MARKKU J. LESKINEN

Male Chronic Pelvic Pain Syndrome

Aetiology, Symptom Evaluation and Treatment

■

ACADEMIC DISSERTATION

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Dedicated to my family
and friends

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LIST OF ORIGINAL COMMUNICATIONS

I. **Leskinen MJ**, Rantakokko-Jalava K, Manninen R, Leppilahti M, Marttila T, Kylmälä T and Tammela TLJ (2003): Negative bacterial polymerase chain reaction (PCR) findings in prostate tissue from patients with symptoms of chronic pelvic pain syndrome (CPPS) and localized prostate cancer. Prostate 55: 105-110.

II. **Leskinen MJ**, Vainionpää R, Syrjänen S, Leppilahti M, Marttila T, Kylmälä T and Tammela TLJ (2003): Herpes simplex virus, cytomegalovirus, and papillomavirus DNA are not found in patients with chronic pelvic pain syndrome undergoing radical prostatectomy for localized prostate cancer. Urology 61: 397-401.

III. **Leskinen MJ**, Mehik A, Sarpola A, Tammela TLJ and Järvelin M-R (2003): The Finnish version of the National Institutes Of Health Chronic Prostatitis Symptom Index correlates well with the visual pain scale: translation and results of a modified linguistic validation study. BJU Int 92: 251-256.

IV. **Leskinen M**, Lukkarinen O and Marttila T (1999): Effects of finasteride in patients with inflammatory chronic pelvic pain syndrome: a double-blind, placebo-controlled, pilot study. Urology 53: 502-505.

V. **Leskinen MJ**, Kilponen A, Lukkarinen O and Tammela TLJ (2002): Transurethral needle ablation for the treatment of chronic pelvic pain syndrome (category III prostatitis): A randomized sham-controlled study. Urology 60: 300-304.

ABBREVIATIONS

BOO	Bladder outlet obstruction
bp	Base pair
BPH	Benign prostatic hyperplasia
CMV	Cytomegalovirus
COX	Cyclo-oxygenase
CP	Chronic prostatitis
CPCRN	Chronic Prostatitis Collaborative Research Network
CPPS	Chronic pelvic pain syndrome
DNA	Deoxyribonucleic acid
EPS	Expressed prostatic secretion
GCPS	Graded Chronic Pain Scale
HPV	Human papillomavirus
HSV	Herpes simplex virus
IC	Interstitial cystitis
IPSS	International Prostate Symptom Score
MC	Mast cell(s)
NIH	National Institutes of Health
NIH-CPSI	National Institutes of Health Chronic Prostatitis Symptom Index
NSAID	Non-steroidal anti-inflammatory drug(s)
PCR	Polymerase chain reaction
Post-M	Post-massage (urine sample)
PPMT	Pre and post-massage test
Pre-M	Pre-massage (urine sample)
PSA	Prostate-specific antigen
PSSI	Prostatitis Symptom Severity Index
QoL	Quality of life
RNA	Ribonucleic acid
rDNA	Ribosomal deoxyribonucleic acid
ROS	Reactive oxygen species
SFQP	Symptom Frequency Questionnaire in Prostatitis
SP	Seminal plasma
TRMH	Transrectal microwave hyperthermia
TUMT	Transurethral microwave thermotherapy
TUNA	Transurethral needle ablation
UTI	Urinary tract infection
VAS	Visual analogue scale

ABSTRACT

Male chronic pelvic pain syndrome (CPPS) is a common disease affecting 4 to 16% of men, but its cause and pathophysiology are mostly unknown and treatments are still empirical, being targeted at alleviating the symptoms rather than curing the disease.

The aim was to determine the role of bacteria or viruses as aetiological factors in CPPS. The presence of microbes in prostate tissue samples obtained by radical prostatectomy from ten patients with localized prostate cancer having moderate to severe symptoms of CPPS and ten non-symptomatic controls was investigated by two broad-range bacterial polymerase chain reaction (PCR) methods to detect bacteria and by viral PCR for herpes simplex viruses (HSV) 1 and 2, cytomegalovirus (CMV) and human papillomaviruses (HPV). Neither clinically relevant bacteria nor viruses were found, suggesting that the prostate does not harbour the normal microbial flora and that a microbial aetiology for CPPS is unlikely.

In order to develop a reliable and valid Finnish instrument for measuring the symptoms of CPPS, the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) was translated into Finnish using the double-back translation method with interim modifications, and the content and construct validity of the Finnish version was tested by presenting the questionnaire to 155 men with CPPS symptoms and to 12 controls without any prior urological history. Convergent validity testing included symptom evaluation using a visual analogue scale (VAS) and the balancing of this against the NIH-CPSI. The results revealed that the Finnish NIH-CPSI has good content, construct and convergent validity. Furthermore, it is readily understandable and easy to use and enables comparisons of symptom severity to be made between Finnish-speaking men and men speaking other languages using the same validated questionnaire. Owing to its high discriminative power, the NIH-CPSI ought to be used as the primary outcome measure in clinical CPPS studies.

The effects of finasteride on the symptoms of CPPS were studied in a randomised, parallel, placebo-controlled trial involving 41 men with moderate to severe symptoms of CPPS, 31 of whom were randomised to 12 months of finasteride treatment, while 10 received placebo treatment. The primary outcome measure was the validated Prostatitis Symptom Severity Index (PSSI). The symptoms of CPPS were relieved statistically more markedly in the finasteride group than in the placebo group. Side-effects were few, and treatment with finasteride was well tolerated. The results

suggest that finasteride may be beneficial in CPPS, and should be considered as a viable treatment option.

The efficacy of transurethral needle ablation (TUNA) for treating CPPS was investigated in a randomised sham-controlled study with 33 men who had moderate to severe symptoms of CPPS. 25 of the participants were randomised to TUNA treatment and 8 to cystoscopy, which was used as a sham treatment. The outcome was evaluated by PSSI at 3, 6 and 12 months after treatment. Equal, statistically significant improvements in symptoms were seen in both groups, and no differences could be detected between them. As the efficacy of TUNA was not superior to that of sham treatment, it cannot be recommended for routine use in cases of CPPS.

In conclusion, the results suggest that a microbial aetiology for CPPS is unlikely and that the Finnish NIH-CPSI is a valid and easily comprehensible tool for measuring the symptoms of CPPS and should therefore be used as the primary outcome measure in clinical trials and in practice. Treatment of CPPS with finasteride has a positive effect on the symptoms, whereas the effect of TUNA thermotherapy is not superior to that of a sham treatment.

INTRODUCTION

Male chronic pelvic pain syndrome (CPPS), formerly chronic non-bacterial prostatitis, is characterized by chronic pain in the pelvis, genital and inguinal area, lower abdomen and perineum, often accompanied by various urinary symptoms (Alexander and Trissel 1996, Krieger et al. 2002). Persistent symptoms may have a serious impact on QoL (Wenninger et al. 1996). CPPS is a common complaint, with a prevalence varying between 4 to 16% (Moon et al. 1997, Mehik et al. 2000, McNaughton Collins et al. 2002), and it therefore poses a great burden for health care.

The aetiology and pathophysiology of CPPS are poorly understood. Several aetiological theories have been proposed, the most popular being bacterial infection (Domingue and Hellstrom 1998, Krieger and Riley 2002), but chemical irritation caused by intraprostatic reflux (Barbalias et al. 1983, Persson and Ronquist 1996, Kaplan et al. 1997) and an autoimmune theory (Alexander et al. 1997, Batstone et al. 2002) are also supported by evidence in the current literature. None of these postulations has been demonstrated to be the only aetiological factor, suggesting a multifactorial aetiology. The pathophysiology will be unclear as long as the aetiology remains so, although there is evidence implying neuroinflammation and MC involvement in the development of the chronic pain associated with CPPS (Donadio and Depiante-Depaoli 1997, Keith et al. 2001)

The lack of understanding of the aetiology and pathophysiological mechanisms of CPPS is reflected in a confusing variety of treatment modalities, most of which are poorly documented, if at all (McNaughton Collins et al. 2000a, 2000b). The development of the NIH-CPSI has been of utmost importance, as it provides a highly discriminative and valid tool for measuring the outcome of treatment for CPPS (Litwin et al. 1999, Nickel et al. 2001c).

The object of this thesis was to explore further the postulated infectious or microbial aetiology of CPPS. PCR methods were used to detect bacteria and viruses in non-contaminated prostate tissue samples obtained during radical prostatectomy. A Finnish version of the NIH-CPSI was created by the double-back translation method and its content, construct and convergent validities were tested. The effects of a 5-α –reductase inhibitor, finasteride, and of TUNA thermotherapy for treating CPPS were investigated in randomised sham-controlled trials.

REVIEW OF THE LITERATURE

1. DEFINITION AND CLASSIFICATION OF PROSTATITIS AND CPPS

The traditional classification of prostatitis, originally suggested by Drach et al. (1978), was based on the differential diagnostic "four-glass" test described by Meares and Stamey (1968), according to which prostatitis was divided into four categories, acute bacterial prostatitis, chronic bacterial prostatitis, chronic non-bacterial prostatitis and prostatodynia, on the basis of inflammatory findings (leukocytes and/or bacteria) in urine and prostatic secretions. The traditional classification was used for more than two decades in spite of practical limitations, especially the difficulty of obtaining prostatic secretions.

A new proposal by the NIH Workshop on Chronic Prostatitis in 1995 included a definition of CPPS and recognized pain as the main criterion, accompanied by variable voiding and sexual dysfunctions. A classification based on this definition and employing mainly inflammatory and bacterial findings in urine and EPS (Table 1) was later validated and approved by the Chronic Prostatitis Collaborative Research Network (CPCRN) (Krieger et al. 1999). Its categories I and II are similar to the traditional classifications of acute and chronic bacterial prostatitis, while category III is divided into two subcategories, III A, representing inflammatory CPPS in which leukocytes are present in the EPS (>10 / high power field), and III B, representing non-inflammatory CPPS, where no inflammatory changes can be found in the EPS. The new classification also includes non-symptomatic, histological prostatitis, category IV.

The NIH classification has proved superior to the traditional one, mainly because it is easier to use in clinical practice and it differentiates between subtypes III A and III B. It has several limitations, however, mostly due to an inadequate understanding of the role of white blood cells in prostatic secretions (Krieger at al. 2000a, Krieger et al. 2002). Healthy, asymptomatic individuals may have leukocytes in their EPS from time to time (Wright et al. 1994), but the diversity in techniques for quantifying these leukocytes and the lack of clear cut-off points make it difficult to determine the true clinical difference between categories III A and III B. In addition, the severity of the symptoms does not seem to correlate with either leukocyte or bacterial counts in prostatic secretions (Schaeffer et al. 2002a).

Table 1. The NIH consensus classification of prostatitis.

Category	Name	Description
I	Acute bacterial prostatitis	Acute infection of the prostate
II	Chronic bacterial prostatitis	Chronic or recurrent infection of the prostate
III	Chronic pelvic pain syndrome (CPPS)	No demonstrable infection
III A	Inflammatory CPPS	Leukocytes in EPS, post-M urine or semen
III B	Non-inflammatory CPPS	No leukocytes in EPS, post-M urine or semen
IV	Asymptomatic inflammatory prostatitis	No symptoms; histological diagnosis or leukocytes in EPS, post-M urine or semen

2. EPIDEMIOLOGY OF CPPS

No systematic studies of the prevalence or incidence of prostatitis had been published before the 1990´s, in spite of the fact that it had been considered a "common" condition, the "third most important disease of the prostate". The NIH report of 1990, for instance, cited more outpatient visits for prostatitis than for any other prostatic disease (McNaughton Collins and Barry 1999). The results obtained in epidemiological studies are greatly affected by the setting and by how prostatitis is defined, both making comparisons difficult. Clinic or physician-based studies tend to overestimate the prevalence relative to population-based studies (Roberts et al. 1999), and urologists are more likely to diagnose prostatitis than are primary care physicians, even in research settings (McNaughton Collins et al. 1998a)

The Olmsted County Study showed the prevalence of a physician-assigned diagnosis of prostatitis to be 11% and the overall incidence to be 3.1/1,000 person-years (Roberts et al. 1998), but considerably lower figures, with prevalences from 4% to 5%, have been reported in other physician-based studies (Moon et al. 1997, McNaughton Collins et al. 1998b).

A prevalence figure of 16% for prostatitis was obtained in a series of 31,681 health care professionals who provided "self-reported" information on their urological symptoms (McNaughton Collins et al. 2002). Men with a history of BPH had 7.7-fold greater odds on experiencing prostatitis, and those with lower urinary tract symptoms 1.8 – 2.8-fold greater odds. The results demonstrate a considerable overlap between urological diagnoses, especially between prostatitis symptoms and BPH, as about 50% of the men with symptoms of prostatitis also had a history of BPH

The prevalence of prostatitis (or prostatitis symptoms) in population-based studies varies from 4% to 14.2%, the latter overall lifetime prevalence figure being recorded in a cross-sectional survey of 2,500 randomly chosen residents of northern Finland (of whom 1,832 responded), the corresponding overall incidence being 3.8/1,000 person years (Mehik et al. 2000a). While 27% of men with symptoms of prostatitis suffered from them at least once a year, 16 % had persistent symptoms. In 63% of cases the symptoms were most prominent during winter months.

Other studies have reported somewhat lower prevalence figures. The overall prevalence of prostatitis in a community-based survey among 2,987 men in Canada (of whom 868 responded) was 9.7 %, the average age of the prostatitis population being 50 years. The prevalence was higher, 11.5 %, in men younger than 50 years, and lower, 8.5%, in men who were 50 years or older (Nickel et al. 2001a). A South Korean survey of 16,321 men aged 20 years reported a prevalence of 6% and, interestingly, a finding that a higher education and a longer time spent in sunlight were inversely correlated with a likelihood of prostatitis symptoms (Ku et al. 2001)

Overall, CP/CPPS is a common disease affecting men of all ages and demographic subgroups. It causes significant impairment of QoL and poses a great health care burden (Wenniger et al. 1996, Schaeffer et al. 2002b).

3. AETIOLOGY OF CPPS

The aetiology of CPPS is still largely unresolved. An infectious aetiology has been strongly suggested, but an autoimmune theory and the possibility of chemical irritation caused by intraprostatic urine reflux are as well supported by evidence in the current literature, although none of these has been indisputably demonstrated to be the only aetiological factor for CPPS. Hence it is most likely that the aetiology is multifactorial.

3.1. Microbial aetiology

3.1.1. Bacteria

The bacterial component is obvious in acute and chronic bacterial prostatitis (Weidner et al. 1991b), but is questionable in CPPS. Nevertheless, a bacterial background for CPPS has been strongly suggested based on both bacterial culture studies and the recovery of bacterial DNA sequences by PCR in expressed prostatic secretion (EPS) and prostate tissue (Krieger et al. 1996a, Riley et al. 1998, Tanner et al. 1999, Krieger et al. 2000b, Krieger and Riley, 2002). The bacteria most frequently encountered in the prostates of men with CPPS have been gram-negative uropathogens such as E. coli and enterococci, but gram-positive staphylococci have also been found, and less frequently Chlamydia trachomatis, Mycoplasma genitalium and corynebacteriae (Domingue and Hellstrom 1998).

It is difficult to interpret these findings and their correlations with clinical or histological prostatitis, since concepts regarding the bacterial flora harboured by a healthy prostate are not uniform, and some studies have not found any normal bacterial flora in the prostate nor any clear connection between bacteria and CPPS (Keay et al. 1999, Hochreiter et al. 2000a). A recently published study by Lee and associates (2003) showed that conventional bacterial cultures of prostate biopsy specimens failed to detect any differences between men with and without CPPS.

The methods available for detecting inflammation or bacterial infection in expressed prostatic secretions (EPS) or urine are contamination-prone and method-dependent (Mueller et al. 2001) and

are therefore less reliable than PCR methods, which should be preferred in clinical studies (Domingue and Hellstrom 1998, Krieger and Riley 2002).

A large variety of microorganisms have been found in the urogenital tract, including the prostate, but their significance for the pathogenesis of clinical manifestations in the urogenital tract such as BPH, prostate cancer, IC and CPPS has remained unclear (Domingue and Hellstrom 1998, Keay et al. 1998).

3.1.2. Viruses

Few reports exist that support the notion of a possible viral aetiology for CPPS. No systematic studies of the viral aetiology of CPPS using PCR techniques have been published. The involvement of viruses in prostatic pathology has been speculated upon the grounds of similarities between secretion granules and virus particles in electron microscopy (Webber and Bouldin 1977). Two systematic studies using viral culture techniques were published in the 1970s, but these gave controversial results, Morriseau and associates (1970) finding that HSV was implicated as a possible causative organism, while Nielsen and Vestergaard (1973) found no viruses in prostate tissue or EPS.

Other papers on viral prostatitis include one case report on HSV prostatitis (Doble et al. 1991) and two on CMV prostatitis in immunocompromised patients (Benson and Smith 1992, McCay et al. 1994). The possibility of a connection between HPV and CPPS has not been studied, and according to the current evidence, HPV does not seem to have any aetiological connection with either BPH or prostate cancer (Syrjänen and Syrjänen 2000).

3.2. Immunological aetiology

The immunological status of the host and the adherence capacity of possible infective agents play a role in inflammatory changes (Fowler and Mariano 1982, Doble et al. 1990, Domingue and Hellstrom 1998).

Batstone and colleagues (2002) found that patients with CPPS had a greater T cell response to autologous SP than did control patients, favouring an autoimmune mechanism in CPPS, whereas a

comparison of leukocyte subpopulations from pre-M and post-M urine sample revealed that all leukocyte subpopulations were over-expressed in post-M samples from CPPS (III A) patients relative to controls, with T cells and granulocytes predominating (Ludwig et al. 2001). This finding suggests both innate and adaptive immune responses in CPPS. Overall, the immune responses in CPPS seem to be mediated more by T cells than by B cells and have CD8 cells (cytotoxic T cells) predominating over CD4 cells (helper T cells) (Alexander et al. 1997, John et al. 2001).

Cytokines are produced as a result of a maladaptive immune response and may play a substantial role in the inflammatory responses in CPPS. Elevated levels of the pro-inflammatory cytokines IL-2, IL-1β, IL-6, IL-8, IL-10 and TNF-α have been found in SP from patients with CPPS (Alexander et al. 1998, Hochreiter et al. 2000b, Miller et al. 2002, Orhan et al. 2001), pointing to inflammatory responses in the prostate or seminal ducts. These findings favour the theory of an altered immunological response, as does the finding of low expression of anti-inflammatory IL-10 in men with CPPS (Shoskes et al. 2002). No logistic correlation has been found, however, between elevated cytokine levels and histological inflammation or inflammatory changes in EPS (Alexander et al. 1998, Nadler et al. 2000).

Reactive oxygen species (ROS) linked to the leukocytes can cause cell membrane damage, reduction of metabolic efficiency and electrolyte leakage (Scandalios 2002). ROS influence the tissue regeneration processes involved in prostatitis (Pasqualotto et al. 2000), but Shahed and Shoskes (2000) showed that they are independent of the leukocyte count in EPS and are a marker of tissue injury rather than a direct cause of it.

3.3. Chemical aetiology and urodynamic aspects

Urine reflux into the prostate has been demonstrated experimentally in humans (Kirby et al. 1982, Chapple et al. 1990, Turner et al. 1996) and in animal models (Nickel et al. 1990), and there is a large body of evidence to support a role for high voiding pressure as a cause of symptoms in a certain group of men with prostatitis (Barbalias et al. 1983, Hellstrom et al. 1987, Barbalias 1990, Ghobish 2000).

Persson and Ronquist (1996), studying the chemical composition of EPS and urine, concluded that urine reflux into the prostatic ducts caused chemical irritation and inflammation, and analogous

findings have been published showing that prostatic calculi are partly composed of the remains of the ingredients of refluxed urine (Ramirez et al. 1980, Klimas et al. 1985). If the prostatic ducts are obstructed by calculi, the rising intraductal pressure or direct irritation from calculi may cause mechanical irritation of the epithelium. As a result of urine reflux into the prostate, chronic inflammation and tissue oedema may lead to voiding disturbances with more reflux. (Barbalias et al. 1983, Hellstrom et al. 1987, Chapple et al. 1990). Video –pressure flow examinations have demonstrated increased maximum urethral closure pressure and decreased flow rates in the proximal prostatic and membranous urethra. The original findings applied to patients with prostatodynia, but they were later confirmed in cases of inflammatory prostatitis (Barbalias et al. 1983, Barbalias 1990, Theodorou et al. 1999).

3.4. Pelvic floor myalgia and neuromuscular aetiology

In some patients the symptoms may be due to tension myalgia in the pelvic floor, i.e. they may arise from habitual contraction or spasm of the pelvic floor muscles. In such cases the pain is often associated with physical activities or periods of sitting that lead to spasms in the pelvic floor. The prostate appears to be normal rather than tender in a rectal examination, but the anal sphincter is often spastic and paraprostatic tenderness is observed (Segura et al. 1979, Shoskes and Moody 1999, Zerman et al. 2001). In addition, pudendal nerve entrapments (Ricchiuti et al. 1999), lumbar disc disease, neoplasms in the pelvis or spine and pubic osteitis have occasionally been described as rare causes of chronic pelvic pain (Shoskes and Moody 1999).

3.5. Psychological aspects

Mental stress has a significant role in all chronic pain syndromes, including CPPS (Keltikangas-Järvinen et al. 1982, De la Rosette et al. 1993, Egan and Krieger 1994, Berghuis et al. 1996). According to Mehik and colleagues (2001), men with symptoms of CPPS experienced mental stress significantly more often than did healthy controls, 43% having sexual disturbances and 17% experiencing a fear of undetected prostate cancer.

4. PATHOGENESIS OF CPPS

4.1. Histopathology of prostatitis

Considerable variation exists in the histological classification of chronic inflammation of the prostate (True et al. 1999). In general, histological prostatitis (category IV) is characterised by multifocal mononuclear cell infiltrates (lymphocytes, monocytes and plasma cells) in the stromal connective tissue around the acini or ducts (Gardner and Bennett 1992, Matsumoto et al. 1992, Bennett et al. 1993).

In acute prostatitis, polymorphonuclear leukocytes (PMNL) and macrophages are present in the glandular ducts, the epithelium and the stroma. Stromal involvement is highly variable and is connected with the density of intraluminal inflammation, which is accompanied by periglandular accumulation of lymphocytes and monocytes, and occasionally plasma cells. This component typically destroys the tissue dividing adjacent glands, creating micro-abscesses. With cessation of the initial acute inflammatory process, the prostatic glands often undergo atrophy and become shrunken and irregular (Boag and Young 1999).

The histopathological changes in CPPS are generally similar to those observed in chronic bacterial prostatitis: glandular atrophy with stromal fibrosis and a mild residual inflammatory reaction, but the pattern of tissue injury does not differ significantly from that which would be expected in non-symptomatic or BPH patients (Boag and Young 1999, Nickel at al. 1999a). In conclusion, CPPS has no specific histopathological characteristics that could be used for diagnostic work-up.

4.2. Pathophysiology of chronic pain in CPPS and neurogenic inflammation

The initiator of the inflammatory process could be a local infection, chemical irritation or immunological response to systemic infection, but regardless of the triggering factor, the inflammatory process causes tissue oedema and increased intraprostatic pressure, which in turn leads to decreased blood flow and tissue hypoxaemia. The concept of increased prostatic tissue pressure in CPPS was introduced by Mehik and colleagues (1999), who showed that intraprostatic pressures were significantly higher in CPPS patients than in BPH patients. The results were later

confirmed with larger group of CPPS patients and controls (Mehik et al. 2000b). Patients with category III A prostatitis seem to have higher intraprostatic pressures than those with category III B prostatitis (Mehik et al. 2002), which may be of clinical relevance for differential diagnosis between these two groups.

CPPS and interstitial cystitis (IC) share many features in common. Neurogenic inflammation and altered mast cell (MC) function have been thought to constitute the most important mechanism of chronic pain in IC (Theoharides et al. 2001). The MC found in the urogenital and gastrointestinal tract are atypical mucosal MC, while typical connective tissue MC are present in the skin and lungs. Mucosal MC promote infiltration of inflammatory cells in the tissue, and T lymphocytes in particular are capable of secreting substances that further activate mucosal MC thus perpetuating the cycle of inflammation (Kops et al. 1984, Kaplan et al. 1985). The role of MC in prostate pathology has been studied by Amir and colleagues (1998) using toluidine blue to detect MC in tissue samples, and they found increased MC counts in benign prostatic hyperplasia (BPH), whereas inflammatory lesions of the prostate expressed significantly decreased MC counts, probably due to the inability of toluidine blue to detect degranulated MC. MC have nevertheless been found in rats with experimental autoimmune prostatitis (Donadio and Depiante-Depaoli 1997) and in spontaneous prostatitis (Keith et al. 2001), suggesting a possible relationship with the development of chronic prostatitis. MC are located adjacent to epithelial cells, vessels and peripheral nerves (Keith et al. 1995, Leppilahti 2002) making their cell products available to a variety of cell types. Activated MC contain several inflammatory mediators, such as histamine, serotonin, cytokines, prostaglandins and nerve growth factor, all capable of producing direct tissue damage. The increased density of sensory nerve fibres in prostatitis (Keith et al. 2001) and the inflammatory reaction promoted by MC degranulation may result in irreversibly altered neurotransmission, and thus at least partly explain the chronic nature of pain in CPPS.

In summary, inflammation causes tissue oedema and increased intraprostatic pressure, leading to tissue hypoxaemia and various mediator-induced tissue changes. The products of inflammatory cells, and particularly MC degranulation, result in tissue damage and altered neurotransmission in sensory nerve fibres. Prolonged inflammation may cause irreversible changes in neurotransmission, thus leading to chronic pain.

5. DIAGNOSTIC EVALUATION OF CPPS

5.1. Symptoms

The essential symptom that defines CPPS is pain or discomfort in the pelvic region and perineum, although low back pain, abdominal pain and pain in the genitalia are also typical. Pain associated with ejaculation is also a common complaint (Alexander and Trissel 1996, Nickel and Sorensen 1996). Voiding symptoms are reported by more than half of the patients, and irritative symptoms (frequency, urgency and nocturia) seem to be more prominent than obstructive ones (Alexander and Trissel 1996). Sexual dysfunction is frequently reported, e.g. 43% of the men with symptoms of prostatitis examined by Mehik and colleagues (2001) reported erectile dysfunction, 24% had decreased libido and 17% had a fear of undetected prostate cancer. Psychosocial distress is common among these patients, and their QoL impact is often significantly impaired (Keltikangas-Järvinen et al. 1989, De la Rosette et al. 1993, Mehik et al. 2001). The sickness impact profile of CP patients resembles that of patients suffering from myocardial infarction, angina or Crohn´s disease (Wenninger et al. 1996).

5.2. Symptom indices

An ideal index for measuring the symptoms of CPPS (or any other pain-related disorder) should be short, practical, self-administered, clinically and psychometrically sensible, valid and reliable (McDowell and Newell 1996). The basic concepts for evaluating the properties of a symptom index are reliability and validity. Reliability refers to the stability of a measurement, in other words, how far it will give the same results on separate occasions. Narrowly interpreted, validity means the extent to which a method measures what it is intended to measure, but the term includes such determinants as content validity, construct validity and convergent validity. Content validity concerns the extent to which a measurement covers all aspects of the topic that it purports to measure, and is therefore probably the most important determinant of validity, construct validity closely resembles content validity, but is used when there is no criterion against which to evaluate the validity of a measurement, while convergent validity describes the extent to which two or more instruments that purport to be measuring the same topic agree with each other (McDowell and Newell 1996).

Several symptom scores have been used to measure the symptoms of CP over the years. The first of these was a four-question instrument developed by Neal and Moon (1994) for use in an α-blockade study of prostatitis. This focuses on pain and measures perineal, scrotal and abdominal/inguinal pain and urethral discomfort on a scale 0 to 3 for each. The Prostatitis Symptom Severity Index (PSSI) described by Nickel and Sorensen (1996) uses a scale of 0 to 10 and includes ten questions about pain in different locations. It was originally designed to be used together with the Symptom Frequency Questionnaire (SFQP), which covers the frequency of symptoms with seven questions and the urinary symptoms with three questions. In addition to its original validation study, which included only 20 subjects, the PSSI has been used in some clinical connections. Other published symptom scores for prostatitis are the 21-item University of Washington Symptom Score (Krieger et al. 1996b), the 21-item Giessen Symptom Score (Brahler et al. 1997) and the 10-item symptom score of Chiang and colleagues (1997). None of these can be regarded as ideal, however, mainly because they focus almost solely on pain and lack formal validation.

The visual analogue scale (VAS) provides a simple way to record subjective estimates of pain intensity and has been used for this purpose since the early years of 20th century. This is a generally recognized and validated means of measuring acute and chronic pain, and its correlations with quality of life and functional performance disability have been well established. It has achieved official acceptance as an outcome measure in clinical studies of pain-related disorders, and might be regarded as the "gold standard" to which other instruments should be compared (Price et al. 1983, McDowell and Newell 1996, Koho et al. 2001).

The CPCRN project launched in 1997 to develop a reliable and valid instrument to measure the all aspects of CPPS, including pain, urinary symptoms and QoL issues, started out from a literature review and proceeded by identifying focus groups for cognitive testing of a 55-item draft questionnaire. In the next step, a multi-disciplinary expert panel revised the questionnaire into 21 questions and submitted it to preliminary validity testing and psychometric analyses. These analyses yielded an index of nine questions that address the above-mentioned three aspects of CPPS experience: pain, urinary symptoms and QoL. Final validation of this NIH-CPSI revealed that it is valid, highly discriminative and has high test-retest reliability and internal consistency (Litwin et al. 1999, Nickel et al. 2001c). Its validity has also been demonstrated in a primary care setting (Turner et al. 2003) and it has been used in epidemiological and clinical trials, where its applicability has

been estimated as good (Shoskes et al. 1999, Schaeffer et al. 2002b, Cheah et al. 2003, Nickel et al. 2003a, Nickel et al. 2003b).

The ways of expressing symptoms and quality of life issues vary between languages, and therefore linguistic validation is called for before adopting a new questionnaire for clinical or research use (Ketovuori and Pöntinen 1981, McDowell and Newell 1996, Kunishima et al. 2002). Linguistic validations of the NIH-CPSI in Spanish, Japanese and German have been published (McNaughton Collins et al. 2001, Kunishima et al. 2002, Schneider et al. 2002), confirming that "non-English" NIH-CPSI´s also have excellent validity and applicability.

5.3. Clinical evaluation

A clinical evaluation aims to determine whether a given patient fulfils the diagnostic criteria of CPPS. The baseline data to be collected from each patient in the case of CPPS include a full history of previous or recurrent urinary tract infections (UTI), sexually transmitted diseases and other genitourinary diseases. Comorbidity that may affect the patient's host defence mechanisms (e.g. diabetes and conditions affecting immunological status) should also be noted (Alexander 1999).

The physical examination should include a digital rectal examination to assess the size, consistency and tenderness of the prostate, and the inguinal regions, scrotum, penis, perineum and lower abdomen should be examined thoroughly to exclude any other disease (e.g. inguinal hernia, Peyronie´s disease) as a cause of pelvic pain (Alexander 1999).

Transrectal ultrasound (TRUS) is useful for determining the size of the gland and for ruling out hypoechoic lesions suggestive of prostate cancer. There are no ultrasonic findings that are specific to CPPS, although calcifications from prostatic calculi are often present and increased blood flow patterns may be detected by colour-Doppler techniques (Wasserman 1999).

Cystoscopy is not routinely necessary for patients with CPPS unless the symptomatology refers to the possibility of a bladder-related disorder such as IC. In addition, cystoscopy is mandatory if urine analysis reveals haematuria (Alexander 1999).

Urodynamic evaluation will not be necessary for every patient suffering from CPPS, but uroflowmetry and residual urine volume measurements are recommended whenever a patient complains of urinary symptoms. Pressure-flow studies with simultaneous sphincteric electromyography and urethral pressure profilometry are indicated in cases where BOO or detrusor-sphincter/bladder neck dyssynergia are suspected clinically or on the basis of uroflowmetry. Increased voiding pressures and/or functional dyssynergia (pseudodyssynergia) have been detected in a subset of CPPS patients, suggesting liberal indications for urodynamic evaluation (Barbalias et al. 1983, Hellstrom et al. 1987, Barbalias 1990, Theodorou et al. 1999, Ghobish 2000).

5.4. Laboratory findings

Urine analysis is an important means of screening in order to exclude UTI and haematuria. Urine cytology should be included in the diagnostic work-up, since carcinoma of the bladder in situ may simulate the symptoms of CPPS (Nickel et al. 2002).

The Meares-Stamey test (the "four-glass test"), introduced in 1968 (Meares and Stamey 1968) was considered a "gold standard" for more than three decades. The test includes four samples: voided first-stream urine (VB1), voided mid-stream urine (VB2), expressed prostatic secretion (EPS) and a voided post-massage (post-M) urine sample (VB3). Each category of prostatitis, together with UTI and urethritis, can be identified from inflammatory and bacteriological findings in these samples. Although never validated and hardly ever used, owing to its complicated nature, this test is well referenced in the literature (McNaughton Collins et al. 2000a).

A simpler method of screening for prostatitis, the pre and post-massage test (PPMT) (Nickel 1999), is based on two urine samples, a voided mid-stream sample (pre-M) and a voided first-stream sample taken after vigorous prostatic massage (post-M). Significant bacteriuria in the pre-M sample points to the possibility of UTI or acute bacterial prostatitis, whereas bacteriuria in the post-M sample indicates chronic bacterial prostatitis. Leukocytes (>10 per high power field) but no bacteria in the sediment of the post-M sample are found in inflammatory CPPS (category III A), but neither leukocytes nor bacteria are present in non-inflammatory CPPS (category III B). Both the sensitivity and the specificity of PPMT have been 91%, and the test is therefore recommended as the first-line means of screening for prostatitis (Nickel 1997).

Semen analysis is rarely used in the diagnostic work-up of prostatitis, although its sensitivity in detecting inflammatory CPPS or chronic bacterial prostatitis can be further enhanced by combining it with EPS and PPMT (Krieger et al. 2000a, Ludwig et al. 2000, Krieger et al. 2002).

Serum prostate-specific antigen (PSA) is an integral part of the laboratory diagnostics for CPPS, especially in order to exclude prostate cancer. Normal PSA levels should be expected in the majority of CPPS patients, although they may be elevated in inflammatory CPPS, so that a correlation has been shown between PSA and the gravity of histological inflammatory changes (Carver et al. 2003). A prostate biopsy should be considered in cases when a slightly elevated PSA level in conjunction with clinical prostatitis does not decrease to normal after a four-week course of antibiotics (Campo et al. 1996, Bozeman et al. 2002).

5.5. Microbiological studies

5.5.1. Microbiological samples and cultures

The microbiological samples used for diagnosing prostatitis or CPPS include urine, EPS, post-M urine, semen and prostate tissue, of which the most commonly used in everyday diagnostics are urine and post-M urine. Urine, EPS and tissue samples from the prostate obtained by needle biopsy techniques are often contaminated with the normal flora from the skin, urethra or bowel (Keay et al. 1998) and are therefore rarely used. Generally accepted precautions such as washing of the glans penis and use of a sterile container are important to avoid contaminations. On the other hand, the sensitivity of bacterial cultures is greatly diminished if the samples are incorrectly stored or not transferred to the culture medium immediately (Nadler and Schaeffer 1999).

A conventional bacterial culture of urine samples or EPS, usually on 5% sheep blood agar, is relatively reliable for detecting the common uropathogens, but isolation of the intracellular chlamydiae requires cell culture techniques and mycoplasmae and certain corynebacteria need special culture media, so that it has been estimated that only 10% of all bacteria in the prostate can be isolated using standard clinical culture methods (Krieger et al. 1996a).

Owing to problems in collecting the samples and performing the cultures, the ideal would be a surgically obtained tissue sample analysed by both culture and nucleic acid-based methods, although this would be far removed from clinical reality (Domingue and Hellstrom 1998).

5.5.2. PCR methods

PCR techniques (Figure 1.) offer modern means of detecting prokaryotic bacterial or viral nucleic acids with high sensitivity and specificity. Body fluids, excretions and tissue samples, even processed ones, are all suitable materials, and as PCR detects nucleic acids, the organisms do not need to be alive, i.e. the tests can detect even residues of dead bacteria or viruses inside leukocytes. In addition, the method is unaffected by the prior use of antibiotics. The high sensitivity of PCR is also its weakness, however, as contamination from sampling or even laboratory reagents may be problematic (Keay et al. 1998, Tanner et al. 1998, Kawai et al. 2002).

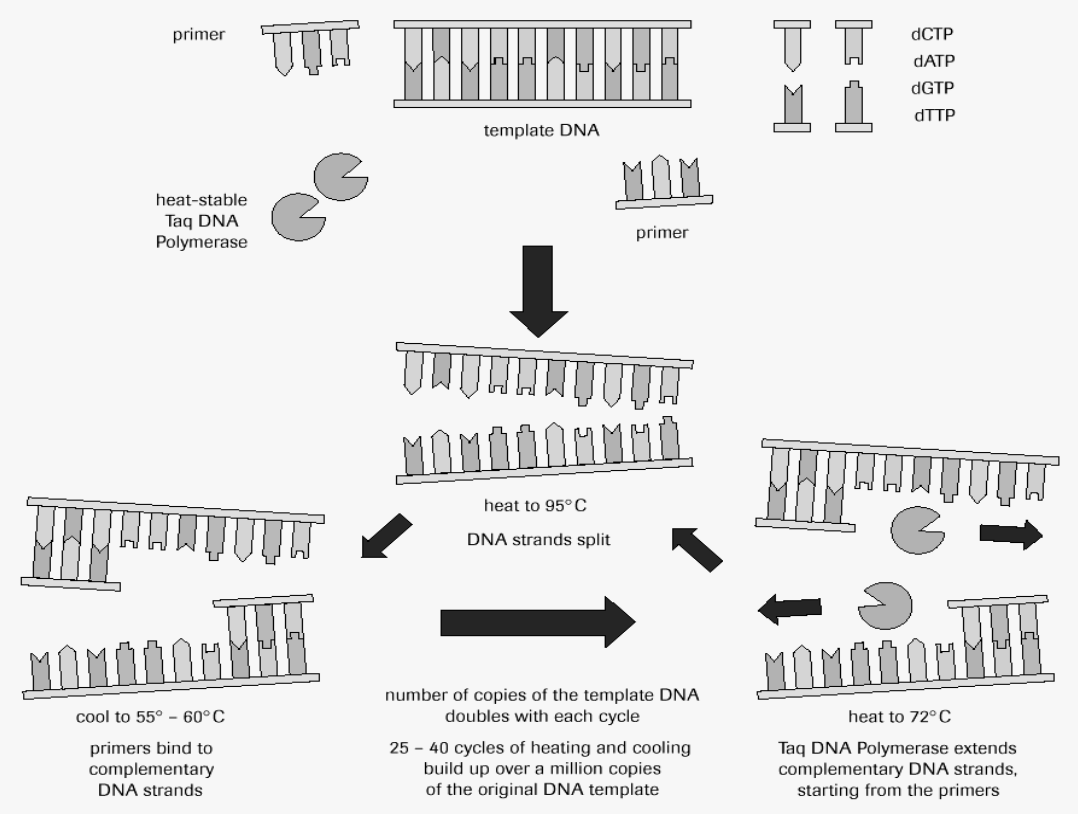


Figure 1. The principle of PCR
(reprinted from: http://206.53.227.20/prod_inf/manuals/pcr_man/Chapter01/CHAP01-Seite2.htm, with the permission of the copyright owner, Roche Diagnostics, Mannheim, Germany).

Basically, all PCR methods include the following phases: first, nucleic acids are extracted from the sample, and the selected nucleic acid fragments are then amplified using appropriate enzymatic reactions to obtain enough DNA for detection, which can be done by agarose gel electrophoresis or with labelled probes which hybridise to the PCR products. Alternatively, in the case of bacteria, the DNA sequence of the amplification product can be determined and the microbe from which it is derived can be identified by comparing the amplified sequence against databases of known DNA sequences (Jalava 2000, Vainionpää et al. 2000).

Broad-range bacterial PCR

Many bacterial species cannot be cultured using currently available methods, but broad-range bacterial PCR may be used to search for such bacteria in clinical samples, so that a greater proportion of the clinically relevant bacteria can be identified (Jalava 2000). 23S rDNA and 16S rDNA are the two most important targets used in broad-range PCR methods. Both genes encode large RNA molecules with highly conserved DNA sequences applicable as targets for broad-range PCR primers and interspersed by more variable sequences that can be used for identification of the bacteria (Gutell et al. 1985). 16S rDNA offers the most extensive databases for sequence comparisons (more than 60 000 bacterial sequences), whereas 23S rDNA sometimes distinguishes better between closely related bacterial species.

The question of optimal analytical sensitivity in broad-range bacterial PCR is a complex one. Since bacterial DNA is present everywhere, including autoclaved and sterile instruments, and also in the high-quality reagents used for sample purification and the reaction compositions of nucleic acid amplification methods (Tanner et al. 1998), aiming at maximal analytical sensitivity may frequently result in the detection of irrelevant bacterial DNA derived from outside the actual sample under analysis. Determination of the target sensitivity level of broad-range bacterial PCR is always a compromise between the sensitivity and specificity of the assay, and the method's inherent sensitivity to contamination may render broad-range bacterial PCR unsuitable for detecting very low numbers of bacteria present in samples (Keay et al. 1998, Kotilainen et al. 1998). To verify the presence of a certain microbe in a sample, two independent PCR procedures should be performed to ensure the presence of the actual microbe in question rather than incidental DNA (Tanner et al. 1998). Hence, due to variations in the sampling techniques, and also differences in PCR techniques, the results of bacterial PCR findings in cases of CPPS (see 3.1.1.) have to be evaluated with great caution.

Viral PCR

The PCR approach is a more sensitive and specific means of detecting viral sequences in a sample than are conventional laboratory techniques (viral cultures). As viral nucleic acids are more heterogeneous in structure than those of bacteria, no broad-range PCR techniques are available for viruses, but instead the viral PCR methods are virus-specific and separate primers and probes need to be used for each virus. Valid PCR methods are available for most clinically relevant viruses, however, and even quantitative analysis is possible for selected ones (Vainionpää et al. 2000). The same limitations regarding contaminations and optimal analytical sensitivity apply as for bacterial PCR.

5.6. Differential diagnostics of CPPS

5.6.1. Other prostatic diseases

CPPS and BHP partly share a similar symptomatology. Epidemiological studies have shown that there is significant overlap between their symptoms and that the prevalence of both increases with age (Mehik et al. 2000a, McNaughton Collins et al. 2002). Histologically, inflammatory changes are often present in BPH, although the clinical significance of such changes in patients without CPPS symptoms remains unresolved (Boag and Young 1999, Nickel et al. 1999a). Overall, a significant proportion of CPPS patients have BPH as well (and vice versa), which may have implications for diagnosis and treatment.

Differential diagnosis between prostate cancer and CPPS is extremely important, bearing in mind that elevated PSA levels are sometimes found in clinical CPPS and in category IV prostatitis. Both histological prostatitis and prostate cancer primarily tend to affect the peripheral region of the gland, which might explain the clinical, although anecdotal, observations regarding a connection between CPPS symptoms and prostate cancer (Henderson et al. 2002). An epidemiological association was implied in the meta-analysis by Dennis and associates (2002), as men with a history of prostatitis were found to have increased risk of prostate cancer, with an odds ratio of 1.6 to 1.8.

5.6.2. Bladder disorders

Bladder cancer, and especially in situ carcinoma, can cause symptoms that mimic those of CPPS:

irritative voiding symptoms, dysuria, and even lower abdominal discomfort. Therefore urine analysis in order to detect haematuria, and preferably urine cytology, are important for the basic diagnostic work-up in these patients (Nickel et al. 2002). In selected cases when urinary symptoms are prominent and/or if urine analysis is abnormal, cystoscopy will be necessary to rule out bladder cancer (Miller et al. 1995, Alexander 1999).

CPPS and IC have a number of basic similarities. In addition to symptoms, some clinical findings are strikingly similar, including bladder petechiae after hydrodistension of the bladder, as described in prostatitis patients (Berger et al. 1998), and findings of a positive potassium sensitivity test in prostatitis (Parsons and Albo 2002). A dysfunctional urinary epithelium (or epithelial leakage), resulting in neurogenic inflammation and altered MC function, has been thought to constitute an important pathophysiological mechanism of IC (Theoharides et al. 2001), and logically the same neuroinflammatory mechanism could explain the persistence of pain in CPPS (Mehik et al. 2003a). The features in CPPS and IC are so closely similar that some authors have proposed that the two constitute the same disease, being only slightly different manifestations of a single pathophysiological process in the lower urinary tract (Miller et al. 1995, Parsons and Albo 2002).

6. TREATMENT

The optimal treatment for CPPS remains exceedingly difficult to define because of a lack of understanding of its aetiology and pathogenesis. The large variety of treatment modalities recommended reveal how little is known about the condition. Most of the treatments are empirical or anecdotal, and only few well-controlled studies exist. In 2000 the Cochrane review found only 15 controlled treatment trials concerned with CPPS, all of them having small sample sizes or being otherwise methodologically weak (McNaughton Collins et al. 2000a), although several well designed and controlled studies have been launched since that review (Propert et al. 2002, Schaeffer 2003) and the results of these are eagerly awaited.

The placebo effect has been substantial in the various CPPS treatment trials reported to date, with up to a 30% improvement in symptoms to be expected from a placebo. Hence regular surveillance

alone with or without any treatment may result in a significant amelioration of symptoms (Nickel and Sorensen 1996, Shoskes et al. 1999, McNaughton Collins et al. 2000b, Nickel et al. 2003b).

6.1. Antibiotics

The role of antibiotics in acute and chronic bacterial prostatitis is indisputable. Fluoroquinolones seem to be an ideal choice owing to their wide antimicrobial spectrum and their pharmacokinetic properties: they are lipid-soluble, and therefore a high concentration can be achieved in the prostatic tissue and fluids (Naber and Madsen 1999). The clinical results obtained with fluoroquinolones have been superior to those achieved using co-trimoxazole or macrolides, for instance (Weidner et al. 1991a, Naber et. al. 2000).

Although controversy exists over the aetiology of CPPS and the justification for the use of antibiotics in its treatment, they are nevertheless widely used as an empirical first-line therapy. More than half of the patients seem to benefit from them (Barbalias et al. 1998, Nickel et al. 2001b, Shoskes et al. 2003) and the correlation has been reported between positive bacterial PCR findings in EPS and a favourable outcome of antibiotic treatment (Shoskes and Shahed 2000), whereas no such correlation has been found between bacterial culture findings, leukocyte counts or antibody status of EPS and the clinical response to antibiotics (Nickel et al. 2001b). Quite recently the Canadian group published the results of a placebo-controlled study in which six weeks of levofloxacin treatment for CPPS resulted in a better short-term outcome than did a placebo (Nickel et al. 2003a). The antimicrobial effect of antibiotics may not be the explanation for the favourable outcome, however, since a number of antibiotics have been found to have alternative mechanisms of action, such as the modulatory effects of fluoroquinolones on inflammatory mediators (Yoshimura et al. 1996, Galley et al. 1997, Hochreiter et al. 2000c, Labro 2000) and the analgesic and anti-inflammatory effects of antibiotics observed in rats (Suaudeau et al. 1993). With few controlled studies to corroborate the axiomatic use of antibiotics in CPPS, several of the aforementioned observations may nevertheless be taken as support for four to six weeks of antibiotic treatment in newly diagnosed cases of CPPS (Bjerklund Johansen et al. 1998, Nickel et al. 2001b, Shoskes et al. 2003, Nickel et al. 2003a).

6.2. α–blockers

The α-adrenergic receptors, with the α-1a subtype predominating in the prostate and bladder neck, regulate smooth muscle tonus, so that the immediate response to an α-blockade is smooth muscle relaxation in the prostate and reduced outflow resistance during micturition. The positive effects of this on BPH symptoms are well documented (Lepor 1993). The theoretical background for the use of α-blockers in CPPS relies mostly on the assumption of dysfunctional voiding and/or intraprostatic urine reflux as an aetiological factor, but an alternative mechanism may be connected with their assumed capability to reduce prostate tissue pressure due to smooth muscle relaxation and hence improve the hypoxaemic conditions in the prostate (Mehik et al. 2003a).

The first report on the effects of an α-blockade on prostatitis was that of Osborn and associates (1981), who found symptomatic improvement in 48% of patients receiving non-selective phenoxybenzamine as compared with 8% of those given a placebo. Some relatively well-controlled studies with more selective α-blockers have been published since, with similar results. Symptomatic improvement has varied, but has clearly surpassed that achieved with a placebo (De la Rosette et al. 1992, Gul et al. 2001, Cheah et al. 2003, Mehik et al. 2003b). The current evidence therefore suggests that α-blockers are beneficial for treating CPPS.

6.3. Anti-inflammatory agents and pain modulators

Non-steroidal anti-inflammatory drugs (NSAID) inhibit prostaglandin (PG) synthesis and block the cyclo-oxygenase (COX) enzymes, thus inhibiting the inflammatory response. Even though NSAID are widely used to treat CPPS, there have been few assessments of their efficacy. One uncontrolled trial using nimesulide reported a positive treatment response (Canale et al. 1993), and the only placebo-controlled study of a NSAID, using the selective COX-2 inhibitor, rofecoxib (Nickel et al. 2003b), showed that the symptoms, measured with NIH-CPSI, improved equally in both groups, with no statistical differences between them, although rofecoxib did prove to have a better impact on QoL than the placebo. The selection of rofecoxib for this trial was based on the assumption that the isoenzyme COX-2 is undetectable in normal tissues but over-expressed in tissues with inflammation and possibly up-regulated by the inflammatory cytokines found in CPPS, IL-1β and TNF-α (Alexander et al. 1998, Nadler et al. 2000). The modest effect of rofecoxib on CPPS

symptoms could be explained by the inhibition of PG synthesis. Since PG also have immunoprotective actions in SP and NSAID treatment has been shown to lower PG levels in SP, it is theoretically possible that NSAID may have a negative impact on CPPS (Bendvold et al. 1985, Batstone et al. 2002). Nevertheless, the use of NSAID is probably justified in the light of empirical experience (Pontari 2002).

Amitriptyline has traditionally been used for many chronic pain syndromes. It has some anticholinergic effects, sedative characteristics and strong H_1-selective antihistaminic activity. A positive effect has been shown in cases of IC (Hanno 1994), and in view of the similarities between IC and CPPS, it might be assumed to be useful in CPPS as well. Interestingly, hydroxyzine, an H_1-selective antihistamine capable of preventing MC degranulation, has also been shown to be beneficial in IC (Theoharides 1994). No controlled studies exist to date that support the use of these drugs in cases of CPPS, although amitriptyline has been reported to be useful against vague voiding symptoms with associated pain (Pranikoff and Constantino 1998) and is relatively commonly used on the grounds of clinical experience.

6.4. 5-α-reductase inhibitors

5-α-reductase inhibitors prevent the conversion of testosterone to dihydrotestosterone in the serum and prostate gland. This results in regression of the glandular component of hyperplastic tissue and reduction in the volume of the prostate. Finasteride was the first commercially available 5–α-reductase inhibitor, and has proved efficacious in reducing the size of the prostate and relieving the symptoms (Boyle et al. 1996) and BOO (Tammela and Kontturi 1993). The theoretical background for the use of finasteride in cases of CPPS might be primarily its effect on BOO, thus reducing the intraprostatic urine reflux. In addition, the reduced volume of the glandular component might result in lower tissue pressure and improved tissue microcirculation.

The first published report of successful finasteride treatment for CPPS included case reports on four patients (Holm and Meyhoff 1996). Later, a North American multi-centre placebo-controlled study confirmed that finasteride is beneficial in CPPS, as symptom improvement, measured with the NIH-CPSI, was 33% in the finasteride group compared with 16% in the placebo group. The outcome

regarding QoL measurements favoured finasteride even more over the placebo (Downey et al. 2002).

6.5. Other medical therapies

The effects of allopurinol were investigated by Persson and associates (1996) in a placebo-controlled study involving 54 patients. There was a statistically significant change in symptoms, favouring allopurinol over the placebo. The study has been strongly criticized, however, on account of methodological faults (McNaughton Collins and Wilt 2000).

Bioflavonoids, which occur naturally in high concentrations, e.g. in red wine, onions and green tea, act as anti-oxidants and may have anti-inflammatory properties that are mediated by stabilizing MC. The bioflavonoid quercetin was tested by Shoskes and colleagues (1999) in a placebo-controlled study involving 30 patients. There was significant improvement of symptoms in the quercetin group and bioflavonoids were thus suggested a viable treatment for CPPS.

Small, uncontrolled studies of various medications, including pentosan polysulphate (Nickel et al. 2000) and several phytotherapeutic agents have been published, mostly reporting positive results (Shoskes 2002). The lack of control groups and the evident placebo effect do not allow their objective analysis, however.

6.6. Thermotherapies

Most thermotherapies were originally developed for the treatment of BPH, but were later applied to CPPS as well. These include transrectal microwave hyperthermia (TRMH) (Montorsi et al. 1993, Shah et al. 1993, Vassily et al. 1999) and transurethral microwave thermotherapy (TUMT) (Nickel and Sorensen 1996). The symptomatic improvement achieved in two sham-controlled trials of TRMH varied from 75% to 55-68%, whereas that of sham treatment was between 52% and 10% measured by unvalidated symptom assessments (Shah et al. 1993, Vassily et al. 1999). In the sham-controlled study of Nickel and Sorensen (1996) TUMT relieved symptoms significantly more than did the sham treatment, as measured by the validated PSSI. The study included only 20 patients, however, and had a short follow-up time, only 3 months, making it difficult to reach any definite

conclusions. Other thermotherapies, such as transurethral balloon laser hyperthermia (Suzuki et al. 1995), have been used to treat CPPS, although the reports can be considered little more than case studies.

Transurethral needle ablation (TUNA) has proved efficacious for treating the symptoms of benign prostatic hyperplasia (BPH). It is minimally invasive, safe and easy to perform as a day-case procedure under local gel anaesthesia (Issa 1996, Bruskewitz et al. 1998). A long-term effect on the α-adrenergic receptors and sensory nerves has been demonstrated in a neurohistochemical study (Zlotta et al. 1997). This surgical α-blockade is probably the most important mechanism of action of TUNA in BPH, and could theoretically be of importance in CPPS. Previous studies of the effects of TUNA on the symptoms of CPPS include two open treatment trials and one randomised sham-controlled study. An uncontrolled trial with seven patients reported by Chiang and associates (1997) showed complete resolution of symptoms in four cases, while the other three evinced partial responses. The short follow-up time of only 3 months and the lack of a control group make it difficult to estimate the long-term value of TUNA for symptoms of CPPS, however. Symptomatic improvement was also noted in a Korean study with 42 patients (Lee et al. 2002), but again neither a control group nor a validated symptom index was involved. A controlled study by Aaltomaa and Ala-Opas (2001) involving 27 patients pointed to a small difference in symptoms in favour of TUNA over a sham procedure, but about half of the patients in the sham group experienced an equal improvement in symptoms.

Overall, the results obtained concerning heat therapies for CPPS are difficult to compare, as validated instruments were rarely used to determine efficacy. In the light of the existing literature, the use of heat therapies for CPPS should be considered experimental.

6.7. Physical therapies

6.7.1. Prostatic massage

Prostatic massage is often considered a historical relic among the treatments proposed for CPPS, as practically no modern data exist to support its effectiveness. An open investigation into the efficacy of repetitive prostatic massage in combination with antibiotic treatment (Nickel et al. 1999b) noted some symptomatic improvement, but at least two thirds of the patients actually had chronic

bacterial prostatitis and no validated symptom measurements were used, thus leaving the efficacy question unanswered with regard to CPPS. There are some data, however, to support the efficacy of prostatic drainage, in that regular ejaculations were found to alleviate persistent symptoms of CPPS in a series of 43 men (Yavasçaoglu et al. 1999).

6.7.2. Biofeedback and relaxation exercises

Little evidence exists for any effect of conventional physical therapies on CPPS. Biofeedback and relaxation exercises have proved beneficial for patients with dysfunctional voiding (pseudodyssynergia) and urodynamically demonstrated dyssynergia (Barbalias 1990, Zermann et al. 2001) and for some with spastic pelvic muscles (Kaplan et al. 1997).

6.8. Surgical therapies

Although CPPS does not in general seem to be a surgically manageable condition, transurethral bladder neck or prostate incision may prove beneficial for those with urodynamically verified BOO (Kaplan et al. 1994). Otherwise, there are no reports in the current literature to corroborate any other kind of surgical therapy for CPPS.

AIMS OF THE RESEARCH

CPPS is an enigmatic condition of unknown, probably multifactorial aetiology. A bacterial background has traditionally been suspected, but never conclusively proved. Viruses as possible causative organisms have not been investigated using modern nucleic acid-based technologies. The lack of reliable symptom measurements for use in clinical research and practice has been problematic and has made interpretation of the results difficult. The NIH-CPSI questionnaire developed by the CPCRN has marked a great improvement in this situation by providing a standardized measure for symptoms of CPPS. Due to our lack of understanding of the aetiology and pathophysiology of CPPS, however, there is no straightforward treatment method, and indeed the treatment modalities have been poorly documented, rarely evidence-based and mostly targeted at relieving the symptoms rather than curing the disease.

The specific aims of the present research were:

1. To study the possible bacterial aetiology of CPPS and to determine whether the prostate harbours a normal bacterial flora,

2. To study the role of viruses, especially HSV, CMV and HPV, as possible aetiological factors in CPPS,

3. To provide a fluent and easily comprehensible Finnish version of the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) and to study its linguistic and convergent validity,

4. To study the efficacy of finasteride for the treatment of CPPS, and

5. To study the efficacy of TUNA for the treatment of CPPS.

MATERIALS AND METHODS

The present research was carried out during the years 1995 – 2002 at the Department of Surgery, Division of Urology, Seinäjoki Central Hospital (I-III, V), at the Department of Urology, Tampere University Hospital and Medical School, University of Tampere (I-III, V), at the Department of Urology, Oulu University Hospital (III-V), at the Department of Microbiology (I) and the Department of Virology and Medicity Laboratories (II), University of Turku, and at the Department of Public Health Science and General Practice, University of Oulu, and Department of Epidemiology and Public Health, Imperial College of Science, Technology and Medicine, London (III). The study designs were approved by the ethical review boards of the respective institutions.

1. AETIOLOGICAL STUDIES

1.1. Patient selection and samples

Consecutive patients suffering from localized prostate cancer with preoperative staging T1c-T2 for whom radical prostatectomy was considered were evaluated for symptoms of CPPS using the NIH-CPSI. Ten patients with moderate to severe CPPS symptoms (NIH-CPSI score $\geq$ 16, pain domain score $\geq$9) and ten with no CPPS symptoms (NIH-CPSI score $\leq$ 2), as controls, were included in the series. None of the patients had had any prior prostatic surgery or radiation, recurrent UTI or history of urethritis or sexually transmitted disease. Written informed consent was obtained from all the participants.

Three tissue samples, each approximately 3 mm in diameter were harvested from a macroscopically non-cancerous region in the central zone of the prostate (middle of either lateral lobe, at least 1 cm from the capsule) immediately after surgical removal of the prostate. To avoid urethral contamination, a different set of instruments was used to dissect the sample, and the urethral mucosa was not touched during sampling. Each sample was flushed with sterile saline, then

immediately frozen, and kept at –70°C until processed. The PCR analyses were performed later, all at the same time and with the clinical and symptomatic patient data masked.

1.2. PCR methods

1.2.1. Bacterial PCR (Paper I)

Half of each biopsy was homogenized by bead beating, and DNA was purified by classic phenol extraction, while the other half was processed according to the tissue protocol of the High Pure PCR Template Preparation Kit with an additional sonication step, as described in the original paper. The presence of bacterial DNA in the specimens was tested for by means of two PCR assays amplifying fragments of bacterial rDNA genes. Primers MS37 and MS38 amplify an approximately 850-bp sequence of the 23S rDNA of most bacteria, and a 1500-bp sequence of 16S rDNA was amplified using the primers fD1mod and rP2. Before addition of the template DNA, all reaction mixes were UV-irradiated for 3 minutes to degrade endogenous bacterial DNA, and adequate isolation and reagent negative controls were included in all runs. The PCR product from 16S rDNA yielding a clear-cut band of the expected size on the analytic agarose gel was purified by electrophoresis. After cloning, the plasmids were isolated and the presence of the 1500-bp insert was verified by electrophoresis. About 450 ng of plasmid DNA was sequenced using primer 533, the ABI Prism Big Dye Terminator Cycle Sequencing v. 3.0 DNA sequencing kit and an ABI Prism 310 Genetic Analyzer (Applied Biosystems, Foster City, California, USA). Sequence comparisons were performed using an in-house algorithm and a local database.

1.2.2. Viral PCR (Paper II)

HSV-1 and HSV-2, and CMV genomes were analyzed by PCR and by liquid-phase hybridization with lanthanide-labelled probes. For PCR, nucleic acids were extracted with the High Pure Viral Nucleic Acid Kit (Roche Diagnostics, Mannheim, Germany). HSV-1 and HSV-2 DNA was amplified by PCR using the biotinylated primers and europium-labelled (for HSV-1) and samarium-labelled (for HSV-2) probes, which were from the glycoprotein D genes (Hukkanen et al. 2000). The PCR products were detected by time-resolved fluorometry, the results being obtained as counts per second. For CMV, the primers (nucleotides 731-755, 1165-1141) and the europium-labelled probe (nucleotides 1140-1121) were from a conserved region of CMV, while for HPV the MY09/MY11 primers targeting the L1 open reading frame of the genome were used. After PCR,

the samples were hybridized with high-risk (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56 and 58) HPV oligonucleotide probe mixtures. The probes were labelled with digoxigenin (DIG Oligonucleotide 3'-End Labeling Kit, Boehringer, Mannheim, Germany), and detection was performed using anti-digoxigenin conjugated to alkaline phosphatase and visualized with the chemiluminescence substrate CSPD (DIG Luminescent Detection Kit, Boehringer, Mannheim, Germany).

2. TRANSLATION AND VALIDATION OF THE NIH-CPSI (PAPER III)

2.1. Translation process

A double-back translation method was employed to create the Finnish NIH-CPSI in which the first forward translation of the original NIH-CPSI into Finnish was performed by two Finnish urologists independently. The versions were compared with each other and several phrases and words were revised to enhance comprehensibility. The reconciled version was then back-translated by a native English, bilingual (English and Finnish) professional translator. Another bilingual professional translator and the authors of the first Finnish version then compared the back-translated version with the original NIH-CPSI. No inconsistencies were found between the versions, and the idiomatic content of the versions was practically identical. Finally, the Finnish grammar and spelling was revised by a native Finn with an M.A. degree in Finnish, after which the questionnaire was taken for trial clinical use by several Finnish urologists. After three months trial use, one adjustment was made to the questionnaire. The word "delighted" in question 9, first translated into Finnish as "mielissään", was revised to "erittäin tyytyväinen" (very happy) to adapt better to the Finnish phraseology.

2.2. Validation

155 men with clinical CPPS and 12 controls without any prior urological history were included in the validation study. The CPPS patients were consecutive referrals with a long history of symptoms, while the control group comprised 12 men from a general surgery waiting list for

haemorrhoidectomy. Written informed consent was obtained from the subjects prior to enrolment. The validation process included symptom evaluation with the Finnish NIH-CPSI and a clinical examination to verify clinical CPPS. The participants completed the Finnish NIH-CPSI by themselves, and this was followed by a clinical examination to confirm clinical CPPS. The CPPS patients were also asked for a subjective opinion of the precision and comprehensibility of the questionnaire on a scale 1 to 5 (1=poor to 5=excellent). The investigator made the same judgement independently. A re-evaluation including a self-completed VAS and a clinical examination by another investigator who was unaware of the subject's previous history or NIH-CPSI score was carried out less than one week later.

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 10.0). A non-parametric Mann-Whitney U test was used for comparisons between the groups. The correlations between the Finnish NIH-CPSI domains and VAS were calculated using the non-parametric Pearson's test, and the consistency between the patients´ and investigator's perceptions using Cronbach´s coefficient α.

3. TREATMENT TRIALS

3.1. Finasteride trial (Paper IV)

The patient series for this placebo-controlled, double-blind, prospective study consisted of 41 men with a long history of CPPS symptoms. The patients who met the eligibility criteria and who gave written informed consent entered a four-week placebo run-in period, after which they were randomised to receive either a 5 mg daily dose of finasteride (31 patients) or a placebo (10 patients) for a period of 12 months. After screening and randomisation, follow-up visits were scheduled at 1, 3, 6 and 12 months. The objective treatment response was evaluated using the following parameters: serum PSA, digital rectal examination and transrectal ultrasound of the prostate, urine flow rate and residual urine volume measurements. Adverse events and altered concomitant treatments were recorded at each visit. The subjective response was recorded at each visit by means of the validated symptom indices PSSI, IPSS and VAS, of which PSSI was used as the primary

treatment response parameter. This uses a scale 0 to 10 and includes ten questions about pain in different locations (Nickel and Sorensen 1996). QoL was measured using the IPSS question No. 8.

The statistical analyses were performed using the Wilcoxon test or the paired t-test for all within-group comparisons, whereas Fisher's exact test was used for comparisons between the groups.

3.2. TUNA trial (Paper V)

A total of 33 patients with CPPS symptoms were enrolled for this randomised, parallel, sham-controlled study. The patients who met the eligibility criteria and gave written informed consent were randomised to receive either TUNA (25 patients) or urethrocystoscopy (US) as a sham treatment (8 patients). The procedures were performed in an operating room under spinal anaesthesia and light intravenous sedation. TUNA was performed using 465 kHz radiofrequency energy and the formal needle insertion technique described by Issa (1996). Treatment was applied on two planes to both lateral lobes of the prostate, so that the target temperature of 50°C at the needle tip was achieved for at least 1 minute. The patients were unaware of whether they had TUNA or the sham treatment, and the procedures were designed to seem externally alike. In the sham group the cystoscope was left in the prostatic urethra for 20 minutes to mimic the TUNA procedure. Single-dose antibiotic prophylaxis prior to the procedure was used in all cases. An indwelling catheter (12 Fr) was left until the next morning. Follow-up visits were scheduled 3, 6 and 12 months after treatment. The objective response to the treatment was evaluated by transrectal ultrasound of the prostate, urine flow rate and residual volume measurements and serum PSA. The subjective treatment response was recorded at each visit using the validated PSSI, IPSS and VAS. PSSI was considered the primary treatment response parameter and it was supported with IPSS question No. 8 as a measure of QoL. Adverse events and altered concomitant treatments were recorded at each visit.

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 9.0) program. All within-group comparisons employed the non-parametric Wilcoxon test. The differences between the TUNA and sham groups were tested using the non-parametric Mann-Whitney U test.

RESULTS

1. AETIOLOGICAL STUDIES

1.1. Patients

The mean duration of CPPS symptoms in the symptomatic patients was 9.1 years (range 2 – 30), the mean NIH-CPSI score was 22 / 43 (range 17 – 31, SD 6.0) and the mean pain domain score 11 / 21 (range 9 – 16, SD 3.9), whereas all patients in the control group had an NIH-CPSI score 0-2 with a pain domain score 0. The two groups were similar in terms of prostate cancer, the only difference between them deriving from the CPPS symptoms (Table 2).

Table 2. Patient characteristics (reprinted from Paper II with permission).

Patient no.	Age (yr)	NIH-CPSI score	Pain score	Duration of symptoms (yr)	pT stage	Gleason score
1.	51	28	15	2	pT2b	3
2.	62	16	9	5	pT2b	6
3.	60	16	9	2	pT2b	5
4.	63	27	12	4	pT2b	8
5.	66	28	11	30	pT2b	5
6.	55	20	9	5	pT2a	7
7.	58	31	16	20	pT2b	7
8.	62	16	9	15	pT3a	7
9.	67	21	13	5	pT3a	7
10.	54	20	10	2	pT2b	5
11.	53	0	0		pT2b	3
12.	59	1	0		pT2b	3
13.	63	0	0		pT2b	6
14.	58	0	0		pT3a	7
15.	68	0	0		pT2b	7
16.	59	2	0		pT2b	7
17.	48	1	0		pT2b	5
18.	66	0	0		pT2b	7
19.	59	0	0		pT2b	7
20.	67	1	0		pT3a	8

1.2. Bacteriological findings (Paper I)

All but one tissue sample were negative for bacterial DNA. The High Pure –purified aliquot of the tissue sample from one symptomatic patient was reproducibly positive in 16S rDNA PCR but negative in 23S rDNA PCR. The nine clones from the first PCR product showed the closest similarity to Lactobacillus crispatus DNA (99.2 to 100% similarity in the 492 to 502 bp sequence). The two clones with an insert from the second PCR product contained Stenotrophomonas maltophilia DNA (with 100% similarity in the 502 bp sequence). None of the negative isolation nor the reagent controls yielded a visible amplicon band after 16S rDNA or 23S rDNA PCR.

1.3. Virological findings (Paper II)

All the samples were negative for HSV 1, HSV 2, CMV and HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 54, 56 and 58.

2. TRANSLATION AND VALIDATION OF THE NIH-CPSI (PAPER III)

The series included 155 CPPS patients with a mean age of 53 years (range 21-79) and a mean duration of CPPS symptoms of 6.6 years. The control group was composed of 12 younger men, with a mean age of 44 years (range 35-65).

2.1. Content and construct validity

The content and construct validity of the Finnish NIH-CPSI were evaluated by comparing the total NIH-CPSI and scores in the different domains between the symptomatic CPPS patients and controls. The scores differed significantly ($p<0.001$) between the groups, the total NIH-CPSI score in the CPPS group being 20.2 (SD 8.6) and that in the control group 5.8 (SD 4.5). In addition, the differences between the groups were significant in the pain and voiding symptom domains, but not in the QoL domain. The patients´ subjective opinion on the comprehensibility and precision of the Finnish NIH-CPSI was 4.2 (SD 0.8) on a scale of 1-5, similar to that of the investigators, 4.2 (SD 0.7). The consistency between the evaluations was 0.65 (Cronbach´s coefficient α).

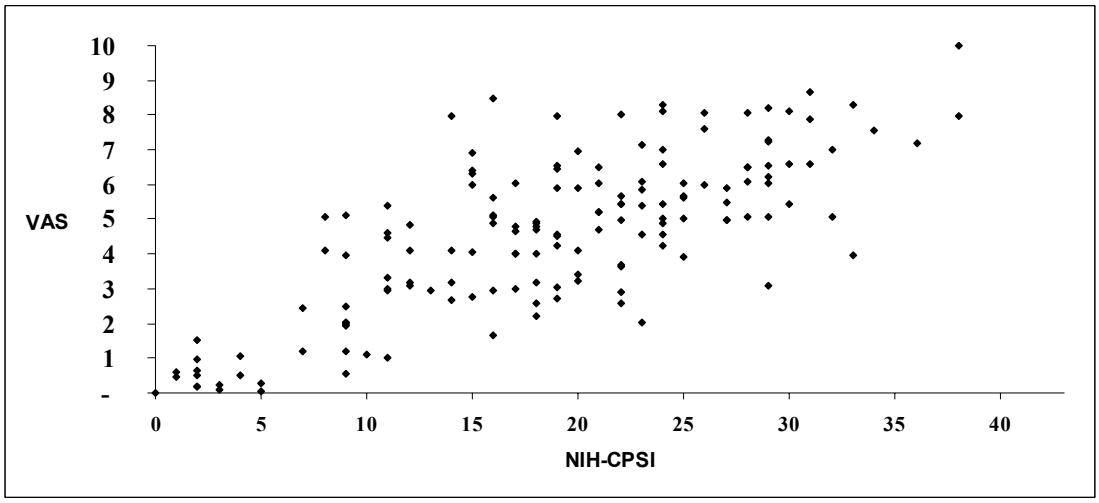
2.2. Convergent validity

The correlation between the total NIH-CPSI score and VAS was used as a determinant of convergent validity. The Pearson correlation between the total NIH-CPSI and VAS was 0.76. Cross-tabulations of the correlations between the domains, total NIH-CPSI scores and the visual pain scale (VAS) are presented in Table 3 and Figure 2.

Table 3. Correlations (Pearson's) between the domains, NIH-CPSI and visual pain scale (VAS) in the CPPS patients (n=155) (reprinted from Paper III with permission).

	Pain	Void	QoL	NIH-CPSI
VAS	0.87	0.27	0.60	0.76
Pain		0.36	0.71	0.89
Void			0.41	0.67
QoL				0.85

Figure 2. Correlations between the NIH-CPSI and VAS presented as a scatter plot diagram (reprinted from Paper III with permission).

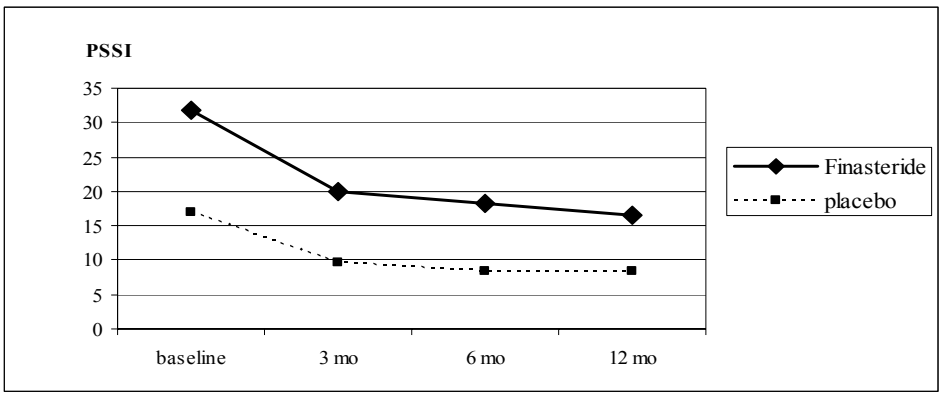


3. TREATMENT TRIALS

3.1. Finasteride trial (Paper IV)

PSSI decreased significantly in both groups ($p<0.001$), but the change was more pronounced in the finasteride group, so that there was a statistically significant difference between the groups ($p<0.05$) at months 3 and 6 (Figure 3). IPSS decreased significantly ($p<0.001$) in the finasteride group, but not in the placebo group ($p<0.05$ between groups). Pain relief (VAS) and an improvement in QoL were noted in both groups, with no statistically significant difference between them. The changes in the volume of the prostate (mean volume from 22 to 18 ml) and serum PSA (mean serum PSA from 1.4 to 0.8) were significant in the finasteride group, but no such changes were noted in the placebo group. Urinary flow did not change markedly in either group. There were no serious adverse events, but three patients in the finasteride group experienced partial impotence during the medication.

Figure 3. Changes in PSSI

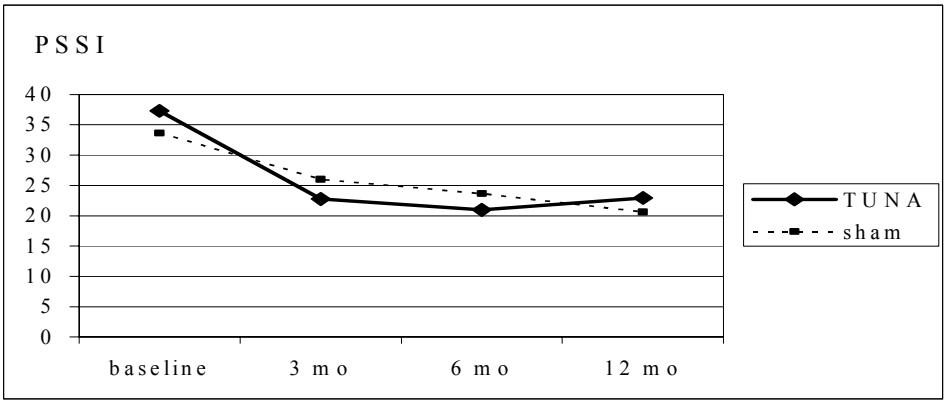


3.2. TUNA trial (Paper V)

PSSI decreased in both groups (TUNA group $p<0.001$, sham group p = n.s.), with no significant difference between them (Figure 4), and the same was true with the IPSS assessment scores (TUNA group $p=0.002$ and sham group $p=0.05$, between groups n.s.). QoL (IPSS-8) was significantly better at 12 months in both groups, but again no difference was detected between them. The changes in the

pain score (VAS) were not statistically significant, and the peak urinary flow rate, residual urine volume, PSA and prostate volume were not altered in either group.

Figure 4. Changes in PSSI (reprinted from Paper V with permission)



DISCUSSION

1. MICROBIOLOGICAL ASPECTS OF CPPS

The NIH-CPSI questionnaire was used here to select patients with CPPS symptoms and non-symptomatic controls for bacterial and viral PCR analysis. To overcome the contamination problems encountered in most of previous PCR studies of CPPS, the tissue samples were collected under sterile conditions during radical prostatectomy. Although the NIH-CPSI score in itself does not define whether a patient has CPPS, the present patients were very similar in terms of prostate cancer, the only difference between the two groups deriving from the CPPS symptoms. Half of the patients had CPPS symptoms while the other half did not, which made it possible to compare the PCR findings between these two groups.

1.1. Bacteria and CPPS

The findings of the present study do not support the concept of the normal prostate harbouring bacteria or the assumption of a bacterial aetiology for CPPS. The PCR analyses intended to detect bacterial DNA were performed using validated techniques which have been applied to a variety of clinical specimens in order to diagnose bacterial infections (Jalava et al. 1995, Kotilainen et al. 1998, Rantakokko-Jalava et al. 2000). The presence of small quantities of bacteria or their DNA in the prostate tissue samples cannot be conclusively excluded, however, as the PCR assays used here have been validated for detecting bacteria in infected tissues and body fluids, where the aetiological agents are usually present in large numbers (Keay et al. 1998, Rantakokko-Jalava et al. 2000). In addition, as the histological inflammatory changes and microbial findings in the prostate have been found to be focal and unevenly distributed (Hochreiter et al. 2000a), it is possible that microbial DNA could have been missed due to the limited size of the tissue sample. The present tissue samples were nevertheless taken from a region of the prostate where histological inflammatory changes most commonly occur (Boag and Young 1999) and the sampling techniques was adjusted to avoid urethral contamination, so that these samples could be regarded as more reliable than those obtained using previously described sampling methods.

The finding of Stenotrophomonas in one of the patients with CPPS probably represents a reagent contaminant, in view of the fact that Stenotrophomonas and similar species have previously been detected even in purified pharmaceutical water (Tanner et al. 1998, Kawai et al. 2002). In addition, the Lactobacillus crispatus DNA could be derived from the reagents rather than organisms present in the prostate, as 16S rDNA was amplified from the template purified by one of the two DNA isolation methods only and no 23S rDNA of this or any other organism could be detected.

The high number of positive bacterial PCR findings reported previously (Krieger et al. 1996a, Riley et al. 1998, Tanner et al. 1999, Krieger et al. 2000b) may be due to differences in settings and contamination-prone sampling techniques, or to the use of excessively sensitive broad-range PCR´s (Keay et al. 1998). Lee and associates (2003) have recently shown that the bacterial flora of the prostate is similar in CPPS patients to that in controls, concluding that the bacteria in EPS or prostatic tissue obtained by biopsy represent colonisation from the urethra rather than causative organisms connected with the CPPS itself. This finding affirms that the mere presence of bacteria in the prostate does not as such constitute an aetiology. In the light of the present findings, the justification for the use of antibiotics for the treatment of CPPS remains unresolved, however, since antibiotics may have secondary actions in addition to their antimicrobial activity.

1.2. Viruses and CPPS

The viruses most frequently reported to be found in the prostate and implicated as having a role in prostate pathology include HSV 1 and 2, CMV, and especially HPV (Boldogh et al.1983, Cuzick 1995, Syrjänen and Syrjänen 2000). Although viruses have been detected both in prostate cancer tissue and in BPH, the current literature does not infer any aetiological relationship (Boldogh et al. 1983, Wideroff et al. 1996, Noda et al. 1998, Strickler et al. 1998, Syrjänen and Syrjänen 2000). Practically no systematic studies exist on the association between HSV or CMV and prostate disease, but several have been carried out into the association between HPV and prostatic neoplasia. Syrjänen and Syrjänen (2000) reviewed the results of 20 studies published on HPV and the prostate by April 1998. Overall HPV detection rate for the entire series of 968 samples was 24.1% and according to the lesion type, HPV DNA was present in 3.1% of BPH samples (10/322), as compared with 12.2% of the normal prostates (7/57) and 22.5% of the prostate cancers (115/510). These figures are lower than those calculated by Cuzick (1995) based on the first 7 reports

published. Overall, the high rate of detection of HPV DNA in previous studies seems to be related either to urethral contamination of the samples or to methodological aspects such as the use of excessively sensitive primers in the PCR analysis rather than actual clinically relevant HPV positivity (Syrjänen and Syrjänen 2000).

Since the involvement of various viruses in the pathogenesis of CPPS has not been systematically studied using modern viral PCR techniques, the present study was designed to investigate this. The PCR analyses used for this purpose were performed by validated techniques with extensive positive internal controls, as have been applied to a variety of clinical specimens to diagnose viral infections (Demmler et al. 1988, Hurskainen et al. 1991, Hukkanen et al. 2000, Syrjänen and Syrjänen 2000), and it was expected that the viruses most frequently reported in the prostate would be detected if they had significant role in the aetiology of CPPS. Due to the small number of patients and the focal nature of the inflammatory changes in the prostate (Hochreiter et al.2000a), it is possible, however, that some viral genomes were missed. Although the viral aetiology of CPPS cannot be ruled out conclusively due to these limitations, the finding that there were no viruses in any of the samples strongly suggests that the viruses investigated here do not have any aetiological relationship with CPPS.

2. SYMPTOM INDICES FOR CPPS

The symptom indices used in connection with CPPS have traditionally focused on measuring pain in different locations, while the impact of the symptoms on daily activities and on QoL has been played down by most questionnaires preceding the NIH-CPSI (Neal and Moon 1994, Nickel and Sorensen 1996, Krieger et al.1996b, Brahler et al.1997, Chiang et al.1997). Of the earlier symptom indices, only PSSI has been used in more than one clinical study. Although this measures pain very precisely, with 10 questions, it does not address QoL issues at all. Thus it is necessary to use a separate QoL questionnaire, such as SFQP or IPSS question No. 8, to gain a perception of the impact of the symptoms on QoL. The combining of two separate questionnaires in this fashion can sometimes be problematic, as the scores represent separate scales that cannot be directly combined either clinically or statistically. The combination of PSSI and IPSS question No. 8 which was used in

the present assessments of the outcome of treatment (papers IV and V) was considered the most practical solution prior to publication of the NIH-CPSI.

The superiority of the NIH-CPSI over previous symptom indices is evident from its capability for addressing different symptom domains and QoL (Nickel et al. 2001c). The original tests performed on the NIH-CPSI also revealed its high reliability, validity and discriminative power (Litwin et al. 1999), and its validity has since been established with respect to Spanish, Japanese and German versions (McNaughton Collins et al. 2001, Kunishima et al. 2002, Schneider et al. 2002). Precise linguistic and cultural validation should always precede the adoption of a new symptom index for use in clinical practice or trials (Boyle 1997). Since the way of expressing symptoms and QoL issues in Finnish differs from that in the major Indo-European languages, an exact word-for-word translation may not result in a comparable, valid outcome (Ketovuori and Pöntinen 1981), and double-back translation is recognised as the method of choice when translating symptom measurement methods and QoL indices into foreign languages (Boyle 1997, Nickel et al. 2001c). This method, with interim analyses and modifications, was used here to produce a Finnish version of the NIH-CPSI.

The content and construct validity testing showed that the Finnish NIH-CPSI has good discriminative power, i.e. it has a good capability for distinguishing the characteristic symptoms of CPPS from other symptoms. The results obtained here are comparable to those of other NIH-CPSI validation studies (Litwin et al. 1999, McNaughton Collins et al. 2001, Kunishima et al. 2002), which also indicate good content and construct validity.

The convergent validity of a symptom questionnaire describes its correlation with other measurements used for the same purpose. VAS is a recognised measure of pain and generally has a good correlation with QoL and various disability measures, so that it is often considered a "gold standard" when measuring pain and related disability (Price et al. 1983, McDowell and Newell 1996, Koho et al. 2001). The NIH-CPSI was recently balanced against the Graded Chronic Pain Scale (GCPS) in a study involving 261 primary care patients with CPPS (Turner et al. 2003), yielding a moderate correlation, which implied that NIH-CPSI had good validity and corresponded well to other pain measurements. This finding is in accordance with the relatively high correlation between the domains of NIH-CPSI and VAS observed here, which further supports the validity of NIH-CPSI.

Combining the concepts of content, construct and convergent validity, it is obvious that NIH-CPSI is the best measure of the outcome of CPPS to date. Its good correlation with VAS indicates a good correspondence with measures of large-scale disability and QoL, but its content and construct validity provide better discriminative power. The use of linguistically validated versions of the NIH-CPSI will enable reliable comparisons to be made between clinical studies conducted in different countries and involving different languages and cultural environments. Hence, the NIH-CPSI and its Finnish version should be used as the primary means of measuring the symptoms of CPPS in Finnish-speaking men in clinical research and practice.

3. 5–α–REDUCTASE INHIBITORS IN CPPS

Finasteride, a 5-α–reductase inhibitor is effective in relieving the symptoms of BPH. It reduces the size of the prostate and relieves BOO (Boyle et al. 1996, Tammela and Kontturi 1993). Anecdotal positive treatment responses achieved with finasteride in BPH patients with CPPS symptoms initially led to the launching of the present trial, and it was only later that Holm and Meyhoff (1996) published their report describing a few cases of the successful use of finasteride to treat CPPS. The present results are mostly similar to those obtained previously regarding finasteride for the treatment of BPH (Boyle et al. 1996), as both the volume of the prostate and PSA decreased significantly in the finasteride group and peak urinary flow increased. Although the limited size of the placebo group and the differences in the baseline symptoms may have influenced the present results, the change in PSSI was clearly more pronounced in the finasteride group. This indicates a significant improvement in symptoms of CPPS, despite the occurrence of a strong placebo effect. Overall, finasteride was well tolerated, with only few side effects. It should therefore be considered beneficial for the treatment of CPPS. This conclusion was supported later by remarkably similar results in terms of symptom relief and other parameters obtained elsewhere (Downey et al. 2002).

The mechanisms by which the inhibition of 5-α–reductase might act on CPPS are not completely understood. The reduction of glandular component of the prostate following 5-α–reductase therapy is most abundant in the periurethral zone, which, for the most part, is responsible for urethral obstruction in BPH patients (Tempany et al. 1993). Hence it may be that the relief of obstruction and reduced

voiding pressures alleviate intraprostatic reflux and the inflammatory response caused by it. In addition, a mere reduction in the size of the prostate could reduce intraprostatic pressure, thus allowing improved microcirculation and tissue oxygenation (Mehik et al. 2003a).

In view of the present results and the current literature, 5-α–reductase inhibitors can be considered a viable treatment option in cases of CPPS. The best candidate for treatment would probably be a CPPS patient with prolonged symptoms and an enlarged prostate for whom antibiotic and/or α-blockade therapy had failed.

4. THERMOTHERAPIES IN CPPS

There is a lot of literature on thermotherapies and prostatitis, but as most data precede the present system of classifying CPPS, comparisons are difficult, even with the literature of the day. Validated instruments have rarely been used to determine efficacy, and most outcome measures have been subjective. Furthermore, thermotherapies have been applied using variable techniques and delivery routes, with variable power settings and target temperatures, which makes it even more difficult to compare their efficacy. Only TRMH, TUMT and TUNA have been studied in controlled settings of some kind, and even then with small populations and variable outcome measures (Shah et al. 1993, Nickel and Sorensen 1996, Vassily et al. 1999, Aaltomaa and Ala-Opas 2001). All these papers conclude that thermotherapies are beneficial for treating CPPS, although complete or durable responses are few and follow-up times are short. The mechanisms by which thermotherapies affect CPPS are in part unclear. A surgical α-blockade is achieved by TUNA, and destruction of the pain-mediating C fibres has been shown as well (Zlotta et al. 1997). TUMT causes direct thermal tissue necrosis, followed by fibrosis and tissue ablation, in addition to which the microwave energy may have direct bactericidal effects (Sahin et al. 1998, Liatsikos et al. 2000).

Previous publications regarding TUNA treatment for CPPS include two uncontrolled trials (Chiang et al. 1997, Lee et al. 2002) and one sham-controlled trial (Aaltomaa and Ala-Opas 2001), none of which used validated symptom measurement. Both of the uncontrolled trials found a significant improvement in symptoms, while the sham-controlled study revealed an improvement in symptoms

in both the TUNA and placebo group, although with a somewhat better outcome in the TUNA group, so that the authors concluded that TUNA might be helpful for some CPPS patients. These results further confirm the strong placebo effect that frequently interferes with CPPS trials. The same placebo effect was clearly noticeable in the present case, as about a 30% reduction in PSSI was found after both TUNA and sham treatment. Therefore, as the efficacy of TUNA is comparable to that of sham treatment, it cannot be recommended as a routine procedure for CPPS. The presence (or absence) of BOO (or BPH) may be the key question here, however, and may determine the outcome after TUNA, so that some CPPS patients with BOO might gain benefit from it.

5. FUTURE ASPECTS

Further research will be needed to determine the role of various aetiological factors in CPPS. As it seems that the microbes known to date do not have any substantial aetiological role, more efforts should be directed to exploring the role of functional and urodynamic abnormalities, altered immunological mechanisms and autoimmunity. In addition, the pathophysiological mechanisms involved in CPPS, especially neuroimmunological mechanisms that can lead to chronic pain, need further clarification. The presence and function of MC in prostatic tissue is poorly understood, and might be crucial for the development of the chronic inflammatory process and chronic pain.

Treatments targeting the inflammatory response involved in CPPS or acting as immunoregulators may provide new and effective ways of controlling inflammation and chronic pain. As the positive treatment responses achieved with antibiotics are probably largely related to their immunomodulatory and anti-inflammatory actions rather than their antimicrobial effects, an exploration of other drugs with similar but more specific actions might result in better outcomes. All treatment assessments should be controlled and should use a sufficiently large patient population to eliminate the placebo effect and should employ standardized, valid outcome measurements.

CONCLUSIONS

1. Using two broad-range bacterial PCR methods, no bacteria were found to exist in prostate tissue samples collected from prostate cancer patients with symptoms of CPPS and non-symptomatic controls. This suggests that the prostate does not harbour a bacterial normal flora and that a bacterial aetiology for CPPS is unlikely.

2. Viral PCR methods failed to reveal the viruses most commonly encountered in the human genitourinary tract (HSV 1 and HSV 2, CMV, and HPV) in the prostate tissue samples collected from prostate cancer patients with symptoms of CPPS and non-symptomatic controls. The result indicates that HSV, CMV or HPV do not constitute aetiological agents for CPPS.

3. A Finnish version of the NIH-CPSI was created by the double-back translation method. Validity testing proved the questionnaire to be a valid and easily comprehensible tool for measuring symptoms of CPPS. The Finnish NIH-CPSI should be used as the primary outcome measure in clinical CPPS studies and in clinical practice among the Finnish-speaking population.

4. The 5-α–reductase inhibitor finasteride alleviates symptoms of CPPS. Its effect surpasses that of a placebo, and it can therefore be regarded as a viable treatment option for CPPS.

5. The effects of TUNA on CPPS are not superior to those of sham treatment. This result, along with the data in the current literature, does not support the routine use of thermotherapies for CPPS.

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APPENDIX: The Finnish NIH-CPSI

Kroonisen eturauhastulehduksen oirekysely (NIH-CPSI)

Kipu

1. Oletteko viimeksi kuluneen viikon aikana tuntenut kipua tai epämukavaa tunnetta
   a) peräsuolen ja kivesten välisellä alueella (=välilihan alueella)? Kyllä(1) Ei(0)
   b) kiveksissä ? Kyllä(1) Ei(0)
   c) siittimen kärjessä (ei virtsaamiseen liittyen)? Kyllä(1) Ei(0)
   d) vyötärön alapuolella, häpyluun tai virtsarakon alueella? Kyllä(1) Ei(0)

2. Oletteko viimeksi kuluneen viikon aikana tuntenut
   a) kipua tai polttavaa tunnetta virtsatessa ? Kyllä(1) Ei(0)
   b) kipua tai epämukavaa tunnetta siemensyöksyn aikana tai sen jälkeen? Kyllä(1) Ei(0)

3. Miten usein viimeksi kuluneen viikon aikana kipua tai epämukavaa tunnetta näillä alueilla on esiintynyt?

ei ollenkaan	(0)
harvoin	(1)
toisinaan	(2)
usein	(3)
yleensä	(4)
aina	(5)

4. Mikä numero kuvaa parhaiten viimeksi kuluneen viikon aikana keskimäärin kokemaanne kipua tai epämukavaa tunnetta niinä päivinä, jolloin sitä esiintyi?

0	1	2	3	4	5	6	7	8	9	10
ei kipua										pahin kipu, jonka voi kuvitella

Virtsaamisoireet

5. Kuinka usein viimeksi kuluneen viikon aikana Teillä on ollut tunne rakon epätäydellisestä tyhjentymisestä virtsaamisen jälkeen?

ei ollenkaan	(0)
harvemmin, kuin joka viides kerta	(1)
harvemmin, kuin puolella kerroista	(2)
noin puolella kerroista	(3)
useammin, kuin puolella kerroista	(4)
melkein aina	(5)

6. Kuinka usein viimeksi kuluneen viikon aikana olette joutunut virtsaamaan uudelleen alle kahden tunnin kuluttua edellisen virtsaamisen jälkeen?

ei ollenkaan	(0)
harvemmin, kuin joka viides kerta	(1)
harvemmin, kuin puolella kerroista	(2)
noin puolella kerroista	(3)
useammin, kuin puolella kerroista	(4)
melkein aina	(5)

Oireiden haittaavuus

7. Kuinka paljon oireenne ovat viimeksi kuluneen viikon aikana estäneet Teitä tekemästä asioita, joita normaalisti teette?

ei ollenkaan	(0)
vain vähän	(1)
jonkin verran	(2)
paljon	(3)

8. Kuinka paljon ajattelitte oireitanne viimeksi kuluneen viikon aikana?

en ollenkaan	(0)
vain vähän	(1)
jonkin verran	(2)
paljon	(3)

Elämänlaatu

9. Jos viimeksi kuluneen viikon aikana kokemanne oireet jatkuisivat samanlaisina loppuelämänne, olisitteko

erittäin tyytyväinen	(0)
tyytyväinen	(1)
enimmäkseen tyytyväinen	(2)
en osaa sanoa (yhtä paljon tyytyväinen ja tyytymätön)	(3)
enimmäkseen tyytymätön	(4)
onneton	(5)
hyvin onneton	(6)

Pisteytys:

kipu:
yhteenlaskettu pistemäärä kohdista 1, 2, 3 ja 4 _____p. / 21

virtsaamisoireet:
yhteenlaskettu pistemäärä kohdista 5 ja 6 _____p. / 10

elämänlaatu:
yhteenlaskettu pistemäärä kohdista 7, 8 ja 9 _____p. / 12

NIH-CPSI Yhteensä _____p. / 43

ORIGINAL COMMUNICATIONS