foreskin length on CP/CPPS. Classification of more levels may have created greater measurement bias because of the certain ductility of foreskin. Third, our results could not explain how the CP/CPPS occurs in circumcised men. On the other hand, no single attempt has shown efficiency for the cure of CP/CPPS,[30] showing there may be multiple disease pathogeneses. Finally, no evidence has indicated the removal of excess foreskin will affect CP/CPPS; further research is recommended to identify this relationship.

## CONCLUSIONS

The results of this study revealed that a redundant prepuce can increase the odds of CP/CPPS. When the foreskin covered up more than half of the glans penis, the incident rate of CP/CPPS increased along with the increase in foreskin length. The possible mechanism for this might be the interaction between pathogens and DCs in the inner foreskin. This interaction activated the T-cells to mediate allergic inflammation in the prostate and consequently produce autoimmunizations to cause the CP/CPPS occurrence.

## AUTHOR CONTRIBUTIONS

YYZ analyzed and interpreted the clinical data, and also wrote the manuscript. DLX interpreted the clinical data and revised the manuscript. WZ designed the study and supervised the project. FJZ, BMH, and YS collected the data; SJX revised the manuscript and supervised the project. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing interests.

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