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慢性前列腺炎/慢性盆腔疼痛综合征诊疗指南

中华医学会男科学分会
慢性前列腺炎/慢性盆腔疼痛综合征诊疗指南编写组

【关键词】慢性前列腺炎/慢性盆腔疼痛综合征; 诊疗; 指南
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慢性前列腺炎/慢性盆腔疼痛综合征(chronic prostatitis/chronic pelvic pain syndrome, CP/CPPS)是泌尿男科常见疾病,对患者身心健康造成不良影响,并严重影响其生活质量。CP/CPPS 发病机制复杂多样,治疗方案繁杂,且疗效不确定,给临床工作带来极大困扰。近年来该领域进展很快,为了规范诊疗方案,更好地指导临床实践,在查阅了最新研究成果,并参考了国内外相关指南和专家共识的基础上,中华医学会男科学分会组织专家进行了广泛的讨论,就 CP/CPPS 相关问题,特别是临床诊治中的原则问题形成共识,编写了 CP/CPSS 诊疗指南,希望能为临床工作者诊治 CP/CPSS 提供有益的指导与帮助。

1 CP/CPPS 定义、分类、流行病学及病因与发病机制

1.1 CP/CPPS 定义与分类 1995 年美国国立卫生研究院(National Institutes of Health, NIH)根据当时对前列腺炎的研究进展将其分为 4 型,CP/CPPS 属于该分型中的Ⅲ型,是指由多种因素引起的,以盆腔区域疼痛或不适、下尿路症状(lower urinary tract symptoms, LUTS)为主的一组症候群。其中根据前列腺按摩液(EPS)、精液或前列腺按摩后尿液(VB3)中白细胞水平是否升高,又将其分为炎症性(ⅢA 型)和非炎症性(ⅢB 型)[1]。但越来越多的研究表明,EPS、精液和 VB3 中白细胞的水平并不能成为 CP/CPPS 的诊断标准和严重程度的判断[2-4]。

由于 NIH 分类系统过于笼统,并不能充分反映 CP/CPPS 的不同病因和临床表现的异质性。Shoskes 等[5]在 2009 年提出了 UPOINT 分类系统,该系统有别于 NIH 分类系统,它能够较为全面地体现 CP/CPPS 的临床表现,从而更准确地指导临床医师对不同患者进行针对性的综合治疗。UPOINT 分类系统包括 6 个独立因素,即排尿症状(urinary)、社会心理症状(psychosocial)、器官特异症状(organ-specific)、感染症状(infection)、神经/全身症状(neurogenic/systemic)、肌痛症状(tenderness of muscles)。既往也有研究将性功能障碍(sexual dysfunction)纳入 UPOINT,即 UPOINT(S),但目前尚有争议[6-7](表 1)。近年来,国内学者探索了慢性盆腔疼痛的机制并取得了积极的成果,建议将 CP/CPPS 更名为前列腺盆腔综合征,有利于对该疾病的认识和诊疗,但仍需要更多的临床应用与验证[8]。

1.2 CP/CPPS 流行病学 前列腺炎是成年男性的常见疾病,前列腺炎患者占泌尿外科门诊患者的 8% ~ 25%[9-10]。国外报告的前列腺炎患病率为 2.0% ~ 16.0%[9,11],国内报告 6.0% ~ 32.9%[10,12-13]。CP/CPPS 是前列腺炎中最常见、最难治疗的类型,占所有前列腺炎的 90% 以上,且 CP/CPPS 发病趋于年轻化[12-13]。

研究表明:职业、环境、辛辣食物、饮酒、久坐、憋尿、性生活习惯及精神因素为 CP/CPPS 发病的主要危险因素。某些特殊职业如司机 CP/CPPS 患病率较其他职业明显增高[14];冬季、气候寒冷、日照时间较短,出现 CP/CPPS 症状可能性较高[15];辛辣食物及饮酒能诱导炎症因子释放,引起前列腺充血,诱发或加重 CP/CPPS 症状[16-18];久坐可引起盆腔静脉充血,加重 CP/CPPS 症状;憋尿与 CP/CPPS 发生明显

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相关,可能与后尿道压力升高,引起尿液反流入前列腺腺管,导致前列腺化学性炎症有关[19];长期禁欲、过度自慰、控制射精、性交中断等不良性生活习惯,亦会造成前列腺充血,诱发无菌性炎症,加重CP/CPPS症状[17-18, 20]。精神过度紧张、心理负担过重及熬夜,常诱发交感神经兴奋;焦虑、抑郁亦可导致自主神经功能紊乱,出现盆底肌痉挛,排尿功能失调及盆底区域疼痛等CP/CPPS症状。

表1　UPOINT(S)分类系统

症状	主要表现
排尿症状	尿频、尿急或夜尿;残余尿>100 ml;慢性前列腺炎症状指数中尿路症状评分>4分。
社会心理症状	临床抑郁症;“灾难化”证据(无助、无望)。
器官特异症状	特异性前列腺痛;EPS中白细胞增加,血精,前列腺内广泛钙化。
感染症状	排除Ⅰ型和Ⅱ型前列腺炎;EPS中有革兰阴性杆菌或肠球菌。
神经/全身症状	腹部和盆腔外疼痛;肠易激综合征;纤维肌痛症;慢性疲劳综合征。
肌痛症状	盆底和腹部肌肉的痉挛和“扳机点”痛。
性功能障碍	勃起功能障碍(ED)、早泄、性高潮障碍等。

1.3　CP/CPPS病因与发病机制　CP/CPPS病因复杂,发病机制尚未完全阐明,存在广泛争议:可能由一种始动因素引起,也可能由多种因素引发,其中一种或几种因素起关键作用并可能交互影响[21];亦有可能是许多难以鉴别的不同疾病,但具有相同或相似的临床表现[22]。目前认为CP/CPPS的主要病因与发病机制包括以下几个方面。

1.3.1　*病原体感染*　虽然CP/CPPS患者行常规细菌培养通常不能分离出病原体,但其仍可能与一些特殊病原体感染有关[23]。此外,泌尿生殖道微生态平衡破坏亦可导致CP/CPPS发生[24]。

1.3.2　*尿液反流*　膀胱出口功能障碍、膀胱颈结构异常或尿道内外括约肌及盆底肌肉痉挛引起的排尿时前列腺尿道压升高,易导致前列腺内尿液反流[25]。尿酸等代谢产物随尿液反流入前列腺,将加重CP/CPPS症状[26]。

1.3.3　*下尿路上皮功能障碍*　下尿路上皮潜在的保护因素和损害因素之间平衡被打破所致的功能障碍可能引起CP/CPPS的发生[27]。CP/CPPS患者前列腺上皮钾离子通道表达异常,钾离子通过上皮间隙渗入基质后可刺激神经纤维并引起疼痛等临床症状[28]。

1.3.4　*神经内分泌因素*　CP/CPPS患者易发生心率和血压波动,表明其自主神经敏感性增高[29]。CP/CPPS患者盆底肌肉功能改变与大脑运动皮层及后岛叶异常兴奋有关[30]。交感神经末梢释放的去甲肾上腺素、前列腺素等物质,亦可导致盆底肌肉功能紊乱,引发疼痛症状[31]。

1.3.5　*精神心理因素*　抑郁和焦虑的男性往往前列腺炎症状评分较高[32],而经久不愈的CP/CPPS患者通常存在明显的精神心理和人格特征改变[33]。使用抗抑郁及抗焦虑药物可改善CP/CPPS症状[34]。

1.3.6　*盆腔相关疾病因素*　研究显示CP/CPPS患者合并精索静脉曲张、痔的比例更高[35],提示盆腔静脉性疾病可能是CP/CPPS的病因之一。

1.3.7　*炎症与免疫反应*　CP/CPPS可能是一种以细胞因子为中介产生的炎症反应性或/和自身免疫性疾病[36-37]。CP/CPPS患者外周血Th1、Th17细胞比例较健康人群显著升高[36],使得机体分泌更多的促炎性细胞因子,通过上调趋化因子等表达,进而诱发前列腺局部免疫反应,造成不利影响[37]。

1.3.8　*氧化应激*　CP/CPPS患者活性氧(reactive oxygen species, ROS)产生过多或/和清除能力相对不足,会导致氧化应激产物或/和副产物增加,从而引起症状加重[38]。

1.3.9　*遗传易感性*　有学者发现位于Xq11-13磷酸甘油酸激酶基因附近的一个短串联重复(short tandem repeat, STR)序列多态性与CP/CPPS有关[39],但遗传易感性是否为CP/CPPS的潜在致病因素尚待进一步研究。

2　CP/CPPS的诊断与鉴别诊断

2.1　*病史*　全面、详细地询问CP/CPPS患者的病史,不仅有助于明确诊断,还能协助评估病情,进一步分析病因、针对性的治疗以及了解预后。病史的采集主要包括主诉、现病史、既往史、个人史4个主要方面。

2.1.1　*主诉*　包括疼痛或不适症状、LUTS以及性功能障碍症状等,部分患者可伴有精神心理症状,应同时询问以上症状持续的时间[40-43]。

2.1.2　*现病史*　应重点询问病程的长短,起病的原

因,疼痛的性质、部位、程度等。应详细询问 LUTS、性功能障碍症状、精神心理症状及相关伴随症状[40-43]。需询问不同症状出现的次序(原发与继发),例如抑郁、焦虑情绪与 CP/CPPS 症状出现先后,可用于鉴别是心理问题继发躯体不适,还是 CP/CPPS 导致的情绪异常。

2.1.3 既往史 应重点询问患者是否存在高血压、糖尿病、甲状腺疾病及泌尿生殖道手术等病史[41-42]。

2.1.4 个人史 应询问患者吸烟、饮酒、熬夜、久坐、疲劳、嗜辛辣食品、憋尿、性交频繁、延迟射精等情况。对患者生活质量、性生活情况和精神心理健康情况的评价也同样重要,因其可影响治疗的选择[40, 43]。

2.2 体格检查 CP/CPPS 患者在全身体格检查基础上重点关注以下内容:下腹部、腰骶部、会阴部、尿道口、阴茎、睾丸、附睾、精索等泌尿生殖系统的检查,注意有无压痛和异常包块,有助于进行诊断和鉴别诊断。注意附睾炎、附睾结节、精索静脉曲张、精索炎、睾丸肿瘤等疾病引起类似的会阴部胀痛等,需要与前列腺炎进行鉴别。

直肠指检对前列腺炎有一定价值,且有助于鉴别前列腺其他疾病及会阴、直肠、神经病变,同时通过前列腺按摩获得 EPS。直肠指检可了解前列腺大小、质地、有无结节、有无压痛及其范围与程度。CP/CPPS 患者直肠指检前列腺饱满、质软,可能有轻度压痛或增大;病程长者,前列腺缩小、变硬、不均匀,有小硬结。检查盆底肌肉的紧张度、盆壁有无压痛,尤其是肌筋膜疼痛的触发点及可能出现的肌肉牵涉痛。

2.3 CP/CPPS 临床症状及相关评估工具

2.3.1 临床症状 大多数 CP/CPPS 患者病情迁延反复,病程常常 3 ~ 6 个月以上,症状个体化差异较大。多数患者存在疼痛症状、LUTS、精神心理症状、性功能障碍等症状中的一种或多种症状。

2.3.1.1 疼痛或不适症状 主要位于会阴部、睾丸、耻骨区、阴茎及下腹部,其次为尿道、肛周、腰骶部、背部的疼痛不适,还可能出现射精痛、阴茎勃起后疼痛不适。

2.3.1.2 LUTS 尿频、尿急、尿痛、尿不尽、排尿不畅、尿灼热感等。

2.3.1.3 精神心理症状 如焦虑、抑郁、睡眠障碍、记忆力下降等症状。

2.3.1.4 性功能障碍 如 ED、早泄、射精无力或困难、性欲低下等症状[20, 40, 44]。

2.3.2 相关评估工具 CP/CPPS 临床症状表现复杂多变,在实际临床诊疗工作中缺乏客观的诊断评估指标。目前认为 NIH 慢性前列腺炎症状评分表(NIH-CPSI)可以相对客观和全面地对 CP/CPPS 患者进行症状评估[45]。NIH-CPSI 包含 3 个分项,分别是疼痛症状、排尿症状和症状对生活质量的影响评分。NIH-CPSI 可作为 CP/CPPS 症状严重程度的辅助诊断评估工具,也可作为 CP/CPPS 治疗随访中重要的疗效评估工具。

CP/CPPS 伴有性功能障碍患者,可以采用国际勃起功能障碍指数(IIEF-5)评估勃起功能[46],早泄诊断工具(PEDT)评估射精功能[47]。对于主要是尿频、尿急为主的储尿期症状患者,可以优先或联合使用膀胱过度活动症(overactive bladder, OAB)患者自我评价量表(OABSS 评分)进行评估[48-49]。患者如有焦虑和抑郁等精神症状,可采取汉密尔顿焦虑量表(HAMA)、汉密尔顿抑郁量表(HAMD)、焦虑自评量表(SAS)[50]、广泛性焦虑障碍量表(GAD-7)[51]进行评估,也可转诊患者到相关科室评估。

2.4 实验室检查

2.4.1 尿液检测

2.4.1.1 尿常规检查 可以排除尿路感染、血尿等其他疾病。

2.4.1.2 前列腺小体外泄蛋白(prostatic exosomal protein, PSEP)检测 PSEP 由前列腺小体分泌。近年来研究发现,CP/CPPS 患者尿中 PSEP 水平升高[52-53],PSEP 水平与 NIH-CPSI 评分相关,同时还与 EPS 中的白细胞浓度相关[54]。PSEP 作为一种无创性检查项目,还需要临床进行更多的研究来提供循证医学证据。

2.4.2 EPS 检查 以前 EPS 是作为前列腺炎分型与确诊的重要指标,长期以来在临床广泛应用。但越来越多的证据表明, EPS 内白细胞的多少,不能反映 CPPS 的严重程度,也不能代表其转归。

采集 EPS 前,应禁欲 2 ~ 7 d。通常取胸膝卧位进行前列腺按摩,标本及时送检。如需进行微生物检测,应进行无菌操作,按摩前先消毒外阴,并使用无菌容器接取标本后及时送检。如怀疑生殖系统结核、肿瘤或急性感染时,不宜作前列腺按摩。一次检测不宜多次重复按摩前列腺,如按摩后收集不到 EPS 时,可嘱患者留取前列腺按摩后首段尿液进行分析。

健康成年男性 EPS 白细胞 < 10 个/HP,卵磷脂小体均匀分布于整个视野,pH 6.4 ~ 6.7,偶见红细胞和上皮细胞。炎症性 CP/CPPS 患者 EPS 白细胞 > 10 个/HP,非炎症性 CP/CPPS 者则正常。白细胞的多少与 CPPS 症状的严重程度不相关。胞质

内含有吞噬的卵磷脂小体或细胞碎片等成分的巨噬细胞,也是前列腺炎的特有表现。

2.4.3 精液检测 对于获取EPS困难的患者,精液检测可以部分替代EPS检测的临床诊断价值,同时有生育诉求的患者还可以了解精液质量。

2.4.3.1 前列腺分泌功能检测 前列腺分泌液中含有大量的锌、柠檬酸、钙、磷酸盐、脂质、激肽酶、抗氧化酶、多胺和白细胞介素等多种物质。世界卫生组织《人类精液检查与处理实验室手册》(第5版)中指出,精液中锌、柠檬酸或酸性磷酸酶含量是检测前列腺分泌功能的可靠指标,而且这些标志物之间存在很好的相关性[55]。

2.4.3.2 精液白细胞检测 当精液白细胞浓度>1×10^6/ml时,提示可能存在生殖道炎症。

2.4.3.3 氧化与抗氧化检测 包括ROS和抗氧化能力检测。

2.4.4 病原微生物检测

2.4.4.1 细菌学检测 CP/CPPS的诊断推荐Meares-Stamey四杯法或两杯法试验,同时建议使用NIH-CPSI问卷来描述疼痛、排尿症状和生活质量方面的疾病特征[40]。

四杯法对首段尿(VB1)、中段尿(VB2)、EPS、按摩前列腺后尿(VB3)分别进行病原体鉴定和白细胞定量。VB1代表尿道,VB2代表膀胱,EPS和VB3代表前列腺。四杯法是CP/CPPS诊断、分型的依据[56]。炎症性CP/CPPS患者EPS和VB3白细胞均升高,非炎症性CP/CPPS者则正常,两者细菌学检测均阴性。

两杯法是一个简化方法,包括VB2和VB3的检测。对于新诊断的患者,两杯法与四杯法具有相似的诊断敏感性[57]。炎症性CP/CPPS患者VB3白细胞升高,非炎症性CP/CPPS者则正常,两者细菌学检测均阴性。

有学者认为,精液分析可以提供生殖道感染的额外信息,这些信息可能在四杯法标本或尿道拭子中无法检测到。研究表明,在分析前列腺感染时,精液比EPS具有更高的敏感性[58]。因此,精液可作为诊断前列腺感染的选择样本,但精液中检测到的炎症标志物或微生物不一定来自前列腺[58]。

2.4.4.2 其他病原微生物检测 目前临床常见检测有解脲支原体、生殖支原体、人型支原体、沙眼衣原体。其他病原微生物,如寄生虫、真菌、病毒、滴虫等,也有少量检测。

2.5 影像学检查及其他特殊检查 影像学检查主要是用来鉴别CP/CPPS之外其他可能引起盆腔区域疼痛和LUTS的疾病,如泌尿系统感染、结石、梗阻、结核,盆腔脏器肿瘤,以及精囊、射精管和阴囊疾病。常用的影像学检查方法包括超声检查、CT和MRI等,其中以超声检查最为常用,包括经体表超声检查和经直肠超声检查。CP/CPPS患者的影像学检查大多无阳性发现,超声和CT检查有时可能发现前列腺回声或密度不均匀,以及钙化或结石等,但这些影像学表现亦常见于无症状男性,并不能作为确定或排除CP/CPPS诊断的依据[59-61]。

其他特殊检查的主要目的也是为了排查需要与CP/CPPS鉴别的疾病,如膀胱出口梗阻、神经源性膀胱功能障碍、膀胱疼痛综合征、膀胱肿瘤、前列腺癌等。这些检查主要包括尿流动力学检查、尿道膀胱镜检查和前列腺穿刺活检等,可根据临床具体情况有针对性选择[59]。

上述检查中,泌尿系统超声可用于大多数需要与CP/CPPS鉴别的疾病排查,超声残余尿量测定和尿流率测定除具有鉴别诊断价值外,对于CP/CPPS患者下尿路症状、功能及疗效评估均具有一定价值,推荐用于CP/CPPS的诊断。其他影像学及特殊检查为可选择性检查项目[59]。

2.6 鉴别诊断

2.6.1 与疼痛相关疾病的鉴别

2.6.1.1 间质性膀胱炎 间质性膀胱炎主要表现为特征性疼痛和尿频,前者即随膀胱的充盈而出现并加重的疼痛,排尿后疼痛可缓解。膀胱镜检查可发现Hunner溃疡即可确诊。对于有尿频和特征性疼痛的患者,膀胱镜检查出现红斑症阳性也具有诊断意义[62]。

2.6.1.2 腺性膀胱炎 腺性膀胱炎和CP/CPPS的临床症状常常相似。炎症性CP/CPPS患者的EPS可表现为白细胞增多、卵磷脂小体明显减少,而腺性膀胱炎患者EPS是正常的。此外,腺性膀胱炎的患者膀胱镜检查,膀胱内可以发现三角区滤泡等病变,病理活检可以确诊[63]。

2.6.1.3 精囊炎 精囊炎常与CP/CPPS同时发生,且可能出现下腹、会阴疼痛及排尿不适。精囊炎患者可出现血精及射精疼痛等,直肠指检可触及肿大的精囊,可能有压痛及波动感;精液常规检查可见大量红细胞;经直肠精囊超声检查可以协助诊断,精囊造影可明确诊断[64]。

2.6.1.4 附睾炎 慢性附睾炎患者查体可触及附睾肿大硬结,压痛不明显,阴囊超声检查可进一步明确诊断[65]。

2.6.1.5 消化系统疾病 如肠易激综合征,是一种

常见的功能性胃肠道疾病,以腹痛及腹部不适为主要表现,可伴有尿频、尿急等肠外症状。此类消化系统疾病症状多与排便有关[66-67]。

2.6.2 与排尿异常相关疾病的鉴别

2.6.2.1 良性前列腺增生(benign prostatic hyperplasia, BPH) BPH 临床表现以 LUTS 为主,疼痛不是典型症状。通过直肠指检、前列腺超声、尿流率等检查可与 CPPS 进行鉴别[68-69]。

2.6.2.2 OAB OAB 是一种以尿急症状为特征的综合征,常伴有尿频和夜尿症状,可能伴有急迫性尿失禁。通过 EPS 和尿动力学检查可予以鉴别[70]。

2.6.2.3 神经源性膀胱 是一类由于神经系统病变导致膀胱和/或尿道功能障碍,进而产生一系列 LUTS 及并发症的疾病总称。因此,神经源性膀胱的诊断必须有明确的相关神经系统病史。通过病史、神经系统检查和尿动力学检查可与 CP/CPPS 鉴别[71]。

2.6.2.4 生殖道感染 CP/CPPS 好发于中青年男性,而中青年男性又是性活动较为频繁的人群。尿道炎患者除 LUTS 外,还可出现尿道口红肿,尿道口分泌物等,可通过尿道分泌物涂片、细菌培养等与 CPPS 鉴别[72-73]。

2.6.2.5 前列腺癌 血清前列腺特异抗原(PSA)、前列腺超声检查、MRI 可予以鉴别,必要时可行前列腺穿刺活检术[74]。

2.6.2.6 膀胱肿瘤 肌层浸润性膀胱癌和膀胱原位癌常可表现为下腹疼痛和膀胱刺激症状,中年以上、尿常规可见红细胞的患者,应行泌尿系超声检查、CT 及 MRI 予以鉴别,必要时可行膀胱镜检查[75]。

2.6.2.7 前列腺结石 可表现为不同程度的 LUTS。通过直肠指检可扪及前列腺有结石摩擦感,前列腺超声检查及 CT 可明确诊断[76]。

2.6.2.8 输尿管下段结石 部分输尿管下段结石患者临床症状不典型,无肾绞痛等明显症状,而仅表现为尿频尿急等下尿路症候群。行尿常规、泌尿系彩超和 CT 可予以鉴别[77]。

2.6.2.9 后尿道结石 不完全梗阻的后尿道结石多表现为尿频、尿急、尿痛、排尿困难等症状,与慢性前列腺炎类似,行尿常规、泌尿系彩超和 CT 可予以鉴别[78]。

2.6.2.10 盆底肌功能障碍 由于盆底肌肉参与男性排尿和生殖系统活动,因此,盆底肌功能障碍常与包括勃起功能障碍和前列腺炎在内的多种疾病共存,可行前列腺液常规检查予以鉴别[79]。

2.6.3 其他相关疾病的鉴别

2.6.3.1 前列腺、精囊结核 前列腺、精囊结核无明显的临床症状,偶感直肠内和会阴部不适,严重者出现血精、精液量减少、性功能障碍和不育等。直肠指检可扪及前列腺、精囊硬结,多无压痛,常有泌尿系结核或其他部位结核史。患者常有泌尿系结核或其他部位结核史:肺部 CT 可明确有无肺部结核病变,泌尿系 CT 可明确有无泌尿系统结核病变,EPS 抗酸染色可找到抗酸杆菌,结核分枝杆菌培养可确诊。

2.6.3.2 腰骶椎、髋关节及运动医学相关疾病 腰椎间盘突出、腰椎滑脱及腰肌劳损等疾病亦可表现为腰骶部不适,髋关节疾病可能表现为同侧腹股沟疼痛,必要时可行 X 线平片、CT、MRI 等相关检查予以鉴别。

2.6.3.3 精神心理疾病 CP/CPPS 患者常伴发焦虑和抑郁等症状,且具有明显的症状严重相关性;而部分焦虑及心境障碍患者可合并排尿异常症状,目前在鉴别诊断上具有一定困难。必要时可请精神科医生会诊协助诊断,辅以精神科药物治疗。

3 CP/CPPS 治疗

3.1 治疗原则 ①积极寻找病因,争取针对病因进行治疗,同时采取对症治疗方案。②对于多数无明确病因且症状显著者,则以对症治疗控制症状,改善患者的生活质量。③多种诊疗方案联合应用,必要时可采用多学科诊疗模式(multiple disciplinary treatment, MDT)[80-81]。

3.2 CP/CPPS 一般治疗

3.2.1 改善生活方式 良好的生活方式对于 CP/CPPS患者的治疗能够起到积极作用[82]。长期憋尿、熬夜或夜间工作、吸烟、饮酒、饮食偏好以及性生活过频等均是诱发 CP/CPPS 的潜在危险因素[83]。因此,纠正上述因素能够减少 CP/CPPS 的发生,减轻由于上述因素诱发的各种症状。

3.2.2 心理咨询 CP/CPPS 的症状会严重影响患者的心理状况,带来焦虑、抑郁、疼痛灾难化等心理问题[84]。因此,泌尿男科医生应重视 CP/CPPS 患者的精神心理状态,结合临床实际情况给予恰当的心理疏导;也可联合心理科等相关科室进行 MDT 诊疗。应建议患者配偶积极配合患者日常活动,保持和谐关系[84]。行之有效的心理咨询往往能使患者的治疗受益更大。

3.2.3 制定自我管理方案 体育活动是 CP/CPPS 患者的一项重要的自我管理内容,研究显示体育活

动与CP/CPPS风险负相关,提示适度的体育活动能够降低CP/CPPS患病风险[85]。此外,规律的性生活也可以帮助CP/CPPS患者改善自身症状;规律的性生活能够促进前列腺腺体炎性物质排出,缓解前列腺区域的疼痛及排尿异常[86]。

3.2.4 *家庭内的物理疗法* 包括热水坐浴、热敷下腹部等[87-88]。

3.3 *CP/CPPS化学药物治疗* CP/CPPS病因多样,临床表现具有异质性,应采取个体化综合治疗提高疗效和生活质量。常用药物有以下几种。

3.3.1 *抗生素* 炎症性CP/CPPS虽没有细菌感染的明确证据[89],但经验性使用抗生素可改善部分患者临床症状,如左氧氟沙星、环丙沙星、洛美沙星和莫西沙星等氟喹诺酮类药物[90-91],大环内酯类药物(如阿奇霉素)或四环素类药物(如米诺环素)[92]。

非炎症性CP/CPPS不推荐使用抗生素治疗。

3.3.2 *α受体阻滞剂* α受体阻滞剂能松弛尿道、膀胱颈和前列腺的平滑肌,是最常用于改善CP/CPPS患者疼痛和LUTS的药物[93-96]。常用的α受体阻滞剂主要有:多沙唑嗪、特拉唑嗪、坦索罗辛、赛洛多辛和萘哌地尔等。建议α受体阻滞剂治疗CP/CPPS时疗程应至少4~12周[42]。需要注意该药的不良反应,如体位性低血压、眩晕等。

3.3.3 *非甾体类抗炎药* 非甾体类抗炎药通过抑制环氧化酶起到抗炎、解热镇痛作用。此类药物的镇痛效果中等,长期服用必须考虑药物带来的不良反应,目前没有足够的证据表明哪种非甾体类抗炎药更好[97-99]。

3.3.4 *抗抑郁药及抗焦虑药* 可选择的药物主要有选择性5-羟色胺再摄取抑制剂(氟西汀、帕罗西汀、舍曲林等)、5-羟色胺-去甲肾上腺素再摄取抑制剂(度洛西汀等)、三环类抗抑郁剂(阿米替林)等[100-102]。抗抑郁药及抗焦虑药适用于合并抑郁、焦虑等心境障碍的CP/CPPS患者,不但可改善患者心理症状,还可缓解疼痛等躯体症状[40,42]。必须注意这些药物的剂量以及不良反应。建议联合精神心理科协同会诊,进行相关评估并指导用药。

3.3.5 *其他药物* M受体阻滞剂等[103](如索利那新、托特罗定等)以及β3受体激动剂[104](米拉贝隆)等,可用于伴有OAB表现,如尿急、尿频和夜尿增多但无尿路梗阻的患者。5α还原酶抑制剂如非那雄胺可能改善CP/CPPS患者排尿及疼痛症状,但证据尚不足,一般并不推荐[95,105-106];如使用单一的镇痛药不能缓解疼痛,可以考虑使用普瑞巴林[107]。

3.4 *植物药治疗* 植物制剂主要是指花粉类制剂与植物提取物,其主要是通过抗炎、抗水肿以及解除平滑肌痉挛等发挥作用,缓解CP/CPPS的症状。目前常用的植物制剂有锯叶棕果实提取物软胶囊、普乐安片等[108-109]。

3.5 *祖国医学治疗* 中医主张辨证论治同时配合综合治疗,注意生活与饮食调护。CP/CPPS发病多责之于湿、热、寒、瘀、郁、虚六端[110],其中"瘀"是病机关键[111],基本治疗原则为清利、补肾、疏肝、化瘀排浊,但应分清主次、权衡用药,切不可一味清利,或过用温补[112]。

3.5.1 *湿热瘀阻证* 若湿热偏盛,以排尿异常症状明显,尿频,尿急,尿痛,尿道灼热,尿后滴沥,排尿终末或排便时偶有白浊,阴囊潮湿,口干口苦。舌红苔黄或黄腻,脉滑数或弦数。治法:清热利湿,佐以活血。推荐方药:程氏萆薢分清饮、八正散、龙胆泻肝汤加减。推荐中成药:龙金通淋胶囊[113]、宁泌泰胶囊[114]、尿清舒颗粒[115]、血尿安胶囊[116]、前列舒通胶囊[117]、黄柏八味片[118]。

若瘀阻偏盛,以骨盆区疼痛症状明显,会阴、腰骶、睾丸、少腹、腹股沟坠胀隐痛或痛如针刺,时轻时重,久坐时加重,舌黯或有瘀点瘀斑,苔薄黄,脉多沉涩。治法:活血化瘀,兼清湿热。推荐方药:前列腺汤、血府逐瘀汤加减。推荐中成药:前列倍喜胶囊[119]、清浊祛毒丸[120]、双石通淋胶囊[121]、前列欣胶囊[122]。

3.5.2 *肝气郁结证* 会阴、下腹、外生殖器区、腰骶或肛周坠胀不适,似痛非痛,小便淋漓不畅;伴胸闷、善太息、性情急躁、焦虑抑郁等,症状随情绪波动加重。舌淡红,苔薄白,脉弦。治法:疏肝解郁,理气止痛。推荐方药:柴胡疏肝散、逍遥散、金铃子散加减。推荐中成药:逍遥丸。

3.5.3 *寒凝肝脉证* 少腹牵引睾丸、会阴等部位冷痛为主,遇寒痛甚,得暖痛减,小便频数,余沥不尽,伴形寒肢冷,舌淡苔白,脉沉迟或弦者。治法:温经通络,暖肝散寒。推荐方药:天台乌药散、少腹逐瘀汤[123]。推荐中成药:少腹逐瘀胶囊。

3.5.4 *肾虚血瘀证* 若偏于肾阴虚,症见尿后余沥,小便涩滞不畅,或会阴坠胀不适,伴腰膝酸软,头晕眼花,失眠多梦,遗精早泄,五心烦热,口干咽燥。舌红少苔,脉沉细或细数。治法:滋补肾阴,清泄相火。推荐方药:知柏地黄丸、大补阴丸加减。推荐中成药:知柏地黄丸[124]。

若偏于肾阳虚,症见小便频数而清长,滴沥不尽,阳事不举,劳则精浊溢出,性欲低下,腰骶酸痛,倦怠乏力,精神萎靡,手足不温。舌淡苔白,脉沉无

力。治法:温补下元,补肾壮阳。推荐方药:济生肾气丸、右归丸加减。推荐成药:桂附地黄丸、右归丸。

3.5.5 气虚血瘀证 病程日久,肛门坠胀明显,小腹、会阴隐痛或绵绵作痛,劳重息轻,小便无力,精神不振,乏力困疲,少气懒言。舌淡红,苔薄白,脉细沉。治法:益气健脾,活血止痛。推荐方药:补中益气汤加减[125]。推荐中成药:补中益气丸。

其他中医特色疗法,如针灸[126]、穴位贴敷[127]、中药直肠滴入[128]等也表明对 CP/CPPS 有一定疗效,但还需要开展更多的临床研究。

3.6 *物理治疗*

3.6.1 *生物反馈* 生物反馈可以改善盆底肌的收缩功能,以增加或减少肌肉张力来缓解疼痛。生物反馈治疗 CP/CPPS 有一定的疗效,能明显改善盆腔疼痛不适和排尿症状[88,129]。生物反馈训练需要长时间的巩固期才能获得长期成功的 CP/CPPS 治疗,短期症状改善程度较小[130]。

3.6.2 *电生理治疗* 电生理治疗能改善 CP/CPPS 患者疼痛和排尿症状[50, 131-132]。

3.6.3 *磁疗* CPPS 患者采用体外磁刺激(EMS)治疗,症状较治疗前有显著改善[133-134];磁振磁电治疗联合中成药治疗的疗效明显高于单独药物治疗[135]。

3.6.4 *微波热疗* 经直肠微波热疗在短期内缓解患者的症状,但对精子质量有一定影响,结束治疗后逐渐恢复[136]。

3.6.5 *低能量冲击波与低能量超声波治疗* 低能量冲击波与低强度脉冲式超声波可以明显改善 CP/CPPS患者疼痛和生活质量[137-141],但仍需要进一步临床与基础研究探明其具体作用机制。

3.7 *心理治疗* 临床中部分 CP/CPPS 患者存在一定的心理问题,常规药物和物理治疗有时难以达到最佳的疗效,而在此基础上辅以心理干预不仅可有效地改善患者心理问题,同时还可以降低患者躯体症状的严重程度[142]。抗焦虑和抗抑郁药物可以改善 CP/CPPS 患者的负面情绪,但对于存在灾难化认知的患者疗效往往欠佳,因此针对这类患者可联合心理干预手段进行综合治疗[143-144]。针对 CP/CPPS 患者的心理治疗主要包括以下几个方面。

3.7.1 *心理支持* 包括耐心解答疑虑,指导患者全面、正确地认识 CP/CPPS 疾病,减轻患者不必要的心理压力。

3.7.2 *放松训练* 主要目的在于训练患者有意识地控制自身的心理与生理活动,降低其唤醒水平,从而改善机体功能紊乱。

3.7.3 *认知行为治疗* 主要用于改变患者异常的认知模式,帮助其正确处理异常的情绪;同时纠正患者对疾病的不良认知,减少其负性思维,降低其对躯体疾病的情绪反应,从而有效地改善患者的躯体不适、排尿症状以及心理问题,并提高生活质量。

3.7.4 *社会/家庭支持* 促进患者与家人的沟通,指导家人理解、鼓励、安慰患者,为其提供一定的心理支持,引导不良情绪的释放。

4 CP/CPPS 共病处理

4.1 CP/CPPS 合并 ED 有研究报道,CP/CPPS 合并性功能障碍的患病率约 62%,其中 ED 占 29%[145]。

CP/CPPS 合并 ED 的发病机制涉及多种因素:CP/CPPS 患者常因久治不愈的疼痛、LUTS 等症状而出现焦虑、抑郁等精神心理障碍,可严重影响勃起和性生活满意度[146];此外,CP/CPPS 合并 ED 还可能与盆底肌群功能失调[147]、性腺功能减退[148]、前列腺钙化[149]等因素有关。

关于 CP/CPPS 合并 ED 的共病治疗方案仍缺乏直接、充分的循证医学依据,有以下几点提示:①治疗 CP/CPPS 相关的疼痛、LUTS 等临床症状,可以同时辅以精神类药物[150-151],不仅可以有效缓解患者的疼痛、LUTS 症状,还可以改善精神心理状态和生活质量,已有研究报道 α 受体阻滞剂[152]、盆底肌群放松训练[153]可以在治疗 CP/CPPS 相关症状的同时改善勃起功能。②多项研究证实,5 型磷酸二酯酶抑制剂联合 α 受体阻滞剂可有效改善 BPH 患者的 LUTS 和 ED 问题[154-155],单独应用他达拉非亦可同时缓解 BPH/LUTS 和 ED 症状[156]。③在 CP/CPPS合并 ED 共病治疗过程中,还需注意对患者进行积极的健康教育、心理疏导,鼓励患者保持良好的饮食作息习惯、规律性生活等。

4.2 CP/CPPS 合并早泄 我国流行病学研究发现,在 CP/CPPS 患者中,早泄的患病率达到 26%[157]。国外研究发现,原发性或继发性早泄的患病率随着 CP/CPPS 患者的盆腔疼痛严重程度而显著增加;在中度至重度盆腔疼痛症状患者中,早泄患病率可达 45%,其 PEDT 与 NIH-CPSI 评分显著正相关[158];多项中国人群的临床研究也得到了类似的发现[159-160]。已证实 CP/CPPS 是继发性早泄的重要器质性病因之一[161-163]。与健康人群相比,原发性或继发性早泄患者的 CP/CPPS 症状均更为显著;CP/CPPS 经过治疗后,部分患者的阴道内射精潜伏时间(IELT)显著延长[164-165]。

CP/CPPS合并早泄的具体机制尚不明确,可能机制有:①早泄的重要病因如精神紧张和思想负担过重,常诱发交感神经兴奋,出现会阴区疼痛不适、LUTS、射精疼痛等CP/CPPS症状;CP/CPPS症状又会加重患者的焦虑、抑郁状态,进而加重早泄[166]。②CP/CPPS可能会影响射精反射中的感觉和调节,而感觉障碍是早泄重要的发病因素之一[167]。③CP/CPPS发病时产生的细胞因子/化学趋化因子刺激前列腺及其周围神经,引起性兴奋阈值下降以及调节射精反射的神经功能改变,从而引起或加重早泄症状[168]。④动物实验表明,CP/CPPS诱导的炎症免疫反应能够显著上调脑室旁核中NMDA受体的表达,通过增强交感神经系统敏感性缩短射精潜伏期从而导致早泄的发生,但此NMDA受体表达上调的机制还需进一步研究[169]。

推荐对CP/CPPS患者进行早泄的病史采集,同时推荐对早泄患者常规进行CP/CPPS筛查[158-159, 165]。对于已经确诊CP/CPPS合并早泄共病的患者,应优先采取针对CP/CPPS的治疗[163]。

应用α1受体阻滞剂和/或抗生素以及盆底物理治疗CP/CPPS时,其伴随的早泄症状可有不同程度的改善[164, 169]。单纯治疗CP/CPPS疗效不佳时,则应予以联合早泄的针对性治疗。联用5-羟色胺再摄取抑制剂,不但可显著改善早泄症状,而且可以缓解患者焦虑、抑郁、躯体疼痛等症状。患者联合用药后,射精次数、IELT、PEDT评分和NIH-CPSI评分等,均显著改善[170]。

4.3 CP/CPPS合并男性不育 男性不育人群中,CP/CPPS伴发率从20%~80%不等[171-172]。一般认为,由CP/CPPS单独导致的男性不育比例通常不到5%[171]。CP/CPPS对精液质量有不利影响[173]。

前列腺液部分成分参与调节生育相关的分子通路,涉及控制射精、调节精液凝固和液化、精子活化和获能等过程,还与激发女性生殖道和免疫系统中的基因表达和细胞变化有关[58]。CP/CPPS影响生育的可能机制包括:氧化应激[174-175]、炎症细胞因子[174, 176-178]、自身免疫反应[179-180]、分泌功能受损[181-182]、精子质量下降[180, 183-184]等。

对于男性不育合并CP/CPPS症状的患者,需与患者仔细沟通并建立完整的病史。有些患者没有Ⅲ型前列腺炎既CP/CPPS症状,在实验室检查时发现EPS/精液中白细胞升高,此时应该鉴别诊断是否存在Ⅳ型前列腺炎[41]。

感染和炎症约发生在15%的男性不育患者中。前列腺炎对不育的影响一直存在争议[185]。部分CP/CPPS患者存在前列腺炎症的证据。一般认为,射精后精子与前列腺液中炎症细胞和炎症介质的接触时间较短,因此,前列腺炎或前列腺精囊炎对精子质量和男性生育力的影响可能与附睾炎或睾丸炎有本质上的不同[186]。

CP/CPPS合并不育症的治疗应重视消除前列腺液和精液中可能存在的病原微生物,改善炎症和腺体分泌功能,提高精子质量以增强生育力。

4.4 CP/CPPS合并焦虑、抑郁 CP/CPSS患者往往合并一系列精神心理问题,包括严重的焦虑、抑郁情绪等[187-188];普通人群中抑郁和焦虑的男性,CP/CPPS症状评分较高[189];抗抑郁、焦虑药物和心理治疗可有效地改善患者的异常情绪和CP/CPPS症状[102, 190]。CP/CPPS和抑郁存在部分共同的发病机制:潜在的心理暗示、激素水平的变化[148],致炎和抗炎细胞因子的产生[191],神经内分泌调节的失常[192],与疼痛有关的中枢神经系统的敏感化等[193]。

结合自评及他评的情绪量表结果,CP/CPPS患者伴有中/重度焦虑、抑郁情绪或明显自杀倾向者,建议首先转至精神/心理科治疗;合并焦虑、抑郁情绪的一般患者,建议在药物治疗的基础上,联合心理治疗,以减轻其不良情绪对疾病躯体症状的影响。常用心理治疗手段参见“3.7 心理治疗”部分。

4.5 CP/CPPS合并BPH/LUTS CP/CPPS的发病贯穿男性青春期后的一生;BPH以中老年人群为主,BPH/LUTS与CP/CPPS的症状有重合。前列腺慢性炎症普遍存在于BPH/LUTS患者中,研究发现,炎症程度与LUTS症状程度弱相关[194]。在BPH/LUTS人群中,有盆腔疼痛或不适等症状的,可能同时存在Ⅲ型前列腺炎既CP/CPPS;此人群中,如无CP/CPPS相关症状,但因前列腺活检发现炎症者,符合Ⅳ型前列腺炎诊断。

CP/CPPS与BPH/LUTS的治疗,有相似的治疗目标即减轻症状、提高生活质量,BPH/LUTS患者还需考虑解除梗阻,预防并发症。因此,两者共病时,治疗措施要兼顾上述目标,在一般治疗、药物治疗的基础上联合物理治疗、手术治疗等。CP/CPPS的治疗方法同样适用于CP/CPPS与BPH/LUTS的共病处理。5α还原酶抑制剂对于合并BPH前列腺体积较大的CP/CPPS患者,效果更显著。手术治疗仅在有BPH/LUTS手术适应证时进行。

手术在解除尿路梗阻的同时,引流和消除可能存在的前列腺炎症病灶。围手术期药物治疗有利于减少并发症,促进术后恢复及症状缓解[195-196]。

5 CP/CPPS 患者健康教育

5.1 *正确认识 CP/CPPS 及其诊治* CP/CPPS 是泌尿外科、男科门诊常见疾病,它引起会阴区域和盆腔的长期疼痛、排尿症状,可能影响性功能及心理健康,从而严重影响患者的生活质量[145]。医患均应认识到,虽然 CP/CPPS 长期伴随部分患者,但不会危及生命和重要器官的功能。CP/CPPS 病因及发病机制目前尚未明确。目前的循证医学证据并没有证实 CP/CPPS 与前列腺增生、前列腺癌以及不育存在必然联系。

由于部分患者缺乏获取医学知识的正确渠道,医学知识匮乏或缺乏正确判断,不堪 CP/CPPS 的心理困扰,影响了睡眠、生活、学习和工作,严重者可以出现抑郁、焦虑等心理疾患[197]。对 CP/CPPS 的正确认识必须建立在及时咨询医生的基础上,尤其要听取专科医生的建议。

治疗前,需要医生明确诊断,正确施治,更需要患者耐心配合。治疗期间,医生应针对患者不同症状,对症处理,同时建议患者戒烟酒、忌辛辣,加强自身调养,保持心情舒畅,起居有常,规律性生活,注意保暖,适度锻炼等。

5.2 *CP/CPPS 患者的运动疗法* CP/CPPS 发病与与缺乏运动有一定的关系:缺乏运动意味着坐卧时间可能延长,而久坐可诱发 CP/CPPS;缺乏运动者血液循环相对缓慢,造成盆腔淤血,前列腺等器官充血水肿;缺乏运动者体质下降,机体抗病能力不足;长期缺乏运动使身体内环境不正常,甚至发生内分泌功能失调等[198-199]。

建议 CP/CPPS 患者进行适度的有氧运动,避免高强度运动引起慢性损伤和外伤。

5.3 *CP/CPPS 患者的饮食疗法* CP/CPPS 病程长,易复发,如能在治疗过程或恢复期辅以饮食疗法,对提高疗效和预防复发将起到积极作用。炎症会导致前列腺锌离子浓度降低,影响前列腺的抗病能力。患者可选择苹果、花生等含锌量较高的食物。患者应注意多喝水、避免长时间憋尿;多吃清淡易消化的食物,并维持排便通畅。

5.4 *CP/CPPS 患者的心理干预* CP/CPPS 患者产生严重身心负担,特别是患者长期受到病痛的影响,容易产生不良情绪,使临床治疗达不到满意效果。部分患者误认为患有前列腺疾病会受到歧视,影响家庭生活和婚姻幸福。

患者应及时接受专业医师的心理疏导,通过医患双方充分的沟通,使患者对疾病有正确认知,身心同时治疗,改善病情。研究表明,药物及物理治疗疗效欠佳的 CP/CPPS 患者,进行心理干预可以有效提高疗效,改善心理状态[200-201]。

慢性前列腺炎/慢性盆腔疼痛综合征诊疗指南编写组成员

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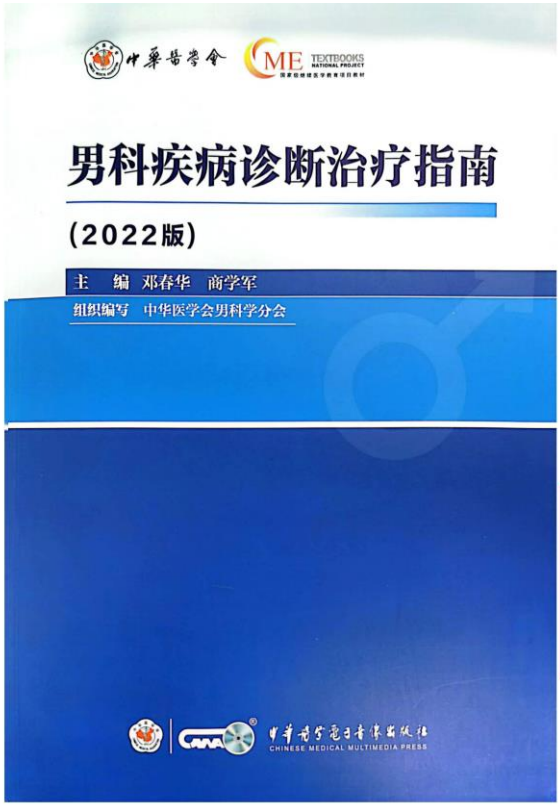


（1）疼痛或不适症状：主要位于会阴部、睾丸、耻骨区、阴茎及下腹部，其次为尿道、肛周、腰骶部、背部的疼痛不适，还可能出现射精痛、阴茎勃起后疼痛不适。

（2）LUTS：尿频、尿急、尿痛、尿不尽、排尿不畅、尿灼热感等。

（3）精神心理症状：如焦虑、抑郁、睡眠障碍、记忆力下降等症状。

（4）性功能障碍：如勃起功能障碍（erectile dysfunction，ED）、早泄、射精无力或困难、性欲低下等症状。

2. 相关评估工具　CP/CPPS 临床症状表现复杂多变，在实际临床诊疗工作中缺乏客观的诊断评估指标。目前认为，美国国立卫生研究院慢性前列腺炎症状评分表（National Institutes of Health chronic prostatitis symptom index，NIH-CPSI）可相对客观和全面地对 CP/CPPS 患者进行症状评估。NIH-CPSI 包含 3 个分项，分别是疼痛症状、排尿症状和症状对生活质量的影响评分。NIH-CPSI 可作为 CP/CPPS 症状严重程度的辅助诊断评估工具，也可作为 CP/CPPS 治疗随访中重要的疗效评估工具。

CP/CPPS 伴有性功能障碍患者，可以采用国际勃起功能指数问卷表（international index of erectile function，IIEF）-5 评估勃起功能，早泄诊断工具（premature ejaculation diagnostic tool，PEDT）评估射精功能。对于主要是尿频、尿急为主的储尿期症状患者，可以优先或联合使用膀胱过度活动症（overactive bladder，OAB）患者自我评价量表（overactive bladder symptom score，OABSS 评分）进行评估。患者如有焦虑和抑郁等精神症状，可采取汉密尔顿焦虑量表（Hamilton anxiety scale，HAMA）、汉密尔顿抑郁量表（Hamilton depression scale，HAMD）、焦虑自评量表（self-rating anxiety scale，SAS）、广泛性焦虑障碍量表（generalized anxiety disorder-7，GAD-7）进行评估，也可转诊患者到相关科室评估。

（四）实验室检查

1. 尿液检测

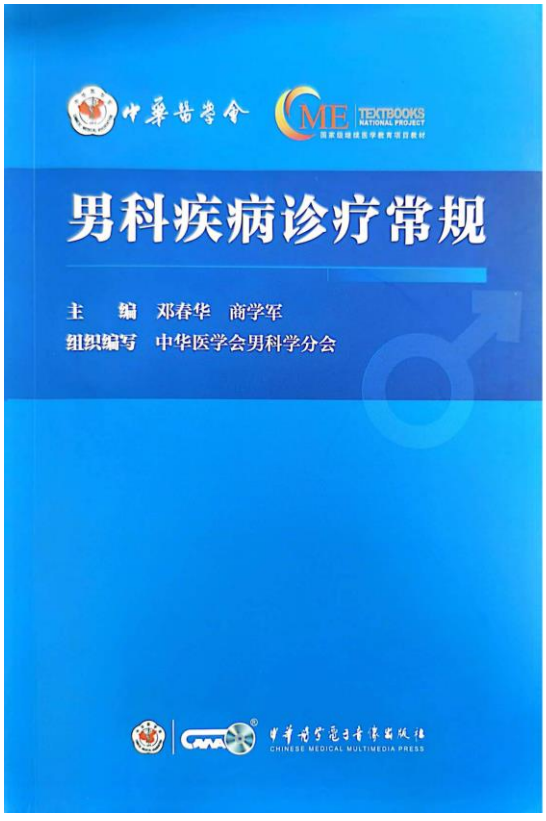
（1）尿常规检查：可排除尿路感染、血尿等其他疾病。

（2）前列腺小体外泌蛋白（prostatic exosomal protein，PSEP）检测：PSEP 由前列

腺小体分泌。近年研究发现，CP/CPPS 患者尿中 PSEP 水平升高，PSEP 水平与 NIH-CPSI 评分相关，同时还与 EPS 中的白细胞浓度相关。PSEP 作为一种无创性检查项目，还需要临床进行更多的研究来提供循证医学证据。

2. EPS 检查　以前 EPS 是作为前列腺炎分型与确诊的重要指标，长期以来在临床广泛应用。但越来越多的证据表明，EPS 内白细胞的多少不能反映 CP/CPPS 的严重程度，也不能代表其转归。

采集 EPS 前，应禁欲 2～7 天。通常取胸膝卧位进行前列腺按摩，标本及时送检。如需进行微生物检测，应进行无菌操作，按摩前先消毒外阴，并使用无菌容器接取标本后及时送检。如怀疑生殖系统结核、肿瘤或急性感染时，不宜做前列腺按摩。一次检测不宜多次重复按摩前列腺，如按摩后收集不到 EPS 时，可嘱患者留取前列腺按摩



正常状态下，PSA 存在于前列腺组织、尿液、精液、EPS 中，而血中 PSA 含量极低，只有在疾病状态时，PSA 大量入血。目前应用于血清 PSA 和游离前列腺特异性抗原（f-PSA）检测的方法有化学发光法、ELISA 法和放射免疫法等。

十三、前列腺小体外泌蛋白检测

前列腺小体外泌蛋白（prostatic exosomal proteins，PSEP）由前列腺小体分泌。研究表明，慢性前列腺炎患者尿中 PSEP 水平升高。多中心研究发现，PSEP 水平与美国国家卫生研究院慢性前列腺炎症状指数评分表（National Institutes of Health-chronic prostatitis symptom index，NIH-CPSI）的评分相关，同时还与 EPS 中的白细胞浓度相关。目前检测多采用 ELISA 双抗夹心法或间接法。检测标本可采集首段尿或中段尿，两者均具有较高的诊断敏感性和特异性。

十四、生殖道病原体检测

1. 淋病奈瑟菌检测　淋病在我国性传播疾病中发病率很高，准确、快速地检测淋病奈瑟菌对淋病防治有着极其重要的意义。目前，淋病奈瑟菌的检测方法有直接涂片法、培养法和分子生物学（如核酸检测法）方法等。

直接涂片法快速、简单，对急性感染阳性率较高，对治疗和慢性感染的检出率较低，同时受其他杂菌的干扰。培养法特异性高，但时间较长，检出率相对较低。核酸检测法敏感性高，简便快速，但需要特定的仪器。

2. 支原体检测　支原体是原核生物中最小、最简单，且无细胞壁的一类微生物。能够从人体分离出的支原体有 16 种，其中 7 种对人体有致病性。支原体在泌尿生殖道存在定植现象，人群中存在着相当数量的支原体携带者而没有症状和体征，常见的可导致泌尿生殖道感染的支原体包括解脲支原体（*U.urealyticum*，Uu）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·指南与共识·

慢性前列腺炎中西医结合诊疗指南*

中国中西医结合学会男科专业委员会**

一、背景、目的与意义

慢性前列腺炎(Chronic prostatitis, CP)是指前列腺在病原体和/或某些非感染因素作用下,患者出现以盆腔区域疼痛或不适、排尿异常等症状为特征的疾病[1]。慢性前列腺炎临床表现复杂、病情缠绵难愈。本病患者常表现为疼痛和下尿路症状,部分患者还伴有焦虑、抑郁、恐惧等精神心理障碍以及勃起功能障碍、早泄等性功能障碍,严重影响患者的身心健康和生活质量,并加重社会经济负担。如何充分运用中医、西医现有的研究成果,进一步规范诊疗,提高临床疗效,改善预后,减轻社会负担,是亟待解决的难题。

本病属于中医学“精浊”、“淋证”、“白浊”等范畴。中医药治疗慢性前列腺炎独具优势和特色,可改善患者疼痛症状、排尿症状和生活质量评分,并且药物不良反应少。西医治疗慢性前列腺炎的方法包括药物治疗、心理治疗、物理治疗、手术治疗等,其主要方法是药物治疗。

近年来,由于慢性前列腺炎的诊断和治疗方面的新理念、新方法、新技术、新药物不断涌现,在学科深度和广度上都有长足的发展和进步,在临床实践中,《慢性前列腺炎中西医结合诊疗指南》(2007 年试行版)、《慢性前列腺炎中西医结合诊疗专家共识》(2015 年版)也逐渐显现出一些不足之处,有必要进行及时地更新和修订,以契合当前的临床诊疗实际,进一步促进慢性前列腺炎诊疗的规范化,提高临床疗效。特别是近年来循证医学的发展、中西医结合治疗慢性前列腺炎研究的开展以及高质量研究证据的产生,为中西医结合诊疗慢性前列腺炎临床指南的制定提供了循证依据。

为此,指南制定工作组邀请中医、西医及中西医结合临床医学专家和方法学专家共同参与,遵循医学指南制定的循证方法,通过广泛地搜集国内外中西医结合防治慢性前列腺炎的研究成果,在进行文献评价及 GRADE(Grading of Recommendations Assessment, Development and Evaluation)系统评价当前最佳证据后,再通过专家论证汇集集体经验和智慧,制定了有证据级别及推荐意见的《慢性前列腺炎中西医结合诊疗指南》(以下简称:本指南)。

本指南适用的疾病范围为慢性前列腺炎(Chronic prostatitis, CP),包括其分类、流行病学、发病机制、诊断、治疗、健康教育与随访等内容。本指南适用于各级中医医院、综合性医院及社区医疗服务中心等医疗机构。

本指南适用人群范围为执业医师(包括从事中医、西医及中西医结合工作的医师)、护理人员和医学院校中从事中医药、中西医结合等相关专业的教学、科研人员。以上人员可在临床及科研、教学实践中参考使用本指南。

二、前列腺炎分类

慢性前列腺炎主要包括慢性细菌性前列腺炎(Chronic bacterial prostatitis, CBP)、慢性前列腺炎/慢性盆腔疼痛综合征(Chronic prostatitis/chronic pelvic pain syndromes, CP/CPPS)。欧洲泌尿外科学会(European Association of Urology, EAU)将前列腺疼痛综合征(Prostate pain syndrome, PPS)重新定义为原发性前列腺疼痛综合征(Primary prostate pain syndrome, PPPS)[2]。该定义突出强调了该综合征的“原发性”。“慢性前列腺炎”一词仍然与 PPS 等同。

前列腺炎的具体分类参照学术界比较公认的 1995 年美国国立卫生研究院(National Institutes of Health, NIH)制定的前列腺炎分类方法(**表 1**)。

前列腺炎常见的类型主要是Ⅱ型、Ⅲ型。Ⅳ型前列腺炎由于缺乏症状而少有主动就诊者。本指南主要论述Ⅲ型前列腺炎,即慢性前列腺炎/慢性盆腔疼痛综合征(CP/CPPS)。

三、流行病学

慢性前列腺炎是泌尿男科常见病、多发病,部分慢性前列腺炎对患者的身心健康造成严重影响。由于国内的各项调查研究所应用的流行病学方法及所选择调

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表 1 NIH 分类的各型前列腺炎及临床特点

类型	Ⅰ型	Ⅱ型	Ⅲ型		Ⅳ型
			ⅢA(炎症性)	ⅢB(非炎症性)	
名称	急性细菌性前列腺炎(Acute bacterial prostatitis, ABP)	慢性细菌性前列腺炎(Chronic bacterial prostatitis, CBP)	慢性前列腺炎/慢性盆腔疼痛综合征(Chronic prostatitis/chronic pelvic pain syndromes, CP/CPPS)		无症状性前列腺炎(Asymptomatory inflammatory prostatitis, AIP)
症状特点	全身症状和尿路刺激症状	反复发作的下尿路感染,具有复发性泌尿道感染的特征,持续超过 3 个月	盆腔区域疼痛或不适至少持续 3 个月以上,伴有下尿路症状和/或性功能障碍		无症状
前列腺液白细胞	增多	增多	增多	正常	增多
致病菌	+	+	-	-	+/-

注:+表示检出,-表示未检出

查人群结构的不同,统计的一般人群发病率差异较大,目前国内报道的慢性前列腺炎发病率为 6.0% ~ 32.9%,高于国外的文献报道[3]。有研究表明组织学炎症检出率更高[4],但前列腺炎症状与组织学前列腺炎严重程度之间,缺乏有临床意义的相关性[5]。

一般认为,慢性前列腺炎主要影响 50 岁以下的中青年男性[6]。关于慢性前列腺炎在人群中的真实患病率的信息非常有限。在国外文献中,以人群为基础的前列腺炎症状患病率为 1% ~14.2%[7-9]。

国内学者对来自北京、安徽、西安、广州、甘肃等省市的 15 000 名符合条件的男性志愿者进行调查,共收集到 12 743 名(占 84.95%)男性志愿者的信息,其中有 1 071 人(占 8.4%)报告了类似前列腺炎的症状,进一步根据病史和前列腺液检查结果显示符合慢性前列腺炎的百分比为 4.48%(571/12 743)[10]。

由于本病症状与其他疾病(如良性前列腺增生症、膀胱疼痛综合征等)症状存在较多重叠,单纯基于症状的病例定义,不能完全反映慢性前列腺炎的真实患病率。

四、发病机制

(一)西医病因病理

1、Ⅱ型前列腺炎致病因素主要为病原体感染,以逆行感染为主,常见致病菌有粪肠球菌、大肠杆菌等[11]。前列腺结石或钙化、生物膜的存在与前列腺感染持续存在相关[12]。

2、Ⅲ型前列腺炎发病机制十分复杂,而且存在诸多争议。疼痛是其主要症状,而作为慢性疼痛综合征的共同特征,尚未发现单一的病因可以解释。这种情况可能发生在暴露于一种或多种起始因素的易感男性中,这些因素可能是单一的、重复的或连续的。一些疾病因素,包括感染、遗传、神经内分泌、氧化应激、盆腔相关疾病因素、免疫(包括自身免疫)或心理机制参与了本病的发生。这些因素可能导致外周自我延续的炎症状态和/或神经源性损伤,产生急性或慢性疼痛。前列腺的慢性组织学炎症与症状进展显著相关[13]。涉及神经可塑性的敏感化可能导致集中性、神经性疼痛状态[14],这也可以解释为什么在 CP/CPPS 中通常未发现组织损伤。越来越多的证据表明 CP/CPPS 的神经病变起源与中枢神经系统的疼痛阈值变化有关,而焦虑似乎是其发展成为 CP/CPPS 的一个危险因素[15]。国内有学者研究还发现年龄[*OR*: 2.828, 95% *CI*(1.239-6.648), *P* = 0.004]、憋尿[*OR*: 2.413, 95% *CI*(1.213-4.915), *P* = 0.005]、焦虑或易怒[*OR*: 3.511, 95% *CI*(2.034-6.186), *P* < 0.001]、禁欲[*OR*: 2.136, 95% *CI*(1.161-3.014), *P* = 0.029]和吸烟状况[*OR*: 1.453, 95% *CI*(1.313-5.127), *P* = 0.013]是与 CP/CPPS 患者疼痛严重程度密切相关的危险因素[16];另一项研究发现,饮酒、吸烟、性交频繁,以及疲劳、压力和睡眠过少也是 CP/CPPS 的危险因素[10]。

肠道微生物在相邻器官中的迁移可能共同参与形成 CP/CPPS。研究表明,CP/CPPS 患者的肠道微生物多样性显著减少,因此推测肠道微生物异常可能是 CP/CPPS 的疾病生物标志物和潜在的治疗靶点[17]。另有研究表明[18],CP/CPPS 患者的尿液微生物有显著的多样性,梭状芽胞杆菌的数量相对较高,不同临床表型之间微生物组差异显著。国内有学者研究发现,80% 以上不明原因的 CP/CPPS 患者存在中央型腰椎间盘突出症,突出的椎间盘压迫硬膜囊造成马尾神经功能损伤,形成炎性反应,从而可能导致 CP/CPPS[19]。

最近,国内学者采用遗传流行病学方法研究发现干扰素基因(Interferon gene, IFNG)、干扰素γ受体 1(Interferon Gamma Receptor 1, IFNGR1)和雄激素受体(Androgen receptor, AR)的遗传多态性,可能是 CP/CPPS 易感性的遗传因素,其进一步的研究可能有助于确定 CP/CPPS 的遗传易感性和遗传模型[20]。

(二)中医病因病机

中医学认为,本病多由于饮食不节,嗜食醇酒肥甘,酿生湿热,或因外感湿热之邪,或因房事不洁,湿热从精道内侵,壅聚于下焦而成;或由于相火妄动,所愿不遂;或忍精不射,相火郁而不散,离位之精化为白浊;或因情志不畅等影响肝气正常疏泄,肝郁不舒而致气滞血瘀,最终精室失藏过泄、瘀浊不散而成。其病机演变初期往往以湿热为主;日久缠绵不愈多表现为气滞血瘀之象;病久则损耗肾气,可致"肾虚则小便数,膀胱热则水下涩"之虚实夹杂证候;或肾阴暗耗,可出现阴虚火旺证候;亦有火势衰微,易见肾阳不足之象。总之,湿、热、瘀、滞、虚出现在慢性前列腺炎的不同阶段[21-25]。久病入络,精室脉络瘀阻,败精瘀浊与湿热互结,是慢性前列腺炎反复发作、缠绵难愈的主要原因[26]。

五、诊断

(一)西医诊断

1、临床症状

国内学者针对慢性前列腺炎症状分布进行研究后发现,尿频占 65.8%,盆腔疼痛和不适占 52.3%,尿痛占 23.0%,性功能相关不适占 21.8%[6]。

(1) 疼痛

作为 CP/CPPS 最主要的临床表现,疼痛最常见于会阴部,其次是睾丸、耻骨区及阴茎;还见于尿道、肛周、腹股沟、腰骶部等。疼痛症状对患者生活质量的影响高于排尿症状[27-28];发生于盆腔外的疼痛对患者的社会心理健康及生活质量的影响更大[29]。射精痛或射精后疼痛不适也是本病常见的临床表现[30]。肌痛是一种经常被忽视的慢性盆腔疼痛形式,51% 的 CP/CPPS 患者存在肌痛[31]。当触诊到盆底肌肉时,CP/CPPS 患者常出现肌肉痉挛和肌肉张力增加以及疼痛[32]。

(2) 下尿路症状

表现为不同程度的下尿路症状(Lower urinary tract symptoms, LUTS),如尿频、尿急、尿痛,尿不尽感,尿道灼热;于晨起、尿末或用力排大便时,尿道有白色分泌物流出(即"尿道滴白"现象,但须除外非本病的因素,如淋菌性尿道炎等);还可有排尿等待、排尿无力、尿线变细、排尿中断及排尿时间延长等。

(3) 精神心理障碍

CP/CPPS 患者中普遍存在焦虑、抑郁、失眠、记忆力下降等精神心理障碍。研究显示,躯体形式障碍(Somatoform disorders, SD)是本病患者最常见的精神障碍类型(91.7%),其次是情绪障碍(Mood disorders, MD)(50.6%)和焦虑(32.1%),疼痛与尿路症状评分和抑郁评分之间呈正相关[33]。

(4) 性功能障碍

CP/CPPS 患者中常伴发性功能障碍,最常见的是勃起功能障碍(Erectile dysfunction, ED)和早泄(Premature ejaculation, PE)。国内学者研究显示 IIIA 型前列腺炎患者中,勃起功能障碍、早泄和射精疼痛的患病率分别为 19%、30% 和 30%[34],而通过自我报告和国际勃起功能指数-5(International Index of Erectile Function, IIEF-5)评估的 ED 患病率分别为 40.5% 和 35.1%,均与年龄显著相关[35]。另一项研究则显示,慢性前列腺炎患者的早泄患病率为 36.9%[36],而且早泄和美国国立卫生研究院慢性前列腺炎症状指数(National Institutes of Health-Chronic Prostatitis Symptom Index, NIH-CPSI)总分之间,存在显著相关[37]。

国内一项大型横断面研究显示,阴道内射精潜伏期(Intravaginal Ejaculation Latency Time, IELT)、国际勃起功能指数-5(IIEF-5)与焦虑和抑郁自评量表得分呈负相关[38]。因此,必须重视 CP/CPPS 患者中普遍存在的心理负担及其引发的性功能障碍问题[33,38-40]。

综上所述,CP/CPPS 可明显地降低患者的生活质量。在诊断 CP/CPPS 时,推荐使用 NIH-CPSI 进行基础评估和治疗监测。社会心理症状和疼痛灾难化在 CP/CPPS 患者中的发生率高[41],心理状况的评估可以通过患者健康问卷(Patient Health Questionnaire, PHQ)及疼痛灾难化评分(Pain catastrophizing scale, PCS)等测量工具来实现[42]。

2、体格检查

包括直肠肛门指诊在内的泌尿生殖系统检查和局部神经肌肉系统检查。

(1)局部体检

检查下腹部、腰骶部、腹股沟、会阴部、阴茎、阴囊、尿道、睾丸、附睾、精索等有无异常,同时有助于进行鉴别诊断。

(2)直肠指检

评估前列腺的大小、边界、质地、中央沟、局部温

度、压痛等情况。同时评估盆底肌肉的压痛及其触发点、紧张度,以及肛门直肠本身的病变。

3、实验室检查

(1)前列腺按摩液检查

Ⅱ型、ⅢA 型前列腺炎患者前列腺按摩液(Expressed prostatic secretion, EPS)中 WBC 数量增多,而ⅢB 型前列腺炎 WBC 数量在正常范围。研究显示,WBC 数量与症状严重程度之间无线性相关[43-46]。EPS 中巨噬细胞的胞质内含有被吞噬的卵磷脂小体或细胞碎片等成分,为前列腺炎的特有表现。当前列腺有细菌、真菌、滴虫等病原体感染时,也可通过 EPS 高倍镜检发现。若 EPS 提取困难,不宜短期内反复多次按摩,可留取前列腺按摩后尿液进行尿液分析。

(2)病原学定位检查

"四杯法"为经典方法,但试验繁杂,不推荐应用于日常诊疗工作。推荐使用"两杯法"(前列腺按摩前、后尿液)或按摩前后试验(Pre and Post Massage Test, PPMT)[47],后者诊断准确率大于 96%[48]。由于仅有 8% 的 CP/CPPS 患者前列腺细菌定位培养呈阳性,这一比例与无症状者相似[49],因此,病原学定位检查对于 CP/CPPS 的诊断价值有限,并非必需。精液微生物培养也有助于前列腺炎的诊断[50],采用尿-前列腺液-精液试验(U-EPS-S 试验),可准确鉴定分离物中的病原体和污染物,有助于诊断和鉴别诊断以及评估不同生殖器官感染的治疗效果[51]。

(3)尿常规分析及尿沉渣检查

在前列腺按摩前留取尿液进行尿液分析,是排除尿路感染和诊断前列腺炎的辅助方法。

(4)其他实验室检查

新近研究证实,使用尿液标本检测的前列腺小体外泄蛋白(Prostatic exosomal protein, PSEP),可以作为辅助诊断前列腺炎的特异性生物标志物[52]。前列腺按摩前、后尿样 PSEP 含量的敏感性分别为 86.93% 和 61.06%,但液体摄入量的差异可能导致尿液浓缩或稀释而影响其结果[53]。

血白细胞 CD64[54]、IL-8、IL-1β、ICAM-1[55] 及 SOD3、CA1[56] 等以及尿前列腺蛋白的 N-糖基化谱[57] 等也可作为新型的前列腺炎诊断标志物,但其临床意义还需要更多的临床研究予以证实。

4、辅助检查

主要有泌尿生殖系统彩超、尿流率、尿动力学、尿道膀胱镜、血清前列腺特异性抗原(Prostate Specific Antigen, PSA)、CT 和 MRI 检查、前列腺穿刺等。彩超检查可发现前列腺回声不均匀或欠均匀、钙化、结石、腺管扩张、精囊增大、盆腔静脉充血等改变,但不推荐单一使用彩超检查结果作为诊断依据。前列腺钙化一般被认为与前列腺慢性炎症和/或感染有关,虽然临床意义不大,但有研究显示前列腺钙化的存在影响抗生素治疗前列腺感染的疗效[58-59]。

上述辅助检查有助于排除泌尿生殖系统以及盆腔脏器可能存在的其他疾病。

(二)中医辨证

本病的辨证分型,主要分为基本证型与复合证型(2 种或 2 种以上基本证型同时存在)。本病常见中医证型包括湿热下注证、气滞血瘀证、肝气郁结证、肾阴亏虚证、肾阳不足证和湿热瘀滞证;实证因素为湿热、气滞、血瘀,虚证因素则主要是肾虚和脾虚。其中,湿热下注证、气滞血瘀证、肝气郁结证、湿热瘀滞证的出现频率较多,其次是肾阳不足证、肾阴亏虚证,且多为兼夹证,湿热、血瘀、肝郁多交互为患[1,21-22,25,60-64]。

证候变化与病程、年龄等因素有关:早期以湿热为主,实证多见,且多有夹瘀兼证;后期则在湿热、瘀血基础上,多伴虚证,以肾虚为主,或伴脾虚、气虚等。

综上,本病主要的基本证型为湿热下注证、气滞血瘀证、肝气郁结证、肾阳不足证、肾阴亏虚证,主要的复合证型为湿热瘀滞证(即湿热下注证 + 气滞血瘀证)。各证型具体表现(**表 2**)。在临床工作中应四诊合参,参考上述证型标准进行辨证。

(三)CP/CPPS 临床表型分类系统(UPOINT)

NIH 分类法和 NIH-CPSI 评分体系的建立,以改善症状、提高生活质量作为前列腺炎的治疗目的,已基本达成共识。但多项基于此的多中心临床试验结果并不十分令人满意。Nickel 等学者于 2009 年提出用于指导 CP/CPPS 诊疗的 UPOINT 表型分类系统和建议的治疗方法[65-69]。

该系统将 CP/CPPS 的临床表现(表型)分为六类,即排尿症状(Urinary symptoms)、社会心理障碍(Psychosocial dysfunction)、器官特异性表现(Organ-specific findings)、感染(Infection)、神经系统/全身性状况(Neurological/ systemic conditions)和盆底肌肉触痛(Tenderness of pelvic floor skeletal muscles),简称 UPOINT。这一分类方法倡导对于造成本病的几个因素进行综合干预,可有效缓解症状,达到临床治愈的目标。UPOINT 表型分类系统对于 CP/CPPS 诊断、治疗和临床研究的指导价值已获得较广泛肯定,表型定向治疗

表 2 CP/CPPS 各证型及其表现

证型	主症	次症	舌脉
湿热下注证	尿频尿急,灼热涩痛	尿液黄浊,尿道滴白,阴囊潮湿,口苦口干	舌红,苔黄腻,脉滑实或弦数
气滞血瘀证	会阴部、外生殖器区、小腹、耻骨区、腰骶、腹股沟及肛周坠胀或疼痛	排尿刺痛,淋沥不畅,血精或血尿	舌紫黯或有瘀点、瘀斑,苔白或黄,脉弦或涩
肝气郁结证	会阴部、外生殖器区、少腹、耻骨区、腰骶、腹股沟及肛周坠胀不适,似痛非痛	胸闷心烦,排尿无力,小便淋沥,疑病恐病	舌淡红,苔白,脉弦细
肾阳不足证	尿后滴沥,劳后白浊	畏寒肢冷,腰膝酸软,精神萎靡,阳痿早泄,性欲低下	舌淡胖,苔白,脉沉迟或无力
肾阴亏虚证	尿频尿急,尿黄尿热	五心烦热,失眠多梦,腰膝酸软,头晕眼花,遗精早泄,性欲亢进或阳强	舌红,苔少,脉细数
湿热瘀滞证	尿频尿急,灼热涩痛,淋沥不畅,会阴部、外生殖器区、小腹、耻骨区、腰骶、腹股沟及肛周坠胀或疼痛	尿液黄浊,尿道滴白,口苦口干,阴囊潮湿,血精或血尿	舌红,苔黄腻,脉弦数或弦滑

注:本病临床表现常呈多样化,其他证型还有肾虚湿热证、肾虚血瘀证、脾肾两虚证、肝郁肾虚证、肝郁脾虚证、中气不足证、肝郁化火证、寒凝肝脉证等。临床需根据实际情况,综合辨证。

可以提高治疗的成功率[2]。这是继 NIH 分类系统之后,临床分型的重大进展,与中医辨证论治不谋而合,将两者结合,可增强中西医结合治疗的精准性,改善患者的疼痛症状、排尿症状、生活质量及 NIH-CPSI 总评分,提高临床疗效[70-72]。

(四)基于 UPOINT 与“病-证”结合为导向的中西医协同分类思路

UPOINT 表型分类和中医“病-证”关系(**表 3**)。

(五)鉴别诊断

上述疼痛不适、排尿异常、性功能障碍等症状并非慢性前列腺炎所特有。本病需与良性前列腺增生、精囊腺炎、尿路感染、膀胱过度活动症、神经源性膀胱、间质性膀胱炎、腺性膀胱炎、泌尿生殖系统结核、肉芽肿性前列腺炎、原发性膀胱颈梗阻、泌尿生殖系统结石、性传播疾病、膀胱肿瘤、前列腺癌、睾丸附睾和精索疾病、肛门-直肠相关疾病、腰椎疾病、中枢和外周神经病变等可能导致盆腔区域疼痛和排尿异常、性功能障碍的疾病进行鉴别。

六、治疗

中西医结合综合治疗 CP/CPPS 主要以改善症状、提高生活质量和促进相关功能恢复为目的[69,73]。在强调辨病-辨证、个体化治疗的同时,需要关注患者的生活质量和纠正不良生活方式。

CP/CPPS 治疗方法繁多,采用单一治疗措施的研究结果常常令人失望,其原因可能与 CP/CPPS 是一种具有多种病因、不同进展途径、症状多样和对治疗反应

表 3 基于 UPOINT 与“病-证”结合为导向的中西医协同分类思路

表型分类	临床表现	中医辨证
排尿症状(U)	CPSI 排尿症状评分 >4 患者主诉令人困扰的尿频、尿急或夜尿 最大尿流率 <15ml/s 和/或呈梗阻模式 残余尿量 >100ml	湿热下注证 湿热瘀滞证 气滞血瘀证 肾阳不足证 肾阴亏虚证 肾虚血瘀证
社会心理障碍(P)	临床抑郁症 不良的应对方式或行为,如灾难化(症状的放大或反刍、绝望)、社交问题	肝气郁结证
器官特异性表现(O)	特异性的前列腺压痛 前列腺液中白细胞增多、血精 广泛的前列腺钙化	湿热下注证 湿热瘀滞证 肝气郁结证 气滞血瘀证
感染(I)	排除 I 型前列腺炎及 II 型前列腺炎感染复发 前列腺液细菌培养阳性 既往抗菌治疗有效	湿热下注证 湿热瘀滞证
神经系统/全身性状况(N)	盆腔或腹部以外的疼痛 肠易激综合征	气滞血瘀证 肝气郁结证
盆底肌触痛(T)	纤维肌痛 慢性疲劳综合征 会阴、盆底或盆侧壁明显触痛和/或痛性痉挛或痛性触发点	气滞血瘀证 肝气郁结证

注:本表每个表型分类和中医证型的对应关系不是绝对的、一成不变的,临证需根据具体病情及其发展阶段,四诊合参,综合辨证,以全面、准确地做出判断。

不一的异质性临床综合征有关,单一治疗措施难以使得所有患者获益[2]。因此,目前尚无特定有显著临床疗效的单一疗法被推荐用于治疗 CP/CPPS[74-75]。

(一) 基础治疗

CP/CPPS 的发生与患者对疾病认知缺乏以及不良的饮食和生活行为习惯相关。对患者进行健康宣教,普及相关知识,指导改变其不良行为习惯是治疗的基础。

(二)西药治疗

最常用的3 种药物是 α-受体阻滞剂、抗生素、非甾体抗炎药(Non-steroidal Anti-inflammatory Drugs,NSAIDs),其他药物(如 M-受体阻滞剂、β3 受体激动剂、抗抑郁药、抗焦虑药等)对缓解症状也有不同程度的疗效。

Nickel 等[68]为 UPOINT 系统的每一类表型提出了针对性的治疗建议和方法。研究显示,使用 UPOINT 系统进行表型定向治疗,可显著降低患者 NIH-CPSI 评分及提高生活质量[58,70,76-77]。

1、α-受体阻滞剂 (推荐强度:强;证据级别:中)

α-受体阻滞剂通过抑制位于前列腺、膀胱颈部平滑肌上的肾上腺素能受体,松弛平滑肌而改善排尿症状。在 CP/CPPS 中使用 α-受体阻滞剂,主要基于该类药物在 LUTS 中的疗效,抗炎作用也是 α-受体阻滞剂发挥治疗作用的可能机制之一[78]。常用的 α-受体阻滞剂有坦索罗辛、特拉唑嗪、多沙唑嗪、阿夫唑嗪和赛洛多辛。多项研究已证实,α-受体阻滞剂能改善 NIH-CPSI 总分[*MD*(平均差) = 5.01;95% *CI*(7.41,2.61)],包括其子评分(疼痛、排尿症状和生活质量)[79]。

总的来说,α-受体阻滞剂对 CP/CPPS 的疼痛、排尿和生活质量评分有中等的治疗效果[80-81]。推荐使用 α-受体阻滞剂治疗病程 < 1 年的 CP/CPPS 患者,可与其他药物联合使用,疗程不应少于6 周[82-83]。应注意该类药物可能导致的眩晕和体位性低血压、逆行射精等不良反应,推荐睡前服用。

2、抗生素(推荐强度:强;证据级别:中)

抗生素治疗对 CP/CPPS 的疼痛、排尿和生活质量评分有中等的治疗效果[2]。

抗菌药物治疗 CP/CPPS 可改善 NIH-CPSI 评分[*MD* = 2.43;95% *CI*(4.72,0.15)][79]。尽管在前列腺液或其他样本中未分离出致病菌的情况下,氟喹诺酮类和大环内酯类药物的应用已被证明对治疗疼痛有效[84],这说明抗生素的治疗效果超出了其抗菌作用,也可能是从抗生素治疗中获益的患者存在未被识别的尿路病原体感染。抗生素联合 α-受体阻滞剂可获得更理想的疗效[80,85]。

ⅢA 型 CP/CPPS 可经验性使用抗生素 2 周 ~ 4 周,再根据疗效反馈决定是否继续使用抗生素治疗。只有在证实患者获益大于风险时,才建议继续应用抗生素,总疗程 4 周 ~ 6 周。推荐使用单一抗生素(喹诺酮类或四环素类)治疗病程 < 1 年,且治疗经历简单的ⅢA 型 CP/CPPS 患者。若超过 6 周无效,应选择其他治疗方法。

不推荐使用抗生素治疗ⅢB 型 CP/CPPS。

对于明确存在沙眼衣原体、解脲支原体和/或人型支原体等感染,可口服大环内酯类、四环素类等抗生素治疗[86]。

对于 II 型前列腺炎,应根据细菌培养结果选择敏感抗生素,常用氟喹诺酮类药物,疗程 4 周 ~ 6 周,并进行阶段性疗效评价。疗效不佳时,可改用其他敏感抗生素。

3、非甾体抗炎药 (推荐强度:弱;证据级别:中)

NSAIDs 是针对 CP/CPPS 相关症状的经验性用药,其主要目的是缓解疼痛和不适。研究显示 NSAIDs 可改善 NIH-CPSI 评分[*MD* = 2.50;95% *CI*(3.74,1.26)][87]。

非甾体抗炎药对本病有中等的整体治疗效果,如塞来昔布[2]。使用该类药物必须考虑其长期使用带来的不良反应,可以联合 α-受体阻滞剂使用[88]。

4、M 受体阻滞剂和 β3 受体激动剂 (推荐强度:弱;证据级别:中)

对伴有膀胱过度活动症(Overactive bladder, OAB)表现如尿急、尿频和夜尿增多,但无尿路梗阻的前列腺炎患者,推荐使用 M 受体阻滞剂(如索利那新、托特罗定等)或 β3 受体激动剂(如米拉贝隆)治疗[89],后者可以显著改善患者 24 h 排尿次数和每次排尿量。

5、抗抑郁、抗焦虑药(推荐强度:弱;证据级别:中)

对合并抑郁、焦虑等心理障碍的患者,可选择使用抗抑郁药及抗焦虑药治疗以改善心理障碍症状,还可缓解排尿症状与疼痛等躯体症状。必须严格掌握这些药物的适应证、禁忌证和不良反应。常用的有三环类/苯二氮卓类抗抑郁药、选择性 5-羟色胺再摄取抑制剂,如舍曲林、氟西汀等[90-91]。

(三)中医辨证论治

辨证论治是中医的优势和特色治疗方法,也是医生临床经验与患者个体化治疗方案结合的最佳体现。本指南所列处方均来源于国家中医药行业高等教育“十四五”规划教材的《方剂学》[92]。在临床应用中,可

结合具体病情和医生个人经验加减化裁,本指南不承担相关法律责任。

1、湿热下注证

治法:清热利湿,导浊通淋

推荐处方:八正散(《太平惠民和剂局方》)加减

推荐备选方:龙胆泻肝汤(《医方集解》)加减、程氏萆薢分清饮(《医学心悟》)加减

推荐中成药:宁泌泰胶囊(推荐强度:强;证据级别:中)

用法用量:口服,每次 3 粒~4 粒,每日 3 次

由四季红、芙蓉叶、仙鹤草、大风藤、白茅根、连翘、三棵针组成的宁泌泰胶囊,能显著改善湿热下注证 CP/CPPS 患者疼痛评分、排尿评分、生活质量评分[93-95],并且不增加不良反应率[95]。与安慰剂比较[93],宁泌泰胶囊可改善 NIH-CPSI 总分[*MD* = -5.12;95% *CI*(-6.11,-4.13)];排尿症状评分[*MD* = -1.52;95% *CI*(-2.03,-1.01)]。与喹诺酮类抗生素单用比较[96],宁泌泰胶囊单用即可改善 NIH-CPSI 总分[*MD* = -4.89;95% *CI*(-6.72,-3.06)],亦可改善 NIH-CPSI 排尿症状评分[*MD* = -1.80;95% *CI*(-2.48,-1.12)]。一项 Meta 分析[97](11 篇 RCT,总样本量 2 079 例)显示,宁泌泰胶囊联合抗生素治疗 CP 与单用抗生素治疗比较,可显著降低 NIH-CPSI 总分[*MD* = -8.14;95% *CI*(-9.39,-6.90)]。

2、气滞血瘀证

治法:行气活血,化瘀止痛

推荐处方:复元活血汤(《医学发明》)加减

推荐备选方:少腹逐瘀汤(《医林改错》)加减

推荐中成药:少腹逐瘀丸(推荐强度:弱;证据级别:低)

用法用量:口服,大蜜丸,每次 9 g,每日 2 次

少腹逐瘀丸用于 CP/CPPS 气滞血瘀证,临床较为常用,患者接受度高。经专家论证认为,该药可以改善气滞血瘀证 CP/CPPS 患者的临床症状,可以进入指南推荐。

3、肝气郁结证

治法:疏肝解郁,行气止痛

推荐处方:柴胡疏肝散(《景岳全书》)加减

推荐备选方:逍遥散(《太平惠民和剂局方》)合金铃子散(《太平圣惠方》)加减

推荐中成药:

① 逍遥丸(推荐强度:弱;证据级别:低)

用法用量:口服,浓缩丸,每次 6 g~9 g,每日 2 次

逍遥丸用于 CP/CPPS 肝气郁结证,临床较为常用,患者接受度高。经专家论证认为,该药可以改善肝气郁结证 CP/CPPS 患者的临床症状,可以进入指南推荐。

② 疏肝益阳胶囊(推荐强度:强;证据级别:中)

用法用量:口服,每次 4 粒,每日 3 次

由蒺藜、柴胡、蜂房、地龙、水蛭、九香虫、紫梢花、蛇床子、远志、肉苁蓉、菟丝子、五味子、巴戟天、蜈蚣、石菖蒲组成的疏肝益阳胶囊,适用于肝气郁结证 CP/CPPS 合并 ED 的患者,联合常规西药方案(盐酸坦洛新缓释片+普适泰片)可显著改善 CP/CPPS 合并 ED 患者 NIH-CPSI、IIEF-5、医院焦虑抑郁量表(HADS)评分[98-101]。

4、肾阳不足证

治法:温肾化气,利水通淋

推荐处方:济生肾气丸(《济生方》)加减

推荐备选方:金匮肾气丸(《金匮要略》)加减

推荐中成药:金匮肾气丸(《金匮要略》)(推荐强度:弱;证据级别:低)

用法用量:口服,每次小蜜丸 9 g 或大蜜丸 1 丸,每日 3 次

金匮肾气丸用于 CP/CPPS 肾阳不足证,临床较为常用,患者接受度高。经专家论证认为,该药可以改善肾阳不足证 CP/CPPS 患者的临床症状,可以进入指南推荐。

5、肾阴亏虚证

治法:滋肾填精,养阴清热

推荐处方:知柏地黄汤(《医宗金鉴》)加减

推荐备选方药:六味地黄丸(《小儿药证直诀》)加减

推荐中成药:知柏地黄丸(《医宗金鉴》)(推荐强度:弱;证据级别:低)

用法用量:口服,每次小蜜丸 9 g 或大蜜丸 1 丸,每日 3 次

知柏地黄丸用于 CP/CPPS 肾阴亏虚证,临床较为常用,患者接受度高。经专家论证认为,该药可以改善肾阴亏虚证 CP/CPPS 患者的临床症状,可以进入指南推荐。

6、湿热瘀滞证

治法:清热利湿,行气活血

推荐方药:龙胆泻肝汤(《医方集解》)合桃红四物汤(《医宗金鉴》)加减

推荐备选方:四妙丸(《成方便读》)合失笑散(《太平惠民合剂局方》)加减

推荐中成药:龙胆泻肝丸合桂枝茯苓丸(《金匮要略》)(推荐强度:弱;证据级别:低)

用法用量:口服,两种浓缩丸均每次各 6 g~9 g,每日 2 次

龙胆泻肝丸联合桂枝茯苓丸用于 CP/CPPS 湿热瘀滞证,临床较为常用,患者接受度高。经专家论证认为,该联合用药可改善湿热瘀滞证 CP/CPPS 患者临床症状,可以进入指南推荐。

(四)基于 UPOINT 与"病-证"结合为导向的中西医协同治疗思路(**表 4**)。

表 4 基于 UPOINT 与"病-证"结合为导向的中西医协同治疗思路

表型分类	西医治疗	中医治法	推荐方药	备选方剂	推荐中成药
排尿症状(U)	α-受体阻滞剂 M-受体阻滞剂 β3 受体激动剂	清热利湿,导浊通淋 温肾化气,化瘀通窍	八正散 龙胆泻肝汤合桃红四物汤 济生肾气丸 知柏地黄汤	程氏萆薢分清饮 龙胆泻肝汤 金匮肾气丸 六味地黄丸	宁泌泰胶囊 龙胆泻肝丸合桂枝茯苓丸 金匮肾气丸 知柏地黄丸
社会心理障碍(P)	心理咨询 认知行为治疗 抗抑郁药、抗焦虑药	疏肝解郁,行气止痛	柴胡疏肝散	逍遥散合金铃子散	逍遥丸 疏肝益阳胶囊
器官特异性表现(O)	α-受体阻滞剂 植物制剂 前列腺按摩 5α-还原酶抑制剂	清热利湿,导浊通淋 活血化瘀,利窍通淋 疏肝解郁,行气止痛	八正散 柴胡疏肝散 复元活血汤	程氏萆薢分清饮 龙胆泻肝汤 逍遥散合金铃子散 少腹逐瘀汤	宁泌泰胶囊 逍遥丸 少腹逐瘀丸
感染(I)	抗生素	清热利湿,导浊通淋 活血化瘀,利窍通淋	八正散 龙胆泻肝汤合桃红四物汤	程氏萆薢分清饮 四妙丸合失笑散	宁泌泰胶囊 龙胆泻肝丸合桂枝茯苓丸
神经系统/全身性状况(N)	神经调节剂 三环类抗抑郁药 加巴喷丁 相关疾病的特异性治疗	疏肝解郁,行气止痛 行气活血,化瘀止痛	柴胡疏肝散 复元活血汤	逍遥散合金铃子散 少腹逐瘀汤	逍遥丸 少腹逐瘀丸
盆底肌触痛(T)	骨骼肌松弛剂 针对盆腔的物理治疗、综合性治疗运动	行气活血,化瘀止痛	复元活血汤	少腹逐瘀汤	少腹逐瘀丸

注:临床中应根据不同患者个体和疾病不同阶段的差异灵活辨证,"病-证"结合,中西医协同治疗,慎防不加辨证地长期过用一方一药。

(五)合并性功能障碍的治疗

对于合并性功能障碍的 CP/CPPS 患者,更详细的诊疗方法建议参照本学会的相关指南。

(六)外治法

1、针灸治疗(推荐强度:强;证据级别:中)

针灸治疗 CP/CPPS 以脏腑辨证为基础进行辨证选穴,调和阴阳,调畅气血,以及远近取穴的选穴循经规律为主[102-103]。可辨证选取:秩边、中极、曲骨、会阴、关元、足三里、三阴交、膀胱俞、上髎、下髎、次髎、中髎、肾俞、气海、阴陵泉、太溪等穴。

针刺对 CP/CPPS 的治疗可从多个层面发挥作用,譬如调节炎性因子的水平,调节免疫;提高机体的抗氧化能力;调节神经递质的释放和自主神经的活动来减轻组织损伤和改善神经功能;调节盆底肌肉收缩,改善尿动力学;改善盆腔瘀血[102],还可调节慢性疼痛疾病相关的脑区功能和结构[104]。多项随机对照研究[105-108]显示针刺疗法可缓解盆腔疼痛和改善排尿症状,降低 NIH-CPSI 评分,随访后发现长期疗效稳定,在改善症状和生活质量方面优于假针灸。

2、栓剂/凝胶塞肛(推荐强度:强;证据级别:低)

对于以会阴部、腰骶部坠胀痛不适为主要表现,伴有或无 LUTS 症状的患者,或不能耐受口服药物治疗、口服药物依从性差的患者,推荐使用栓剂或凝胶,睡前排便后塞肛。多项研究证实栓剂(前列安栓、前列泌尿栓)/凝胶(含纳米银成分)对 CP/CPPS 具有较好疗效,能显著改善慢性前列腺炎患者 NIH-CPSI 评分、中医证候评分,可与其他治疗措施联合应用[109-116]。

3、中药贴敷、脐疗(推荐强度:弱;证据级别:低)

研究证实中药贴敷、脐疗也可取得一定疗效[117-119]。其中一项系统评价[117]纳入 22 项 RCT 共涉及 1 087 例患者,结果显示,穴位贴敷疗法可显著提高慢性前列腺炎患者的有效率[$OR=0.30$;95% CI(0.22, 0.40)],改善患者 NIH-CPSI 评分[$OR=-2.28$;95% CI(-2.84, -1.72)]及中医证候评分[$OR=2.70$;95% CI

(0.38,5.02)]。

4、中药保留灌肠(推荐强度:弱;证据级别:低)

中药保留灌肠使药物直接从直肠黏膜吸收,有效成分迅速到达病变的前列腺组织,避免了消化酶、酸碱环境对药物的影响和破坏作用,可提高药物的生物利用度[120]。中药灌肠可显著改善 NIH-CPSI 评分、中医症状评分、前列腺液中白细胞数量和卵磷脂小体数量[121]。

(七)物理治疗

1、磁振磁电治疗、生物反馈和电刺激治疗(推荐强度:弱;证据级别:低)

磁振磁电治疗通过磁场、机械波、磁振波、低频声波及脉冲电刺激,具有增强前列腺生物膜通透性,改善局部微循环和组织代谢,减轻间质水肿的作用。磁振磁电联合药物、生物反馈和电刺激联合治疗 CP/CPPS 有协同作用,能明显改善 CP/CPPS 患者排尿症状,缓解疼痛与不适症状,提高生活质量[122-123]。

2、前列腺按摩(推荐强度:弱;证据级别:低)

前列腺按摩可促进前列腺血液循环、腺体排空,促进引流,并增加局部的药物浓度。按摩手法如经直肠盆骶经络揉推治疗还具有刺激神经末梢,放松盆底痉挛的肌肉,提高局部疼痛感受器阈值,降低中枢传递疼痛感觉的神经元兴奋性,促进各种镇痛物质的自身分泌,缓解 CP/CPPS 患者的疼痛等症状[124],联合其他治疗可有效缩短病程[122]。

3、热疗(推荐强度:弱;证据级别:低)

主要利用多种物理方法所产生的热力作用,促进前列腺腺体内温度均匀升高、血管扩张、血流加快、血液循环改善,加快局部代谢产物排出,促进炎症消退,降低结缔组织张力和增强免疫力[125-126],有效缓解前列腺炎症状,但需慎用于未生育男性。

(八)心理治疗 (推荐强度:强;证据级别:中)

针对 CP/CPPS 设计的认知行为疗法可以改善疼痛和生活质量,对于有明显心理困扰的 CP/CPPS 患者,建议进行心理治疗[2]。心理干预能够改善患者的疼痛症状、灾难化心理和生活质量[127-128]。

(九)CP/CPPS 主要治疗方法、证据和推荐意见汇总(**表 5**)

表 5 CP/CPPS 主要治疗方法、证据和推荐意见

证据总结	推荐意见	推荐强度	证据等级
α-受体阻滞剂对 CP/CPPS 的疼痛、排尿和生活质量评分有中等治疗效果	对于 CP/CPPS 持续时间少于 1 年的患者,推荐使用 α 受体阻滞剂	强	中
抗生素治疗对 CP/CPPS 的疼痛、排尿和生活质量评分有中等治疗效果	使用单一抗生素(喹诺酮类或四环素类)治疗病程少于 1 年且治疗经历简单的ⅢA 型 CP/CPPS 患者	强	中
非甾体抗炎药对 CP/CPPS 有中等的治疗效果	为有适应证的 CP/CPPS 患者提供非甾体抗炎药物。必须考虑长期使用带来的不良反应	弱	中
M-受体阻滞剂可以改善排尿症状	为伴有 OAB 表现如尿急、尿频和夜尿,但无尿路梗阻的 CP/CPPS 患者提供 M-受体阻滞剂	弱	中
β3 受体激动剂可以改善患者 24 小时排尿次数和每次尿量	为伴有 OAB 表现的 CP/CPPS 患者使用 β3 受体激动剂	弱	中
抗焦虑、抗抑郁药可改善 CP/CPPS 患者心理障碍症状、排尿异常与疼痛等躯体症状	对合并抑郁、焦虑等心理障碍的 CP/CPPS 患者,使用抗抑郁药、抗焦虑药治疗	弱	中
宁泌泰胶囊能显著改善湿热下注证 CP/CPPS 患者疼痛评分、排尿评分、生活质量评分	为有适应证的 CP/CPPS 患者提供宁泌泰胶囊	强	中
疏肝益阳胶囊能显著改善心理性勃起功能障碍(肝郁肾虚证)	为有适应证的 CP/CPPS 患者提供疏肝益阳胶囊	强	中
针灸在改善 CP/CPPS 症状和生活质量方面优于假针灸	为有适应证的 CP/CPPS 患者提供针灸治疗	强	中
栓剂/凝胶塞肛可以改善 CP/CPPS 患者疼痛和排尿症状	为有适应证的 CP/CPPS 患者提供栓剂或凝胶塞肛治疗	强	低
中药贴敷、脐疗可以改善 CP/CPPS 患者 NIH-CPSI 评分	为有适应证的 CP/CPPS 患者提供中药贴敷、脐疗	弱	低
中药保留灌肠可显著改善 CP/CPPS 患者 NIH-CPSI 评分	为有适应证的 CP/CPPS 患者提供中药灌肠治疗	弱	低
磁振磁电治疗、生物反馈和电刺激联合治疗能改善 CP/CPPS 患者排尿症状,缓解疼痛与不适,提高生活质量	为有适应证的 CP/CPPS 患者提供磁振磁电治疗或生物反馈和电刺激治疗	弱	低
前列腺按摩可缓解 CP/CPPS 患者疼痛等症状	为有适应证的 CP/CPPS 患者提供前列腺按摩	弱	低
热疗可以有效缓解 CP/CPPS 症状	为有适应证的 CP/CPPS 患者提供热疗	弱	低
心理干预能够改善 CP/CPPS 患者的疼痛症状、灾难化心理和生活质量	对有明显心理困扰的 CP/CPPS 患者进行心理治疗	强	中

七、健康教育与随访

慢性前列腺炎具有病程长、治疗周期长、易反复发作等特点，容易给患者造成不同程度的精神心理压力，影响正常工作生活。患者对本病缺乏正确认识、存在不良习惯、治疗依从性差等因素严重影响治疗效果。因此，实施慢病管理，对慢性前列腺炎患者的健康教育和随访，显得十分重要。实施个体化健康教育，普及相关知识，有助于缓解患者的紧张、焦虑，改善由此引发的躯体症状；随访有利于及时获得治疗及康复反馈信息，用于指导治疗方案的调整。有效的健康教育和随访有助于提高疗效，有利于治疗的连续性，同时提高患者满意度，提高患者依从性，有利于疾病的康复。在日常诊疗中，医生应耐心倾听，并择机进行细致的诊间口头宣教，也可以充分利用现代多媒体，采取多元化的宣教方式实现诊间、诊后宣教。

（一）健康教育

1、科普疾病知识

向患者普及慢性前列腺炎相关知识，缓解、消除焦虑恐慌，树立战胜疾病的信心。如前列腺的解剖、病理生理，前列腺炎的病因、临床表现、治疗方法和效果、易复发的原因、用药指导、生活健康指导、心理指导等。明确告知患者前列腺炎是一种常见病、多发病，不威胁生命，并非所有的前列腺炎都需要治疗。前列腺液白细胞检查主要用于指导诊断分类，与病情严重程度、症状的严重程度无必然联系，减少或消除白细胞数量并不是治疗的目的，改善症状、提高生活质量、促进相关功能恢复，才是最重要的。

2、纠正不良习惯

应纠正过量饮酒、嗜食辛辣、久坐、频繁自慰、忍精不射、纵欲等不良习惯。应杜绝不洁性行为、预防尿路感染。保持心情愉悦，缓解紧张焦虑情绪，加强体育锻炼，注意防寒保暖。

3、适时心理干预

抑郁和/或焦虑状态可能是慢性前列腺炎易感或致病因素，还会影响本病的预后。对于慢性前列腺炎患者普遍关注的癌变、性功能障碍、不育等问题，应耐心细致地解释。鼓励患者保持积极向上的生活工作态度，勿过度关注某些症状。必要时请心理科、疼痛科等多学科参与诊疗。

4、坚持规范诊疗

强调遵从医嘱的重要性和必要性。症状的缓解和消除，是评价慢性前列腺炎治疗效果的主要依据。治疗的重点不应仅仅放在药物上，并非所有患者都需要药物治疗。心理支持、改变不良习惯等非药物干预方法，同样重要。

5、中医养生保健

在辨证的前提下，慢性前列腺炎患者的饮食，以清淡、清补之品为主。炙煿、辛辣燥热之物宜忌食或少食。通过不同的中医保健方法（如收腹、提肛、摩腹等），调息、调心、调身，调节脏腑经络气血可改善症状。

（二）随访

定期随访，及时获取患者治疗效果、心理状态等反馈信息，并进行针对性调整，给予必要的健康指导及复诊信息。可每 2 周～4 周随访一次。建议采用 NIH-CPSI 阶段性随访评估慢性前列腺炎的治疗效果。

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·临床研究·

前列腺小体外泄蛋白在前列腺癌诊断中的意义

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The clinical significance of prostatic exosomal protein in the diagnosis of prostate cancer

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ABSTRACT: Objective　To evaluate the clinical significance of prostatic exosomal protein (PSEP) in the diagnosis of prostate cancer. Methods Urine samples and clinical information were collected from 870 patients who underwent s prostate needle biopsy during Mar. 2015 and Mar. 2017. The PSEP level was detected with enzyme-linked immunosorbent assay. The association between PSEP level and prostate cancer was analyzed. Results Of all 870 cases, 370 were positive and 500 were negative. Compared with negative cases, prostate cancer cases had advanced age and increased prostate specific antigen (PSA) level ($P<0.001$), lower incidence of histological inflammation ($P<0.05$), and lower PSEP level ($P=0.013$). Subgroup analysis showed that when PSA was 4～10 ng/mL, there was correlation between PSEP level and incidence of histological inflammation ($P=0.009$, $r=0.094$). Conclusion Histological inflammation is associated with a low risk of prostate cancer. PSEP level is correlated with histological inflammation. Patients with prostate cancer have decreased PSEP level. Urine PSEP may be helpful to avoid unnecessary prostate needle biopsy in patients with PSA 4－10 ng/mL.

KEY WORDS: prostate cancer; prostatic exosomal protein; inflammation

摘要：**目的**　探讨前列腺小体外泄蛋白(PSEP)指标在前列腺癌诊断中的价值。**方法**　2015 年 3 月至 2017 年 3 月间收集 870 例前列腺穿刺活检患者的穿刺前尿样，收集相关临床资料，采用酶联免疫法检测尿样中 PSEP 浓度，分析尿液 PSEP 浓度和前列腺癌的相关性。**结果**　经病理诊断穿刺阳性 370 例，穿刺阴性 500 例。前列腺癌患者的年龄和前列腺特异抗原(PSA)水平均高于阴性组($P<0.05$)。前列腺癌患者穿刺组织中伴随炎症的比例低于阴性组($P<0.05$)，尿 PSEP 浓度亦低于阴性组($P=0.013$)。亚组分析显示在 PSA 4～10 ng/mL 这一区间中，两组之间的尿 PSEP 浓度存在差异($P=0.038$)。PSEP 与前列腺组织学炎症存在相关性($P=0.009$，$r=0.094$)。**结论**　伴随组织学炎症者确诊前列腺癌的风险较低，尿液 PSEP 与前列腺组织学炎症有关，前列腺癌患者尿 PSEP 浓度显著降低，尿液 PSEP 检测作为辅助指标有助于减少 PSA 灰区患者因炎症干扰造成的不必要前列腺穿刺活检。

关键词：前列腺癌；前列腺小体外泄蛋白；炎症

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目前临床主要通过前列腺特异抗原(prostate specific antigen，PSA)检测来判断可疑患者是否接受前列腺穿刺活检[1]。然而，PSA 是组织特异性抗原而非肿瘤特异性的抗原，因而对前列腺癌诊断的特异性较差，前列腺良性疾病如炎症等也可导致 PSA 增高，尤其在 4～10 ng/mL 时(诊断灰区)其诊断特异性明显不足[2]。国内大样本临床研究显示前列腺穿刺阳性率仅为 25.5%，其余大部分为前列腺炎症等良性疾病造成的过度穿刺[3]。前列腺小体外泄蛋白(prostatic exosomal protein，PSEP)已被证实可作为前列腺炎症的特异性生物标志物[4-7]，本研究目的在于评估 PSEP 检测在前列腺癌诊断中的价值。

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1　材料与方法

1.1　研究对象　收集 2015 年 3 月至 2017 年 3 月在

复旦大学附属肿瘤医院行前列腺穿刺的 870 例患者穿刺前尿样，无需前列腺按摩。排除尿常规明显异常者。标本收集后于-20℃冰箱冻存，待标本达到 20 例后集中送检。本研究获得医院伦理委员会批准，研究对象均签署知情同意书。

1.2 检测方法 采用酶联免疫吸附法（enzyme-linked immunosorbent assay，ELISA），试剂盒由昂科生物医学技术（苏州）有限公司提供，按照操作说明书对收集的标本进行检测。用酶标仪测定各反应孔在双波 450 nm、630 nm 处的 A 值。根据不同浓度的标准品 A 值绘出标准曲线，得出待测样本的 PSEP 浓度。按照 PSEP 检测试剂盒说明书设定，以≤1.0 ng/mL 判定为 PSEP 阴性，＞1.0 ng/mL 判定为 PSEP 阳性。

1.3 统计学分析 采用 SPSS 19.0 统计软件进行数据处理。不符合正态分布的计量资料以中位数（范围）表示并采用非参数检验，计数资料采用 χ^2 检验。应用 spearman 相关系数分析 PSEP 浓度与前列腺组织学炎症之间的相关性。$P<0.05$ 定义为差异有统计学意义。

2 结 果

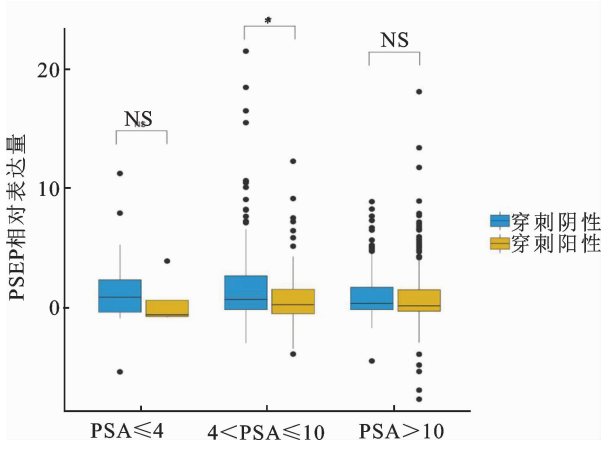
2.1 研究对象的基本特征 经病理诊断 370 例（阳性）确诊为前列腺癌，500 例（阴性）为前列腺良性组织。前列腺穿刺阳性与阴性患者的基本特征见表 1。前列腺癌患者的年龄和 PSA 水平均高于阴性组（$P<0.05$）。前列腺癌患者穿刺组织中伴随炎症的比例低于阴性组（$P<0.05$），尿 PSEP 阳性率亦低于阴性组（$P=0.013$）。以上差异均有统计学意义。

表 1 前列腺穿刺患者的基本特征 [例(%)]

指标	阴性组（$n=500$）	阳性组（$n=370$）	P 值
年龄[（岁，中位数（范围）]	65(31～91)	69(44～91)	＜0.001
PSA(ng/mL)			＜0.001
＜4	28(5.8)	4(1.1)	
4～10	260(54.1)	56(15.9)	
＞10	193(40.1)	292(83.0)	
组织学炎症			＜0.001
有	180(36.0)	47(12.7)	
无	320(64.0)	323(87.3)	
PSEP(ng/mL)			0.013
≤1.0	258(51.6)	223(60.3)	
＞1.0	242(48.4)	147(39.7)	

PSA：前列腺特异性抗原；PSEP：前列腺小体外泄蛋白。37 例患者 PSA 值缺失。

2.2 各 PSA 水平区间尿液 PSEP 浓度差异 进一步分析在不同水平 PSA 区间中，两组之间的尿 PSEP 浓度是否存在差异。结果显示 PSA 在 4～10 ng/mL 这一区间中，前列腺癌患者的尿 PSEP 阳性率低于阴性组，其差异具有统计学意义（$P=0.038$，图 1），而在 PSA≤4 ng/mL 和 PSA＞10 ng/mL 这两个区间未观察到该差异（$P=0.600$ 和 0.346）。



* $P<0.05$。

图 1 各 PSA 区间穿刺病例的 PSEP 浓度

2.3 组织学炎症与 PSEP 的关系

PSA 4～10 ng/mL 的患者穿刺标本中伴随炎症的比例显著高于 PSA＞10 ng/mL 的患者，差异具有统计学意义（$P=0.004$，表 2）。

前列腺组织学炎症患者的尿 PSEP 阳性比例高于无炎症患者（50.2% *vs.* 42.6%），其差异具在统计学上达到边界水平（$P=0.052$）。PSEP 与前列腺组织学炎症存在相关性（$P=0.006$，$r=0.094$）。

表 2 各 PSA 区间穿刺患者的组织学炎症分布情况[例(%)]

	PSA			P 值
	≤4 ng/mL	4～10 ng/mL	＞10 ng/mL	
伴随炎症				0.004
无	24(75.0)	213(67.4)	378(77.9)	
有	8(25.0)	103(32.6)	107(22.1)	

PSA：前列腺特异性抗原。

3 讨 论

本研究发现伴随组织学炎症者确诊前列腺癌的可能性较低。相较于问卷法[8]，组织学诊断炎症更为精确可靠，避免了回忆偏差、无症状前列腺炎等可能的干扰因素。组织学炎症在前列腺穿刺标本中常见，发生率约为 68%～82%[9]。虽然这种组织学炎症往往没有相应的临床表现，但常与其他病变伴随出现。此前已有研究关注前列腺组织学炎症与前列腺癌的关系。近期一项荟萃分析对其进行了总结，纳入 25

项研究共20 585例前列腺穿刺患者，分析结果显示穿刺组织中伴随炎症者确诊前列腺癌的概率较无炎症者低54%(OR：0.46，95%*CI*：0.34～0.57)，亚组分析表明无论急性或慢性组织学炎症，穿刺阳性的概率均低于无炎症者[9]。国内的研究也证实前列腺组织学炎症位置和炎症范围分级与穿刺阳性概率呈负相关[10]。出现这种现象的原因可能是：①患者由于组织学炎症而非前列腺癌造成的PSA升高从而接受穿刺活检；②肿瘤细胞存在免疫逃逸现象，而局部炎症反应会识别和清除肿瘤特异抗原，客观上可能加强免疫监视作用，从而抑制前列腺癌的发生[9]。现有的研究解释了部分炎症“保护作用”的机制，但组织学炎症和前列腺癌之间的机制仍需进一步的生物学研究阐明。

作为前列腺炎症的生物标志物，本研究发现穿刺阴性患者的尿PSEP浓度显著高于前列腺癌者，从另一个角度验证了伴随组织学炎症者确诊前列腺癌的概率较低的结果。PSEP由前列腺小体分泌生成，前列腺小体是由前列腺上皮细胞产生的胞外囊泡，主要由脂质、核酸和蛋白组成，由前列腺导管上皮细胞通过胞吐作用分泌到管腔。当前列腺组织受到炎性细胞的浸润，释放出各种活性物质和趋化因子，前列腺小体生成增多，PSEP分泌也随之增加，通过解剖通道分泌进入男性生殖道[7]。研究证实在炎症状态下，PSEP浓度明显升高，通过尿液检测就能达到诊断前列腺炎的目的[4-7]。本研究证实了组织学炎症患者的PESP浓度显著高于无炎症患者，尿PSEP浓度与组织学炎症呈正相关。值得注意的是，在PSA 4～10 ng/mL的灰区中，前列腺癌患者的尿PSEP浓度显著低于穿刺阴性者，这是由于这一区间的患者炎症比例高于PSA＞10 ng/mL的患者(32.6% *vs*. 22.1%)，提示PSEP可作为辅助指标有助于综合判断，减少因炎症干扰而造成的不必要的前列腺穿刺活检。PSA的升高受到多种因素的影响，除了前列腺肿瘤和前列腺炎症，良性前列腺增生、射精、医疗操作等都会造成PSA升高。本研究未发现PSEP水平和PSA水平之间存在关联性，既往文献也未报道两者之间存在关联性[4]。

本研究也存在一定的局限性。尽管研究报道PSEP检测试剂对前列腺炎诊断的灵敏度为93%，特异度为95%，总体符合率达到94%，说明两者具有良好的一致性，但仍有少量假阳性和假阴性，考虑为液体摄入差异造成尿液的浓缩或稀释所致。当实施PSEP检查时，液体摄入量或尿液排出量和平时生活状态差异显著可能会影响到即时尿样的测量值[7]。因此选择穿刺当天的晨尿进行检测最合适。

综上所述，本研究发现伴随组织学炎症者确诊前列腺癌的风险较低，在病理报告中完整评估前列腺组织学炎症的情况将有助于穿刺阴性者重复穿刺的决策。其次尿液PSEP检测作为一种简便易行、非侵入性、无痛的方法，可以作为临床辅助诊断前列腺炎症的指标，减少PSA灰区患者不必要的前列腺穿刺活检。

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Original Article

Clinical significance of urine prostatic exosomal protein in the diagnosis of prostate cancer

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Abstract: PSA may be elevated in non-malignant conditions such as prostatitis and leads to unnecessary prostate needle biopsy. Urine prostatic exosomal protein (PSEP) has been proved to be a promising biomarker of prostatic inflammation. The aim of this study is to determine the relationships between PSEP and the diagnosis of prostate cancer (PCa), and their association with histologic prostatic inflammation. Prostate needle biopsies from 674 patients were evaluated for the presence of histological inflammation and PCa. The urine PSEP levels were measured using an enzyme-linked immunosorbent assay kit. 286 cases were diagnosed as PCa and prostatic inflammation was observed in 33.7% of the biopsies. The presence of histological inflammation was significantly associated with a lower PCa risk ($P < 0.001$). The urine PSEP levels was significantly lower in PCa patients compared to the controls ($P = 0.003$). When subanalyzed by PSA levels, the difference was more evident in cases with PSA 4-10 ng/ml ($P = 0.039$). The urine PSEP levels was correlated with histological inflammation on prostate needle biopsy ($P = 0.018$, $r = 0.12$). Urine PSEP examination may be helpful to eliminate false positive PSA levels due to prostatic inflammation and reduce unnecessary prostate needle biopsy in cases with PSA grey zone.

Keywords: Prostate cancer, prostatic exosomal protein, inflammation, prostatitis

Introduction

Prostate cancer (PCa) is usually suspected on the basis of elevated prostatic specific antigen (PSA) levels. Men with a positive PSA test result may undergo a transrectal ultrasound-guided core needle biopsy of the prostate to diagnose PCa. PSA is organ but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy, prostatitis and other non-malignant conditions [1]. Of biopsies performed, 60.6%-75.8% cases did not result in a PCa diagnosis [2, 3].

Considering that inflammatory infiltrate is a common histological finding on prostate needle biopsy, varying from 68% to 82% [4], it is an important factor contributing to increased levels of PSA in men without PCa. Unfortunately, most prostatic inflammation are asymptomatic and can be detected only upon histological examination of a prostate specimen [5]. For urologists, a predisposing marker to eliminate false positive PSA levels due to prostatic inflammation would considerably avoid unnecessary prostate needle biopsy.

Prostasomes are extracellular vesicles produced by prostatic epithelial cells and excreted with urine [6]. Over 400 distinct protein compositions of prostasomes have been identified. Among these proteins, prostatic exosomal protein (PSEP) has been proved to be a promising marker of prostatic inflammation [7].

To date no studies have looked for associations between PSEP and risk of PCa. Herein, we evaluated the relationships between PSEP and the diagnosis of PCa, and their association with histologic prostatic inflammation.

Table 1. Characteristics of prostate needle biopsy cases

		Negative n = 388	Positive n = 286	*P* value
Age		65 (33-91)	69 (44-90)	< 0.001
PSA, ng/ml[a]	≤ 4	17 (4.5%)	3 (1.1%)	< 0.001
	4-10	203 (54.0%)	45 (16.5%)	
	> 10	156 (41.5%)	225 (82.4)	
Inflammation	Yes	180 (46.4%)	47 (16.4%)	< 0.001
	No	208 (53.6%)	239 (83.6%)	
PSEP, ng/ml		1.01 (-4.99-18.8)	0.61 (-7.28-18.5)	0.003

[a]25 cases' PSA data were unavailable.

Materials and methods

Study population

Prospective and observational study was carried out in 674 consecutive prostate biopsy done from January 2015 until December 2016 due to elevation of serum PSA (> 4.0 ng/ml) and/or suspicious DRE digital rectal examination (DRE) and/or positive imaging findings. Informed consent for both procedures and study participation was obtained. The study was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center.

Transrectal Ultrasound Guided Prostate Needle Biopsy Prostate needle biopsy was performed as an out patient procedure under local anesthesia. An end-fire ultrasound transducer (Falcon 2101, B-K Medical, Inc.) and a 16-gauge automated biopsy needle (Bard, Inc.) were used. A minimum of 12 cores were obtained, and two to eight additional cores were taken as determined by age and prostate volume. Tissue specimens were fixed in 10% buffered formalin, processed and subjected to H&E staining according to routine protocol.

Clinical and demographic data were abstracted from patients' medical records. Diagnoses of prostatic inflammation were based upon histology by experienced pathologists. The presence of prostatic inflammation was defined as presence of inflammatory cell infiltration in the glands and stroma of the prostate, using the Histopathological Classification System of Prostatic Inflammation [8].

PSEP measurement

In order to minimize the bacterial interference, midstream urine samples were collected without massage and stored at -80°C until PSEP measurement. PSEP levels were measured with PSEP diagnostic kits (enzyme-linked immunosorbent assay) (Onco Biomedical Technology, Suzhou, China) according to the manufacturer's manuals [7]. The absorbance values were read in the dual-wavelength mode on a BIO-RAD 680 microplate reader. A linear standard curve was generated by plotting the graph using the standard concentrations on the y-axis and the corresponding absorbance on the x-axis. The sample concentration was determined according to the standard curve, and the value was multiplied by the dilution factor if there was one.

Statistical analysis

Quantitative variables were expressed as medians semi-interquartile range. Qualitative variables were expressed as rates. Univariate analysis included x^2 test to analyze the association between qualitative variables. Mann-Whitney U test was performed to compare quantitative variables. SPSS program V.20 was used to perform statistical analysis.

Results

A total of 674 participating patients were analyzed. PCa was identified in biopsies from 286 cases. There were significant age and PSA levels difference between the cancer and non-cancer group ($P < 0.001$, **Table 1**). In general, histological inflammation was a frequent finding, observed in the biopsy specimens from 227 (33.7%) patients. A significant but inverse association was found between presence of inflammation and presence of PCa ($P < 0.001$, **Table 1**). PCa cases had lower levels of PSEP compared with normal subjects ($P = 0.003$, **Table 1**).

In PSA levels stratified analysis, the presence of prostatic inflammation were more prominently in cases with PSA 4-10 ng/ml than in cases with the other two PSA levels ($P = 0.002$, **Table 2**). Accordingly, decreased levels of PSEP were still associated with an increased risk of PCa in cases with PSA 4-10 ng/ml ($P = 0.039$, **Figure 1**). This association was not observed in the other two PSA levels ($P = 0.564$ and 0.379, respectively). An ROC curve

Table 2. PSA levels and Histological prostate inflammation

		PSA ≤ 4 ng/ml	PSA 4-10 ng/ml	PSA > 10 ng/ml	*P* value
Inflammation	No	12 (60.0%)	145 (58.5%)	274 (71.9%)	0.002
	Yes	8 (40.0%)	103 (41.5%)	107 (28.1%)	

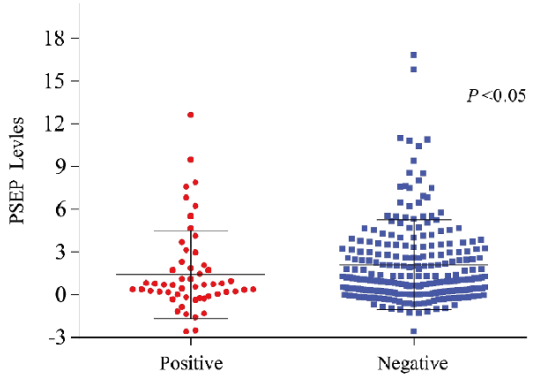

Figure 1. Urine PSEP levels in prostate needle biopsy cases with PSA 4-10 ng/ml.

was developed to identify the cut-off value distinguishing men with PCa from controls in PSA 4-10 ng/ml group. Youden's Index reached a maximum at a cutoff value of 0.35 ng/ml. The diagnostic sensitivity was 62.2%, and the specificity was 72.4%. The negative predictive value was 89.6% and positive predictive value was 34.6%. In multivariate logistic regression analysis, PSEP levels < 0.35 ng/ml was not significantly associated with PCa risk in PSA grey zone. Compared with men with PSEP levels < 0.35 ng/ml, men with PSEP levels > 0.35 ng/ml were associated with a decreased risk of PCa (OR: 0.57, 95% CI = 0.29-1.12, *P* = 0.102). When the cut off value was 5.52 ng/ml, using PSEP levels would screen out 90% of PCa patients with PSA 4-10 ng/ml.

The PSEP levels were positively correlated with prostatic inflammation (*P* = 0.018, r = 0.12). The PSEP levels were higher in urine isolated from prostatic inflammation patients [1.04 (-6.52-18.8) ng/ml] compared with normal subjects 0.76 (-7.28-18.5) ng/ml, *P* = 0.048]. The difference was more prominently in cases with PSA 4-10 ng/ml (**Table 3**).

Discussion

Inflammatory infiltrates are frequently found in routine biopsies performed, although the prevalence is variable, perhaps because the inflammation is not frequently reported by pathologists [8]. In this study we report a high prevalence of prostatic inflammation on prostate needle biopsy. Multiple previous studies have evaluated the relationship between inflammation and the subsequent diagnosis of PCa and have reached differing conclusions. Iczkowski et al. reported that atrophy with inflammation showed some preferential spatial association to PCa [9]. Benedetti et al. and Gurel et al. found that prostate inflammation was associated with a higher incidence of PCa while some studies presented that inflammation in benign prostate is inversely associated with future PCa risk. Meta-analyses by Dennis [10] and Jiang [11] et al. showed a positive association between clinical prostatitis and PCa. These studies comprised pooled analyses of cohort or case-control studies and the presence or absence of prostatitis was determined by chart review or personal interview. While these studies provide an important clinical link between clinical prostatitis and PCa, they relied on patient definitions and recall of prior prostatitis, which may be vulnerable to recall bias. Moreover, clinical prostatitis is not always accompanied by histological signs of inflammation and vice versa. Thus, these studies are not well suited to determine the association of histological inflammation and PCa. Similar with our results, a meta-analysis of 25 studies reported that histological inflammation on prostate needle biopsy was associated with a lower PCs risk [12].

Prior studies have shown that asymptomatic histological inflammation and latent infection are common findings in men, particularly those with benign prostatic hyperplasia and concomitant urological conditions [13]. Given that subclinical inflammation may be present in many men, in our study we used histology to better determine the association between histological inflammation and the subsequent development of PCa. The high prevalence of inflammation in pathological samples of prostate tissue from surgery or biopsy suggested a possible link between inflammation and PCa.

While the molecular pathogenesis of PCa has been characterized by genes and proteins involved in pro-inflammatory pathways, previ-

Table 3. Urine PSEP levels stratified by PSA levels

		Without Inflammation	With Inflammation	*P* value
PSA, ng/ml	≤ 4	1.46 (-4.99-8.29)	-0.028 (-0.44-2.57)	0.280
	4-10	0.98 (-3.06-16.8)	1.27 (-3.50-18.8)	0.027
	> 10	0.72 (-7.28-18.5)	0.94 (-6.52-13.8)	0.061

ous study has shown that inflammation has a protective role on PCa incidence [12]. The ability of premalignant cells to evade and downregulate the host immune defenses determines the survival and neoplastic potential of premalignant cells. The inflammatory response can prevent this carcinogenesis by recognizing and eliminating tumor specific antigens, a process known as immunosurveillance. Therefore, in the PCa milieu a balance exists between immune system up-regulation and downregulation. Inflammation is a hallmark of immune system up-regulation. Thus, it is plausible that it favors host defense mechanisms with a lower risk of PCa in the current study. Our results implicate inflammation and immunomodulation as candidate targets for pharmacological intervention to prevent and potentially treat PCa.

Proteomic profiling of prostasomes isolated from urine identified hundreds of proteins, many of which can serve as biomarkers for prostate diseases was recently validated for prostate cancer and prostatitis [6]. One advantage of collecting prostasomes from urine, as compared with blood, is that such isolates are more enriched in prostasomes relative to other constituents [6]. Cells and most apoptotic bodies are considerably larger than prostasomes and can thus be easily separated from prostasomes by differential centrifugation. In a recent study, PSEP displayed sensitivities above 60% at 94.2% specificity at a detection threshold with positive values for prostatitis patient samples and negative values for control samples [7]. Compared with expressed prostatic secretions, urine PSEP measurement was more convenient and less painful. In the current study, the PSEP levels were positively correlated with prostatic inflammation as expected. It is noteworthy that The PSEP levels were significantly lower in urine isolated from PCa patients with PSA 4-10 ng/ml compared with normal subjects. Histological inflammation was more frequently found (41.5%) in cases within PSA grey zone, which may account for the difference we observed. As a potential biomarker for prostatic inflammation, urine PSEP may be helpful to eliminate false positive PSA levels due to prostatic inflammation and reduce unnecessary prostate needle biopsy in cases within PSA grey zone.

There are several potential implications of our study. Since we found that histological prostate inflammation is associated with lower PCa risk, followup guidelines for these patients might be adjusted for the reduced PCa risk. As such, our results encourage pathologists to systematically evaluate and report prostate inflammation on biopsy as it may have implications for a repeat prostate biopsy strategy. Furthermore, the use of urine PSEP examination to predict prostatic histological inflammation is appealing, which could potentially allow for more tailored prostate needle biopsy decision.

This study had the limitation of not being designed to explore the mechanisms linking inflammation to lower prostate carcinogenesis. With these implications, studies evaluating the biology of inflammation and how it relates to carcinogenesis are needed since they may identify areas for PCa prevention therapies. As a non-invasive method, PSEP will be helpful to discriminate prostatic inflammation from PCa based on the relatively high negative predictive value. While the relatively small sample size of men in PSA grey zone in the current study might limit the power to reveal an optimal PSEP cutoff which should be confirmed in a larger-scale study.

In conclusion, histological inflammation was associated with lower PCa risk. Urine PSEP levels were correlated with histological inflammation on prostate needle biopsy. The urine PSEP levels were significantly decreased in PCa patients with PSA 4-10 ng/ml.

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Disclosure of conflict of interest

None.

Abbreviations

PCa, prostate cancer; PSA, prostate-specific antigen; PSEP, prostatic exosomal protein.

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Original Article

A urine-based biomarker for chronic prostatitis/chronic pelvic pain syndrome: a retrospective multi-center study

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Contributions: (I) Conception and design: X Shang, H Li, Y Zeng; (II) Administrative support: X Shang; (III) Provision of study materials or patients: X Shang; (IV) Collection and assembly of data: Z Wu, X Hu, J Yang; (V) Data analysis and interpretation: W Liang, X Hu, J Yang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) is one of the most common diseases in young and middle-aged men, accounting for 30% of outpatient men in urology OPD. There are no definitive diagnostic criteria for CP or CPPS and no accepted therapies that cure the disease.

Methods: We identified 372 patients with CP diagnosed from 2015 to 2018 and collect the information of age, routine urinary test, express prostatic secretion (EPS), and NIH-Chronic Prostatitis Symptom Index (NIH-CPSI).

Results: Our study proved a correlation between the increase of prostatic exosomal proteins (PSEPs) level and NIH-CPSI scores. Spearman's correlation coefficient showed a significant level correlation between NIH-CPSI and PSEP level (rs=0.194, P=0.0035). In the meantime, the correlation was found between the PSEP level and EPS-white blood cells. Spearman's correlation coefficient showed that there was a significant hierarchical correlation between EPS-white blood cells and PSEP level (rs=0.183, P=0.001).

Conclusions: These findings highlight the potential of PSEP is a practical indicator of the symptomatic progression of CP/CPPS. Applications of PSEP assay may guide drug discovery and lead to better treatment to improve the patient's quality of life.All in all, PSEP detection in urine is safe and effective, and it is worthy of further promotion and application in clinical practice.

Keywords: Chronic prostatitis (CP); prostate exosomal protein; chronic pelvic pain syndrome (CPPS); urine-based biomarker

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Introduction

Chronic prostatitis (CP) or chronic pelvic pain syndrome (CPPS) is one of the most common diseases in young and middle-aged men and accounts for up to 30% of the outpatient male observed in the urological clinics (1). From the epidemiological survey, 4.5–10% of the male population presents symptoms of prostatitis worldwide, and 50% of men have prostatitis at some points during their lifetime (2,3). Thus, CP/CPPS is of paramount importance as a medical problem for health care internationally. However, despite the intense research in the past decades, the etiology and pathogenesis of CP/CPPS are still unclear. Also, the clinical manifestation of CP/CPPS lacks specificity, making clinical diagnosis and treatment challenging (4,5). The cause of CPPS has not yet been clarified, but the basic viewpoint is: CP/CPPS is a complex disease involving physical and mental factors. Even if there are obvious physical lesions that can cause pelvic pain, psychological and social factors cannot be ignored. Treatment requires the use of a multidisciplinary and comprehensive approach, including surgery, drugs, physiotherapy, psychotherapy, etc. (6). The purpose of treatment is to relieve pain, improve function and eliminate psychological barriers. Many biomarkers have also been confirmed to be involved in inflammation (7). So the research of biomarkers is not only helpful for the accurate diagnosis of CP/CPPS, but also for the development of new targeted drugs for CP/CPPS, which is important for the individualized and precise treatment of CP/CPPS.

The diagnosis of CP/CPPS has included a combined process of recording clinical symptoms and signs, routine urine tests, or culture and the express prostatic secretion (EPS), which can be retrieved by performing a rectal exam with a massage on the prostate (8). However, this is a clinical process that requires a qualified doctor to operate and often disturb the patients. Also, the EPS index may exclude other potential pelvic pain associated with urological disorders. There is a lack of effective tools for the evaluation of the disease and the judgment of effect. At present, the NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) is a questionnaire most commonly used internationally. It was developed by experts organized by the National Institutes of Health. Most practice clinics and hospitals in our country (for example, the Jinling hospital in Nanjing; the Taicang People's Hospital and Military General Hospital in Jinan) carry out the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) to document the patient symptoms and responses to diagnose CP/CPPS. In this process, the patient must answer several questions. The doctor should calculate the NIH-CPSI score according to medical history and clinical symptoms. Therefore, it is imperative to find and introduce a valid tool of CP/CPPS surrogate for diagnosis.

Also, studies have shown increased risks of prostate cancer (PCa) for men with a history of prostatitis compared with the case-control. For example, Tomas *et al.* found the atypical hyperplasia in epithelial cells with dark, swelling, and prominent nucleoli in the tissue slide showing a lesion of inflammatory atrophy. Inflammatory atrophy can supply a favorable breeding ground for PCa development (9).

Exosomes are small, membrane-bound storage vesicles that mediate transport of a cytosolic cargo between the cells and to the extracellular space (10). Exosomes are produced in many cell types, including the prostate epithelial cells, where they are termed prostasomes (11). They can also be excreted to the interstitial tissue compartments when infiltrating leukocytes accumulate in response to inflammation. Thus, prostasomes can be found in seminal plasma, and urine (12). Prostasomes have been reported to elicit antioxidant effects, antibacterial activity, and immunomodulation (13,14). It has been proposed prostasomes may reduce the production of reactive oxygen species (ROS) (15). Studies also suggested prostasomes inhibit the NADPH oxidase activity of polymorph nuclear neutrophils by lipid transfer from prostasomes to the plasma membrane of these cells (16). The molecular composition of human prostasomes is varied and comprises hundreds of known and unknown proteins. Prostate diseases, including prostate cancer, benign prostatic hyperplasia (BPH), and prostatitis, present unique phenotypes at the level of their respective proteasomal proteomes (17).

Recently, antibodies against human prostasomes were generated and found to be reactive to urine samples of CP/CPPS patients. The proteins that are immune reactive to the antibodies are appointed as prostatic exosomal proteins (PSEPs) (18,19).

A multi-center clinical trial performed in China showed that CP/CPPS patients present elevated PSEP in the void urine when compared to the healthy men (20). Subsequent applications of the PSEP test confirmed the utility in many clinics across China; however, these applications have not addressed the relationship between PSEP test and current methods of diagnosing CP/CPPS. In this study, we intended to be the first to reveal the potential relationship between PSEP in urine samples and EPS indexes, including white blood cells (WBC) and lecithin corpuscles and NIH-CPSI. Our studies highlight the potential value of PSEP as an

indicator for CP/CPPS symptoms and disease progression.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/tau-20-1268).

Methods

Subjects

From Sep 2015 to May 2018, 372 patients (age ranging from 20 to 61 years old, male) were recruited and diagnosed as having CP/CPPS at the Jinling Hospital Affiliated to the Nanjing University School of Medicine, the Nanjing University of Chinese Medicine Affiliated Integrated Traditional and Western Medicine, Jinan Military General Hospital. Of the 372 patients, 225 underwent an NIH-CPSI questionnaire survey (21). For inclusion into this study, CP/CPPS patients must meet the following criteria: males with CP/CPPS history and clinical symptoms, including urinary frequency, urgency, and retention, the inflammatory reaction, or reflective (perineal pain, abdominal bulge, and discomfort). A portion of patients presented with premature ejaculation or other symptoms includes infertility. Upon rectal exam, CP/CPPS patients confirmed changes of EPS found over the average person, including WBC and lecithin corpuscle (phosphatidylcholine) in secretion. Also, routine urinary tests or culture showed no significant anomaly of acute inflammatory cell types or other urinary tract infections. An NIH-CPSI questionnaire survey was used to report pain, symptoms of abdominal discomfort, finding urination symptoms, and quality of life to give rise to a total score.

The Institutional Research Ethics Committee approved all research analysis. The written informed consent was retrieved from all individuals, and case-report-forms (CRF) were administered during outpatient visits to collect the information of age, routine urinary test, EPS and NIH-CPSI, etc. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

Sample collection

Midsegment urine samples were attained in the morning and were at once frozen. They were stored at –20 ℃ until ready for use. Subjects were excluded when there were incomplete clinical data, inadequate quantities of urine samples, or grossly bloody and thick urine, or with alcohol consumption.

PSEP assay

The double-blinded PSEP-ELISA assay was performed as described according to the manufacturer's instruction [Onco Biomedical Technology (Suzhou) CO., Ltd] (20). Void human urine samples were added to the 96-well microplate trays and incubated at 37 ℃ for one hour. After antibody incubation, the reaction was visualized by the addition of chromogenic tetramethylbenzidine (TMB). The resulting color development shows the amount of PSEP in urine samples. The absorbance of the samples was read at 450 nm/630 nm.

Statistical analysis

The statistical analysis was performed blindly. For the cross-sectional study analysis, a database collected all information from each patient, including age, routine urinary test, EPS, including WBC, and lecithin corpuscle in secretion and NIH-CPSI. WBC and lecithin corpuscle stratified data in secretion and NIH-CPSI, respectively, according to different classification methods. The mean of PSEP concentration and detection rate of PSEP are calculated, respectively. Contingency tables and Spearman's correlation coefficient were used to test for independence between PSEP positive/negative status and concentration with Chi-square test statistics by SAS9.4 (The SAS software was developed by The State University of North Carolina, the USA in 1966) for each factor including WBC and lecithin corpuscle and NIHCPSI. Data were stratified by counting methods to minimize potential confounding factors when testing for association between PSEP and CP/CPPS status. The differences were significant when $P<0.05$. We conduct power analyses for the assessment of our sample size by G power software.

Results

The relationship between urine PSEP level and EPS-WBC number with "+/–" as an indicator of disease severity

All 372 patients were documented with EPS-WBC numbers in their case report forms (CRFs). This method stratified them from documenting WBCs, as shown in *Table 1*.

They were divided into distinct groups according to their WBC number in EPS. WBC number less than 9

Table 1 Relationship between urine PSEP level and WBC numbers in EPS

WBC grade	Case number	PSEP positive	PSEP negative	Positive rate (%)	Mean ($\bar{x}$±s)
WBC±	58	31	27	53.4	2.56±2.62
WBC+	116	76	40	65.5	3.23±3.29
WBC++	75	51	24	68.0	3.17±2.78
WBC+++	72	55	17	76.4	4.63±3.91
WBC++++	51	42	9	82.4	4.08±2.78

Chi-Square test χ^2=13.200, P=0.010. Spearman's correlation coefficient analysis rs=0.183, P<0.001. WBC±: WBC number less than 9/HP; WBC+: WBC number 10–20/HP; WBC++: WBC number 21–30/HP; WBC+++: WBC number 31-40/HP; WBC+++: WBC number >40/HP. P<0.05 is statistically significant. PSEP, prostatic exosomal protein; WBC, white blood cells; EPS, express prostatic secretion.

Table 2 The relationship between urine PSEP level and the density of EPS-lecithin corpuscles

Lecithin grade	Case number	PSEP positive	PSEP negative	Positive rate (%)	Mean ($\bar{x}$±s)
+	89	61	28	68.5	3.37±3.08
++	99	68	31	68.7	3.55±3.38
+++	117	80	37	68.4	3.74±3.48
++++	67	46	21	68.7	3.18±2.69

Chi-Square test χ^2=0.003, P=0.999. Spearman's correlation coefficient analysis rs<0.001, P=0.994. PSEP, prostatic exosomal protein; EPS, express prostatic secretion.

under the high-power microscope is considered negative or set as ±; WBC number 10–20 is set as +; WBC number 21–30 is set as ++; WBC number 31-40 is set as+++; WBC number >40 is set as ++++. As is shown in *Table 1*, with the increase of EPS-WBC number, the positive rate of PSEP showed a trend of increase. The mean PSEP concentration appeared to increase. PSEP concentration in urine sample change significantly when we analyze the dataset with the contingency table chi-square test (χ^2=13.200, P=0.01). Spearman's correlation coefficient showed a significant rank correlation between EPS-WBC and PSEP concentration either (rs=0.183, P=0.001). These data suggested that, in the current cohort of 372 patients, there was a statistically significant correlation between the number of WBC and the concentration of PSEP in the urine of CP/CPPS patients.

Relationship between urine PSEP level and EPS-lecithin corpuscles

Although the vitality EPS examination has been questioned, EPS is still widely used in the clinic because there is no ideal specific diagnostic marker. We, therefore, examined EPS-lecithin corpuscles for all patients. All 372 patients had records of the EPS-lecithin corpuscle in their CRFs. The grade of EPS-lecithin corpuscle density stratified them, as shown in *Table 2*. In normal EPS, a full field of lecithin corpuscles was observed with a high-power microscope, which was appointed as ++++. The density of EPS-lecithin corpuscles lower than 50% (++) per vision field under the high-power microscope is considered a sign of CP/CPPS in urological clinics. From *Table 2*, the data showed there was no statistical significance (χ^2=0.003, P=0.999) between the density of lecithin corpuscles and PSEP concentration in the urine of CP/CPPS patients when we analyzed them with contingency tables chi-square test. Also, the Spearman's correlation coefficient showed no significant rank correlation between the two either (rs=0.001, P=0.994).

Relationship between urine PSEP level and NIHCPSI

The CP symptom index developed by the NIH of the United States (NIHCPSI) is an established scoring method to record the symptoms of the patients. According to the severity of symptoms, NIH-CPSI is divided into mild (1–14 points), moderate (15–29 points), or severe (30–43 points) (21). Increases of NIH-CPSI are used as the indication that CP/CPPS becomes more pronounced with more severe symptoms.

Table 3 The relationship between the urine PSEP level and the NIH-CPSI

NIH-CPSI	Case number	PSEP positive	PSEP negative	Positive rate (%)	Mean ($\bar{x}\pm s$)
≤15	113	70	43	61.95	3.56±3.60
16–30	89	66	23	74.16	3.39±3.17
>30	23	21	2	91.30	5.20±3.82

Chi-Square test χ^2=9.149, P=0.0091. Spearman's correlation coefficient analysis rs=0.194, P=0.0035. PSEP, prostatic exosomal protein; NIH-CPSI, NIH-Chronic Prostatitis Symptom Index.

From the 372 CP/CPPS patients, 225 patients had NIH-CPSI records. The correlation between urine PSEP level in urine and NIH-CPSI was examined. As shown in *Table 3*, the rising NIH-CPSI was correlated with the increase of patients with a positive rate of PSEP. We analyzed them with the contingency table chi-square test (χ^2=9.149, P=0.0091). Spearman's correlation coefficient showed a significant rank correlation between NIH-CPSI and PSEP concentration (rs=0.194, P=0.0035). Although the correlation between NIH-CPSI and PSEP is weak, these data suggest an increased PESP concentration in the urine sample is correlated with the severity of symptoms and the advanced stages of CP/CPPS.

We have conducted a power analysis by the G power software to assess the sample size. Power (1 – β) =0.99, which means the power of the test is well, and the sample size is enough to have valid results (*Figure 1*).

Discussion

CP/CPPS is caused by the interaction between immune, neurological and endocrine systems and psychological factors (22). The theories behind the disease include stress-induced dysfunction of the hypothalamic-pituitary-adrenal axis (23), abnormal adrenal cortex hormones (endocrine) (24), neurogenic inflammation (25) and muscle fascia pain syndrome (26). In the latter two categories, local nervous system disorders are caused by past trauma, infection or anxious personality. Chronic unconscious tightening of the pelvis (regulated by the release of substances from nerve cells, such as substance P can also lead to inflammation. The prostate and other parts of the urogenital tract: bladder, urethra, testis can also be inflamed by long-term activation of mast cells at the ends of the pelvic nerves. Similar stress-induced genitourinary inflammation has been found in experiments of other mammals (27). However, there is no correlation between the histological examination of prostatitis and the chronic prostatitis symptom index of the NIH-CPSI (28).

CP/CPPS is a frustrating clinical condition for both practitioners and patients. In developing countries, the situation is worse because often CP/CPPS is not correctly diagnosed using a combination of multiple methodologies, including NIH-CPSI, EPS, 2- and 4 cup tests, and so on (29). Instead, clinician experience sometimes dictates the treatment of self-described abdominal and urinary discomfort with a frequent prescription of antibiotics to observe treatment response to the anticipated CP/CPPS.

At present, there is no uniform standard and "gold standard" for the diagnosis of CP/CPPS, and laboratory diagnosis lacks widely accepted biomarkers, and the methodology that can be used in clinical research is very limited. There is no doubt that CP changes the local microenvironment of the prostate, and the corresponding biomarker changes will inevitably occur. Quick *et al.* (30) found CCL-2 and CCL-3 of CP/CPPS patients has a key inflammatory mediator effect. The results of Paulis *et al.* (31) showed that IL-6 in EPS of CP/CPPS patients was significantly higher than that in healthy controls, and its increased level was related to CP/CPPS symptom score (NIH-CPSI). Hochreiter *et al.* (32) found that IL-8 in EPS of type IIIA patients was significantly higher than type IIIB group and the control group, it is believed that IL-8 can be used to distinguish type IIIA and IIIB CP/CPPS. Miller *et al.* (33) measured NGF, IL-6, IL-8, and IL-10 in semen of CP/CPPS patients, and found that the level of NGF in semen was related to the severity of pain. These findings are consistent with the findings of Watanabe *et al.* (34) that the NGF in EPS is related to the NIH-CPSI pain score, and the level of NGF is significantly reduced after successful treatment. As a new member of the costimulatory molecule family, B7-H3 plays an important role in regulating the immune system. Wei *et al.* (35) reported that the B7-H3 in EPS of the control group was significantly higher than other subtypes group, and the B7-H3 level of CP/CPPS III B patients was higher than that of CP /CPPS IIIA patients.

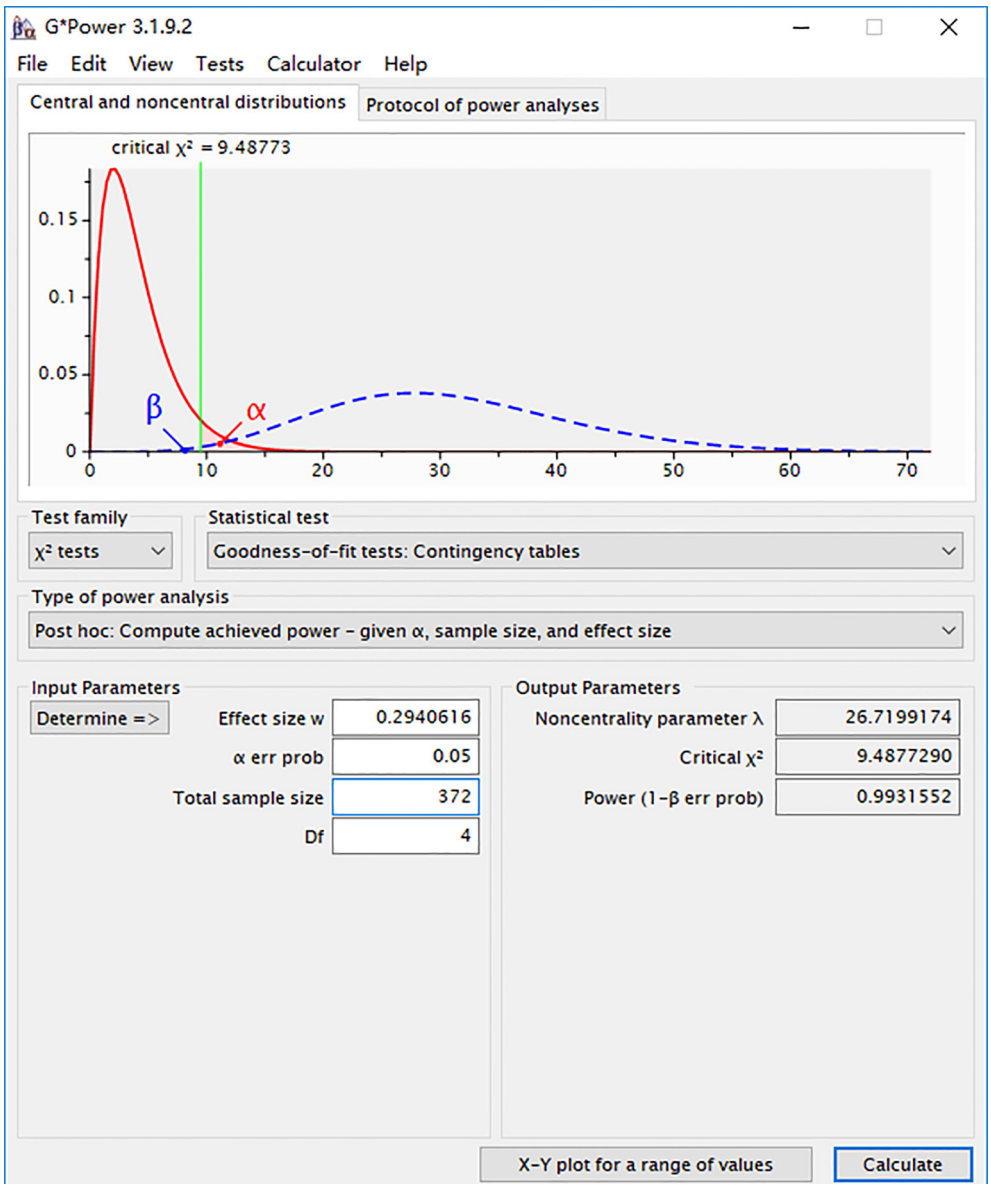

Figure 1 The power analysis by the G power software.

Traditional routine testing methods, including EPS and urine routine diagnostic examination are challenged. It has limited significance for clinical guidance. Therefore, we need to find a new biomarker to guide the diagnosis and treatment of CP/CPPS.

The available PSEP–ELISA assay as a simple, objective and non-invasive urine test supplies the clinician as a biological surrogate to aid in the diagnosis of CP/CPPS. In the past couple of years, the PSEP test became adopted in hospitals and clinics in China and received some positive responses. However, the correlation of urine PSEP level with EPS and/or NIH-CPSI was only described in meetings and conferences anecdotally. Therefore, the current study is the first to confirm that the PSEP level is associated with the increasing WBC counts and NIH-CPSI scores. Thus, an increasing PSEP level in the urine can be a sign of the severity of CP/CPPS and may guide the best treatment plan. However, it is a pilot study that only elaborates on the correlation of urine PSEP level with EPS and/or NIH-CPSI. Therefore, further study should focus on the cut-

off point of PSEP to distinguish between IIIa and IIIb categories avoiding prostatic massage.

During the chronic prostatic process, leukocytes exudate and swarm to the inflammation region; leukocytes engulf lecithin, causing lecithin bodies to decrease.

In our current study, we do not find a strong correlation between urine PSEP level and density of EPS-lecithin corpuscles. We noticed this result and had extensive discussions with other clinicians. We believe that further study may be needed to test this relationship more closely in a study with a larger sample size.

There is intense research ongoing to find better and more practical biomarkers for CP/CPPS. Studies have shown that inflammatory cytokines in seminal plasma of CP/CPPS patients are increased significantly, including IL-1, IL-6, IL-8, IL-10, and TNF-a (36). Polymorph nuclear (PMN) elastase in EPS was significantly higher in IIIa compared to IIIb (37,38). Other pathogens than bacteria, including chlamydia, are associated with increased WBC counts and pain severity in men with CP/CPPS. Perhaps the most thorough survey of the protein biomarkers came from mass spectrometry of seminal plasma proteomes of prostatitis patients (39). This study identified 418 proteins associated with prostatitis versus 280 present in healthy individuals with 1,662 proteins present in both populations. While these are encouraging steps towards the development of vial biomarkers for CP/CPPS, they are derived from EPS or require sophisticated equipment to perform analysis. Therefore, they are not of practical value for general clinical application at this moment.

While PSEP-ELISA assay is simple to perform on voided urine, much still is to be learned. For example, it would be essential to confirm our study by more independent hospitals and clinics around the world for different ethnic backgrounds. There are reports that in some regions, pathogens may be more closely related to CP/CPPS. Also, the mechanism of PSEP involvement in CP/CPPS is entirely unknown. It would be essential to understand why PSEP is elevated in CP/CPPS and whether it is causative, or it is a mere biomarker surrogate. The understanding of PSEP biology would also be necessary for drug development. For example, many animal models are currently being used to investigate the etiology and drug response of experimental prostatitis in animal models (40). PSEP may be used to monitor the disease course and drug treatment outcomes. There are still some shortcomings in this study. There is no NIH classification of CP. The correlation between PSEP in urine of CP patients with different types and WBC, SPL counts in EPS, and NIH-CPSI score needs further study. We are preparing to carry out a multidisciplinary, multi-center, prospective, large-sample clinical study of evidence-based medicine. Moreover, CP/CPPS is often clinically associated with symptoms of urinary dysfunction. Currently, research on PSEP only confirms that it is related to the severity of symptoms, but cannot locate the cause. It may be necessary to combine UDS examinations, which is more conducive to accurate treatment of patients. UDS examination can identify specific types of lower urinary tract dysfunction in patients with CP/CPPS (41), and then take targeted treatment.

Conclusions

Our study proved a correlation between the increase of PSEP level and NIH-CPSI scores. In the meantime, the correlation was found between the PSEP level and EPS indexes. These findings highlight the potential of PSEP is a practical indicator of the symptomatic progression of CP/CPPS. Applications of PSEP assay may guide drug discovery and lead to better treatment to improve the patient's quality of life.

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Footnote

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Ethical Statement: The authors are accountable for all

aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The Institutional Research Ethics Committee approved all research analysis. The written informed consent was retrieved from all individuals, and case-report-forms (CRF) were administered during outpatient visits to collect the information of age, routine urinary test, EPS and NIH-CPSI, etc. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013).

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Clinical Evaluation of Urine Prostatic Exosomal Protein in the Diagnosis of Chronic Prostatitis

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Keywords
Prostate · Prostatitis · Prostasome · Prostatic exosomal protein · Biological markers

Abstract
Objective: To evaluate the clinical potential of urine prostatic exosomal protein (PSEP) as a diagnostic biomarker of chronic prostatitis (CP). ***Materials and methods:*** Using an enzyme-linked immunosorbent assay kit, urine PSEP levels were detected in 103 control cases as well as 283 cases of CP, with 82 cases fulfilling the definition of the USA National Institutes of Health category II (NIH-II), 108 cases of NIH-IIIa and 93 cases of NIH-IIIb. The values of age, body mass index, prostate volume, serum prostatic specific antigen (PSA) urine PSEP levels, and seminal parameters were analyzed. ***Results:*** The PSEP levels were significantly higher in patients of NIH-II (2.09 [2.35] ng/mL), NIH-IIIa (1.80 [2.95] ng/mL) and NIH-IIIb (1.64 [2.48] ng/mL) compared to the value of 0.24 (0.76) ng/mL in the controls. ROC identified a cutoff value of 1.387 ng/mL, with a sensitivity of 59.0% and specificity of 94.2%. The area under the ROC curve was 0.833. PSEP levels positively correlated with serum PSA levels in the NIH-IIIb group, and with EPS WBC count in the NIH-IIIa group, and with semen WBC count in each CP subgroups but negatively correlated with sperm motility in both the NIH-IIIa group and the NIH-IIIb group. ***Conclusion:*** Urine PSEP could be a potential biomarker for CP.

Introduction

Prostatitis is a common disease in adult males, with a prevalence of 8.2% reported in a systematic review that included more than 10,000 participants [1]. Chronic prostatitis (CP), which could have significant mental and physical impact on patients' quality of life [2], consists of 3 categories defined by the USA National Institutes of Health (NIH-II) (chronic bacterial prostatitis), NIH-III (CP/chronic pelvic pain syndrome), and NIH-IV (asymptomatic prostatitis) [3]. Currently, multiple clinical evaluations and the exclusion of other conditions must be completed for diagnosis and severity assessment in CP because a specific biomarker is still not available [4].

Prostasomes are nanosized vesicles produced by prostatic epithelial cells and are enriched in semen and prostatic fluids. Under normal conditions, a small amount of prostasomes is released into the posterior urethra and then excreted with urine [5]. Recently, several studies had

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revealed that some protein components of prostasomes could be promising candidates as diagnostic biomarkers for prostate diseases [6, 7, 8]. Among these proteins, prostatic exosomal protein (PSEP) is thought to be a potential marker of CP and was evaluated in this study.

Materials and Methods

A total of 283 patients with CP who visited our clinic were enrolled in this study between May 2014 and November 2015, and were classified into 3 groups: NIH-II, NIH-IIIa and NIH-IIIb. Additionally, 103 males were recruited as controls from routine physical examination for fertility, with normal seminal WBC count (no more than 1×10^6/mL), and without a history or any symptoms of prostatic diseases or urinary tract infection as well. Individuals were excluded if they had sexual activity within 48 h before measurement or catheterization within 2 weeks.

The diagnosis of CP was made based on clinical symptoms and laboratory findings of urine and expressed prostatic secretions (EPS) and on the exclusion of other circumstances such as urethritis, cystitis, urogenital cancer, and urinary calculus. A post-massage urine test was performed in case of EPS collection failure. Each patient had a review of the history and symptom severity assessment using the National Institutes of Health CP Symptom Index (CPSI), which was reported as subscores for pain, urinary symptoms, and quality of life, as well as the total score. EPS were collected for regular testing and culture. Data of body mass index (BMI) calculated as the weight (in kilograms)/height (in square meters), prostate volume (PV) measured by ultrasound, serum prostatic specific antigen (PSA) were collected. Semen samples were collected from 198 cases of CP patients (59 cases of NIH-II, 73 cases of NIH-IIIa, 66 cases of NIH-IIIb group) and all controls. Data of semen volume, semen WBC count, sperm concentration, and motility were compared.

In order to minimize the bacterial interference, midstream urine samples were collected before massage and stored at –80°C until PSEP measurement. Samples were thawed before analysis and assayed using PSEP diagnostic kits (enzyme-linked immunosorbent assay) manufactured by Onco Biomedical Technology Co. Ltd. (Suzhou, China) [9]. Indirect ELISA was performed. Urine samples were added to the microplate wells and incubated for 1 h at 37°C. The plates were washed 5 times. Then, 100 μL per well of blocking solution (1% BSA in PBS) was added and incubated for 40 min at 37°C. The wells were washed 5 times and then PSEP antibody was added. The plate was incubated for 40 min at 37°C. After washing, secondary antibody conjugated with horseradish peroxidase (HRP) was added and incubated for 20 min at 37°C. After washing, substrate solution was added into each well and incubated for 20 min. Color development was stopped and the absorbance values were read in the dual-wavelength mode (450 nm as the test wavelength and 630 nm as the reference wavelength) on a BIO-RAD 680 microplate reader. A linear standard curve was generated by plotting the graph using the standard concentrations on the y-axis and the corresponding absorbance on the x-axis. The sample concentration was determined according to the standard curve, and the value was multiplied by the dilution factor if there was one.

Values of PSEP, WBC in EPS, CPSI total, and subscores were reported as the median (interquartile). The Kruskal-Wallis test was used to compare these values between groups. Analysis of variance was used to compare values of age, BMI, PV, PSA levels, urine WBC count, semen volume, semen WBC count, sperm concentration, and motility between groups. An ROC curve was developed to determine the optimal cutoff value for PSEP. Correlations between PSEP and age, BMI, PV, PSA, WBC count in EPS, WBC count in semen, semen volume, sperm concentration, sperm motility, as well as NIH-CPSI scores were assessed using the Spearman correlation coefficient. Significance was set at $p < 0.05$. SPSS version 20.0 was used for statistical analysis.

Results

The demographic characteristics of the study groups are shown in Table 1. There were no differences in distribution of age, BMI and PV between the CP and control groups. The PSA levels were slightly elevated in each CP subgroup compared to the control group. CPSI scores were collected from CP patients, while individuals in control group gave almost negative response to the questionnaire. CPSI total score, pain, urinary symptom subscores, and symptom impact did not significantly differ among the subgroups of CP. Patients of NIH-II and NIH-IIIb group had slightly decreased sperm motility. There were no differences of WBC count in semen, sperm concentration, and semen volume between CP and the control group.

The PSEP detected in midstream urine showed a non-normal distribution in the CP and control groups. The PSEP levels in each group are listed in Table 1. The median (interquartile range) PSEP levels were 2.09 [2.35] ng/mL, 1.80 [2.95] ng/mL and 1.64 [2.48] ng/mL in the NIH-II, NIH-IIIa, and NIH-IIIb group respectively. The values were significantly higher in each CP subgroup compared to the value of 0.24 [0.76] ng/mL in the controls. However, no difference in PSEP was found among the NIH-II, NIH-IIIa, and NIH-IIIb groups (Fig. 1).

An ROC curve was developed to identify the cutoff value distinguishing men with CP from controls (Fig. 2). Youden's Index reached a maximum at a cutoff value of 1.387 ng/mL. The diagnostic sensitivity was 59.0%, and the specificity was 94.2%, corresponding to the cutoff. The area under the ROC curve was 0.833 (95% CI 0.794–0.873).

The associations between PSEP and other parameters were assessed by spearman correlation coefficient (Table 2). There were no correlations between PSEP level and age, BMI, PV in both control and CP subgroups. It was found that urine PSEP levels positively correlated with

Table 1. Characteristics of patients with CP and controls enrolled in the study

	Control (n = 103)	NIH-II (n = 82)	NIH-IIIa (n = 108)	NIH-IIIb (n = 93)
Age, years, mean (SD)	35.8 (7.9)	35.1 (9.3)	34.7 (9.0)	33.5 (9.3)
BMI, kg/m^2 mean (SD)	23.0 (2.0)	22.9 (1.5)	23.1 (2.1)	23.2 (1.8)
PV, mL, mean (SD)	19.5 (6.4)	19.0 (6.9)	18.4 (6.3)	17.6 (6.7)
PSA, ng/mL, mean (SD)	1.14 (0.62)[1–4]	1.37 (0.65)[1, 2]	1.50 (0.70)[1, 3]	1.38 (0.76)[1 ,4]
PSEP, ng/mL, median (IQR)	0.24 (0.76)[5–8]	2.09 (2.35)[5, 6]	1.80 (2.95)[5, 7]	1.64 (2.48)[5, 8]
WBC in urine (/hpf), mean (SD)	1.9 (0.7)[9, 10]	6.7 (3.6)[9–12]	2.7 (0.6)[9, 11]	2.0 (0.7)[9, 12]
WBC in EPS (/hpf), median (IQR)	4.5 (6.25)[13–15]	19.5 (7.25)[13–16]	23.5 (8.25)[13, 15, 17]	6.0 (6.0)[13, 16, 17]
CPSI total score, median (IQR)	0.0 (0.0)[18–21]	20.0 (7.25)[18, 19]	20.0 (11.0)[18, 20]	21.0 (7.75)[18, 21]
Pain domain, median (IQR)	0.0 (0.0)[22–25]	6.5 (4.5)[22, 23]	7.5 (5.0)[22, 24]	7.0 (4.0)[22, 25]
Urinary domain, median (IQR)	0.0 (0.0)[26–29]	6.0 (5.0)[26, 27]	5.0 (4.75)[26, 28]	6.0 (3.0)[26, 29]
QOL, median (IQR)	0.0 (0.0)[30–33]	8.0 (4.0)[30, 31]	9.0 (5.0)[30, 32]	9.0 (4.0)[30, 33]
Number of cases with semen sample	103	59	73	66
Semen volume, mL mean (SD)	3.5 (2.2)	3.4 (1.9)	3.5 (2.0)	3.3 (1.8)
WBC in semen, 10^6/mL mean (SD)	0.4 (0.5)	0.6 (0.8)	0.5 (0.7)	0.5 (0.9)
Sperm concentration, 10^6/mL mean (SD)	117.5 (89.6)	104.1 (95.0)	123 (83.5)	115.9 (90.7)
Sperm motility, (A+B%) mean (SD)	60.2 (18.8)[34–36]	53.6 (16.3)[34, 35]	55.0 (15.7)[34]	52.9 (18.1)[34, 36]

BMI, body mass index; PV, prostate volume; PSA, prostatic specific antigen; PSEP, prostatic exosomal protein; WBC, white blood cell; EPS, expressed prostatic secretions; CPSI, Chronic Prostatitis Symptom Index; QOL, quality of life.

[1] p = 0.014, one-way ANOVA test.
[2] p = 0.023, one-way ANOVA, LSD method.
[3] p < 0.001, ne-way ANOVA, LSD method.
[4] p = 0.012, One-way ANOVA, LSD method.
[5–8] p < 0.001, Kruskal-Wallis test.
[9] p = 0.037, One-way ANOVA test.
[10] p = 0.045, One-way ANOVA, LSD method.
[11] p = 0.017, One-way ANOVA, LSD method.
[12] p = 0.029, One-way ANOVA, LSD method.
[13–33] p < 0.001, Kruskal-Wallis test.
[34] p = 0.030, One-way ANOVA test.
[35] p = 0.037, One-way ANOVA, LSD method.
[36] p = 0.028, One-way ANOVA, LSD method.

serum PSA levels in the NIH-IIIb group (r = 0.210, p = 0.043), but not in NIH-II, NIH-IIIa, or control groups. The associations between PSEP levels and inflammatory markers of WBC count both in EPS and semen were assessed. PSEP positively correlated with EPS WBC count in the NIH-IIIa group (r = 0.141, p = 0.039), PSEP also positively correlated with semen WBC count in each CP subgroups: NIH-II (r = 0.192, p = 0.015), NIH-IIIa (r = 0.234, p = 0.027), NIH-IIIb (r = 0.173, p = 0.045). Besides, a negative correlation was found between PSEP and sperm motility in both the NIH-IIIa group (r = –0.184, p = 0.026) and the NIH-IIIb group (r = –0.191, p = 0.041). No correlations were found between the PSEP levels and semen volume, sperm concentration, CPSI total or subscore in control and CP subgroups. Furthermore, the values of age, BMI, PSEP, and PSA were compared according to PV both in the control and overall CP groups (Table 3). Individuals with lager PV (≥20 mL) were obviously elder than those with smaller ones (<20 mL). Serum PSA levels were significantly higher in patients with larger PV compared to patients with smaller PV

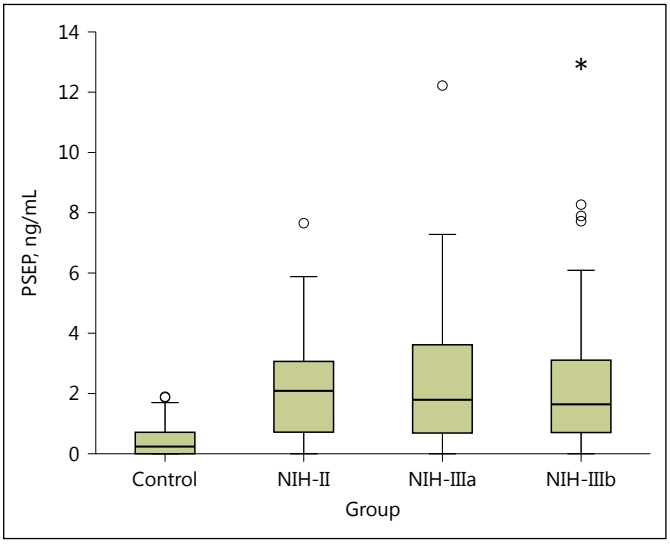

Fig. 1. Comparison of PSEP between CP subgroups and the control group. PSEP values were significantly higher in the NIH-II, NIH-IIIa and NIH-IIIb groups compared to those values in the control group (p < 0.01). No significant difference was observed in the 3 subgroups of CP.

Table 2. Correlation coefficients between PSEP and age, BMI, prostate-related parameters in CP and controls

	Control		NIH-II		NIH-IIIa		NIH-IIIb	
	r value	*p* value	*r* value	*p* value	*r* value	*p* value	*r* value	*p* value
Age, years	–0.002	0.987	–0.064	0.567	0.001	0.998	0.056	0.593
BMI, kg/m^2	0.142	0.153	0.135	0.226	–0.011	0.906	–0.032	0.760
PV, mL	0.042	0.670	–0.020	0.857	0.015	0.882	0.076	0.468
PSA, ng/mL	–0.035	0.727	–0.133	0.232	0.031	0.748	0.210	0.043*
WBC in EPS (/hpf)	–0.027	0.676	0.137	0.061	0.141	0.039*	0.087	0.103
WBC in semen, 10^6/mL	0.113	0.105	0.192	0.015*	0.234	0.027*	0.173	0.045*
Semen volume, mL	–0.117	0.783	0.048	0.626	–0.006	0.896	0.089	0.753
Sperm concentration, 10^6/mL	0.030	0.806	–0.108	0.691	0.077	0.872	–0.094	0.635
Sperm motility (A + B%)	–0.095	0.173	–0.148	0.061	–0.184	0.026*	–0.191	0.041*
CPSI total score	–0.064	0.468	0.167	0.378	0.014	0.923	0.107	0.471
Pain domain	0.083	0.570	0.052	0.785	–0.198	0.178	0.119	0.419
Urinary domain	0.076	0.635	0.193	0.306	0.054	0.713	–0.040	0.786
QOL	–0.031	0.349	–0.005	0.981	0.141	0.338	0.019	0.900

BMI, body mass index; PV, prostate volume; PSA, prostatic specific antigen; PSEP, prostatic exosomal protein; WBC, white blood cell; EPS, expressed prostatic secretions; CPSI, Chronic Prostatitis Symptom Index; QOL, quality of life.

r, spearman rank correlation coefficient.

* Indicate statistically significant correlation ($p < 0.05$).

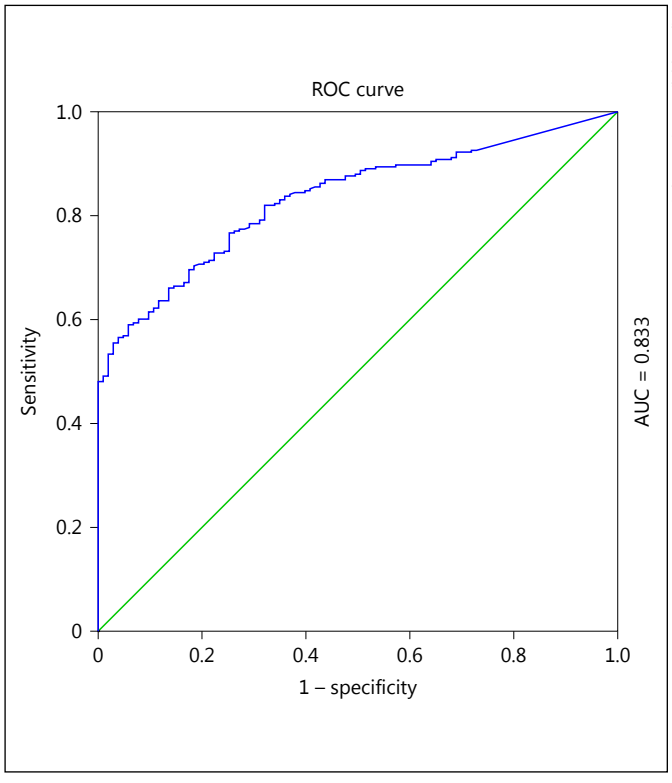

Fig. 2. Youden's Index reached a maximum at a cutoff value of 1.387 ng/mL; the sensitivity was 59.0% and the specificity was 94.2%. The area under the ROC curve was 0.833 (95% CI 0.794–0.873).

within the overall CP group. However, such difference of PSA was not found within the control group. The BMI and PSEP levels were not varied according to PV in both groups.

Discussion

The symptoms of CP mainly include pelvic pain, low urinary tract symptoms, psychological symptoms, and sexual dysfunction [10]. Differential diagnosis is important during clinical assessment, given that the symptoms of CP are not specific. Many other conditions may share the same symptoms as CP, such as cancer of the pelvic organs; prostatic abscess; urinary tract infection; urethral stricture; benign prostate enlargement; urinary stones; epididymo-orchitis; and bladder dysfunction [11]. Currently, validated symptom-scoring instruments, including NIH-CPSI, IPSS, UPOINT, and IIEF-5, could help in assessing symptom severity and guiding therapy, but a proper biomarker is still unavailable during diagnosis/differential diagnosis and the classification of CP [4].

Prostasomes, first reported in 1977 [12], are nanosized extracellular vesicles produced in prostatic epithelial cells that are released into prostatic ducts by a fusion process [13]. Prostasomes were found in 3 different locations: intracellular storage vesicles, the prostate acinar lumen and

Table 3. Comparison of age, BMI, PSEP, and PSA levels according to PV in both the CP and the control groups

	Control (n = 103)			CP (n = 283)		
	PV <20 mL (n = 58)	PV ≥20 mL (n = 45)	p value	PV <20 mL (n = 178)	PV ≥20 mL (n = 105)	p value
Age, years, mean (SD)	30.7 (5.3)	42.5 (5.6)	<0.001*	29.2 (6.3)	43.3 (5.9)	<0.001*
BMI, kg/m^2, mean (SD)	23.1 (2.0)	22.9 (2.1)	0.556	23.0 (1.8)	23.1 (2.0)	0.876
PSEP, ng/mL, median (IQR)	0.19 (0.62)	0.31 (0.78)	0.643	1.88 (2.65)	1.51 (2.60)	0.701
PSA, ng/mL, mean (SD)	1.09 (0.63)	1.20 (0.60)	0.360	1.28 (0.59)	1.66 (0.82)	0.021*

BMI, body mass index; PV, prostate volume; PSA, prostatic specific antigen; PSEP, prostatic exosomal protein. Student t test was used to compare the mean values of the age, BMI, PSA; Mann-Whitney U test was used to compare median values of PSEP levels.

* Statistically significant difference ($p < 0.05$).

other locations, where prostatic fluid is excreted [13]. There appear to be 2 distinct subpopulations of prostasomes, which have a mean diameter of 150 nm and range from 40 to 500 nm under electron microscopy [14]. More recently, 2 distinct prostasome subpopulations in centrifuged seminal plasma were detected with dynamic light scattering, with an average hydrodynamic radius of 80 and 300 nm [15]. Prostasomes comprise a variety of proteins, lipid compounds (the majority of which is sphingomyelin) and nucleic acids (including mRNA, miRNA, and small DNA fragments). There are hundreds of protein compositions in human prostasomes, including 6 different categories: enzymes; transport/structural proteins; GTP-binding proteins; chaperone proteins; signal transduction proteins; and other annotated proteins [16]. Prostate diseases, such as prostate cancer, BPH, and prostatitis, present unique phenotypes at the level of their respective prostasomal proteomes. Some of these proteins have already been tested as potential biomarkers of prostate cancer [6, 7, 8].

Prostasomes perform a wide variety of physiological functions, the most important of which is intercellular communication by membrane fusion. Prostasomes fuse with spermatozoa, thus playing an important role in capacitation and the acrosome reaction [5]. Other proposed functions of prostasomes include immunosuppressive and complement inhibitory activity, antioxidant capacity and antibacterial properties [17, 18]. We speculate that prostasome excretion could be increased in the case of chronic inflammation of the prostate and that the protein composition may change. Thus, CP could be distinguished from a normal status by detecting PSEP, a protein complex of prostasomes specific to inflammatory disorders of the prostate that was discovered by Onco Biomedical Technology [9].

In this report, intergroup urine PSEP levels were compared. Our data demonstrated significantly higher urine PSEP levels in all CP subgroups compared to the control group. An ROC curve identified a cutoff value of 1.387 ng/mL; the corresponding sensitivity was 59.0% and the specificity was 94.2%, and the area under the curve was 0.833 (95% CI 0.794–0.873). Due to the positive correlation of PSEP and WBC count in EPS, and semen, PSEP levels could probably reflect the severity of prostate inflammation. These findings suggest that urine PSEP is potentially capable of serving as a biomarker, with favorable specificity in the diagnosis of symptomatic CP. The decline of semen quality in patients with CP has been gradually confirmed in the past years. One of the possible pathogenic mechanisms is the inactivation of systemic and local epigenetic C-X-C chemokine receptor type 4 (CXCR4) due to promoter hypermethylation [19]. Decreased sperm motility in CP patients was also found in our study. Interestingly, PSEP levels were negatively correlated with sperm motility. Either delayed semen liquefaction or abnormal function of the prostasomes may be the potential cause, which needs to be further explored. In addition, we found that PSA levels in each CP subgroups were slightly higher than those in the control group. As a widely used and studied diagnostic marker of prostate cancer, PSA is related to factors like age, PV, and so on. Does PSEP have the same characteristics as PSA? Our data showed no difference of PSEP between larger PV and smaller PV individuals both in the control and CP groups. Spearman correlation coefficient showed a weak correlation between urine PSEP and serum PSA only in the NIH-IIIb group, but no such correlations were found in NIH-II, NIH-IIIa or the control group. Moreover, urine PSEP was not associated with factors of age, BMI, or PV either in the control group or in CP subgroups ac-

cording to spearman correlation coefficient. Therefore, we believe that PSEP is less affected by factors of age, PV and metabolic status; however, the relationship of PSEP and PSA needs to be further explored.

CP is caused by multiple etiologies, with the involvement of complicated pathological changes, including pathogenic, immunological, and neuroendocrine inflammation. Our present study demonstrated that the common feature of these pathological changes is the elevated levels of PSEP, which was supported by the data that no difference in PSEP was found among the CP subgroups. Thus, PSEP did not seem to be capable of identifying etiology or pathological changes in CP with regard to NIH classification of CP subtypes, although additional studies are needed to reach a conclusion with a larger sample size. Several recent publications reported other biomarkers of CP. Watanabe et al. [20] reported research from 20 cases, which revealed that nerve growth factor levels were significantly elevated in EPS from men with CPPS (NIH-III prostatitis) compared to controls. Wei et al. [21] reported that the levels of B7-H3 were significantly lower in EPS from men with CPPS compared to controls. However, the clinical application of these biomarkers is limited in the case of EPS collecting failure, which may be attributed to the prostatic ducts obstruction caused by stricture, intraprostatic calcification or even prostatic stones, as patients with prostatic stones have more severe symptoms [22]. From our perspective, PSEP can potentially be widely applied in clinical evaluations. PSEP can be very beneficial for patients with CP based on the advantages of urine sample tests being more convenient, more acceptable and less painful than EPS.

There are still some limitations of PSEP. The sensitivity of PSEP can be improved by testing initial urine or post ejaculation urine. However, the secondary antibodies in this ELISA kit is HRP-labeled antibody and bacteria in initial urine can interfere with the HRP and make the false positive result. Diagnostic sensitivity may be improved by detecting post ejaculation urine instead of midstream urine. However, most patients are not willing to provide post-ejaculation urine because the process is cumbersome. We think that midstream urine is more acceptable for PSEP detection at present, while efforts should be made to establish better detection methods to avoid the interference of bacteria in initial urine. The correlation between PSEP level and symptom severity was also analyzed in CP patients. Although it is disappointing that there were no significant correlations between PSEP and CPSI total or sub scores, it remains to be seen whether PSEP is a reliable indicator for evaluating symptom severity in further studies.

Conclusion

The urine PSEP level was significantly elevated in patients with CP, indicating that PSEP could be a potential biomarker for CP. PSEP level was less affected by factors of age, PV, and metabolic status. However, the relationship of PSEP and PSA needs to be further explored. The correlation between PSEP and CP symptom severity requires further investigation.

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Ethical Standards: this study was approved by the Ethics Committee of the First People's Hospital of Taicang.

Disclosure Statement

The authors declare that there are no conflicts of interest to be disclosed.

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·论　　著·

前列腺小体外泄蛋白(PSEP)在慢性前列腺炎诊断中的临床应用

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[摘要] 目的:运用前列腺小体外泄蛋白(PSEP)检测试剂盒对确诊的慢性前列腺炎患者进行检测,观察该体外诊断试剂对慢性前列腺炎的诊断价值。方法:对我院2015年6月至2016年12月收治确诊的慢性前列腺炎患者和正常对照共211例,运用前列腺小体外泄蛋白(PSEP)检测试剂盒,对患者尿液中PSEP进行定量检测,运用灵敏度、特异度和总符合率等指标,比较PSEP诊断体系与临床诊断标准的差异。结果:前列腺小体外泄蛋白PSEP检测试剂对慢性前列腺炎诊断的灵敏度为92.65%,特异度为94.67%,总符合率为93.36%,Kappa=0.858,说明两种系统具有良好的一致性。结论:前列腺小体蛋白检测方法建立,可弥补临床上诊断慢性前列腺炎主观性强,检测方法有一定痛苦等不足,可为慢性前列腺炎患者的诊断提供一种新颖的简便易行、非侵入性、无痛的分子检测方法。

[关键词] 前列腺小体外泄蛋白(PSEP);慢性前列腺炎;灵敏度;特异度;总符合率

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Clinical application of prostatic exosomal protein (PSEP) in the diagnosis of chronic prostatitis

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[**Abstract**] **Objective**: To evaluate and analyze the value of in vitro diagnostic reagents, prostatic exosomal protein (PSEP) detection kit, in the diagnosis of chronic prostatitis. **Methods**: 211 cases of chronic prostatitis patients

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[引文格式] 杨志超,杨建军,曾燕,等.前列腺小体外泄蛋白(PSEP)在慢性前列腺炎诊断中的临床应用[J].东南大学学报:医学版,2017,36(5):800-803.

and normal controls were diagnosed from 2015 .6 to 2016 . 12 . Quantitative detection of PSEP in urine, including the sensitivity, specificity and coincidence rate was inspected with prostatic exosomal protein (PSEP) detection kit. The difference between the PSEP system and the gold standard of clinical diagnosis was compared. **Results**: The sensitivity of prostatic exosomal protein (PSEP) detection reagent for the diagnosis of chronic prostatitis was 92.65%, while specificity 94.67%. The total coincidence rate was 93.36%, Kappa = 0.858. Good consistency was found in two kinds of system. **Conclusion**: Prostasomes protein for the clinical diagnosis of chronic prostatitis is objective and painless. It could be a novel, simple and non-invasive molecular method for diagnosing chronic prostatitis.

[**Key words**] prostatic exosomal protein (PSEP); chronic prostatitis; sensitivity; specificity; consistency

慢性前列腺炎患者的临床主诉较多，虽然这些症状并不危及患者生命，但常常影响患者的工作及生活。在临床工作中依据患者的主诉作出诊断带有一定的主观片面性，因此首先需要尿常规检查排除单纯的泌尿系感染，其次，需要前列腺液（expressed prostatic secretious，EPS）镜检、细菌学培养等检查明确诊断。而后两项检查需要经肛门指检并按摩前列腺后取得前列腺液才能进行，实际工作中经肛门指检并按摩前列腺会给患者带来不适，一部分患者放弃前列腺液常规检查，另有部分患者即使按摩前列腺后仍然无法取得前列腺液而难以诊断，这样导致慢性前列腺炎的诊断缺乏客观指标。

本课题组采用昂科生物医学技术（苏州）有限公司研发的前列腺小体外泄蛋白（prostatic exosomal protein，PSEP）检测试剂盒，对我院经尿常规和前列腺液常规检测而临床确诊的 136 例慢性前列腺炎患者，和 75 例正常对照组的尿样进行检测，探讨 PSEP 检测在慢性前列腺炎诊断中的价值。

1 材料与方法

1.1 病例选择

参照《前列腺炎诊断治疗指南（2014 版）》中慢性前列腺炎临床诊断标准[1]，慢性前列腺炎患者的诊断依据：主诉、尿常规、肛门指检前列腺及前列腺液常规检查。收集自 2015 年 6 月至 2016 年 12 月在我院就诊的慢性前列腺炎患者 136 例和健康对照 75 例的尿液标本，取材时采用中段尿样，年龄 18 ~ 60 岁，平均 37 岁。慢性前列腺炎患者及健康对照组均常规行尿常规和 EPS 检测。该研究在医院伦理委员会讨论通过后进行。

1.2 排除标准

前列腺癌患者；急性前列腺炎患者；二周内置入导尿管者；48 h 内有性生活者；由于精神行为障碍不能配合者；有严重的脏器功能疾病；有严重的肛肠部位疾病，不适合性前列腺按摩检测者，病情危重，难以对有效性和安全性做出确切评价者。

1.3 尿液样本收集与检测

1.3.1 尿液样本收集 利用随机号码表编制 211 个随机数字，对收集的尿液样本进行编号，采用双盲法，尿液收取后 10 min 内置入 -80 ℃冰箱保存。待尿液标本集中达到 20 份以上即行检测。

1.3.2 检测 前列腺小体外泄蛋白（PSEP）试剂盒由江苏太仓昂科生物技术有限公司提供。用间接 ELISA 方法检测 136 例慢性前列腺炎和 75 例正常人尿液样本。参照文献[2]，并根据 PSEP 试剂盒操作说明对收集的尿液样本进行检测，统计 PSEP 阳性例数及阴性例数，根据不同浓度的标准品 OD 值建立标准曲线。将患者的数值与阳性标准孔数值比较，计算测试样本的实际前列腺小体外泌蛋白浓度。样本检测：计算检测标本中 PSEP 蛋白含量。各样本重复 3 次测量取平均值。将尿液标本检测的阳性及阴性标本与临床诊断病例比较，根据 PSEP 试剂盒 Cutoff 值（1.2 ng · ml^{-1}）统计出真阳性，假阳性，假阴性，真阴性，求出检测灵敏度、特异度、阳性值，阴性值。

1.4 检测效率评价

（1）计算 PSEP 试剂盒的临床检测的灵敏度、特异性、阳性预期值、阴性预期值等指标。（2）临床检测效率以总符合率（一致百分率）表示：总符合率 = 真阳性 + 真阴性 /（真阳性 + 假阳性 + 真阴性 + 假阴性）× 100%，评价该检测方法与临床诊断标准的等效性。（3）进行统计分析试验系统和对照系统的一致性：进行 Kappa 一致性分析，Kappa 系数 > 0.75，为高度一致，认为两系统等效；0.4 < Kappa 系数 < 0.75 认为一致，需进行阳性符合率和阴性符合率比较并进行统计学分析；Kappa 系数 < 0.4 则认为两系统不一致，两系统不等效。（4）ROC 曲线分析：绘制 ROC 曲线，以曲线下面积（Aera Under the Curve，AUC）评价 PSEP 检测试剂盒的诊断价值。ROC 曲线下面积 AUC（AUC 一般

情况:0.5 ~ 0.6 为无意义、0.6 ~ 0.7 为差、0.7 ~ 0.8为一般、0.8 ~ 0.9 为好、0.9 ~ 1.0 为优秀,采用 AUC > 0.7表示该指标诊断准确性较高)。

1.5　统计学处理

采用 SPSS 16.0 统计软件进行统计学处理。慢性前列腺炎患者与健康对照组的样本差异比较采用秩和检验和配对 t 检验。$P<0.05$ 为差异有统计学意义。

2　结　　果

2.1　灵敏度和特异度检测结果

按照临床诊断标准及 PSEP 试剂盒检测统计阳性及阴性数(见表 1),计算 PSEP 试剂盒临床检测的灵敏度、特异性、阳性预期值、阴性预期值等指标。

表 **1**　灵敏度和特异度检测结果

PSEP 试剂盒 \ 临床诊断标准	阳性	阴性	合计
阳性	126	4	130
阴性	10	71	81
总数	136	75	211

灵敏度为 92.65%,特异度为 94.67%,阳性预期值为 96.92%,阴性预期值为 87.65%,阳性似然比为 17.37,阴性似然比为 0.08。

2.2　临床检测效率

临床总符合率为 93.36%。

2.3　**PSEP** 试剂盒和临床诊断标准的一致性检验

结果显示 Kappa = 0.858 (95% *CI* = 0.786 ~ 0.93),说明两系统具有高度一致性(表 2)。ROC 曲线下面积为 0.891(表 2 及图 1),表示 PSEP 试剂盒对慢性前列腺炎具有较好的诊断价值。

表 **2**　**PSEP** 试剂盒和临床诊断标准的一致性检验

ROC 曲线下面积(AUC)	0.891
SE	0.029 2
95% *CI*	0.830 ~ 0.936
Z 值	13.386
P 值	<0.000 1

3　讨　　论

慢性前列腺炎的病因和发病机制复杂,Pontari 等总结了 Medline 上 1966 年至 2003 年关于慢性前列腺炎的文献,认为发病时各种因素引起的感染、免疫、内分泌、神经、精神因素等相互作用所导致的炎症过程,包括前列腺长期充血、各种原因引起的感染、尿液返流、甚至是炎症介质的异常[3,4];慢性前列腺炎的临床症状与季节、饮食、性活动、泌尿生殖道炎症以及精神心理因素等有关,有文献认为其可被看做是一种症状性疾病,患者主诉症状比较多而且没有特异性,在临床诊断中往往主观性强,实验室和影像学检查方法有限[5,6]。因此,急需一种无创、快捷简便,同时结果又准确可靠的生物标记物和诊断手段,为慢性前列腺炎的筛选和诊断提供有效的工具。

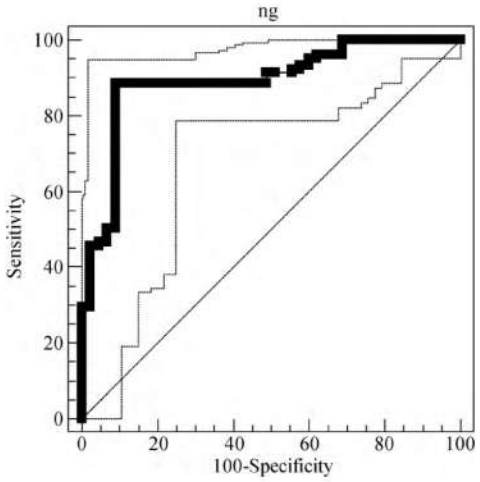

图 **1**　**PSEP** 试剂盒检测结果的 **ROC** 曲线

前列腺小体(prostasomes)为慢性前列腺炎患者中前列腺组织释放出的一种活性物质,它是人类前列腺上皮细胞分泌,前列腺小体有多重生理功能,在 CD59、CD52、CD55 的参与下通过一系列生化反应,可以保护酸性环境中的精子,延迟顶体反应,增强精子的活力。前列腺小体可抑制 PMN (polymorphonuclear leukocytes) 细胞的 NADPH 酶的活性,使得反应性氧核素 ROS 减少,并具有抑制病毒活性及抗菌作用。前列腺小体蛋白属于外泄蛋白,有包括上百种复杂的蛋白质,它是存在于正常人尿液中的前列腺蛋白质,早期的实验研究发现在慢性前列腺炎患者的尿液中,PSEP 含量升高[7-11]。为此江苏太仓昂科生物医学技术有限公司研发出 PSEP 试剂盒,在此基础上,我们通过尿液的检测的方法探讨其在慢性前列腺炎诊断中的价值。

本研究临床标本共收集 211 例,包括慢性前列腺炎 136 例和正常对照 75 例,检测前必须排除可能影响前列腺小体蛋白检测的因素,包括肛门指检、导尿、细菌性尿路感染、膀胱镜检查等。经统计分析结果显示:

前列腺小体蛋白检测方法灵敏度约 92.65%，特异度 94.67%，说明该方法可靠性较强，作为慢性前列腺炎的临床检测具有可操作性和较好的临床价值，可用于临床对于慢性前列腺炎的诊断，并可作为治疗慢性前列腺炎的疗效评价指标之一。

慢性前列腺炎的临床诊断主要包括：症状、肛门指检、尿常规、前列腺液检查及培养。肛门指检及按摩、前列腺液检查是必须的，而肛门检查并按摩前列腺有一定痛苦和轻微的侵袭性，部分患者难以忍受，甚至极少部分患者出现一过性晕厥现象，部分患者放弃行肛门指检；部分患者肛门指检并按摩前列腺后，因无前列腺液滴出难以行前列腺液检查；影响 EPS 的因素较多，包括检测前患者性生活时间、EPS 量、检验人员的经验等；IIIB 型慢性前列腺炎缺乏客观的、特异性的诊断依据。通过 PSEP 试剂盒检测患者的尿液来诊断慢性前列腺炎可弥补以上缺憾，减少诊断慢性前列腺炎主观性。本研究结果显示：PSEP 试剂盒尿液检测结果与临床标准诊断（主要为前列腺液检查）比较，其临床总符合率为 93.36%，Kappa = 0.858（95% *CI*：0.786 ~ 0.93），具有良好的一致性，该方法可为慢性前列腺的诊断提供一种新颖的简便易行、非侵入性、无痛的分子检测方法。

尽管前列腺小体外泄蛋白 PSEP 检测试剂对慢性前列腺炎诊断的灵敏度为 92.65%，特异度为 94.67%，总符合率为 93.36%，说明两种系统具有良好的一致性，但是仍然有少部分假阳性和假阴性，考虑为液体摄入量的差异导致了尿液的浓缩或稀释，最后影响结果的判断。当实施 PSEP 检查时，液体摄入量或尿液排出量和平时生活状态差异显著时，可能会影响到即时尿样的测量值。因此我们建议患者以晨尿检查为合适，可以减少稀释或浓缩作用导致的影响。

本研究是以临床诊断标准作为依据，由于未进行前列腺液的细菌培养，难以作出 II、IIIA、IIIB 型慢性前列腺炎分型诊断，不能比较慢性前列腺炎各型组间差异。但临床工作中，III 型前列腺炎约占慢性前列腺炎的 90% 以上，诊断慢性前列腺炎主要依靠前列腺液检查，很少行前列腺液培养，主要原因为培养结果对临床治疗指导意义小，而且培养阳性率很低。目前用 PSEP 试剂盒检测需要时间约 3 小时，而且需要超过 20 份标本行批量检测，正在研发的 PSEP 胶体金产品可对一份尿样标本检测而且可以更快速得到检测结果。

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· 论 著 ·
Clinical Research
(临床研究)

前列腺小体外泄蛋白与 EPS 常规指标和 NIH-CPSI 的相关性分析

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【摘要】 目的: 研究慢性前列腺炎(CP)患者尿液中的前列腺小体外泄蛋白(PSEP)的含量与前列腺按摩液(EPS)中的白细胞(WBC)、卵磷脂小体(SPL)及 NIH-CPSI 评分之间的关系。 方法: 收集 2017 年 11 月至 2018 年 8 月前来东部战区总医院男科门诊就诊的 367 例 CP 患者的中段尿进行 PSEP 含量检测,显微镜下观察 EPS 中的 WBC 和 SPL 计数,指导患者独立填写 NIH-CPSI 量表,统计分析 CP 患者尿液中的 PSEP 含量与 EPS 中的 WBC、SPL 计数及 NIH-CPSI 评分之间的相关性。 结果: CP 患者尿液中的 PSEP 含量随 EPS 中的 WBC 数量增加而增加,二者具有显著相关性($r = 0.19$, $P = 0.047$),与 EPS 中的 SPL 计数无明显相关性($r = 0.02$, $P = 0.48$),与 NIH-CPSI总评分显著相关($r = 0.31$, $P = 0.02$)。 结论: PSEP 对临床诊断 CP 和评估 CP 的炎症程度具有一定意义。

【关键词】慢性前列腺炎; 前列腺小体外泄蛋白; 卵磷脂小体; 尿液; 前列腺按摩液; 美国国立卫生研究院慢性前列腺炎症状指数
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Correlation of the prostatic exosomal protein content with conventional indicators of EPS and NIH-CPSI

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【**Abstract**】 ***Objective***: To study the relationship of the content of prostatic exosomal protein (PSEP) in the urine with the counts of WBCs and small particles of lecithin (SPL) in the EPS and NIH-CPSI in patients with chronic prostatitis. ***Methods***: We collected mid-stream urine samples from 367 chronic prostatitis patients in the Department of Andrology of the General Hospital of Eastern Theater Command from November 2017 to August 2018. We measured the content of PSEP in the urine, counted WBCs and SPLs in the EPS of the patients, obtained their NIH-CPSI scores, and analyzed the correlation of the PSEP level with the WBC and SPL counts and NIH-CPSI scores of the patients. ***Results***: The PSEP level in the urine was elevated with the increase of the WBC count in the EPS of the patients ($r = 0.19$, $P = 0.047$) but not significantly correlated with the SPL count in the EPS ($r = 0.02$, $P =$

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0.48). A significant correlation was observed between the PSEP level and the NIH-CPSI scores of the patients (r = 0.31, P = 0.02). ***Conclusion***: The PSEP content in the urine can be used as an indicator in the clinical diagnosis and assessment of the inflammation degree of chronic prostatitis. ***Natl J Androl*, *2019*, *25* (*6*): *500-503***

【**Key words**】chronic prostatitis; prostatic exosomal protein; small particles of lecithin; urine; expressed prostatic secretion; NIH-chronic prostatitis symptom index

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前列腺炎,尤其是慢性前列腺炎(chronic prostatitis,CP),是青壮年男性泌尿生殖系统最常见的疾病之一,占泌尿外科门诊就诊男性的30%[1]。在流行病学调查的基础上,5%~9%的男性人群在全球范围内出现前列腺炎症状[2],50%的男性在其一生中的某个时间点患有前列腺炎[3]。因此,CP被视为国际卫生保健中至关重要的医学问题。然而,尽管在过去几十年中进行了大量研究,但CP的病因和发病机制尚未完全清楚[4-6]。此外,CP的临床表现缺乏特异性,病程迁延不愈,不仅会对患者造成身体上的痛苦,还会产生精神上的压力,使得CP的临床诊断和治疗都非常具有挑战性[7]。目前尚没有CP的客观诊断标准,其诊断在很大程度上取决于患者所描述的临床症状和体征,以及尿常规、四杯法、前列腺按摩液(expressed prostatic secretion,EPS)常规和美国国立卫生研究院慢性前列腺炎症状指数(NIH-CPSI)的问卷调查等综合评估。EPS可通过直肠指检按摩前列腺获得,但这是一个复杂有创的操作过程,往往对患者具有侵袭性,临床很多患者因恐惧心理甚至会拒绝该项检查,导致很多情况下只能根据患者临床表现联合NIH-CPSI量表来诊断CP,大大降低了CP临床诊断的准确性。EPS常规检查通常包括显微镜下观察WBC和卵磷脂小体(small particles of lecithin,SPL)计数,缺乏对CP的客观和简单的检测,严重影响CP的有效治疗及预后结果。前列腺小体外泄蛋白(prostatic exosomal protein,PSEP)是近年来用于CP诊断与疗效判定的一个新指标,前期研究显示,与健康男性相比,CP患者尿液中的PSEP明显升高[8-11]。我们初步的研究结果也证实,尿液中的PSEP含量对CP诊断的敏感度和特异性均较强[12]。为进一步探索CP患者尿液中的PSEP与其EPS中WBC、SPL计数及CP症状严重程度之间的相关性,本研究对前来东部战区总医院男科门诊就诊的367例CP患者进行样本收集分析和问卷调查研究。

1 资料与方法

1.1 一般资料

1.1.1 纳入标准 参照《前列腺炎诊断治疗指南(2014版)》中的CP临床诊断标准,收集2017年11月至2018年8月前来东部战区总医院男科门诊就诊的CP患者367例的中段尿标本,患者年龄20~60岁,平均32.58岁。本研究获得东部战区总医院伦理委员会批准,所有纳入的研究对象均签署知情同意书。

1.1.2 排除标准 ①急性前列腺炎患者;②2周内留置导尿管者;③48 h内有过性生活者;④近1个月有泌尿系感染或服用抗生素的患者;⑤有泌尿系统手术史的患者;⑥明确诊断为良性前列腺增生、前列腺癌的患者;⑦有附睾炎或性传播疾病病史的患者;⑧由于精神心理障碍等因素不能配合或不适合行前列腺按摩检查的患者;⑨有严重的肛直肠部位疾病者;⑩有全身其他系统疾病或脏器功能衰竭等严重疾病,⑪难以对实验研究的安全性和有效性做出确切评价者。

1.2 EPS收集与检测 由同一名有经验的男科医师采用前列腺按摩的方法收集所有患者的EPS,并立即通过湿涂片法在显微镜下完成EPS中的WBC及SPL计数。WBC计数方法[13]:400倍显微镜下观察3~5个视野,取平均值,依据平均值分为5组:偶见或少许(<10个/HP)、+(10~20个/HP)、++(21~30个/HP)、+++(31~40个/HP)、++++(>40个/HP)。SPL计数方法:400倍显微镜镜下观察5个视野,根据平均值分为5组:++++(SPL满布视野)、+++(占视野3/4)、++(占视野1/2)、+(占视野1/4)、-(无或散在)。

1.3 NIH-CPSI评分 由经过培训的泌尿男科医师指导患者根据上1周自身情况独立填写NIH-CPSI量表。NIH-CPSI量表是用于记录患者症状的既定评分方法,内容较为细化且全面,一共包含9个问

题,主要对 CP 的 3 个主要症状进行了量化评分,包括疼痛和不适评分、排尿症状评分、症状对生活质量的影响评分。根据症状的严重程度,NIH-CPSI 分为轻度(1~14 分)、中度(15~29 分)、严重(30~43 分)。

1.4 尿液标本收集与标本检测

1.4.1 尿液标本收集 嘱患者留取中段尿标本前一天晚上必须清洁饮食,避免饮酒,禁止排精活动,留取尿液标本前需要憋尿 2 h。标本收集后送至 -20 ℃冰箱冻存,待标本达到一定数量后集中送检,但标本保存时间严格控制在 1 个月内,标本禁止反复冻融。所有患者进行 EPS 常规检查均需在留取尿液标本后进行,以排除前列腺按摩对尿液标本的影响。当患者的临床数据不完整或尿液标本量过少时,受试者被排除在外。

1.4.2 尿液中的 PSEP 含量检测 采用间接 ELISA 法,试剂盒由昂科生物技术公司提供,在 450 nm/630 nm 双波长下检测吸光度(A)值,根据标准曲线换算得出样本中 PSEP 的浓度。正常人尿液中的 PSEP 浓度≤1.20 ng/ml,诊断 CP 阳性的参考标准为 PSEP > 1.20 ng/ml。

1.5 统计学分析

数据采用 SPSS 22.0 统计软件进行统计分析,计量资料采用 $\bar{x} \pm s$ 表示。CP 患者尿液中的 PSEP 含量与 EPS 中的 WBC 及 SPL 计数、NIH-CPSI 评分之间的相关性分析采用 Spearman 相关分析,$P \leq 0.05$ 表示差异有统计学意义。

2 结果

2.1 PSEP 含量与 EPS 中 WBC 计数的相关性 随着 EPS 中 WBC 数量的增加,尿液中的 PSEP 含量也逐渐增多,阳性率也大致呈增加趋势。见表 1。相关性分析显示 CP 患者尿液中的 PSEP 含量与 EPS 中 WBC 计数存在显著相关性($r = 0.19$, $P = 0.047$)。

表 1 CP 患者尿液中 PSEP 含量与 EPS 中 WBC 计数的关系

Table 1. WBC count in the EPS and the content of prostatic exosomal protein (PSEP) in the urine of the chronic prostatitis patients

WBC count	n	PSEP positive n(%)	PSEP level (ng/ml)
+	51	40(78.43)	3.47 ± 3.46
+	131	107(81.68)	3.75 ± 3.07
+ +	75	61(81.33)	3.98 ± 2.96
+ + +	73	62(84.93)	4.36 ± 3.53
+ + + +	37	33(89.19)	5.78 ± 4.56

2.2 PSEP 含量与 EPS 中的 SPL 计数的相关性 随着 EPS 中的 SPL 计数的增加,尿液中的 PSEP 含量并没有随之减少,阳性率也没有呈现出规律变化(表 2)。相关性分析表明,CP 患者尿液中的 PSEP 含量与 EPS 中的 SPL 计数没有显著的相关性($r = 0.02$, $P = 0.48$)。

表 2 CP 患者尿液中 PSEP 含量与 EPS 中 SPL 计数的关系

Table 2. Count of small particles of lecithin (SPL) in the EPS and the content of prostatic exosomal protein (PSEP) in the urine of the chronic prostatitis patients

SPL count	n	PSEP positive n(%)	PSEP level (ng/ml)
+	84	68(81.43)	4.35 ± 3.69
+ +	108	84(77.78)	3.81 ± 3.79
+ + +	132	115(87.12)	5.67 ± 3.98
+ + + +	43	36(83.72)	4.94 ± 3.43

2.3 PSEP 含量与 NIH-CPSI 评分的相关性 本研究所纳入的 367 例 CP 患者中,NIH-CPSI 量表填写合格者有 352 例。相关性分析显示,NIH-CPSI 和 PSEP 浓度存在显著的等级相关性($r = 0.31$, $P = 0.02$)。见表 3。

表 3 PSEP 含量与 NIH-CPSI 评分之间的关系

Table 3. NIH-CPSI scores and the content of prostatic exosomal protein (PSEP) in the urine of the chronic prostatitis patients

NIH-CPSI	n	PSEP positive n(%)	PSEP level (ng/ml)
<15	177	116(65.54)	3.47 ± 3.61
15 - 29	139	104(74.82)	3.71 ± 3.09
>29	36	32(89.66)	5.24 ± 3.87

3 讨论

前列腺炎是泌尿外科和男科最常见的疾病之一,发病率较高,根据流行病学调查的结果显示,在我国成年男性人群中,10% 以上具有前列腺炎样症状,并且其中一部分人群的生活质量因此受到了严重的影响,对我国的公共卫生医疗事业造成了巨大的经济负担[14]。

目前常采用 CP 诊断的方法有 EPS 常规检查、影像学检查等,这些检查方法不但耗时长,而且特异性较差,准确率也较低,导致 CP 病程迁延,病情反复,难免会在某种程度上对患者造成身体和心理上的负担。目前临床上缺少能够准确诊断 CP 及其病

原体的快捷高效的诊断方法，尿液中的 PSEP 含量检测方法是近年来研发出的新技术。前列腺炎患者的前列腺组织通常会受到炎性细胞的侵袭浸润，释放出多种活性物质和趋化因子，而前列腺小体就是其中重要的一种[15]。PSEP 是由前列腺小体分泌生成的一类蛋白质的总称，在炎症发生时，前列腺小体的外泌或排出增加，PSEP 在尿液中的含量也会随之增多，通过生理解剖通道分泌进入到男性尿道、生殖道中[16]。相比于以前应用于临床中的前列腺炎诊断方法，该检测方法具有快速、精确、无创等优点。

国内对于尿液中的 PSEP 的检测尚处于起步阶段，曾燕等[9]对 CP 患者及正常人尿液中的 PSEP 采用 ELISA 方法进行检测，结果发现 CP 患者尿液中的 PSEP 明显高于正常人群。Li 等[8]研究结果表明，尿液中的 PSEP 含量检测对 CP 有良好的诊断价值，可能是 CP 诊断的一种潜在的生物标志物，但 PSEP 与 PSA 的关系以及 PSEP 在评估 CP 的严重程度等方面的问题，还需要进一步的研究与探索。我们前期的研究已证明 PSEP 诊断 CP 的敏感度和特异性均较强，本研究进一步对 PSEP 与 EPS 中的 WBC 和 SPL 计数以及 NIH-CPSI 指数的关系进行了研究。

本研究对所有纳入研究的 367 例 CP 患者的中段尿进行了 PSEP 检测，分别对 CP 患者 EPS 中的 WBC、SPL 计数分级，分析 PSEP 与 CPSI 评分、EPS 中 WBC 及 SPL 计数等指标之间的相关性。结果表明 CP 患者尿液中的 PSEP 与其 EPS 中的 WBC 计数存在显著相关性（$P=0.047$），这与 Li 等[8]的研究结论相符，但相关系数较小（$r=0.19$），表明线性相关性不是很强；与 EPS 中的 SPL 计数无线性相关关系（$P=0.48$）；与 NIH-CPSI 存在线性相关关系（$P=0.02$），这与 Li 等[8]的研究结果不同。我们认为，可以通过进一步扩大研究所纳入的样本量，从而更准确地评估这种关系。陈曦等[13]对不同 NIH 分型前列腺炎患者前列腺液中的 WBC 及 SPL 计数与 NIH-CPSI 评分的关系进行研究的结果认为，不同分型前列腺炎患者前列腺液中 WBC、SPL 计数与患者症状严重程度之间无明确相关性，WBC 与 SPL 计数用于评估 CP 病情可靠性差。而本研究发现，PSEP 与 CP 的炎症程度存在线性相关，而与 EPS 中的 WBC 也存在一定的相关性，这从一定程度上弥补了 EPS 中的 WBC 和 SPL 计数在 CP 诊断和炎症评估方面的不足。

本研究尚存在一些不足之处，没有对 CP 进行 NIH 分型，不同分型的 CP 患者尿液中的 PSEP 与 EPS 中的 WBC、SPL 计数以及 NIH-CPSI 评分之间的相关性需要进一步的研究。此外，泌尿男科门诊医生的工作量大，NIH-CPSI 问卷耗时较长，故本研究并未获得所有患者的 NIH-CPSI 评分。在后续的研究工作中，我们会扩大样本量，细化 CP 分型，深入研究尿液中的 PSEP 含量对治疗前后的评估作用。

综上所述，CP 的诊断与评估不仅应包括 EPS 的常规检查，还应重视包括临床症状严重程度、心理评估等方面，EPS 中的 WBC 计数并不能完全作为诊断及炎症程度的评价指标，PSEP 对临床诊断 CP 和评估 CP 的炎症程度具有一定意义。

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前列腺小体外泌蛋白在男性不育症合并Ⅲ/Ⅳ型前列腺炎诊断中的意义

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慢性前列腺炎是较为常见的男科疾病，患病率在10%左右[1]，据统计约50%的男性在一生中的不同时期会出现前列腺炎相关的症状[2]。研究表明，慢性前列腺炎与男性不育症关系密切，其中Ⅲ型前列腺炎（慢性前列腺炎/慢性骨盆疼痛综合症）是其主要类型。男性不育症是临床上较为常见的一种生殖疾病，10%-15%的育龄夫妇存在不孕问题，其中男方因素占30%左右[3]。为了研究本地区男性不育症患者Ⅲ/Ⅳ型前列腺炎的发病情况，以及前列腺小体外泌蛋白在男性不育症合并Ⅲ/Ⅳ型前列腺炎诊断中的意义，我们选取2016年1月-2016年12月本院生殖医学科门诊就诊的男性不育症患者200例，根据是否患有慢性前列腺炎分为两组进行对照研究。

1　材料与方法

1.1　研究对象与方法

200例研究对象均为婚后同居1年以上，性生活正常而配偶未能怀孕的男性不育症患者。年龄20-44岁，平均32.46岁。男性不育症患者中慢性前列腺炎的临床诊断方法包括：①临床症状：美国国立卫生研究院（NIH）的前列腺炎症状指数（CPSI）评分来评估；②前列腺液（EPS）常规检查，EPS检查≥10个白细胞/高倍视野，提示炎症性前列腺炎；③细菌培养：前列腺炎的细菌定位培养方法采用前列腺按摩前后“二杯法”（PPMT）尿培养确定。通过CPSI评分＞1分，EPS/精液/VB3细菌培养阴性，常规显微镜检下EPS的白细胞计数来综合诊断炎症性（ⅢA）和非炎症性（ⅢB）。Ⅳ型为无症状性慢性前列腺炎：病人无明显自觉症状，前列腺液（EPS）、精液中有白细胞[4]。卵磷脂小体是男性前列腺液中的正常成分，正常人前列腺液镜检发现卵磷脂小体极多、几乎满视野（3＋、4＋），当卵磷脂小体少于50%（2＋）时，对诊断前列腺炎有重要的参考价值。上述前列腺炎患者尿液中前列腺小体外泌蛋白＞1.24 ng/ml为阳性。精液参数的分析方法：全部入选的男性不育症患者采用计算机辅助精子分析（CASA）技术进行精液分析，并按照世界卫生组织（WHO）第五版标准进行诊断，即前向运动精子PR＜32%为弱精子症，精子总数＜39×10^6为少精子症。精液常规化验完毕后，3 000 g，15分钟离心精液，弃沉淀取精浆测定锌浓度，锌＜2.4 μmol/一次射精为异常。精液常规检查与前列腺液常规检查间隔2-7天。

1.2　统计学方法

采用SPSS 16.0统计学软件进行数据分析，计量资料数据用均数±标准差（$\bar{x}\pm s$）表示，两组间比较采用t检验；计数资料用率表示，组间比较采用χ^2检验；相关性分析采用Spearman检验；以$P<0.05$为差异有统计学意义。

2　结果

2.1　男性不育症患者中慢性前列腺炎的发生情况

200例男性不育症患者，经过CPSI评分、EPS常规检查和细菌培养共确诊Ⅲ/Ⅳ型前列腺炎123例（61.5%），其中ⅢA型前列腺炎46例（23.0%）、ⅢB型前列腺炎63例（31.5%）、Ⅳ型前列腺炎14例（7.0%）。123例前列腺炎患者中，少、弱精子症患者40例（32.53%），精液正常患者83例（67.47%）。

2.2　慢性前列腺炎患者的前列腺小体外泌蛋白阳性率

Ⅲ/Ⅳ型前列腺炎123例，Ⅲ/Ⅳ型前列腺炎患者前列腺小体外泌蛋白阳性率91.06%。非炎症对照77例，前列腺小体外泌蛋白阳性率11.69%。ⅢA型前列腺炎46例，EPS-WBC平均为17±5个/HP，前列腺小体外泌蛋白阳性率91.30%、ⅢB型前列腺炎63例，EPS-WBC平均为8±3个/HP，前

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列腺小体外泌蛋白阳性率90.48%。Ⅳ型前列腺炎14例，EPS-WBC平均为19±7个/HP，前列腺小体外泌蛋白阳性率92.86%。前列腺炎患者前列腺小体外泌蛋白含量与患者精浆锌含量呈负相关（r=−0.613）。与前列腺炎患者精液前向运动精子PR、精子总数无相关性（r=0.143、r=0.059），见表1、表2。

表1 各组不育症患者精液参数及尿PESP比较

组别	n	精子总数（个）	PR(%)	液化(分钟)	精浆锌(nmol/L)	PESP(ng)	PESP阳性率(%)
非前列腺炎组	77	149±59	48.1±23.7	30	10.95±5.27	0.91±0.52	11.69%
ⅢA型前列腺炎组	46	160±65	44.3±35.2	45	3.49±1.85	2.73±1.65	91.30%
ⅢB型前列腺炎组	63	104±44	44.6±33.9	45	3.37±2.43	2.58±1.63	90.48%
Ⅳ型前列腺炎	14	136±51	46.4±28.4	45	3.18±1.96	2.36±1.43	92.86%

表2 不育症患者前列腺检查指标比较

组别	例数(个)	卵磷脂小体(+)	白细胞(个/HP)	液化(分钟)	PESP(ng)
前列腺炎组	123	1.57+	14.39±3.57	30	2.45±1.09
非前列腺炎组	77	1.81+	3.75±3.13	45	0.91±0.52

3 讨论

精液由精子和精浆两部分组成，精子在睾丸精曲小管产生后，经过形态学成熟和功能学成熟发育阶段，最终储存于附睾中，射精时附睾中的精子与前列腺和精囊腺的分泌物一起排出体外进入女性阴道后穹隆部位，随后精子游动到子宫，最终到达输卵管壶腹部与卵子结合受精，完成受精过程。前列腺液占精浆总体积约1/5，前列腺液中的液化因子与精囊液中凝固因子共同参与精液的液化过程，前列腺液中高浓度的锌是保证精子活力必不可少的物质[5]。由此可见，虽然目前慢性前列腺炎导致男性不育症的机理不确切，但引起男性精液异常进而导致不育是肯定的。本研究结果显示，男性不育症患者前列腺炎发病率高达61.5%，也从侧面证实了这一观点。至于男性不育症合并前列腺炎患者精液常规正常率高达67.47%，笔者认为有如下几个原因，第一，本研究主要针对Ⅲ/Ⅳ型前列腺炎进行研究，此型前列腺炎无病原微生物感染，白细胞平均14.39±3.57，仅仅略高于正常参考值。第二，本研究前列腺患者CPSI评分，轻度77.42%，中度22.58%。笔者认为前列腺导致男性精液异常是前列腺炎病情累积量变的结果。第三，本研究仅仅对前列腺患者精液宏观指标进行分析，精子微观学改变有无异常尚需进一步探讨。

前列腺小体外泌蛋白是由人类前列腺上皮细胞分泌的一种亚细胞结构，主要成分是鞘磷脂，含有磷酸胆碱和神经酰胺。由前列腺导管上皮通过胞吐和胞透作用分泌至管腔[6]。当前列腺受到炎细胞浸润，前列腺小体外泌蛋白通过解剖通道分泌进入男性生殖道，前列腺小体蛋白有抗菌抗氧化作用，可中和白细胞的ROS作用，尤其在精液中抗菌作用更强[7]。本研究的200例尿样中，前列腺炎患者组尿液中前列腺小体外泌蛋白浓度明显高于非前列腺炎患者组，有显著差异性。前列腺炎患者样本检测到的前列腺小体外泌蛋白阳性率高达91.06%，灵敏度较高。前列腺小体外泌蛋白外泌蛋白检测取材于尿液，简单无痛苦，准确率特异性高[8]，为前列腺炎的诊断治疗提供了简便可靠的检测手段。

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前列腺小体外泄蛋白在男性不育诊断治疗中的应用观察

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摘　要：目的　探讨和观察前列腺小体外泄蛋白（prostatic exosomal protein，PSEP）指标在男性不育诊断治疗中的应用价值。方法　随机选择我院门诊60例男性不育患者，作为实验组，收集尿液标本后并收取其精液标本。同时选取180例体检男性尿液作为对照组。采用酶联免疫法检测实验组和对照组尿样中的PSEP浓度。（1）分析实验组和对照组PSEP浓度水平的差异；（2）在实验组中，分析PSEP浓度和精液量、精子浓度、精子活性、精子正常形态率、酸性磷酸酶、精浆锌之间的相关性。结果　经测试，实验组PSEP阳性率（62.5%）显著高于对照组PSEP阳性率（17.4%）（$P<0.001$）。在实验组中，PSEP浓度和b级活性精子数量呈显著负相关（$P=0.039$，$r=-0.277$），和精子PR（a+b）指标也较明显负相关（$P=0.054$，$r=-0.259$）；PSEP浓度和精液量呈正相关（$P=0.028$，$r=0.293$），PSEP浓度和其他精液指标暂未发现相关性。结论　尿液PSEP在男性不育患者中有较高的阳性率，且PSEP浓度和精子活性呈现负相关；尿液PSEP指标对男性不育诊断中的病因研究分析和指导治疗具有较大临床意义，应继续扩大样本量进一步研究探讨。

关键词：前列腺小体外泄蛋白；前列腺疾病；男性不育；精液分析

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Application of prostatic exosomal protein in diagnosis and treatment of male infertility.

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Abstract：Objective：To investigate and observe the application value of prostatic exosomal protein（PSEP）in the diagnosis and treatment of male infertility. Methods：60 male infertility patients in our hospital were selected. The urine was collected before the operation as the experimental group. 180 male urine samples were selected as the control group. The semen indicators corresponding to each patient in the experimental group were recorded. The concentration of PSEP in the urine samples of the experimental group and the control group was determined by Enzyme-linked immunosorbent assay.（1）Analyze the difference of PSEP concentration levels between the experimental group and the control group；（2）Analyze the PSEP concentration and semen volume，sperm concentration，sperm activity，normal sperm morphology rate，acid phosphatase，and seminal plasma zinc in the experimental group. Results：The positive rate of PSEP in the experimental group（62.5%）was significantly higher than that in the control group（17.4%）（$P<0.001$）. In the experimental group，there was a significant negative correlation between PSEP concentration and b-level active sperm count（$P=0.039$，$r=-0.277$），and negative correlation with sperm PR index（$P=0.054$，$r=-0.259$）；PSEP concentration There was a positive correlation with semen volume（$P=0.028$，$r=0.293$），and no correlation was found between PSEP concentration and other semen indicators. Conclusion：Prostate small in vitro protein as an auxiliary index for the diagnosis of prostate disease，also has a high positive rate in male infertility patients，and PSEP concentration and sperm activity are negatively correlated，so the urine PSEP index in the diagnosis of male infertility etiological research analysis and guided treatment have superior significance，and further expansion of sample size will be further studied.

Key words：Prostatic exosomal protein；Prostate disease；Male Infertility；Semen Analysis

慢性前列腺炎（chronic prostatitis，CP）是目前临床上常见的男科疾病，发病率约 15%[1]，同时弱精子症是男性不育的常见原因。引起弱精子症原因很多，CP 与精液质量的关系仍是研究热点之一[2]。近年来，随着对前列腺疾病认识的不断加深，以及临床快速诊断 CP 方法的普及，使前列腺与精浆疾病与男性不育关系的研究得以开展。前列腺导管上皮细胞分泌的前列腺小体外泄蛋白（prostatic exosomal protein，PSEP）作为临床快速检测 CP 特异性的标志物[3]，是否与精液质量相关并最终影响妊娠结局值得探究。本研究探讨了 PSEP 指标和精子质量之间的关系，以及 PSEP 指标在男性不育诊断及治疗中的应用价值。

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1　材料与方法

1.1　研究对象

随机选取 2019 年 6 ～ 7 月在首都医科大学附属北京妇产医院生殖男科门诊的 60 例男性不育者作为实验组，同时收集精液标本及取精前收集尿液标本；选取 180 例体检男性尿液作为对照组。排除尿常规明显异常者。尿液标本 -20℃冰箱冻存集中检测。

1.2　检测方法

记录实验组患者各项精液指标，按照《WHO 人类精液检查与处理实验室手册》（第 5 版）进行测量，包括量、精子浓度、精子活力、精子正常形态率等。采用酶联免疫法试剂盒（昂科生物医学技术（苏州）有限公司）对收集的尿样进行检测。用酶标仪测定反应孔在双波 450/630nm 处

的 OD 值。根据不同浓度的标准品 OD 值绘出标准曲线，得出待测样本的 PSEP 的浓度。

1.3 统计分析

采用均值和标准差分析实验组和对照组尿液 PSEP 浓度水平的差异。根据数据情况采用非参数检验，计数资料采用 χ^2 检验。考察 Spearman 相关系数以分析实验组中 PSEP 浓度与精液量、精子浓度、精子活动能力、精子正常形态率等之间的相关性。采用 SPSS 19.0 统计软件进行数据处理，以 $P < 0.05$ 定义为有统计性差异。

2 结果

经测试，实验组和对照组尿液样本的 PSEP 浓度存在显著差异（表 1）。实验数据反映了实验组和对照组 PSEP 浓度水平的基本特征：实验组 PSEP 浓度均值为 3.02ng/ml，阳性率为 62.5%；而对照组中 PSEP 浓度均值为 0.78ng/ml，阳性率为 17.4%。两组间差异具有明显统计学意义（$P < 0.001$）。

表1 实验组和对照组PSEP指标水平的差异

分组	例数	均值 (ng/ml)	标准差	标准误	阳性率
实验组	60	3.02	2.27	0.05	62.5%*
对照组	180	0.78	0.57	0.04	17.4%*

* $P < 0.001$

同时，比较实验组 PSEP 浓度和精液各指标之间的相关性结果（表 2）。在实验组中，PSEP 浓度和 b 级活性精子数量呈显著负相关（P=0.039，r=−0.277），和精子 PR（a+b）、a 级活力指标也接近统计学负相关；PSEP 浓度和精液量呈正相关（P=0.028，r=0.293）。PSEP 浓度和其他精液及精浆指标暂未发现相关性。

表2 实验组中尿液PSEP指标和精液各参数比较

精液指标	r	P 值
精液量	0.293	0.028
b 级活力	0.277	0.039
a 级活力	−0.258	0.055
PR (a+b)	0.259	0.054
精子浓度	0.146	0.282
精子正常形态率	0.164	0.227
酸性磷酸酶	0.078	0.569
精浆锌	0.170	0.213
对照组	180	0.78

3 讨论

前列腺液是精浆的主要组成部分。因辅助生殖技术的发展、前列腺功能检查的缺失，导致 CP 对男性不育的影响长期被忽视。CP 作为泌尿外科和男科门诊的常见疾病，其发病原因、临床症状均存在多样性和复杂性，其患者往往在性生活质量和生育力方面受到巨大的困扰。已有文献报道，CP 患者对比正常人群，可以降低精浆质量，从而进一步损害精子功能或者精子生存环境。CP 患者中也存在精液量增加，精液液化时间延长，精子浓度和精子活动力下降等的情况 [4, 5]。

前列腺小体是由人类前列腺上皮细胞分泌的一种亚细胞结构，平均直径 150 nm，存在于前列腺导管上皮细胞顶部富含高尔基体的地方。由前列腺导管上皮通过胞吐作用和胞透作用分泌至管腔 [6]。其外泌的前列腺小体外泄蛋白（PSEP）可作为临床快速诊断 CP 的特异性生物标志物 [7]，但是否可以通过其检测前列腺功能来评估其对男性生育力的影响仍然值得探究。

我们知道，前列腺小体具有抗菌、抗氧化和多重免疫调节的功能。反应性氧核素（ROS）是男性特发性不育的主因，不育病人精液中 40% 发现 ROS 增高，前列腺小体能够抑制多形核白细胞的 NADPH 氧化酶活性，从而减少 ROS 反应。此外前列腺小体包含的氨基肽酶（CD13）、二肽基肽酶 4（CD26）和脑啡肽酶或中性内肽酶 NEP（CD10）在精子运动过程中起着重要作用 [8]。

本研究发现，前列腺小体外泌的 PSEP 可在尿液中较为稳定出现，PSEP 指标在男性不育患者中也有较高的阳性率；同时 PSEP 指标和精子活力呈现负相关，与精液量呈现正相关。本研究结果推测，前列腺功能可能通过影响精子环境从而影响其前向活力，进而导致男性生育力下降。研究中发现部分数据 P 值接近 0.05 界限，提示应进一步扩大样本量完善研究结论。

PSEP 作为诊断前列腺疾病的辅助指标，与精液参数也有相关关系，具有一定的男性不育的诊断和病因学研究价值；在男性不育的病因学分类、育前体检及临床生育力评估与诊治等方面具有重要意义，为探讨前列腺功能对精液质量的影响开启了研究新思路。

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临床医学

前列腺小体外泌蛋白 ELISA 检测方法的建立和初步评价*

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[摘 要] **目的** 建立前列腺小体外泌蛋白 ELISA 检测方法并评价其作为慢性前列腺炎辅助诊断的可行性。**方法** 从慢性前列腺炎患者尿液中提取并纯化前列腺小体外泌蛋白,以纯化的前列腺小体外泌蛋白为抗原免疫实验 BALB/c 小鼠,得到单克隆抗体经过纯化后,建立 ELISA 检测方法。并对笔者所在医院的 140 例慢性前列腺炎患者尿液及正常人 60 例尿液中的前列腺小体外泌蛋白含量进行检测和评价。通过正交试验确定特异性抗体和酶标抗体的最佳工作浓度,并对试剂盒进行了 4 ℃,12 个月保存实验。确定该检测方法的临界值。**结果** 慢性前列腺炎症患者尿液中前列腺小体外泌蛋白含量明显高于正常人尿液中含量,有显著性差异(Z=10.74,P<0.05)。实验室临界值为 1.24 ng/ml。在 140 份慢性前列腺炎患者尿样中,阳性率为 88.5%;特异性为 90%。将前列腺小体外泌蛋白试剂盒测定结果与临床金标准比较[*Kappa*=0.75(95%CI=0.652 to 0.848),P<0.01],该检测试剂盒与临床金标准有高度一致性。试剂盒各个成分在低温保存 12 个月可以保持稳定。**结论** 前列腺小体外泌蛋白的检测试剂盒灵敏度高,特异性强,稳定性合格,可以为临床前列腺炎诊断提供可靠的依据。

[关键词] 前列腺小体外泌蛋白;ELISA 检测方法;评价

[中图分类号] R697.33 [文献标志码] A

Establishment of ELISA detection method for prostatic exosomal protein, and its primary evaluation

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[**Abstract**] **Objective** To shape ELISA detection method for prostatic exosomal protein [PESP] and to evaluate the method of applying indirect ELISA for the assistant diagnosis of chronic prostatitis in its feasibility. **Methods** PEP was isolated from the urines of chronic prostatitis patients and used as the immunogen for generating mouse monoclonal antibodies; the purified antibodies were used to establish an indirect ELISA detection method to study 140 urine samples of chronic prostatitis patients and 60 normal control's urine samples collected from the department of urology in Jinan Military Greneral Hospital. The optimal dilution of specific antibody and secondary antibody were surveyed through the orthogonal trial. The kits stored at 4℃ for 12 months were tested. Differences between two groups and critical value were evaluated by using SPSS 16.0 software. **Results** The content of PESP in chronic prostatitis sample was much higher than the normal control samples, that had significant differences between the two groups(Z=10.74, P<0.05). The critical value in the laboratory is 1.24ng/ml. There were perfectly consistent compared with the results of PESP testing kits and clinical gold standard (*Kappa*= 0.75 [95%CI=0.652 to 0.848], P<0.01). The components of the prostasomes kits can be stabilized storing at 4℃ for 12 months. **Conclusion** The prostasomes ELISA kits is specific, sensitive, stable, and may provide a simple rapidly and reliable method for clinic prostatitis diagnosis.

[**Key words**] Prostasomes(prostatic exosomal protein, PESP); Prostatic disease; Indirect ELISA

慢性前列腺炎(chronic prostatitis, CP)是泌尿外科中青年男性患者最常见的疾病之一,据报道其占门诊量的 30%。据流行病学调查,我国成人男性人群中,10%以上有前列腺炎样症状,50%男性不同时期均患过前列腺炎[1]。在前列腺癌中,炎症的存在及细胞上皮组织损伤后再生被认为是恶性转化的关键因素。文献指出,大约 12%前列腺炎如不及时治疗可转化为前列腺癌。所以前列腺炎严重影响男性健康[2-4]。前列腺炎临床表现因患者个体差异而缺乏特异性,因此在临床上治疗效果一直不满意。根据 1997 年美国国立卫生研究院(NIH)对前列腺炎的分类,临床上通常以Ⅲ型慢性前列腺炎多见,约占 90%左右。在临床实际工作中,泌尿男科医师对首诊的 CP 患者选择的检查方法前 3 位的是尿液分析、前列腺液检查、直肠指检。前列腺液检查和直肠指检对患者有一定侵入性,因此非常需要简便无侵入性,同时准确可靠的分子诊断方法[5]。

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前列腺小体(prostasomes)是由人类前列腺上皮细胞分泌的一种亚细胞结构，平均直径 150 nm，存在于前列腺导管上皮细胞顶部富含高尔基体的地方，由前列腺导管上皮通过胞吐作用和胞透作用分泌至管腔[6,7]。Alba Minelli 等在前列腺疾病患者血清中检测到前列腺小体[8]。本文提供一种基于前列腺小体外泌蛋白定量的间接酶联免疫吸附方法，作为前列腺炎辅助诊断，现报告如下。

1　资料与方法

1.1　一般资料　按照《中国泌尿外科疾病诊断治疗指南》中前列腺炎的诊断标准[2]，2012 年—2013 年从济南军区总医院收集慢性前列腺炎 140 例。年龄 16~72 岁，平均 34 岁。正常人体检尿液 60 份，年龄 20~68 岁，平均 34 岁。尿常规均正常。尿液收取后立即检测，或放-20 ℃冰箱保存。2 个月之内检测完毕。

1.2　试剂和仪器　前列腺小体外泌蛋白和特异性鼠抗人前列腺小体外泌蛋白检测抗体由美国 EliOnco 公司提供。96 孔聚苯乙烯检查板由美国 Becton-Dickson 及美国 Thomas Fisher Scientific 提供。HRP 标记的羊抗鼠 IgG 购自 Sigma 公司。自配清洗液、显色剂、终止液。清洗液为含 0.5%吐温-20 的 PBS 溶液；显色剂 A 含柠檬酸、乙酸钠、过氧化脲；显色剂 B 含柠檬酸、EDTA、TMB 盐酸盐、硫代硫酸钠溶液；终止液为 2 mol/L H_2SO_4。

DEM-Ⅲ自动酶标洗板机，采用北京拓普分析仪器有限公司。酶标仪(680 型)购自 BIO-RAD 公司。WHS 型智能恒湿恒温箱，购自宁波江南仪器厂。微量移液器，采用 Eppendorf，Gilson 品牌。

1.3　ELISA 检测方法建立　将稀释为一定比例的前列腺小体外泌蛋白标准品包被在 96 孔板中(B1-F1 孔)，其余孔加尿液标本，37 ℃恒温箱孵育 1 h，洗板机洗板 5 次后，加 1%BSA 封闭，每孔 100 微升，37 ℃恒温箱孵育 40 min，洗板 5 次。加入特异性前列腺小体外泌蛋白检测抗体，37 ℃恒温箱孵育 40 min，洗板后，加入 HRP 标记的羊抗鼠 IgG，37 ℃恒温箱孵育 20 min，洗板后避光显色 20 min，加入终止液，终止反应。用酶标仪测定各反应孔在双波 450，630 nm 处的 OD 值。根据不同浓度的标准品 OD 值绘出标准曲线，将患者的数值与阳性标准孔数值比较，从而得出被测试者尿样本的实际前列腺小体外泌蛋白浓度。

样本检测：用间接 ELISA 方法检测 140 例前列腺炎症和 60 例正常人尿样本。根据临床样本检测真阳性 a，假阳性 b，假阴性 c，真阴性 d，求出检测灵敏度，特异度，阳性预期值，阴性预期值并计算 Cutoff 值。

1.4　方法学鉴定

1.4.1　分析精密度　批内变异：用两个浓度水平的样本(炎症和正常人)各重复检测 10 次，计算 10 次测量浓度结果的平均值 M 和标准差 SD，得出变异系数 CV。批间差：用 3 个批号的试剂盒分别检测同样两份标本，各重复 10 次，计算 30 次结果的平均值 M 和标准差 SD，求出变异系数 CV。

1.4.2　各组成部分的稳定性实验　将检测酶联板，特异性抗体，酶标抗体，显色剂，阳性标准品等各组成部分放入 4 ℃冰箱，检测 1 次/m，观察有效期限。

1.4.3　正交实验　把特异性结合抗体按照 1:50；1:100 稀释；酶标抗体按照 1:2000；1:2500；1:3000；1:5000 稀释，然后先加样本 37 ℃孵育 1 h，洗板封闭后，加不同浓度的特异性抗体后，37 ℃孵育 40 min，洗板 5 次后加入不同浓度的酶标抗体，37 ℃孵育 20 min 后，洗板显色。根据 OD 值数据选出最佳的特异抗体和酶标抗体的使用浓度。

1.4.4　检测方法比较 (ELISA 双抗夹心法和间接法)　检测方法的确定对于检测效果具有至关重要的作用，在确定了抗体和试剂及测试时间以后必须对检测方法进行筛选，然后比较了双抗夹心法和间接法对检测结果的影响。

1.5　统计学处理　采用 SPSS16.0 统计软件进行统计学处理。前列腺炎症患者与正常人的样本差异比较采用秩和检验和配对 t 检验。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　临床样本检测结果　前列腺炎症患者尿样和正常人尿样本 PESP 检测，炎症患者尿液中前列腺小体外泌蛋白含量与正常人相比较明显升高，有显著性差异[(3.013±2.199) ng/ml vs (0.734±0.574) ng/ml，$Z=10.74$，$P<0.05$]。

2.2　方法学鉴定结果

2.2.1　灵敏度、特异度、符合率评价　按方案要求对 200 例样本进行临床金标准和考核试剂的两种检测。计算前列腺小体外泄蛋白检测试剂盒临床检测的灵敏度、特异性、总符合率、阳性预期值、阴性预期值等统计学结果。根据临床金标准选择慢性前列腺炎 140 例，正常对照 40 名，用本试剂盒在 140 例炎症患者中检出阳性 124 例，阴性 16 例。在正常对照 60 名中，阳性 16 名，阴性 44 名。

灵敏度=a/(a+c)×100%=124/140×100%=88.5%；特异度=d/(b+d)×100%=54/60×100%=90%；总符合

率=(a+d)/(a+b+c+d)=(124+54)/200×100%=89%。

2.2.2 一致性分析 采用 SPSS 16.0 统计软件对前列腺小体外泌蛋白检测试剂盒和临床诊断金标准进行一致性检验，结果显示 *Kappa*=0.75 (95%CI= 0.652 to 0.848)，*P*<0.01，一致性具有非常显著性统计学意义。

2.2.3 准确性检验（ROC 曲线分析）评价 采用 SPSS 16.0 统计软件对前列腺小体外泌蛋白试剂盒检测结果进行 ROC 曲线拟合，结果见图 1。

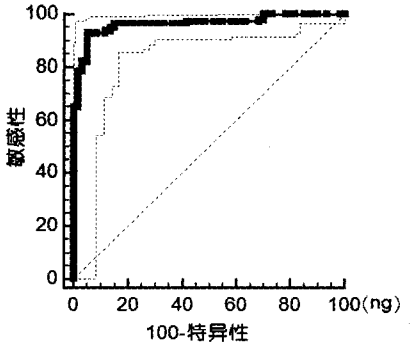

图 1 前列腺小体外泌蛋白的 ROC 曲线

如图 1 所示，ROC 曲线下面积为 0.963 (SE= 0.0125，95% CI 0.927~0.985，*Z*=36.948，*P*<0.01)，表示前列腺小体外泌蛋白试剂盒对慢性前列腺炎具有较好的诊断价值。选择 Youden 指数最大的点对应的界值作为慢性前列腺炎的诊断标准，得出前列腺小体外泌蛋白的诊断点为 1.24 ng。

2.2.4 精密度分析 用两个浓度水平的样本(阳性和阴性)各重复检测 10 次，计算 10 次测量浓度结果的平均值 M 和标准差 SD，得出变异系数 CV< 8%。用 3 个批号的试剂盒分别检测同样两份标本，(阳性和阴性)各重复 10 次，计算 30 次结果的平均值 M 和标准差 SD，其变异系数 CV 为 10.1%。结果见表 1。从以下数据可以看出该试剂盒反应体系具有良好的精密度。

表 1 反应体系的精密度检测

批内差(*n*=10)				批间差(*n*=30)			
标本	$\bar{x}$	SD	CV	标本	$\bar{x}$	SD	CV
阳性	0.69	0.04	5.8%	阳性	0.67	0.06	9.0%
阴性	0.13	0.01	7.7%	阴性	0.19	0.02	10.1%

2.2.5 试剂盒保存的稳定性实验评价 试剂盒置 4 ℃条件下干燥保存，每月定期抽检直至 12 个月，检测前列腺炎阳性样本和正常人样本。结果见表 2。从表 2 可见 1~12 月，阳性样本 ng 值每月无明显降低，阴性样本数值稳定，均在 1 ng 以下。P/N>4.7。各个月的标准品曲线 R^2 值都在 0.99 以上，非常接近 1。在保存 12 个月后，阳性样本ng 值依然达到正常情况的 90%。说明试剂盒各个成分在低温保存 12 个月可以保持稳定。

3 讨 论

慢性前列腺炎中组织受到炎性细胞的浸润，从而释放出各种活性物质和趋化因子，一种称为前列腺小体的外泌蛋白通过解剖通道分泌进入男性生殖道。研究提示，前列腺疾病中可能存在表达前列腺小体蛋白质组的独特表型，已知的分子功能是多种多样的，包括结构膜蛋白、酶、监管蛋白和信号转导分子等[9]。慢性前列腺炎病程中，多种致病因子启动 Wnt 途径，Wnt 信号通路异常表达，相应下游活性物质增加，与前列腺小体的释放和表型的变化均有密切的关系[6]。高浓度的前列腺小体可以在精液、前列腺液中发现，电镜下有两种形态：小、黑色的，外面紧包电子致密物；大的，浅色的，不致密的结构，直径 40~500 nm。有脂质双层膜，多层融合排列，富含胆固醇。相似的结构也可以在前列腺细胞系的培养液中发现。前列腺小体的主要成分是鞘磷脂，含有磷酸胆碱和神经酰胺。胆固醇和磷脂的比例是 2:1，而典型的哺乳动物细胞膜上的此种比例是 1:1[10-13]。前列腺小体蛋白有多重生理功能。抑制 PMN 中 NADPH 氧化酶的活性，从而起到抗菌抗氧化作用[14,15]。在体外培养实验条件下，小剂量的前列腺小体呈现出对肺炎球菌、地衣形杆菌、侧孢杆菌、Megatenium 杆菌的强烈抑制作用，这种抗菌活性与细胞膜的变性密切相关。在扫描电镜下，可直接观察到前列腺小体黏附到光滑的细菌包膜表面，是其外观逐渐变粗破裂，引起细菌死亡。

在精液中前列腺小体比中性粒细胞发挥更强的抗菌功能。前列腺小体可作为强有力的抗氧化剂，中和白细胞的 ROS 作用。前列腺小体的特殊的脂质结构和成分是其抗氧化抗菌功能的关键因素，推测在炎症的过程中可以检测到前列腺小体，同时此研

表 2 试剂盒 4 ℃保存实验

样本(ng)	时间(月)											
	1	2	3	4	5	6	7	8	9	10	11	12
阳性标本	4.4	4.3	4.2	4.2	4.4	4.2	4.1	4.3	4.1	4.2	4.0	4.0
阴性标本	0.8	0.9	0.8	0.8	0.7	0.7	0.8	0.7	0.6	0.7	0.6	0.6
R^2	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99

究为开发新类型的抗菌药物提供了理论基础[16]。根据在炎症状态下前列腺小体外泄蛋白质组的独特表型，设计特异性抗体，仅仅通过尿液检测，就能达到对慢性前列腺炎的早期明确诊断的目的。

从本检测的 200 例尿样中，可以看出前列腺炎患者和对照组正常人尿液中前列腺小体外泌蛋白含量的分布存在显著性差异，患者样本检测到的前列腺小体外泌蛋白的浓度明显高于对照组中前列腺小体外泌蛋白的浓度。其灵敏度为 88.5%；特异度为 90%，总符合率达到 89%。并且临床诊断金标准与本检测结果相比有很好的一致性。

前列腺小体外泌蛋白外泌蛋白的检测可以为临床前列腺炎诊断提供一个可靠的检测方法。同时该试剂盒经过严格的 4 ℃条件下长时间保存实验，检测结果稳定，符合国家食品药品监督管理总局体外诊断试剂考核标准。此检测方法简便可靠，适用于临床慢性前列腺炎的辅助诊断。

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· 论　著 ·
Clinical Research
（临床研究）

尿液中前列腺小体外泄蛋白检测两种 ELISA 方法的比较

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【摘要】 **目的**：比较两种前列腺小体外泄蛋白（PSEP）ELISA 检测方法。　**方法**：不同 ELISA 检测方法的比较（双抗夹心法和间接法）；验证稀释液基质（0.1 mol/L PBS 缓冲液）标曲系统和尿液基质标曲系统同时测试 30 例临床尿液样本，验证标准品与待测标本在不同基质情况下的表现是一致的。　**结果**：用 ELISA 双抗夹心法和间接法分别检测 100 例 IIIA 型前列腺炎患者样本，100 例正常人样本，其灵敏度分别为 89% 和 87%，特异度分别是 91% 和 90%，总符合率分别为 90% 和 88.5%，两者无统计学差异。分别以稀释液基质标曲系统和尿液基质标曲系统测试 30 例临床尿液样本，测试结果在散点图上绘制回归线，$R^2 = 0.999$，具有良好的线性，说明稀释液基质与临床尿液样本没有明显的基质差异，互换性良好。　**结论**：根据 PESP 其自身特性，PSEP 检测试剂盒 ELISA 间接法用于临床检测前列腺炎切实可行。

【关键词】 前列腺小体外泄蛋白；前列腺炎；ELISA 间接法；基质效应
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Study on the Detection Method of Prostatic exosomal protein ELISA Kit

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【Abstract】 ***Objective***: Comparison of two ELISA detection methods for prostatic exosomal protein (PSEP). ***Methods***: Comparison of different detection methods (Double antibody sandwich ELISA method and Indirect ELISA method). Validation of diluents (0.1 mol/L PBS buffer) standard system and the urine standard curve system were used to test 30 clinical urine samples at the same time. Validation of standard and specimen under the condition of different substrates for testing is same. ***Result***: Double antibody sandwich ELISA method and indirect ELISA were used to test 100 samples of IIIA CP and 100 samples of normal persons. The sensitivity (89% and 87%), specificity (91% and 90%) and total coincidence rate (90% and 88.5%) were similar. There was no statistical difference between the two groups. (2) Validation of diluents (0.1 mol/L PBS buffer) standard system and the urine standard curve

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system were used to test 30 cases clinical urine samples at the same time. The test results were plotted on a scatter plot with R^2 = 0.999 and good linearity. No significant difference was found in results with clinical urine sample in different diluents, showing good interchangeability. ***Conclusion***: Base on its own characteristics, the indirect method of PSEP ELISA kit for clinical detection of prostatitis is both practical and feasible. ***Natl J Androl*, *2020*, *26*($): -**

【Key words】 prostatic exosomal protein; prostatitis; indirect ELISA method; matrix effect

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临床上前列腺炎分为4型:Ⅰ型:急性细菌性前列腺炎;Ⅱ型:慢性细菌性前列腺炎;Ⅲ型:慢性前列腺炎(chronic prostatitis, CP)/慢性骨盆疼痛综合征,此型根据前列腺按摩液、精液中白细胞计数又分为炎症性(ⅢA)和非炎症性(ⅢB)2个亚型;Ⅳ型:无症状炎症性前列腺炎。其中,CP是成年男子的常见疾病,主要类型是Ⅱ型、ⅢA型和ⅢB型[1-2]。尽管CP是泌尿外科最多的疾病之一,但由于患者的症状多样、病因复杂,临床上急需简便易行、非侵入性的CP检测方法,来辅助并提高CP的检出率。

Ronquist等[3-5]先后报道在良性和恶性前列腺上皮细胞中都存在的前列腺小体(prostasomes),前列腺小体或又称前列腺外泌体,属于外泌体(exosome),是一种具有双层脂膜的微小囊泡,可以从局部分泌(胞内出芽、胞吐),也可以顶分泌(表面泄出)。高浓度的前列腺小体可以在精液、前列腺液、尿液中发现,由富含胆固醇的脂质双层膜多层融合排列。用超速离心、葡聚糖凝胶柱纯化的方法可以在精液和尿液中分离出前列腺小体[6]。Minelli等[7]用抗前列腺小体抗体的ELISA方法在前列腺疾病患者(BPH、前列腺炎、前列腺癌)血清中检测到前列腺小体。

本课题组前期研究发现了前列腺小体外泌蛋白(prostatic exosomal protein, PSEP),及其对应的小鼠抗人PSEP单克隆抗体,建立并优化了PSEP检测试剂盒[8]。基于前期研究,本文对不同ELISA检测PSEP方法(双抗夹心法和间接法)进行评估和比较,并且验证在稀释液基质(0.1 mol/L PBS缓冲液)和尿液基质体系下,标准品与待测标本的一致性情况。

1 材料与方法

1.1 标本采集 按照《中国泌尿外科疾病诊断治疗指南》中前列腺炎的诊断标准,从东部战区总医院和江苏省人民医院收集到完全符合临床综合诊断的ⅢA型CP的尿样100例,正常人尿液100份,平均年龄分别为31岁和39岁。样本尿常规均正常,样本-20 ℃冷冻待测。

1.2 试剂和仪器

1.2.1 主要试剂 PSEP标准品、小鼠抗人PSEP单克隆抗体、兔抗人PSEP单克隆抗体购自EliOnco公司提供,96孔反应板购自Thomas Fisher公司,HRP标记羊抗小鼠IgG购自Sigma公司,清洗液、显色剂、终止液均自配,其余试剂购自国药集团化学试剂苏州有限公司。

1.2.3 主要仪器 DEM-Ⅲ自动酶标洗板机采用北京拓普分析仪器有限公司,酶标仪(680型)购自Bio-Rad公司,WHS型智能恒湿恒温箱购自宁波江南仪器厂。

1.3 实验方法

1.3.1 双抗夹心法 将兔抗人PSEP单克隆抗体(20 μg/ml),100 μl/孔,37 ℃包被于微孔板1 h,洗板,以1% BSA进行封闭。将CP患者尿液、正常人尿液标本以及PSEP标准品(浓度分别为0.1、1、2、5、10 ng/ml)各100 μl分别加入微孔板的孔位上,37 ℃孵育1 h,洗板,然后加入小鼠抗人PSEP单克隆抗体(20 μg/ml),100 μl/孔,37 ℃孵育40 min,洗板。再加入HRP标记羊抗小鼠IgG(0.1 μg/ml),37 ℃孵育20 min,洗板。加入显色剂,避光显色20 min。终止显色后,采用酶标仪读出*A*值,将数值与阳性标准孔数值比较,计算浓度值。

1.3.2 间接法 100 μl PSEP标准品分别以0.1、1、2、5、10 ng/ml浓度包被在微孔板上,4 ℃过夜,洗板。将100 μl CP患者尿液、正常人尿液标本分别加入微孔板,37 ℃孵育1 h,洗板5次,再加入100 μl 1% BSA,37 ℃封闭1 h,洗板。然后加入小鼠抗人PSEP单克隆抗体(20 μg/ml),后续步骤同双抗夹心法。

1.3.3 互换性评价 选择间接法测试体系,使用稀释液基质(0.1 mol/L PBS)标曲系统以及尿液基质标曲系统同时测试一系列浓度的临床尿液样本,将稀释液基质标曲系统测得浓度值的算术平均值作为X轴,尿液基质标曲系统测得浓度值的算术平均值作为Y轴,绘制散点图并进行线性回归分析。

1.4 统计学分析 采用 SPSS 16.0 统计软件进行统计学处理。根据临床样本检测灵敏度、特异度、总符合率,两种检出方法的比较采用 χ^2 检验,$P \leqslant 0.05$ 为差异有统计学意义

2 结果

2.1 不同检测方法测试尿液样本的结果比较 结果见表 1、2。

2.2 基质互换性验证 分别以稀释液基质标曲系统和尿液基质标曲系统测试 30 例临床尿液样本,结果绘制散点图见图 1。

表 1 两种检测方法检测 PSEP 的临床数据

Table1. The clinical data of protein exudation from prostatic bodies were detected by different methods

Results	Clinical gold standard results		*P*
	Positive (*n*)	Negative (*n*)	
Double antibody sandwich ELISA			
Positive	89	9	
Negative	11	91	<0.01
Indirect ELISA			
Positive	87	10	
Negative	13	90	<0.01

表 2 两种检测方法检测 PSEP 的灵敏度、特异度和总符合率比较

Table 2. The statistical results of protein exudation from prostatic bodies were detected by different methods

	Double antibody sandwich ELISA	Indirect ELISA
Sensitivity (%)	89	87
Specificity (%)	91	90
Total coincidence rate (%)	90	88.5

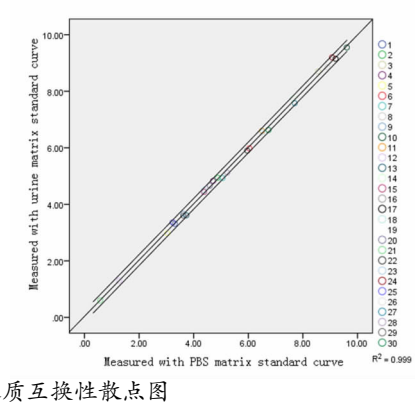

图 1 基质互换性散点图

Figure 1. Scatter plot of matrix interchangeability

3 讨论

前列腺小体是由人类前列腺上皮细胞分泌的一种亚细胞结构,平均直径 150 nm(50 ~ 500 nm),由前列腺上皮细胞通过胞吐作用和胞透作用分泌或外泄至管腔,可位于细胞囊泡内、细胞外腺泡管、或前列腺液和精液等,也可在前列腺细胞系的培养液中发现。由于前列腺的排泄管开口于尿道前列腺部的后壁,并且许多前列腺腺泡直接开口于尿道,故前列腺小体可进入尿液和前列腺液中,并非来源于膀胱。据此采用特异性 PSEP 单克隆抗体,建立了基于尿液检测 PSEP 的技术,并经大量临床样本检测验证[9-13]。

前列腺小体的主要成分包括鞘磷脂,含磷酸胆碱和神经酰胺。胆固醇和磷脂的比例是 2∶1,而典型的哺乳动物细胞膜上的此比例是 1∶1。与其他外泌体相比,前列腺小体富含胆固醇、鞘磷脂、钙、二磷酸鸟苷和许多跨膜蛋白(CD13、CD46、CD55、CD59),CD59 是反应性细胞溶解的膜抑制剂[14-16],有抗菌、抗氧化和多重免疫调节的功能[17-18]。前列腺小体相关蛋白可以作为一类很好的前列腺疾病标记物[19]。也已有报道,前列腺小体与前列腺疾病及其相关的不育不孕有密切关系[20-24]。此外,PSEP 在前列腺癌诊断中的意义也进行了大样本研究,临床发现,前列腺组织炎症和前列腺癌的低风险具有相关性。PSEP 水平在前列腺组织穿刺中和组织炎症相关性显著,而在 PSA 处于 4 ~ 10 μg/L 的前列腺癌病例的尿液中 PSEP 水平显著下降[25]。

本研究中,分别采用双抗夹心法和间接法两种 ELISA 法,分别检测 100 例ⅢA 型 CP 的尿样,和 100 例正常人尿液。两组方法的测试结果,经配对样本 *t* 检验,*P* 值为 0.324,说明两组数据有很好的一致性。同时,分别统计了两种方法测试后的灵敏度、特异性和总符合率。由表 1、2 可见,虽然双抗夹心法灵敏度、特异性和总符合率略高于间接法,但两组基本一致,均满足临床的需求。考虑双抗夹心法成本高于间接法,因此在产品转化中,更推荐间接法。此外,本研究考虑到尿液基质中含有复杂的成分,其基质效应可能会影响目标物 PSEP 的测定。因此分别采用稀释液基质(0.1 mol/L PBS)标曲系统和尿液基质标曲系统同时测试一系列浓度的临床尿液样本。从图 1 绘制的散点图可见,两组结果的相关性 R^2 为 0.999,具有良好的线性相关性。同时结果在散点图上的位置,均落在 95% 可预测区间线内,说明稀释液基质与临床尿液样本没有明显的基

质差异,PBS基质和尿液基质互换性良好,本检测方法能够客观反映尿液中PSEP的含量。因此根据PESP检测项目的其自身特点,PSEP检测试剂盒ELISA间接法用于临床检测慢性前列腺炎可行。

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· 论　著 ·

Clinical Research
（临床研究）

首段和中段尿中前列腺小体外泄蛋白对慢性前列腺炎诊断价值的比较

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【摘要】 目的：通过检测首段和中段尿的前列腺小体外泄蛋白（PSEP）来评估其在慢性前列腺炎（CP）诊断中的临床价值，并比较两段尿中的 PSEP 含量是否存在差异。 方法：纳入研究对象为 2017 年 11 月至 2018 年 5 月门诊就诊的患者 358 例，其中临床诊断为 CP 269 例，正常 89 例，ELISA 法检测其首段和中段尿标本中的 PSEP。分别计算首段和中段尿 PSEP 检测的灵敏度、特异度、总符合率等指标，绘制受试者工作特征（ROC）曲线，比较 PSEP 检测与临床诊断结果的差异，同时比较两段尿中的 PSEP 含量之间的差异。 结果：首段尿中的 PSEP 含量为（3.82 ±3.74）ng/ml，中段尿中的 PSEP 含量为（3.77 ±3.90）ng/ml，两者无明显差异（$P=0.46$）。首段和中段尿 PSEP 检测对 CP 的诊断灵敏度为 81.41%、86.99%，特异度为 89.89%、88.76%，总符合率为 83.52%、87.43%。 结论：首段和中段尿检测 PSEP 均可以作为临床辅助诊断 CP 的指标，其诊断敏感度和特异性均较强。

【关键词】前列腺小体外泄蛋白；慢性前列腺炎；灵敏度；特异度；诊断
中图分类号：R697⁺.33　　文献标志码：A　　doi：10.13263/j.cnki.nja.2018.10.007 ①

Value of prostaticexosomal protein contentsin the first- and mid-stream urine for the diagnosis of chronic prostatitis

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【Abstract】 *Objective*: To detect the contents of prostaticexosomal protein (PSEP) in the first- and mid-stream urine and assess their clinical value in the diagnosis of chronic prostatitis (CP). *Methods*: This study included358 male outpatientsat Nanjing General Hospital from November 2017 to May 2018, 269 diagnosed with and the other 89 without CP. Wemeasured the contents of PSEP in the first- and mid-stream urine samples collected from the subjectsby ELISA anddetermined the sensitivity and specificity, and total coincidence rate ofthe PSEPcontents in the diagnosis of CP. Using the ROC curve, we compared the PSEP levels in the two different urine samples and the results of diagnosis of CPbetween the PSEP detection method and clinical diagnostic criteria. *Results*: No statistically

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significant difference was observed between the contents of PSEP in the first- and mid-stream urine samples ([3.82 ± 3.74] *vs* [3.77 ± 3.90] ng/ml, $P = 0.46$). In the diagnosis of CP, the PSEP contents in the first- and mid-stream urine samples manifested a sensitivity of 81.41% *vs* 86.99%, a specificity of 89.89% *vs* 88.76%, and a total coincidence rate of 83.52% *vs* 87.43%. ***Conclusion***: Both the content of PSEP in the first-stream and that in the mid-stream urine can be used as auxiliarydiagnostic indicators of chronic prostatitis, bothwith high sensitivity and specificity. *Natl J Androl, 2018, 24(10): 898-902*

【Keywords】 prostaticexosomal protein; chronic prostatitis; sensitivity; specificity diagnosis

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慢性前列腺炎(chronic prostatitis,CP)是中青年男性泌尿生殖系统中最常见的疾病之一,CP患者约占泌尿男科门诊就诊量的30%[1]。流行病学调查研究表明,在全球范围内4.5%~10%的男性会出现前列腺炎症状,50%的男性在其一生中的某个时间点曾患有前列腺炎[2]。因此,CP作为国际医疗保健中的极为重要的问题而备受关注。然而,尽管在过去几十年中进行了较为深入的研究,CP的病因和发病机制仍不完全清楚。此外,CP的临床表现缺乏特异性,使得临床诊断和治疗非常具有挑战性[3]。

目前,CP的诊断依据包括患者主诉,尿及前列腺按摩液(expressed prostatic secretion, EPS)常规检查或培养、直肠指检等,尿、EPS常规检查缺乏特异性,EPS显微镜下观察具有很强的主观性,尿及前列腺液培养十分复杂且相当耗时,存在较高的假阴性和假阳性结果;直肠指检难免会在一定程度上对患者造成一定的侵入性伤害,造成身体和心理上的双重压力,不利于疾病的诊治和预后。由于CP缺乏客观和简单的诊断方法,也影响了CP的治疗和预后。因此寻找一种诊断CP的客观指标具有重要的临床价值。前列腺小体外泄蛋白(prostatic exosomal protein,PSEP)是由前列腺小体分泌生成的一类蛋白质的总称,前列腺小体是由前列腺上皮细胞产生的一种外泌体,具有很强的抗菌和抗氧化作用。在炎症发生时,前列腺小体的外泌或排出增加,PSEP在尿中的含量也会随之增多。本研究对门诊就诊的CP患者的首段尿和中段尿分别进行PSEP定量检测,评估其在CP诊断中的价值,并比较PSEP在首段尿和中段尿中的差异。

1 资料与方法

1.1 病例选择

1.1.1 纳入标准 参照《前列腺炎诊断治疗指南(2014版)》中的CP临床诊断标准,CP患者的诊断依据患者主诉、尿常规检查、直肠指检及EPS常规检查。收集2017年11月至2018年5月前来南京军区南京总医院门诊就诊的患者358例的首段和中段尿标本和EPS,其中临床诊断为CP 269例,正常89例,年龄20~64岁,平均年龄33.02岁。对收集的标本均行尿常规和EPS常规检查。本研究获得医院伦理委员会批准,研究对象均签署知情同意书。

1.1.2 排除标准 明确诊断的前列腺癌者;急性前列腺炎者;两周内留置导尿管者;48 h内有过性生活者;由于精神心理障碍等因素不能配合或不适合行前列腺按摩检查者;有严重的肛直肠部位疾病者;有全身其他系统疾病或脏器功能衰竭等严重疾病,难以对实验研究的有效性和安全性做出确切评价者。

1.2 标本收集与检测

1.2.1 标本收集 严格按照无菌操作收集患者首段尿、中段尿,嘱患者留取尿标本前晚必须清洁饮食,避免饮酒,禁止排精活动。对收集的尿标本采用随机号码表方法进行编号,采用双盲法,标本收集后送至-20 ℃冰箱冻存,待标本达到一定数量后集中送检,但标本保存时间严格控制在1个月内。所有患者进行EPS常规检查均须在留取尿标本后进行,以排除前列腺按摩对尿标本的影响。

1.2.2 PSEP检测 采用ELISA法,试剂盒由江苏太仓昂科生物技术公司提供,按照操作说明书对收集的尿标本进行检测。在450 nm/630 nm双波长下检测吸光度(A),根据标准曲线换算得出样本中PSEP的浓度。正常人尿中的PSEP浓度为≤1.20 ng/ml,诊断CP的参考标准为PSEP >1.20 ng/ml。

1.5 统计学分析 采用SPSS 22.0统计软件进行

分析，首段尿和中段尿检测的 PSEP 数据采用配对 t 检验。$P \leqslant 0.05$ 为差异有统计学意义。PSEP 检测与临床诊断结果一致性检验采用 Kappa 一致性分析，Kappa 系数 >0.75，为高度一致，认为两组等效；0.4 < Kappa 系数 <0.75，认为一致；Kappa 系数 <0.4则认为两组不一致，两组不等效。PSEP 在诊断 CP 方面的准确性采用 ROC 曲线统计分析，以曲线下面积（aera under the curve，AUC）来评价首段尿和中段尿 PSEP 在 CP 诊断中的临床应用价值。AUC 一般评价标准：0.5 ~0.6 为无意义、0.6 ~0.7 为差、0.7 ~0.8 为一般、0.8 ~0.9 为好、0.9 ~1.0 为优秀。

2 结果

2.1 首段尿和中段尿中 PSEP 含量的比较 首段尿 PSEP 含量为（3.82 ±3.74）ng/ml，中段尿为（3.77 ±3.90）ng/ml，经配对 t 检验，两者无明显差异（t = 0.74，P =0.46）。

2.2 PSEP 检测的灵敏度和特异度

2.2.1 首段尿 PSEP 检测结果 按照 CP 临床诊断标准和 PSEP 检测结果统计阳性数及阴性数（表 1），PSEP 检测灵敏度为 81.41%，特异度为 89.89%，阳性预期值为 96.05%，阴性预期值为 61.54%，假阳性率为 10.11%，假阴性率为 18.59%，临床总符合率为 83.52%。

2.2.2 中段尿 PSEP 检测结果 按照 CP 临床诊断标准和 PSEP 检测结果统计阳性数及阴性数（表 2），PSEP 检测灵敏度为 86.99%，特异度为 88.76%，阳性预期值为 95.90%，阴性预期值为 69.30%，假阳性率为 11.23%，假阴性率为13.01%，临床总符合率为 87.43%。

表 1 358 例患者首段尿 PSEP 检测与临床诊断比较

Table 1. Clinical diagnostic criteria *versus* prostaticexosomal protein (PSEP) content in the first-stream urine for the diagnosis of chronic prostatitis (CP)

	Based on clinical diagnostic criteria		Total
	CP-positive (n = 269)	CP-negative (n = 89)	
Based on PSEP content in first-stream urine			
CP-positive (n)	219	9	228
CP-negative (n)	50	80	130

表 2 358 例患者中段尿 PSEP 检测与临床诊断比较

Table 2. Clinical diagnostic criteria *versus* prostaticexosomal protein (PSEP) content in the mid-stream urine for the diagnosis of chronic prostatitis (CP)

	Clinical diagnosis		Total
	CP-positive (n = 269)	CP-negative (n = 89)	
Based on PSEP content in mid-stream urine			
CP-positive (n)	234	10	244
CP-negative (n)	35	79	114

2.3 首段和中段尿 PSEP 检测的 ROC 曲线比较 PSEP 检测与临床诊断结果的一致性检验显示：Kappa =0.62 和 0.69，说明首段尿和中段尿 PSEP 与临床诊断结果相比，均具有一致性。首段尿和中段尿 PSEP 检测的 ROC 曲线下面积分别为 0.92、0.93（图 1），表明 PSEP 诊断 CP 的准确性很高，首段尿和中段尿 PSEP 检测在诊断 CP 均有较高的临床应用价值，但是两条曲线存在交点，意味着两段尿 PSEP 检测各有所长，并不存在一种明显优于另一种的情况。

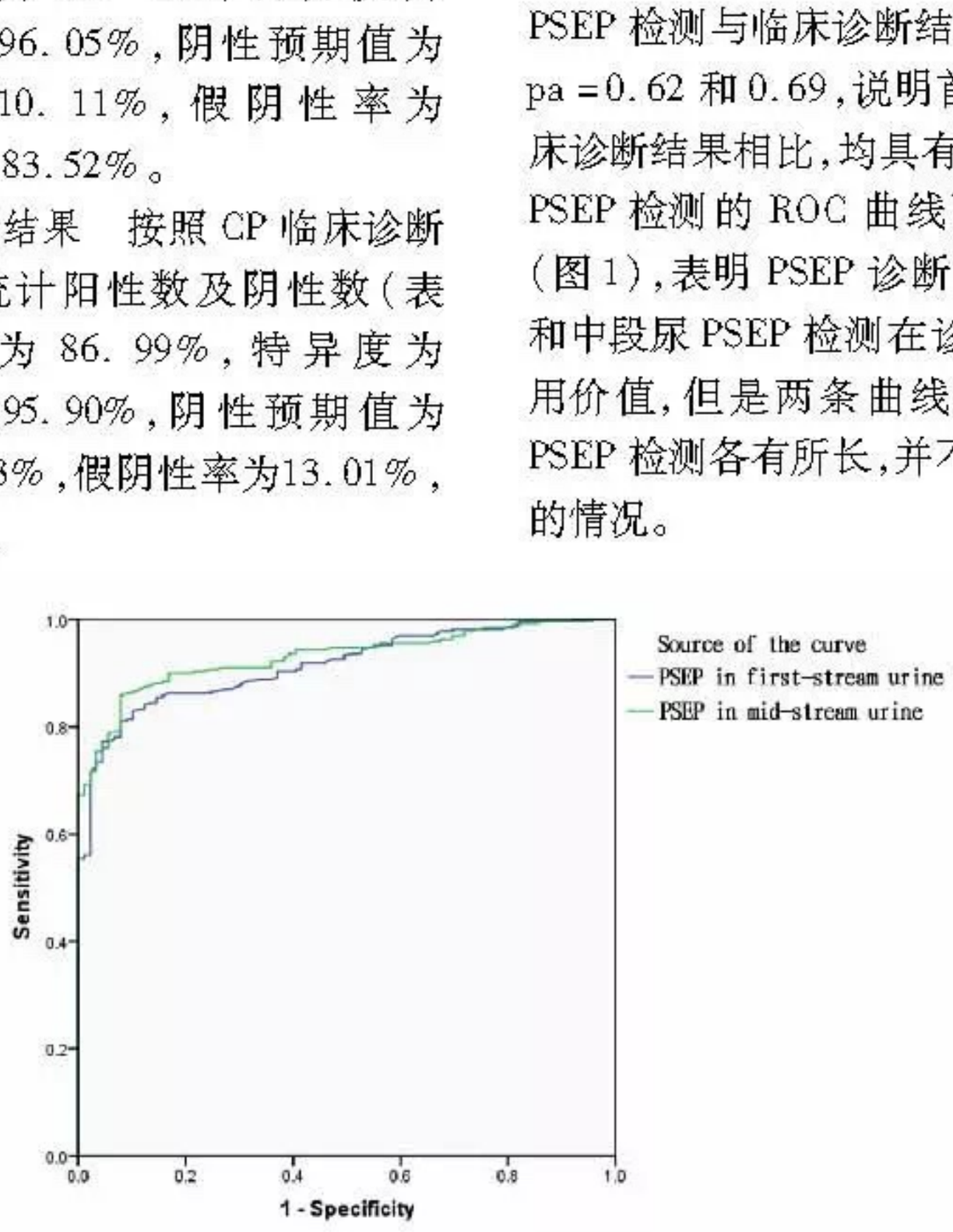

图 1 首段尿和中段尿 PSEP 检测的 ROC 曲线

Figure 1. ROC curve for the sensitivity and specificity of prostaticexosomal protein (PSEP) contents in the first- and mid-stream urine in the diagnosis of chronic prostatitis

3 讨论

CP是泌尿男科门诊最常见的疾病之一，CP的症状多样，主要表现为尿急、尿频、尿痛及排尿困难等症状，并伴有下腹部疼痛不适，性功能障碍，神经衰弱及心情烦躁等[4]。目前临床上所采用的诊断CP的方法有：尿分析、EPS常规检测等检查方式，而EPS检查对患者有一定的侵入性，造成患者的痛苦与不适。目前临床上尚缺少能够诊断CP及其病原体的准确有效的分子诊断方法[5]。

PSEP由前列腺小体分泌生成，前列腺小体是由前列腺上皮细胞产生的一种纳米囊泡，平均直径为100～150 nm，存在于前列腺导管上皮细胞顶部富含高尔基体的区域，由前列腺导管上皮通过胞吐作用分泌到管腔[6]。在正常情况下，少量前列腺小体被释放到后尿道，然后随尿排出体外。前列腺小体的主要成分是鞘磷脂，含有磷酸胆碱和神经酰胺以及数百种蛋白质。最近，有研究表明，一些前列腺小体的蛋白质组份可能作为诊断性生物标志物应用于前列腺疾病的临床诊断[7-9]。前列腺小体蛋白具有相当复杂的生理功能，包括抑制病毒活性及细菌的作用。在CD59、CD52、CD55的共同作用下，通过一系列的生化反应，保护人体的酸性环境中的精子，延迟顶体反应，增强精子的活力。前列腺小体通过减少活性氧（reactive oxygen species，ROS）起到抗氧化作用，可以通过抑制NADPH氧化酶的活性，从而发挥抗菌、抗炎以及抗氧化的作用。CP患者前列腺组织受到炎性细胞的浸润，释放出各种活性物质和趋化因子，前列腺小体生成增多，PSEP也随之分泌增加，通过解剖通道分泌进入男性生殖道。

Li等[10]推测，CP患者的前列腺小体排泄会增加，因此蛋白质也很有可能会随之发生改变。Watanabe等[11]的对20例慢性非细菌性前列腺炎/慢性骨盆疼痛综合征（chronic prostatitis/chronic pelvic pain syndrome，CP/CPPS）患者研究显示，与对照组相比，CP/CPPS患者EPS中的神经生长因子水平显著升高；Wei等[12]报道，与对照组相比，CP/CPPS患者EPS中B7-H3的水平显著降低。但是，在临床应用中，这些生物标志物在收集EPS时会因为操作复杂等诸多不利因素而造成失败率较高，这可能是由于CP患者的前列腺导管较为狭窄所致[13]。与这些生物标记物相比较，PSEP更有可能被广泛应用于临床评估。在炎症过程中，PSEP的释放及其表型均会产生变化，通过对不同表型的PSEP进行检测，有助于对CP的诊断与治疗。PSEP基于CP患者尿样本检测，比EPS检测更方便，减少了患者检测过程中的痛苦，更容易让患者接受，PSEP可能更适合于CP的临床诊断，

本研究PSEP检测的灵敏度和特异度低于杨志超等[14]报道的结果，但明显高于邵雪峰等[15]结果，而与曾燕等[16]的结果最为接近。首段和中段尿中的PSEP含量在统计学上没有明显差异，在CP的临床诊断应用中，可以优先选择中段尿作为PSEP的检测标本，但如果因为某些原因无法获取中段尿，采用首段尿进行PSEP检测，也可以获得满意的结果。首段尿和中段尿PSEP检测与临床诊断结果比较，其临床总符合率分别可以达到83.52%和87.43%，Kappa = 0.62和0.69，具有良好的一致性，表明该检测方法可靠性良好，可以作为临床上诊断CP的生物标志物，并且可以作为治疗CP的疗效评价指标之一。

但是，本研究尚存在一些不足之处，由于标本收集的量和时间的因素，可能会导致尿标本的浓缩或稀释，进而影响最后的检测结果，产生一些假阳性和假阴性结果。由于研究条件的限制，尿标本不能在收集后立即冷藏或送检，所以冷藏前的常温下保存时间对检测结果是否有影响尚不得而知。本研究纳入样本时并没有对CP病例进行分型，所以并不清楚各型CP的分布情况，不能排除样本分布不均所造成的结果误差。在我们的后续研究中会进一步针对尿标本的量、送检时间以及CP分型方面进行相关分析。除此之外，我们会进一步研究PSEP与CP患者EPS中的白细胞、卵磷脂小体等的相关性。

总而言之，首段和中段尿检测PSEP均可以作为临床辅助诊断CP的指标，两者的诊断敏感度和特异性均较强，可为CP的诊断提供一种新颖、简便易行、非侵入性、无痛的检测方法。

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UROLOGY - ORIGINAL PAPER

The clinical value of the prostatic exosomal protein expression in the diagnosis of chronic prostatitis: a single-center study

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Abstract

Objective Levels of urinary prostatic exosomal protein (PSEP) were detected to evaluate the clinical potential of PSEP as a diagnostic marker of chronic prostatitis (CP).

Materials and methods The level of urinary PSEP was measured in 412 cases by an enzyme-linked immunosorbent assay kit, including 202 controls and 210 CP cases. Of the CP patients, 116 cases met the definition of the USA National Institutes of Health category III (NIH-III), with 60 cases of NIH-IIIA and 56 cases of NIH-IIIB. The ages, body mass indexes (BMI), white blood cell (WBC) levels in expressed prostatic secretions (EPS), lecithin body counts in EPS, urine PSEP levels both before and after prostate massage obtained from the CP patients and NIH-CPSI scores were analyzed.

Results In the diagnosis of CP, the PSEP contents in the urine samples before and after prostate massage manifested a sensitivity of 86.93% vs. 61.06%, and a total coincidence rate of 85.24% vs. 61.06%, respectively. The area under the ROC curve was 0.926 vs. 0.709 for the before and after massage PSEP contents, respectively. Besides, during the follow-up of patients with CP, the improvement in symptoms was not correlated with the level changes of PSEP.

Conclusion Measurement of PSEP levels for the clinical diagnosis of CP is objective and painless. It could be a novel, simple, and noninvasive method for the diagnosis of CP. However, differences in fluid intake may result in a concentration or dilution of urine, which would ultimately affect the judgment of PSEP results.

Keywords Prostate · Chronic prostatitis · Prostatic exosomal protein · Diagnosis

Introduction

Chronic prostatitis (CP) is one of the most common diseases in the genitourinary systems of young and middle-aged men. CP patients account for approximately 30% of patients in urology and men's outpatient clinics [1]. Epidemiological studies have shown that between 4.5 and 10% of men worldwide have prostatitis symptoms, and 50% of men will have prostatitis at some point in their lifetime [2, 3].

CP has significant physical and psychological effects on the quality of life of patients [4]. It consists of three categories: NIH-II (chronic bacterial prostatitis), NIH-III (CP/chronic pelvic pain syndrome), and NIH-IV (asymptomatic prostatitis), as defined by the National Institutes of Health [5, 6]. Despite intensive research in the past few decades, the etiology and pathogenesis of CP are still not fully understood. In addition, the lack of specificity in the clinical presentation of CP makes clinical diagnosis and treatment very challenging [7]. The current lack of objective and straightforward

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diagnostic methods for CP also affects the treatment and prognosis of CP. Therefore, finding an objective indicator for diagnosing CP has outstanding clinical value.

PSEP (prostatic exosomal protein) is secreted by prostate corpuscles, a type of nanovesicle produced by prostate epithelial cells with an average diameter of 100–150 nm. It is present in the upper part of prostate ductal epithelial cells rich in Golgi by the prostate ductal epithelium. They are secreted to the lumen by exocytosis [8]. The main component of the prostate gland is sphingomyelin, which contains phosphorylcholine, ceramide, and hundreds of proteins. Recently, studies have shown that the proteome of some prostatic bodies may be used as a diagnostic biomarker for the clinical diagnosis of prostate disease [9–11]. Among these proteins, PSEP is a promising CP diagnosis marker and was, thus, evaluated in this study.

Materials and methods

Patient summary

A total of 210 CP patients who visited our hospital participated in this study from May 2017 to May 2019. In addition, 202 men were recruited from routine physical examinations as controls; they did not have any history or symptoms of prostate disease or urinary tract infection. If the individual had had a catheterization within 2 weeks or had had sexual activity within 48 h before the measurements, his data were excluded. The diagnosis of CP is based on clinical symptoms and laboratory results of urine samples and expressed prostatic secretions (EPS) and excludes other conditions such as urinary calculi, urethritis, genitourinary cancer, and cystitis. Each patient was assessed for his history and severity of symptoms using the National Institutes of Health's CP Symptom Index (CPSI), which is reported as subscores of pain, urinary tract symptoms, and quality of life, and a total score.

The patient's PSEP was collected for routine testing

Body mass index (BMI) data calculated in body weight (kg)/height (m^2) were collected. Urine samples were collected from all controls and 202 patients with CP (including 60 cases of NIH-IIIA and 56 cases of NIH-IIIB). Among them, urine was also collected from 113 patients after prostate massage. To minimize the bacterial interference, midstream urine samples from each patient were collected in strict accordance with aseptic procedures and stored at − 80 °C until PSEP was detected. After the sample was thawed, the experiment was carried out, and a PSEP diagnostic kit (enzyme-linked immunosorbent assay) produced by Angke Biomedical Technology Co, Ltd. (Suzhou, China) was used for the test [12]. The collected urine specimens were tested according to the manufacturer's operating instructions. Absorbance (A) was measured at a dual wavelength of 450 nm/630 nm, and a standard curve was established based on the OD values of the standards. The patient's value was compared to the strict standard of good value to calculate the actual PSEP concentration of the test sample.

Statistics

The median (interquartile) values of PSEP, the CPSI total score, and subscores between groups were compared using a Kruskal–Wallis test. The variance analysis method was used to compare the differences in age, BMI, EPS lecithin counts, and WBC counts in EPS. The Spearman correlation coefficient was used to evaluate the correlation between p value and age, BMI, NIH-CPSI scores, WBC counts in EPS, and lecithin content in EPS. The significance level was $p < 0.05$. Statistical analysis was performed using SPSS 22.0. The consistency of the PSEP test and clinical diagnosis results were analyzed with Cohen's Kappa coefficient. A Kappa coefficient > 0.75 indicates highly consistent testing, and the two groups would be considered equivalent; a Kappa coefficient between 0.4 and 0.75 would be consistent; and a Kappa coefficient < 0.4 would be inconsistent. In the latter case, the two groups would not be considered equivalent. The accuracy of PSEP in diagnosing CP was analyzed using ROC curve statistical analysis. The area under the curve (AUC) was used to evaluate the clinical application value of urine PSEP before prostatic massage and urine PSEP after prostatic massage in CP diagnosis. The AUC general evaluation criteria were as follows: 0.5–0.6, meaningless; 0.6–0.7, poor; 0.7–0.8, normal; 0.8–0.9, good, and 0.9–1.0, excellent.

Results

Quantification of PSPE in different subgroups

The demographic characteristics of the study groups are shown in Table 1. The PSEP levels were slightly elevated in each CP subgroup compared to the control group. CPSI scores were collected from CP patients; while individuals in the control group gave an almost negative response to the questionnaire, the CPSI total score, the pain, and urinary symptom subscores and symptom impact on the quality of life did not differ significantly among the subgroups of CP. The PSEP detected in midstream urine showed a non-normal distribution in the CP and control groups. The PSEP level in each group is listed in Table 1.

PSEP levels in patients with CP were significantly higher than those in the control group. However, no difference in PSEP was found among the urine obtained from the patients

Table 1 Clinical characteristics of enrolled chronic prostatitis patients

	Control	Before the prostate massage	After the prostate massage	NIH-III A	NIH-III B
Ages, years, median (IQR)	42.00 (16.25)	32.00 (13.00)	–	32.50 (11.00)	29.00 (13.50)
BMI, kg/m^2, mean (SD)	–	23.328 ± 2.654	–	23.475 ± 2.454	23.081 ± 2.696
CPSI total score, median (IQR)	0.00 (0.00)	23.00 (11.75)	23.00 (11.50)	22.50 (12.75)	24.00 (10.50)
Pain domain, median (IQR)	0.00 (0.00)	9.00 (7.00)	9.00 (7.00)	9.00 (6.75)	9.00 (7.25)
Urinary domain, median (IQR)	0.00 (0.00)	5.00 (4.00)	5.00 (4.00)	4.00 (5.00)	5.00 (5.00)
QOL, median (IQR)	0.00 (0.00)	9.00 (5.00)	9.00 (5.00)	9.00 (4.75)	10.00 (5.25)
Severity of symptom, median (IQR)	0.00 (0.00)	13.00 (9.00)	13.00 (9.00)	12.50 (9.00)	13.00 (8.00)
lecithin body counts in EPS(/hpf), median (IQR)	–	2.00 (2.00)	2.00 (2.00)	2.00 (2.00)	2.00 (1.75)
WBC in EPS(/hpf), median (IQR)	–	1.00 (1.75)	0.50 (1.00)	1.00 (2.00)	0.00 (0.00)
PSEP, ng/mL, median (IQR)	0.29 (0.83)	3.47 (6.02)	3.51 (5.66)	3.46 (3.75)	3.65 (7.08)

BMI body mass index, *CPSI* chronic prostatitis symptom index, *QOL* quality of life, *EPS* expressed prostatic secretions, *WBC* white blood cell, *PSEP* prostatic exosomal protein

before the prostate massage, the urine collected from the patients after the prostate massage, and the urine from the NIH-IIIA and NIH-IIIB groups ($p > 0.05$, Fig. 1). A difference in PSEP was found among those in pre-therapy and post-treatment ($p = 0.001$, Fig. 2).

ROC curve

A ROC curve was determined to identify the cutoff value in the urine of patients with CP before prostate massage and that of the controls (Fig. 3). Youden's index reached a maximum, with a cutoff value of 1.26 ng/mL. The diagnostic sensitivity was 86.9%, and the specificity was 85.2%, corresponding to the cutoff. The area under the ROC curve (AUC) was 0.926 (95% CI 0.904–0.944). A second ROC curve was determined to identify the cutoff value in the urine of patients with CP after prostate massage and the controls (Fig. 4); Youden's index reached a maximum, with a cutoff value of 0.126 ng/mL, and the diagnostic sensitivity was 61.1%, and the specificity was 85.2%, corresponding to the cutoff. The area under the ROC curve was 0.709 (95% CI 0.656–0.759).

Correlation between PSEP and clinical pathological features

The associations between PSEP and other parameters were assessed by the Spearman correlation coefficient (Table 2). There were no correlations between PSEP level and age in either the control or CP subgroups. There was

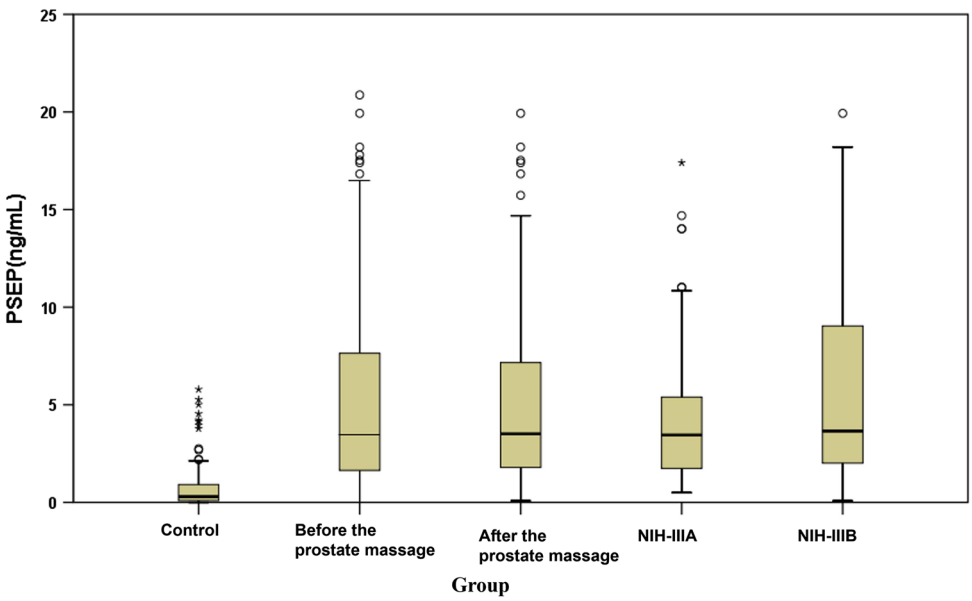

Fig. 1 Comparison of PSEP between CP subgroups and the control group. The values were significantly higher in each CP subgroup compared to the value in the controls ($p < 0.01$). No significant difference was observed in the four subgroups of CP

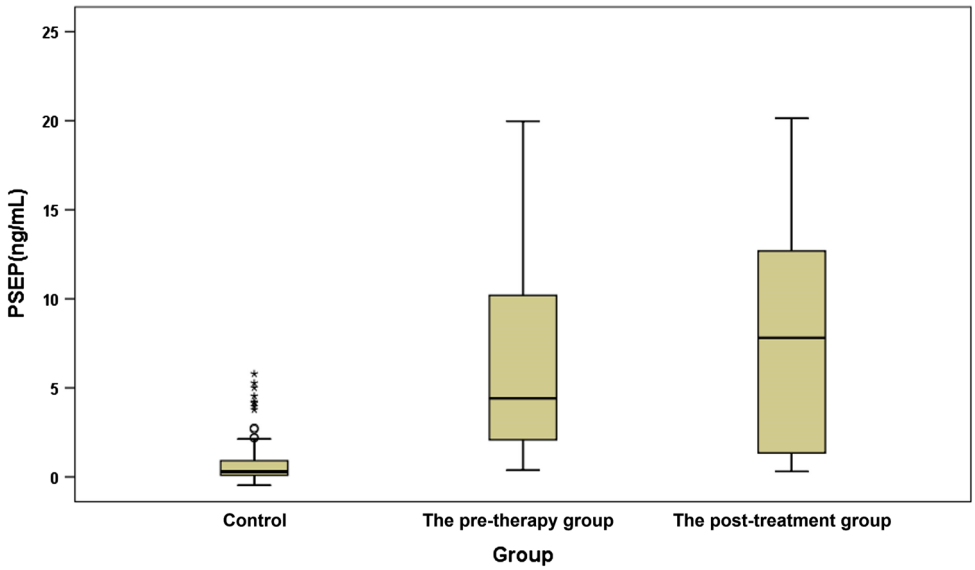

Fig. 2 Comparison of PSEP between the follow-up group and the control group. The values were significantly higher in the pretherapy and the post-treatment group compared to the value in the controls ($p < 0.01$). No significant difference was observed in the follow-up group of CP

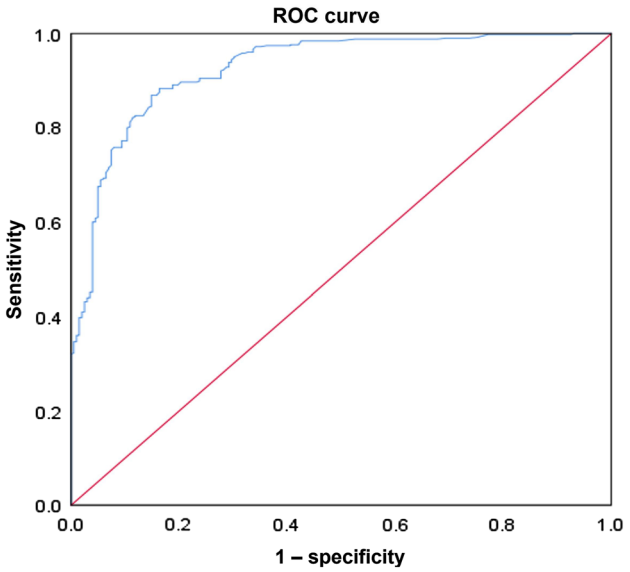

Fig. 3 ROC curve for the sensitivity and specificity of prostatic exosomal protein (PSEP) contents the urine before prostate massage obtained from the patients in the diagnosis of CP

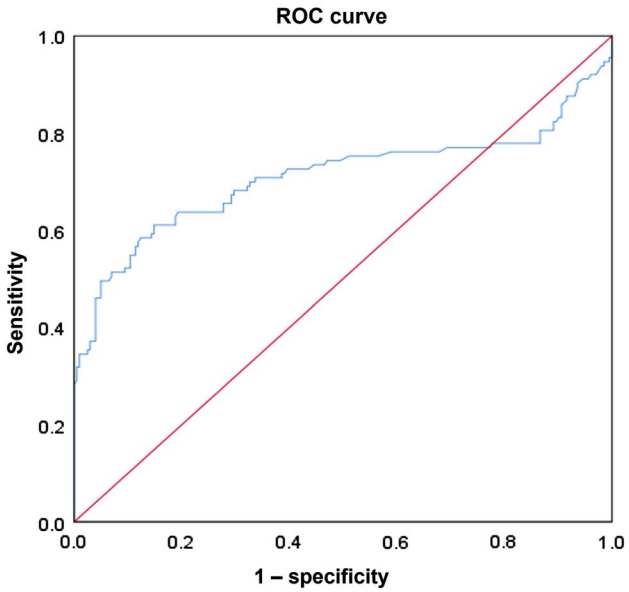

Fig. 4 ROC curve for the sensitivity and specificity of prostatic exosomal protein (PSEP) contents the urine after prostate massage obtained from the patients in the diagnosis of chronic prostatitis

no correlation between the PSEP level and BMI, WBC count in EPS, and the lecithin body count in EPS in the CP subgroups. The associations between PSEP levels and the CPSI total or subscores were assessed. It was found that urine PSEP levels negatively correlated with CPSI total scores ($r = -0.331$, $p = 0.014$) and with the pain domain subscore ($r = -0.369$, $p = 0.006$) in the NIH-IIIB group but not in the urine before prostate massage obtained from the patients, urine after prostate massage obtained from the patients, or the urine from the NIH-IIIA or control groups.

Interestingly, the association between PSEP and CPSI scores and subscores before and after treatment was evaluated in 36 follow-up patients (Table 3). Patients in the follow-up group had no significant difference in urination symptoms before and after treatment. However, the NIH-CPSI score, pain symptom score, quality of life score, symptom severity score, and PSEP were significantly different. There was no correlation between PSEP level and age, CPSI total or subscore in the total 36 follow-up patients (Table 4).

Table 2 Correlation coefficients between PSEP and age, BMI, the NIH-CPSI score, prostate-related parameters in the study

Features	Control		Before the prostate massage		After the prostate massage		NIH-III A		NIH-III B	
	r	*p*	*r*	*p*	*r*	*p*	*r*	*p*	*r*	*p*
Ages, years	0.067	0.345	0.023	0.739	0.003	0.972	0.117	0.373	−0.060	0.662
BMI, kg/m^2	–	–	−0.136	0.151	−0.114	0.243	0.020	0.883	−0.141	0.328
CPSI total score	–	–	−0.125	0.175	−0.128	0.176	−0.088	0.505	−0.331	0.014
Pain domain	–	–	−0.128	0.164	−0.134	0.158	0.003	0.981	−0.369	0.006
Urinary domain	–	–	−0.009	0.926	−0.016	0.867	−0.053	0.685	−0.017	0.904
QOL	–	–	−0.102	0.269	−0.094	0.321	−0.174	0.184	−0.209	0.130
Severity of symptom	–	–	−0.106	0.251	−0.114	0.229	−0.034	0.794	−0.314	0.021
lecithin body counts in EPS(/hpf)	–	–	0.169	0.070	0.149	0.125	0.134	0.306	0.199	0.142
WBC in EPS(/hpf)	–	–	−0.114	0.223	−0.073	0.450	−0.077	0.560	–	–

BMI body mass index, *CPSI* chronic prostatitis symptom index, *EPS* expressed prostatic secretions, *WBC* white blood cell, *QOL* quality of life, *PSEP* prostatic exosomal protein

Table 3 Clinical characteristics of the follow-up of patients with CP enrolled in the study

Parameters	The pre-therapy group	The post-treatment group	*p* value
Ages, years, median (IQR)	29.00 (11.50)	–	–
CPSI total score, median (IQR)	26.50 (11.75)	20.50 (8.75)	< 0.001
Pain domain, median (IQR)	11.00 (6.75)	7.00 (5.75)	< 0.001
Urinary domain, median (IQR)	5.00 (4.00)	4.00 (5.75)	0.400
QOL, median (IQR)	10.00 (2.00)	9.00 (4.00)	0.001
Severity of symptom, median (IQR)	16.50 (10.25)	11.00 (7.50)	0.001
PSEP, ng/mL, median (IQR)	4.41 (8.31)	7.81 (11.38)	0.001

CPSI chronic prostatitis symptom index, *QOL* quality of life, *PSEP* prostatic exosomal protein

Table 4 Correlation coefficients between PSEP and age, the NIH-CPSI score in the follow-up of patients with CP

Parameters	The pre-therapy group		The post-treatment group	
	R	*p*	*r*	*p*
Ages, years	0.093	0.590	0.185	0.279
CPSI total score	−0.047	0.785	0.016	0.924
Pain domain	0.012	0.943	−0.230	0.177
Urinary domain	−0.029	0.866	0.169	0.324
QOL	0.035	0.841	−0.039	0.821
Severity of symptom	0.003	0.984	−0.034	0.844

CPSI chronic prostatitis symptom index, *QOL* quality of life

Discussion

The etiology and pathogenesis of chronic prostatitis are complicated. The existing literature on chronic prostatitis indicates that chronic prostatitis is an inflammatory process caused by the interaction of various factors, such as infection and immune, endocrine, nervous, and mental factors, including long-term hyperemia of the prostate, infection caused by multiple causes, urine reflux, and even abnormalities of inflammatory mediators [13, 14], clinical symptoms and seasons of chronic prostatitis, diet, sexual activity, genitourinary tract inflammation and related mental psychology factors. Some studies suggest that CP can be regarded as a symptomatic disease: patients complain of more symptoms and no specificity, and it is often subjective in clinical diagnosis, with limited laboratory and imaging methods to verify it [15, 16]. Therefore, there is an urgent need for a biomarker and a noninvasive, quick and straightforward, and accurate and reliable diagnostic method that provides a useful tool for screening and diagnosing chronic prostatitis.

Prostasomes are active substances released from the prostate tissue in patients with chronic prostatitis, secreted specifically by human prostate epithelial cells. Prostasomes contain a series of regulating proteins, such as CD59, CD52, and CD5. Biochemical reactions can protect sperm in acidic environments, delay acrosome reactions, and enhance sperm motility. Prostate corpuscles inhibit the activity of NADPH

enzymes in PMN (polymorphonuclear leukocytes), resulting in a decrease in reactive oxygen species (ROS), thereby exerting antibacterial, anti-inflammatory, and anti-oxidative effects. Prostatic body proteins, which are prostate proteins found in normal human urine, are exogenous proteins that include hundreds of complex proteins. Under normal conditions, a small number of prostatic bodies are released and secreted into the male reproductive tract through the anatomical passage and then discharged with the urine. The prostate tissue of CP patients is infiltrated by inflammatory cells that release various active substances and chemokines, increasing the production of prostatic bodies and increasing the secretion of PSEP, which is secreted into the male reproductive tract through the anatomical channel. Early experimental studies have also found elevated levels of PSEP in the urine of patients with chronic prostatitis [8, 17–21].

Watanabe et al. [22] showed that, compared with a control group, 20 patients with chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) patients, nerve growth factor levels in EPS were significantly elevated; Wei et al. [23] reported a significant reduction in B7-H3 levels in EPS in patients with CP/CPPS compared with controls. However, in clinical applications, these biomarkers may have a high failure rate when collecting EPS due to many unfavorable factors, such as complex operation, which may be due to the narrowing of the prostate duct of CP patients [24]. Compared with these biomarkers, PSEP is more likely to be widely used in clinical evaluation. Yin et al. [21] reported that the level of PSEP in the urine of patients with CP was significantly increased. PSEP, TNF-α, and IL-10 could be used as the basis for the diagnosis of CP, and their combination may provide more accurate diagnostic information for CP clinical types. During the inflammatory process, the release of PSEP and its phenotype will change. The detection of PSEP by different phenotypes will help to diagnose and treat CP. PSEP is based on urine sample tests in CP patients, which is more convenient than EPS detection, reducing the pain in the patient's testing process and makes it easier for patients to accept. PSEP may, thus, be suitable for clinical diagnoses of CP.

The results of this study showed that the urine test results from the PSEP kit were compared with the standard clinical diagnosis, and the total clinical coincidence rate was 85.24% (Kappa = 0.85), indicating good consistency. There was no statistically significant difference in the content of PSEP in the urine before and after the massage. In the clinical diagnosis of CP, pre-massage urine can be preferentially selected as the specimen for PSEP. After the massage, when the urine PSEP test was compared with the clinical diagnosis results, the total clinical coincidence rate was 61.06% (Kappa = 0.61), but there were still a small number of false positives and false negatives observed. We speculate that when the PSEP test is performed following substantial changes in liquid intake, urine output, and/or living conditions, it may cause changes in the concentration or dilution of the urine, affecting the measurement of the urine sample and, ultimately, the judgment of the result. The difference in liquid intake leads to urine concentration or dilution, which can eventually affect the interpretation of the results. Therefore, in clinical diagnostic applications of CP, we recommend that patients be tested in the morning to reduce the effects of dilution or concentration. Besides, the mean age of the control group was inconsistent with the experimental group, but in the previous study of Li et al. [25], there was no correlation between age and PSEP. Notably, we also analyzed changes in PSEP level during the CP patients' follow-up. We found that the patient's symptoms improved after the treatment, but the improvement in clinical symptoms was not correlated with the changes in PSEP level. There was no statistically significant difference in urine PSEP content and NIH-CPSI score and sub-score before and after treatment among CP patients ($p > 0.05$). All these results suggested that the PSEP could be served as a diagnosis marker instead of to be a prognosis indicator.

There are some shortcomings in this study, as it is based on clinical diagnostic criteria. Because of the lack of a bacterial culture of the prostatic fluid, it is challenging to make a type II, IIIA, or IIIB chronic prostatitis diagnosis, and thus the differences between groups of chronic prostatitis could not be appropriately compared. Because all the CP cases were not classified, detailed distribution of each type of CP was not precise, and therefore, error in the results caused by the uneven distribution of the samples could not be excluded. However, in clinical work, type III prostatitis accounts for more than 90% of chronic prostatitis. Diagnosing chronic prostatitis mainly relies on prostatic fluid examination, and few prostatic fluid cultures are used. The main reason is that the culture results have little significance for clinical treatment guidance after they are cultivated. The positive rate is meager. In this study, the result may not fully represent patients with urinary tract infection, although we excluded routine cases of urinary tract infections through regular urine tests. However, the lack of bacterial culture of the urine, it is challenging to make a precise diagnosis of chronic prostatitis. In the follow-up work, we will delve into the relationship between urine culture results and PSEP in urine. At present, it takes approximately 3 h to detect CP with the PSEP kit, and the specimens need to be tested in batches. Due to the research conditions of this study, the amount of specimen collected may cause concentration or dilution of the urine, which in turn would affect the final test results, resulting in some false positives and false negatives. The false-positive result is the difference in fluid intake resulting in the concentration of urine, which ultimately affects the judgment of the results. When the PSEP examination is performed, if the patient's fluid intake is reduced or the urine output is

increased, and the living conditions are significantly different, it may cause concentration of urine, which may affect the false positive of the measured value of the urine sample. Therefore, we recommend that patients take morning urine tests as appropriate to reduce the effects of dilution or concentration. Furthermore, urine specimens cannot be sent immediately after collection; it is not known whether storage time at average temperature before the test influences the test result. In our follow-up study, we will further analyze the number of urine specimens, time of submission, and the detailed distributions of each type of CP.

Conclusion

Measurement of PSEP in urine can be used as an indicator for a clinically assisted diagnosis of CP, and its diagnostic sensitivity and specificity are favorable. This test could be a novel, simple, and noninvasive molecular method of diagnosing chronic prostatitis. However, differences in fluid intake can result in the concentration or dilution of urine, which would ultimately affect the judgment of the PSEP results. The correlation between PSEP and the severity of CP symptoms needs further study.

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Compliance with ethical standards

Conflict of interest The author(s) declare that they have no conflict of interest.

Ethical standards The research contents and research programs were reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Anhui Medical University. (anyiyifuyuanlunshen-kuai-PJ-2019-09-11).

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