Review

Update on treatment aspects of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

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Abstract: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a frequent disease affecting men of all ages. Chronic prostatitis can significantly impair quality of life. Symptoms attributed to CP/CPPS are heterogenous. Patients with CP/CPPS present an individual etiological and symptomatology profile resulting in an unique clinical phenotype. Research efforts were made to define multimodal therapeutic strategies addressing the wide array of signs and symptoms. A clinical phenotyping system has been suggested clinically directive to focus on the symptoms of the patients. This system contains six major complain domains of CP/CPPS patients: urinary, psychosocial, organ specific, infection, neurologic and tenderness of skeletal muscles (UPOINT). Recently, the system was modified by adding the sexual dysfunction as a domain to create UPOINTS. Promising results have currently been reported from multimodal approaches of CP/CPPS therapy as it aims to offer a personalized combination therapy.

Key words: Prostatitis; Chronic pelvic pain syndrome; UPOINTS; Phenotype; Treatment.

INTRODUCTION

According to the National Institutes of Health (NIH) 1995 classification Chronic Prostatitis/ Chronic Pelvic Pain Syndrome (CP/CPPS) represents category III of prostatitis with no bacteria detectable in urine or expressed prostatic secretion. CP/CPPS can be inflammatory with an elevated white cell count in prostatic secretion (NIH IIIa) or non-inflammatory with no white cells in the prostatic secretion (NIH IIIb)[1]. The leucocyte count does not correlate with the severity of symptoms[2]. The worldwide prevalence of CP/CPPS is between 2.7 and up to 16%[3,4]. CP/CPPS has a significant negative impact on quality of life[5]. In a large European study 21 % of patients with chronic pain syndrome had a depression. 19% of patients lost and 13% changed their occupation because of pain[6]. CP/CPPS is likely to have different causal determinants and different disease progression pathways[7]. It has been suggested that the cause may be infectious, autoimmunal, hormonal, psychological or associated with an intraprostatic urinary reflux. CP/CPPS may cause anxiety, impair emotional function, and cause insomnia and fatigue[5,8]. Genetic components are evident as family clusters and an accumulation of pain syndromes in twins have been observed[9,10]. An upregulation of the corticotropin-releasing hormone has been suggested as a hormonal risk factor. Chlamydia trachomatis[11], Ureaplasma urealyticum[12], Mycoplasma hominis[13], Trichomonas vaginalis[14], Viruses[15], Candida[16] and parasites have been described to be associated with the infectious forms of CP/CPPS. Monotherapy strategies for CP/CPPS have been shown to be ineffective[17]. These discouraging results show that the complex symptom array of CP/CPPS patients cannot be targeted by a single therapeutic agent. The UPOINT/UPOINTS system has been proposed in order to classify patients with CP/CPPS clinically and to offer patients a symptom related therapy.

Recently a possible etiological pathway has been described that was recognized by many experts. According to this mechanism, an unfavorable event (trauma, infection etc.) leads to an injury-response of the tissue. Inflammation and the upregulation of cytokines may lead to additional organ damage involving nerves, blood vessels, smooth muscles and the loss of bladder epithelial integrity. The resulting pain may produce contraction of pelvic smooth and skeletal muscles, finally leading to lower urinary tract symptoms, ejaculatory pain and pain in other regions such as back and abdomen. Prolonged pain may sensitize central and peripheral nervous systems and finally cause hyperalgesia and allodynia. Chronic pain may have damaging psychological effects and cause a depressive state[18,19].

METHODS

We performed a selective literature search for chronic prostatitis/chronic pelvic pain syndrome.

RESULTS

As there are no biomarkers of CP/CPPS to guide therapy the validated outcome index is the National Institute of Health Chronic Prostatitis Index (NIH-CPSI)[20]. A clinical phenotyping was proposed to classify patients with CP/CPPS to offer therapy according to the individual complains. The UPOINT system was validated in several clinical trials[21,22]. A strong correlation between the number of positive UPOINT domains and the total score of the NIH-Chronic Prostatitis Symptom Index (CPSI) measured in patients was shown. Shoskes et al.[21] first demonstrated that a majority (84%) of patients treated based on the UPOINT phenotype had a clinical improvement of CP/CPPS symptoms measured by an at least 6-point improvement in the total score of the NIH-CPSI symptom questionnaire. This strategy was followed in other studies[22].

In a large German-Italian study, a total of 1,227 patients with CP/CPPS were evaluated. The correlation between the UPOINT and CP/CPPS was confirmed for the total and for the Italian subgroup whereas, in the German subgroup the correlation was achieved only after sexual dysfunction (ED) was added as a domain to create UPOINTS[23]. The authors suggested that adding sexual dysfunction to the domain system may be helpful, as sexual dysfunction is a frequent complaint of patients suffering from CP/CPPS. Two additional studies from China and Canada supported this observation[24,25]. The prevalence of sexual dysfunction is 65%[26]. CP/CPSS has been clearly shown as a risk factor of ED[27].

Several therapy options are available for each UPOINT domain. In a prospective randomised placebo-controlled study Pollen extract (Cernilton) was shown to significantly improve the total score of the NIH-CPSI as well as the pain and the quality of life domains in patients with inflammatory CP/CPPS (NIH IIIa)[28]. The treatment with Pollen extracts can be more helpful when supplements are added[29]. Alpha-receptor blockers alone and with Pollen extract improve urinary flow parameters in patients with prostatitis[30,31]. The probability of the beneficial effects of alpha-receptor blockers is higher in the presence of storage and voiding symptoms in CP/CPPS patients (U in UPOINT)[31]. Even though 5-alpha-reductase

inhibitors are not recommended in general (EAU Guidelines 2017) some studies showed a tendency to improve symptoms. Phosphodiesterase-5 inhibitors may help to improve sexual function. Antidepressants may be effective to treat the psychological domain of the UPOINT system. Xia et al., reported that an antidepressive therapie with Fluoxetin not only had a positive effect on the depression score but also significantly improved the quality of life and urinary domains of CPSI[32]. Special physiotherapy treatment options such as myofascial physical therapy may be helpful as it releases tightness of soft tissue and helps to release pain[33]. Acupuncture has been shown to be an effective therapy especially in decreasing pain[34,35]. According to the EAU guidelines NSAIRs have a moderate treatment effect. Celecoxib was shown to be significantly beneficial and improved the pain subscore, the QoL subscore and the total NIH-CPSI score in placebo controlled clinical studies[36].

In placebo-controlled studies antibiotics were proven not to significantly improve the symptoms of CP/CPPS if no infection in prostate is present[37]. In contrast with these findings a network meta-analysis showed a significant benefit of antibiotic treatment in total symptom, pain, voiding and QoL scores in CP/CPPS patients[38]. In the EAU guidelines the use of quinolones or tetracyclin for a treatment period of at least six weeks is recommended if an antibiotic treatment is applied (EAU Guidelines 2017). It has been assumed that an antibiotic treatment helps in cases of an infectious cause of CP/CPPS when microbiological cultures failed to detect uropathogens that are present in the prostatic fluid. In 8% of patients with suggested CP/CPPS positive prostatitis cultures can be found[36].

Investigations show that treatment of some UPOINT(S) domains may be beneficial for other domains. In a large Italian study patients with CP/CPPS NIH-III were treated with alpha-receptor blocker alfuzosin and S repens extract alone or in combination with supplements lycopene and selenium[22]. Only after a positive microbiological culture of prostate-specific specimen an antibiotic ciprofloxacin or azithromycin was added to the therapy. Although no therapy for the erectile dysfunction was given 54% of patients had an improvement of sexual function. The authors suggested a two-step algorithm for CP/CPPS patients. As a first treatment option a combination of an alfa-blocker, phytotherapy (pollen extract) optional with supplements (lycopene and selenium) and in the case of proven or highly suspected infection an antibacterial agent. In case of persistent complains antidepressant, anxiolytics, myorelaxants and other agents can be added as a second step to the treatment.

CONCLUSION

The recent treatment strategies of CP/CPPS take into account the multimodal origin of this disease as well as its heterogenous phenotype. There are diverse options available for patients and treating doctors to achieve significant symptom relief. Clinical results are promising so far. Based on the modern understanding of the etiology, future investigations may provide further therapeutic options in a multimodal setting[39]. However, treatment of CP/CPPS remains challenging and requires from the treating doctor fundamental knowledge in different fields of modern medicine.

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Multidisciplinary comment

We have read the review by Hoffmann et al. regarding the treatment of chronic prostatitis/Chronic pelvic pain syndrome with interest. According to the National Institute of Health classification for prostatitis, there are 4 different types of prostatitis syndromes[1,2]. Syndromes I&II have a proven bacterial infection (acute and recurrent respectively), allowing a fairly straightforward approach. Syndrome IV is asymptomatic and so rarely requires treatment. Hoffmann et al. in their review have focused on category III, in which no source of infection is found. These patients may or may not have inflammatory findings in the semen (IIIA and IIIB respectively), in either case they are symptomatic.

Patients with chronic nonbacterial prostatitis/chronic pelvic pain syndrome (CP/CPPS) typically present primarily with chronic pain and as such have a strong negative impact on their quality of life. The UPOINT classification system, initially described in 2009, uses a clinical phenotype-based system that helps to profile specific patients and assists in choosing individual treatment targets[3,4]. Treatment results are usually assessed using the NIH-CPSI score[5,6].

Without a clear cause, management of CPPS is challenging and frustrating to both the patient and physician, also involving a significant economic burden[7]. Patients with CP/CPPS typically have a history of repeated physician visitations, involving multiple doctors. These patients typically undergo multiple diagnostic investigations and treatment trials. Sadly, as described by the authors, although several therapeutic agents exist, they are moderately effective at best, and these patients frequently require multimodality strategies. Considering this, patients suffering from CP/CPPS can benefit from referral to centers of excellence experienced in treating them. Centers of excellence can reduce unnecessary diagnostic tests, reassure patients regarding their diagnosis and prognosis, and implement an early individualized multimodal therapeutic regimen achieving the best long-term results.

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