

ANTI-NANOBACTERIAL THERAPY FOR MEN WITH CHRONIC PROSTATITIS/CHRONIC PELVIC PAIN SYNDROME AND PROSTATIC STONES: PRELIMINARY EXPERIENCE

DANIEL A. SHOSKES,^{*,†} KIM D. THOMAS AND EYDA GOMEZ

From the Department of Kidney Transplantation, Cleveland Clinic Florida, Weston, Florida

ABSTRACT

Purpose: Category III chronic prostatitis/chronic pelvic pain syndrome (CPPS) is a common debilitating condition of unclear etiology. Patients often have prostatic calcifications but a link to symptoms is controversial. Nanobacteria are implicated in stone formation in the urinary tract and, therefore, therapy to eliminate nanobacteria and the stones that they produce might have an impact on CPPS symptoms.

Materials and Methods: A total of 16 men with recalcitrant CPPS refractory to multiple prior therapies were treated with comET (Nanobac Life Sciences, Tampa, Florida), which consists of 500 mg tetracycline, a proprietary nutraceutical and an ethylenediaminetetraacetic acid suppository daily. The National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI), transrectal ultrasound, and blood and urine tests for nanobacterial antigen were performed at the start and conclusion of 3 months of therapy. One patient was lost to followup.

Results: Mean NIH-CPSI total score $\pm$ SD decreased from 25.7 ± 1.6 to 13.7 ± 2.0 ($p < 0.0001$). Significant improvement was seen in each subscore domain. A total of 12 patients (80%) had at least 25% improvement on NIH-CPSI and 8 (53%) had at least 50% improvement. Nanobacterial antigen or antibody was found in 60% of serum and 40% of urine samples. In 10 patients who underwent transrectal ultrasound after therapy prostatic stones were decreased in size or resolved in 50%.

Conclusions: Therapy designed to eliminate nanobacteria resulted in significant improvement in the symptoms of recalcitrant CPPS in the majority of men, whether due to the treatment of stone producing nanobacteria or through some other mechanism. Prospective placebo controlled trials are warranted.

KEY WORDS: prostate, calcinosis, prostatitis, pelvic pain, bacteria

Category III chronic prostatitis/chronic pelvic pain syndrome (CPPS) is a common syndrome of unclear etiology with significant impact on quality of life.¹ A subset of patients have refractory symptoms despite multiple treatment approaches.² A feature associated with treatment failure in some studies has been prostatic calculi.³

The role of prostatic calculi in producing symptoms and disease is controversial, particularly because of the high prevalence in older, asymptomatic men. There is a clear correlation between age and the incidence of prostatic calculi,⁴ although their presence in younger men is often associated with inflammation⁵ and prostatitis symptoms.⁶ Prostatic calculi are presumed to form by the precipitation of prostatic secretions and calcification of the corpora amylacea. Crystallographic analysis has shown a core of apatite in 98% of cases.⁷ Interestingly apatite is the mineral formed by nanobacteria, a newly described microorganism implicated in biomineralization in the kidney⁸ and blood vessels.⁹

A treatment developed to eradicate calcification formed by nanobacteria, comET, consists of an antibiotic (tetracycline), a nutraceutical that purportedly allows the antibiotic to penetrate the stone and a suppository containing ethylenediaminetetraacetic acid (EDTA) to dissolve the stone. Anecdotally several patients in a clinical trial to assess similar comET

treatment for coronary artery disease reported the complete resolution of concomitant CPPS symptoms.¹⁰ Therefore, we studied comET therapy in men with CPPS unresponsive to conventional therapies who had documented prostatic stones.

MATERIALS AND METHODS

From July 2003 to January 2004 comET therapy was offered to men attending a specialized CPPS clinic provided that they fulfilled certain criteria, namely 1) symptoms greater than 9 months in duration, 2) failure of appropriate antibiotic therapy, 3) failure of anti-inflammatory therapy (quercetin, or nonsteroidal anti-inflammatory drugs), 4) absent painful pelvic side wall spasm on rectal palpation, 5) prostatic calculi on transrectal ultrasound (TRUS) (other than diffuse stippled calcification or calcification exclusively along the surgical capsule) and 6) no allergy to tetracycline. In most men all other treatment modalities that we could offer had failed. About 40% of the patients attending our clinic fulfilled the clinical criteria. Of those who had TRUS available about 50% had significant prostatic calcification. Therefore, this treatment was suitable for about 20% of the patients in our practice. Symptoms were quantified by the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI).¹¹ All patients had a complete history, physical examination, wet mount examination, culture of urine and expressed prostatic secretions (EPS), and TRUS available (fig. 1). Prior to therapy urine and prostatic fluid were tested for nanobacterial antigen using the rapid

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* Correspondence: Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, Florida 33331 (telephone: 954-659-5180; e-mail: dshoskes@mac.com).

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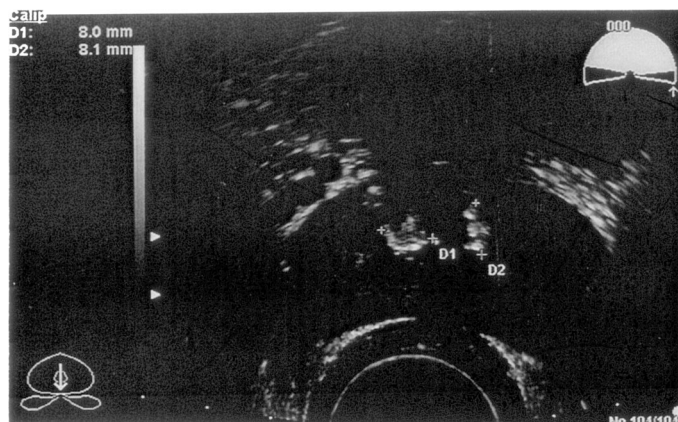


FIG. 1. Typical TRUS appearance of prostatic calculi in study patient.

nanobacterial antigen test (Nanobac Life Sciences). Serum was sent elsewhere to be tested for nanobacterial antigen and antibody using enzyme-linked immunosorbent assay (ELISA) methods. Patients were treated with comET for 3 to 4 months.

Treatment received at bedtime consisted of: 1) 500 mg tetracycline orally, 2) nanobacOTC supplement (Nanobac Life Sciences), a proprietary blend of vitamin C, selenium, EDTA, coenzyme Q10, bromelain, grapeseed extract, hawthorn berry, quercetin, L-arginine, vitamins B3, B6 and B9, L-lysine, L-ornithine, trypsin and papain) and 3) a rectal suppository containing 1,500 mg EDTA. At the end of therapy the NIH-CPSI, transrectal ultrasound and nanobacterial tests were repeated. Comparison of NIH-CPSI was made before and after therapy by the paired t test. The study had the approval of our institutional review board.

RESULTS

A total of 16 men began therapy and 1 was lost to followup, leaving 15 evaluable, of whom all completed at least 3 months of therapy. Side effects were minimal. One patient was fatigued during therapy and 1 had rectal discomfort during week 1 of therapy only. Mean patient age was 44.6 years (range 30 to 57) and mean symptom duration was 6.3 years (range 1 to 30, median 3). Using a definition of EPS inflammation of at least 10 white blood cells per high power field 7 men had category IIIa (inflammatory) and 8 had category IIIb disease. The initial mean NIH-CPSI $\pm$ SD was 25.7 ± 1.6 for total score, 11.3 ± 1.1 for pain, 4.7 ± 0.8 for urinary and 9.7 ± 0.6 for quality of life. Nine men (60%) had nanobacterial antigen or antibody detected in the blood, 6 (40%) had nanobacterial antigen in the urine and none had detectable levels in EPS.

Figure 2 shows that following therapy there was a significant decrease in NIH-CPSI for total score (25.6 to 13.7, $p < 0.0001$), pain (11.3 to 4.9, $p < 0.0001$), urinary (4.7 to 3.1, $p = 0.01$) and quality of life (9.7 to 5.7, $p < 0.0001$). Previous studies have suggested that the minimal improvement in NIH-CPSI that is perceived by patients as significant is 25% and 50% improvement is perceived by patients as extremely significant.² Figure 3 shows that 3 patients had less than 25%, 4 had 25% to 49% and 8 had greater than 50% improvement. Given the small number of patients, it is difficult to analyze meaningfully factors predicting treatment success. However, the 3 patients with less than 25% improvement in total NIH-CPSI score were the only ones with NIH-CPSI urinary scores of 7 or higher. Two of these 3 patients had undetectable nanobacteria in the blood and urine, and 1 had positive blood and urine results. In contrast, only 2 of the 12 patients who improved had no nanobacteria in the blood or

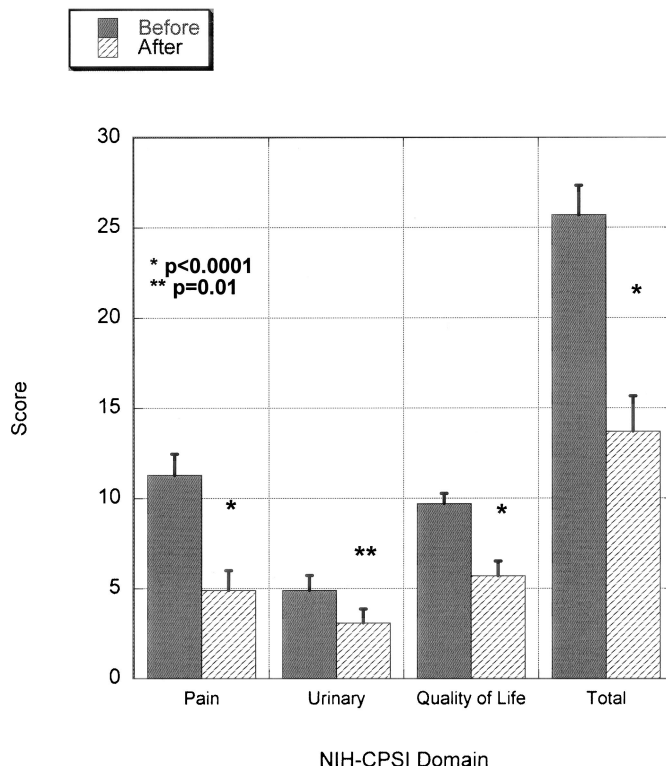


FIG. 2. Change in NIH-CPSI score after comET therapy

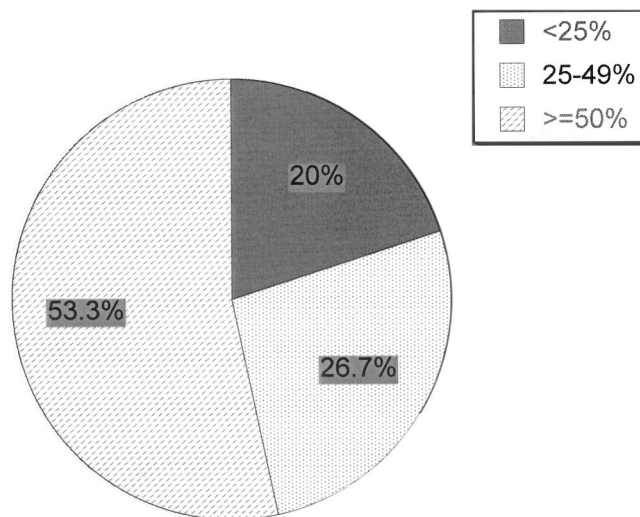


FIG. 3. Proportion of patients with given level of symptom improvement in total NIH-CPSI score after comET therapy.

urine. The patient with the lowest improvement in total NIH-CPSI score (5.9%) had a pain score of 0 and a urinary score of 10 at the onset of treatment. Age, symptom duration, symptom level and degree of stone burden did not influence treatment success. Ten patients underwent TRUS after therapy. By gross calculation stones were unchanged in size in 4 cases, decreased in number and/or size in 5 and resolved in 1.

Since stopping therapy 2 patients had symptom recurrence, which was resolved after restarting comET therapy. Seven patients who were examined at least 3 months after stopping therapy had no recurrence or worsening of symptoms. Two patients who had been on complete medical disability have returned to work.

DISCUSSION

We treated a group of patients with prostatic stones and long-standing CPPS symptoms unresponsive to conventional therapies with a treatment designed to eliminate stone forming nanobacteria and found that 80% had a significant improvement in symptoms after 3 months. Clearly no further conclusions can be drawn from an open label pilot study such as this regarding the mechanism of action and durability of effect. Nevertheless, the study population represented a truly hard-core group of patients in whom multiple previous therapies had failed, including antibiotics, phytotherapy, α -blockers, neuromuscular therapies and prostatic massage. A response of such magnitude even in an uncontrolled study is noteworthy in this patient population.

Nanobacteria have recently been described as novel microorganisms characterized by small size (0.2 to 0.5 μ), slow growth and ability to form calcium phosphate crystals at neutral pH, and at physiological calcium and phosphate concentrations. They are gram-negative, have a unique structure and apparent nucleic acid, and their growth in vitro is best inhibited by tetracycline.⁹ There is evidence that nanobacteria may initiate kidney stone formation via Randall's plaques¹² and they have been found in renal stones,¹³ polycystic kidney cyst fluid¹⁴ and calcified blood vessels.⁹ Not all studies have confirmed nanobacteria in stones¹⁵ and some groups have questioned their existence as a distinct microorganism.¹⁶ While to our knowledge prostatic stones have not directly been analyzed for nanobacteria, the documented apatite core⁷ of 98% of prostatic stones could be consistent with a nidus formed by nanobacteria. We found indirect evidence of nanobacteria on ELISA in 60% of blood and 40% of urine samples in our patients with CPPS. This compares with a 5% incidence in the serum of healthy adults in Finland (O. Kajander, unpublished data). The lack of nanobacterial antigen detected in EPS was likely due to a limitation of the urine assay, which requires capillary action to pull the fluid through the development chamber, an action that viscous EPS could not provide.

Any hypothesis of a relationship between prostatic stones and CPPS symptoms must account for the fact that such prostatic calcifications are often seen in asymptomatic men. As with urinary tract calculi, the key factor in symptoms may be obstruction. Indeed, 1 study showed increased intraprostatic pressure in men with CPPS compared to controls.¹⁷ Calcification within ducts draining prostatic glands could cause obstruction, secondary inflammation and increased intraprostatic pressures. Such a mechanism could explain the temporary relief obtained with anti-inflammatories, prostatic massage and antibiotics, which have direct anti-inflammatory effects. Persistent pain and inflammation in the area could then lead to persistent pelvic nerve and muscle irritation, resulting in an autonomous syndrome including pain and lower urinary tract symptoms. Nanobacteria in the urine could reflux into the prostatic ducts and induce the formation of apatite crystals, starting the process.

The symptomatic benefit experienced by most men in this study could have come from any combination of the 3 treatment components or from a placebo effect, although in studies with men as heavily pretreated as in our study with a long symptom duration, such a placebo effect is typically in the 20% range.¹⁸ Tetracycline alone can be an effective antimicrobial for prostatitis,¹⁹ although all men had negative cultures and previous prolonged courses of antibiotics had failed. Tetracycline can also have a direct anti-inflammatory effect independent of its ability to kill bacteria. Phytotherapy can be effective for CPPS and the nutraceutical capsule contained bromelain, quercetin and papain, which are 3 ingredients in the bioflavonoid compound Prosta-Q (Farr Labs, Santa Monica, California), which has proven efficacy for CPPS.¹⁸ However, all patients in this group had undergone failed therapy with Prosta-Q or a similar anti-inflammatory

nutraceutical. Furthermore, the dose of quercetin used in this treatment was approximately a twentieth that used for CPPS in previous clinical trials. As a first attempt at treatment, we used the same nutraceutical combination that had been applied in studies to eradicate nanobacteria in coronary artery plaque but we do not know whether this would be the optimal combination for the treatment of CPPS. EDTA binds to calcium and it can dissolve calculi in vitro. Systemic use has been advocated for cardiovascular disease by alternative medical practitioners but valid supportive data are sparse. Rectal absorption via the suppository occurs and systemic blood levels have been measured (Nanobac Life Sciences, unpublished data). However, the degree of prostatic calcification decrease did not correlate with symptom improvement, so that it is unlikely that the EDTA acted alone. It is possible that daily insertion of a suppository had some placebo effect by focusing relaxation to the rectal and pelvic nerves and muscles.

CONCLUSIONS

We report on a group of men with recalcitrant CPPS associated with prostatic calculi treated with combination therapy to eradicate nanobacterial calcification. There was significant improvement in symptoms after 3 months with minimal toxicity. This therapy warrants further study in larger, placebo controlled trials designed to control for the placebo effect, and explore the role of nanobacterial infection as a cause of prostatic stones and the role of prostatic stones in the etiology and symptoms of CPPS.

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