

## **CHRONIC PROSTATITIS AT AUA 2016**

Based on the number of presentations at this past year's American Urological Association (AUA) meeting, chronic prostatitis research activity took a welcome leap up in the last year. The 16 presentations more than double the number of presentations last year and haven't been equaled since 2009.

Most studies concerned the possible causes, course, and potential markers of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), with some interesting new ideas. The mix of organisms, mainly bacteria, that live inside us is a hot research topic today, and now CP/CPPS researchers are looking at how the mix in both the gut and the urinary tract differs from normal in men with CP/CPPS. The results may help with both diagnosis and treatment targets. Also implicated as potential causes were environmental toxins and even the health of your gums. Numerous studies in the past linked psychological factors with CP/CPPS, but which comes first, the chicken or the egg? Most studies implicated the chicken, but an intriguing new study points to the egg—the possibility that inflammatory cytokines released from an inflamed prostate may enter the brain and cause anxiety and depression rather than mental processes prompting the pain.

The treatment studies presented were few but promising. A small study showed that men who had ejaculatory pain got relief from injections of anesthetic into pelvic floor muscle trigger points. And an animal study of the prostate enlargement drug, dutasteride, showed it eases inflammation and bladder symptoms, so it has potential for CP/CPPS.

## **CAUSES, DIAGNOSIS, AND NATURAL HISTORY**

### **Gut Microbiome Is Different in Men with CP/CPPS**

Analysis of Gut Microbiome Reveals Significant Differences Between Men with Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Controls

Daniel Shoskes, Jessica Altemus, Alan Polackwich, Barbara Tucky, Hannah Wang, Charis Eng, Cleveland, OH

The organisms that live in our guts are increasingly thought to play a role in health. An unhealthy mix of gut bacteria may play a role in inflammatory diseases, immune dysfunction and autoimmune disease, cancer, and more. By using DNA sequencing and taxonomic and bioinformatic computer analysis, these researchers have now found—at least in a small study group—that the gut bacteria (from rectal samples) in men with CP/CPPS differ from those in control men who had only urinary symptoms. Compared with the 24 controls, the 25 men with CP/CPPS had more of 5 different types of microbes, including *Varibaculum* bacteria, and fewer of some 80 other types, such as *Prevotella*. There was a tendency, although not statistically significant, for a different mix in the men with CP/CPPS who had pain as their major symptom. The differences may have some implications for the physiologic pathways that might be involved in CP/CPPS, but that is not yet clear. Checking the makeup of a man's gut microbiome might ultimately prove useful for diagnosing CP/CPPS and might provide a treatment target, noted the researchers.

## **Urinary Microbiome Is Different in Men with CP/CPPS**

The Urinary Microbiome Differs Significantly Between Patients With Chronic Prostatitis/Chronic Pelvic Pain Syndrome and Controls as Well as Between Patients With Different Clinical Phenotypes

Daniel Shoskes, Jessica Altemus, Alan Polackwich, Barbara Tucky, Hannah Wang, Charis Eng, Cleveland, OH

The urinary tract microbiome is different in men with CP/CPPS, too, discovered the same research team at the Cleveland Clinic. Bacterial DNA sequencing in 25 men with CP/CPPS and 25 controls who had only urinary symptoms showed that certain organisms were over-represented in men with CP/CPPS, including bacteria in the Clostridia class, and other bacteria were under-represented, such as *Eichenella*. In addition, there were microbiome differences between men with more severe or less severe symptoms (scores over or under 26 on the NIH-Chronic Prostatitis Symptom Score or NIH-CPSI), shorter or longer duration of symptoms (over or under 48 months), total number of symptom types in the UPOINT classification, and between the psychosocial and the neurologic/systemic groups in that classification. As with the gut microbiome differences, the urinary tract differences also suggested physiologic pathways that might be involved in CP/CPPS, such as indole alkaloid synthesis and flavone/flavonoid synthesis. The difference between the microbiomes is enough to be a potential biomarker for CP/CPPS, and the differences between the symptoms types may suggest some treatment targets.

## **Prostate Inflammation May Predict CP/CPPS Will Get Worse**

Chronic Prostate Inflammation Predicts Symptom Progression in Chronic Prostatitis/Chronic Pelvic Pain Patients

J. Curtis Nickel, Kingston, Canada, Stephen Freedland, Durham, NC, Ramiro Castro-Santamaria, King of Prussia, PA, Daniel Moreira, Rochester, MN

Chronic inflammation in the prostate can predict that CP/CPPS symptoms will likely get worse in men who are already showing some symptoms. Inflammation doesn't distinguish men who have CP/CPPS from those who don't, however. Researchers came to this conclusion after looking at data from the REDUCE trial, a drug study aimed at reducing the risk of prostate cancer. Because the men in the trial all underwent prostate biopsy at the start and had comprehensive health examinations, the data offered a great opportunity to study CP/CPPS and its relationship to acute or chronic inflammation that can be seen in prostate tissue under the microscope. The majority of men—93%—of the nearly 3,000 who had NIH-CPSI questionnaire results available did not have CP/CPPS at the start. Of the nearly 2,200 men who answered the questionnaire later, CP/CPPS-like symptoms developed in about 15%; acute or chronic inflammation found in their prostate tissue didn't reveal who was going to develop the symptoms, however. On the other hand, of the 145 men who had CP/CPPS symptoms at the start as well as a year later, 109 got worse, and their prostate tissue was much more likely to have shown chronic inflammation at the start of the study. These results don't imply that men with CP/CPPS should have biopsies just to see if their symptoms will get worse, but when men with CP/CPPS have a biopsy for other reasons and it shows inflammation, they and their doctors should do all they can to help keep the symptoms in check.

## **IBS Often Comes First in Men with CP/CPPS**

Chronic Prostatitis/Chronic Pelvic Pain Syndrome Is Associated with Irritable Bowel Syndrome: A Population-based Study

Shyi-Chun Yii, Chun-Hou Liao, New Taipei City, Taiwan, Shiu-dong Chung, New-Taipei City, Taiwan, Heng-Ching Lin, New Taipei City, Taiwan

This large study based on records from Taiwan's national health insurance program show that men with CP/CPPS were twice as likely as men without it to have had irritable bowel syndrome before they got their CP/CPPS diagnosis. The researchers used a database of medical data for 1 million individuals and identified almost 5,000 who got a definite diagnosis of CP/CPPS from 2001 through 2013. Nearly 8% of the men diagnosed with CP/CPPS had IBS that was diagnosed before CP/CPPS, whereas only about 5% of control men did. Based on age and adjusting for other factors such as income, urban or nonurban living, and cardiovascular health, the men with CP/CPPS were nearly twice as likely to already have IBS as the controls. That relationship was similar no matter what age the men were. The researchers urged urologists to be alert for CP/CPPS in their patients who already have IBS.

## **Analysis Links Environmental Toxins with Prostatitis**

Urinary Polycyclic Aromatic Hydrocarbons: Exposing a Novel Culprit in Prostatitis

Golnaz Naderkhani, Norman Smith, Dariush Mirsattari, London, Canada

Could environmental toxins play a role in causing CP/CPPS? To investigate possible links, these researchers analyzed data from the US National Health and Nutrition Examination Survey of 2002-2010, which collected information on prostatitis symptoms as well as on urinary concentrations of chemicals such as polycyclic aromatic hydrocarbons (PAHs), heavy metals, arsenic, pesticides, nicotine metabolites, phthalate, phenol and paraben. Among 7,947 American adults that answered the health questionnaire on prostatitis, 110 reported symptoms of prostatitis. Statistical analyses showed a correlation between prostatitis symptoms and just one group of toxins—the PAHs. Men with prostatitis had higher levels of PAHs and PAH metabolites in their urine than other men. PAHs are a large group of environmental contaminants that come from natural processes and human activities, such as smoking tobacco (first- or second-hand), smoking or grilling meat, and burning coal, oil, gasoline, trash, tobacco, or wood. PAHs have been linked with acute and chronic inflammation, endocrine and reproductive problems, and other physical and mental health problems.

## **Bad Gums, Bad Prostate?**

Possible link between periodontal disease and chronic prostatitis

John Estemalik, Nabil Bissada, Nishant Joshi, Catherine Demko, Eswar Shankar, Donald Bodner, Sanjay Gupta, Cleveland, OH

Periodontal or gum disease has previously been linked with cardiovascular disease and, lately, with other conditions from arthritis to Alzheimer's. Now a small study links periodontal disease

with prostatitis and benign prostatic hyperplasia (BPH or prostate enlargement). That makes sense because dental plaque bacteria can drive inflammation, and the bacteria themselves have been found in unexpected places, such as in arteries. In this pilot study, the researchers assessed periodontal disease and looked at prostatic secretions in 24 patients who had either CP/CPPS or BPH. Prostatic secretions in 17 of the men showed one or more of the bacteria common in dental plaque, such as *Porphyromonas gingivalis* and *Treponema denticola*. Although establishing a link with prostate inflammation will require a bigger study, and researchers have not yet established any cause-and-effect relationship between oral health and disease, it certainly can't hurt to make a regular habit of brushing and flossing.

### **Could Ulcer Bug Be Linked with Prostate Problems?**

Statistical and Biological Evidences of Link between *Helicobacter pylori* Exposure and Prostate Inflammatory Diseases

Dong-Ru Ho, Chih-Shou Chen, Wei-Yu Lin, Yun-Ching Huang, Jian-Hui Lin, Kuo-Tsai Huang, Pey-Jium Chang, Pu-Z City, Taiwan

These researchers both analyzed population health data and performed laboratory experiments to look for a link between infection with *Helicobacter pylori* (famous as a cause of stomach ulcers) and benign prostate diseases. The population study of nearly 25,000 subjects showed benign prostate disease in about 16% of those with *H pylori* infection and 14% of those without, yielding a slightly increased odds (about 20%) of a relationship. The team also injected an *H pylori* protein extract under the skin of the back in male rats, who showed some increased hypersensitivity to touch at the base of the scrotum. The rats also had increased blood levels of some inflammatory chemicals and inflammation that could be seen in their prostate tissue. Although the study suggests the possibility of a link, the researchers said that this may be only a part of the whole picture and suggested that prostate inflammation may be induced by a response to an antigen elsewhere in the body.

### **Pelvic Pain Is Common in Older Men**

The painful pelvic symptoms in aging men. The results of population-based sample of men

Elcio Nakano, Paulo Sajovic de Conti, Eduardo Muracca Yoshinaga, William C Nahas, Miguel Srougi, Alberto Antunes, Sao Paulo, Brazil

Among men age 50 to 75, pelvic pain is fairly common and associated with urinary symptoms, found these researchers who looked at the records of 870 Brazilian men who were screened for prostate cancer. That means urologists who see older men for typical complaints, such as erectile dysfunction and urinary frequency, need to stay alert for pain problems. Among the screened men, who averaged age 61, 22% had painful urination, 20% had pain over the pubic area, 18% had testicular pain, 16% had perineal pain, 10% had pain after ejaculation, and 9% had penile pain. The pain problems showed a relationship with education, race, younger age, high blood pressure, and unhealthy cholesterol levels. But pain wasn't related to erectile dysfunction, diabetes, body mass index, or waist-to-hip ratio.

## **Could Prostate Inflammatory Chemicals Prompt Anxiety, Depression?**

The role of inflammatory cytokines and MAPK signaling in chronic prostatitis/chronic pelvic pain syndrome with related mental health disorders

Chao Hu, Hualan Yang, Yanfang Zhao, Xiang Chen, Yinying Dong, Yehao Dong, Jiefeng Cui, Tongyu Zhu, Ping Zheng, Shanghai, China, People's Republic of, Ching-Shwun Lin, San Francisco, CA, Jican Dai, Shanghai, People's Republic of China

This study looked at levels of inflammatory cytokines and anxiety and depression-type symptoms in both men with CP/CPSPS and rats with a kind of induced CP/CPSPS. Levels of the inflammatory cytokines interleukin (IL)-1 alpha, IL-1 beta, IL-4, IL-13, and TNF alpha were significantly elevated in the men with CP/CPSPS who also had anxiety or depression as well as in the rats' prostate tissue. The rats also had elevated levels of ERK1/2 phosphorylation in certain brain areas and reduced levels in others. Behavioral tests of the rats demonstrated anxiety- and depression-like symptoms as well as memory problems. Although the results aren't conclusive, they suggest that the inflammatory chemicals do get into the brain and may play a role in prompting the anxiety and depression that occurs so often—estimated at 78%—in men with CP/CPSPS.

## **Ureaplasma Microbes Not Responsible for CP/CPSPS**

Presence of urinary *Ureaplasma urealyticum* or *Ureaplasma parvum* is not associated with the occurrence of chronic prostatitis/chronic pelvic pain syndrome

Yu Seo, Gil Lee, Cheonan, Republic of Korea

Ureaplasmas, tiny parasites that inhabit the urogenital tract, sometimes cause urethral inflammation. Some have speculated that these organisms might be responsible for CP/CPSPS. Using genetic sequencing, these researchers looked for the two common species, *Ureaplasma urealyticum* and *U parvum*, in more than 600 urine samples collected from men who had come to a urology outpatient clinic for various reasons and who did not have gonorrhea or chlamydia. About 4% of the men had the first organism in their urine and 6% the latter organism. There was no correlation, however, between the presence of either organism and the risk of having symptoms and signs of CP/CPSPS. In addition, the average NIH-CPSI score totals for pain, urinary, and quality-of-life items were no different among men who had one or the other organism or neither.

## **Men with Low T Have More Prostatitis Symptoms, Higher Urethra Pressure**

Testosterone and Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Propensity Score Matched Analysis

Jun Ho Lee, Sung Won Lee, Seoul, Republic of Korea

For some time it has been known that men with CP/CPSPS tend to have low testosterone (T) levels. This study approached the question from the other direction—do men with low T have CP/CPSPS symptoms? From some 8,000 health examinations of men in their 40s and 50s, the researchers selected records of 948 men with T levels below a 3.5 ng/mL cutoff and compared their NIH-CPSIs with those of nearly 5,000 controls. (The average adult male T level is about

6.8 ng/mL, and the normal range is 2.7 to 10.7 ng/mL.) Men were considered to have prostatitis-like symptoms if they reported perineal or ejaculatory pain and had an NIH-CPSI pain score of 4 or more. A pain score of 4 to 8 was considered mild, and a score of 8 or more was considered severe pain. Somewhat more men with T below the cutoff (27%) had higher total symptom scores than men with T at or above the cutoff (24%) and higher moderate-to-severe symptoms (9%) than men at or above the cutoff (6%). The differences, although modest, were statistically significant. Pain and quality of life scores were also higher in men with lower T levels. In addition, somewhat more men with lower T had severe lower urinary tract symptoms (15% vs 13%), low maximal urine flow rates (5% vs 4%), and higher volumes of residual urine after voiding (6% vs 4%), considered statistically significant differences. These last differences support the idea that higher prostatic urethra pressure may be a cause of CP/CPPS.

### **Rat Model May Aid Study of Sexual and Other Symptoms in CP/CPPS**

Category III prostatitis affect premature ejaculation through brain and spinal cord serotonin system: a preliminary study

Yadong Zhang, Tao Zheng, Xiangan Tu, Qiyun Yang, Kunlong Lv, Minkuan Zhou, Kai Xia, Xiangzhou Sun, Chunhua Deng, Guangzhou City, People's Republic of China

To understand the CP/CPPS causes, symptoms, and potential treatments, researchers use experimental animals treated in some way to reproduce characteristic symptoms. Many animal models are created by injecting irritants into the prostate, but more recently researchers have been manipulating the immune system to develop autoimmune models. This rat model was produced by injecting Freund's adjuvant, which is a solution of antigen in mineral oil, into the prostate. That produced effects often seen in men with CP/CPPS: It raised blood levels of the inflammatory chemicals IL-1beta and TNF-alpha. The brain's hippocampus and spinal cord tissue had abnormally low levels of 5-HT (also known as serotonin), which is typical in depression. Levels of other compounds involved in the serotonin system were low. The researchers noted that the injected rats also showed characteristics of decreased sexual libido and premature ejaculation.

## **TREATMENT**

### **Trigger Point Injections Ease Pain with Sex**

The Efficacy of Trigger Point Injections in the Treatment of Sexual Pain

Sonia Bahlani-Khanna, New Hyde Park, NY, Alexandra King, Hempstead, NY, Robert Moldwin, New Hyde Park, NY

Trigger point injections are injections of small quantities of an anesthetic combination (lidocaine and marcaine) into the pelvic floor muscles at specific spots that hurt when they are touched. They are a hallmark of pelvic floor dysfunction (PFD), which occurs frequently in men with CP/CPPS and in women with interstitial cystitis/bladder pain syndrome (IC/BPS). Trigger point injections are known to reduce pain, and this study aimed to find out how effective they are specifically for sexual pain. The 31 patients who received these injections all reported improved aspects quality of life, including decreases in urinary hesitancy, nighttime urination, and constipation. Of the 19 female patients with sexual pain, 12 got improvement, and all 3 of the

men with ejaculatory pain felt improvement. Although the study is very small, it highlights the potential of trigger point injections for ejaculatory pain.

### **Dutasteride May Ease Nonbacterial Prostatitis**

Effects of dutasteride on prostatic inflammation mediated by estrogen receptor beta in a rat model of nonbacterial prostatitis

Shinsuke Mizoguchi, Kenichi Mori, Fuminori Sato, Yufu, Japan, Naoki Yoshimura, Pittsburgh, PA, Hiromitsu Mimata, Yufu, Japan

Dutasteride is a drug commonly used for prostate enlargement (BPH), but it can reduce inflammation. It does this, in part, by stimulating estrogen receptor beta. Based on that potential, this research team looked at how the drug affects prostatitis symptoms, the expression of estrogen receptors (ERs), and levels of inflammatory chemicals when rat prostates were irritated. The rats that got only a placebo before irritation had problems, such as overactive bladder-like symptoms and urinary frequency, but rats that got dutasteride did not. Rats that got the placebo had higher expression of ER alpha and the inflammatory chemicals IL-1 beta and IL-18 and lower expression of ER beta. The rats that got placebo also had a significantly decreased ratio of ER beta to ER alpha, whereas that ratio increased in the rats that received dutasteride. Because these experiments showed that dutasteride improved not just inflammation but also bladder symptoms, these researchers think dutasteride could be a valuable treatment for nonbacterial prostate inflammation as well as for BPH.

### **Place Your Bets on CB2 as CP/CPPS Treatment Target**

Upregulation of prostatic cannabinoid receptor type 2 following castration and capsaicin-induced prostatitis in the rats

Teng-Lung Lin, Taipei, Taiwan

Cannabis-related substances in the body known as cannabinoids play a role in inflammation and pain, so the receptors are potential treatment targets. But which ones should be the targets in CP/CPPS? This team looked for receptors with the greatest potential by inducing prostate inflammation in rats and measuring the expression of cannabinoid receptors types 1 (CB1) and 2 (CB2), fatty amide hydrolase (FAAH, a cannabinoid degradation enzyme), and cyclooxygenase 2 (COX-2, an enzyme that plays a role in inflammation). After the prostates were irritated, the expression of COX-2 and CB2 rose, but CB1 expression stayed the same, and that of FAAH was unaffected. Based on those results, the researchers concluded CB2 may be a promising treatment target.

### **Social Study Suggests Problem-solving Therapy May Help**

Social Problem Solving, Perceived Stress and Daily Stressful Events in Chronic Prostatitis

Meghan M. Colosimo, Christine Maguth Nezu, Arthur M. Nezu, Philadelphia, PA, Frank M. Nezu, Columbia, MD, Jennifer Y. Fariello, James F. Squadrito Jr., Bryn Mawr, PA, Stacey Lau, Melinda J. Webster, Philadelphia, PA

In this study, 61 men with chronic prostatitis answered questionnaires about perceived stress, daily stress, and social problem solving. Analysis of the results showed a relationship between symptoms and higher scores on perceived and daily stress and lower scores in social problem solving. Since the last was the strongest relationship, the authors suggested that problem-solving therapy may help treat pelvic pain that doesn't respond to other treatments. That remains to be tested, however.