Review Article

Gut microbiome and chronic prostatitis/chronic pelvic pain syndrome

Hans C. Arora[1], Charis Eng[2], Daniel A. Shoskes[1]

[1]Glickman Urological & Kidney Institute, Cleveland Clinic, Cleveland, OH, USA; [2]Genomic Medicine Institute, Cleveland Clinic, Cleveland, OH, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: C Eng, DA Shoskes; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: HC Arora; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Daniel A. Shoskes, MD. Cleveland Clinic, 9500 Euclid Avenue, Q10-1, Cleveland, OH 44195, USA. Email: dshoskes@gmail.com.

Abstract: Analysis of the human microbiome continues to reveal new and previously unrealized associations between microbial dysbiosis and disease. Novel approaches to bacterial identification using culture-independent methods allow practitioners to discern the presence of alterations in the taxa and diversity of the microbiome and identify correlations with disease processes. While some of these diseases that have been extensively studied are well-defined in their etiology and treatment methods (colorectal cancer), others have provided much more significant challenges in both diagnosis and treatment. One such condition, chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), has several etiological and potentiating contributions from infection, inflammation, central nervous system (CNS) changes, stress, and central sensitization—all factors that play important roles in the crosstalk between the human body and its microbiome. No singular cause of CP/CPPS has been identified and it is most likely a syndrome with multifactorial causes. This heterogeneity and ambiguity are sources of significant frustration for patients and providers alike. Despite multiple attempts, treatment of chronic prostatitis with monotherapy has seen limited success, which is thought to be due to its heterogeneous nature. Phenotypic approaches to both classify the disease and direct treatment for CP/CPPS have proven beneficial in these patients, but questions still remain regarding etiology. Newer microbiome research has found correlations between symptom scores and disease severity and the degree of dysbiosis in urine and gut (stool) microbiomes in these patients as compared to un-afflicted controls. These findings present potential new diagnostic and therapeutic targets in CP/CPPS patients.

Keywords: Microbiota; prostatitis; chronic pain; pelvic pain

Submitted Aug 18, 2016. Accepted for publication Sep 12, 2016.
doi: 10.21037/atm.2016.12.32
View this article at: http://dx.doi.org/10.21037/atm.2016.12.32

Increasing interest has been directed towards the study of the human microbiome, defined as the ecological community of commensal, symbiotic, and pathogenic microorganisms and their genetic content inhabiting the human body (1). While our own human genome contains approximately 20,000 protein-encoding genes, it has been estimated that the sheer number of microbiota living on and inside of us is at least 10 times the number of somatic and germ cells in our bodies (2). As we are beginning to understand the role of the microbiome in healthy humans, it is becoming increasingly clear that there exists interplay and symbiotic relationships between our bodies and these microorganisms, the most abundant of which can be found in the gut. Deviations from the "normal" human gut microbiome have been discovered in a variety of diseases and conditions, including inflammatory bowel disease, colorectal cancer, obesity/metabolic syndrome, type 2 diabetes mellitus, breast cancer, autoimmune disease, autism spectrum disorder, post-traumatic stress disorder and responsiveness to visceral pain (3-10). Studies in small mammals are revealing even more relationships between the gut microbiome and the central nervous system (CNS) than

previously thought, suggesting the existence of a "gut-brain axis" whereby the gut microbiome modulates the CNS and/or vice versa (11-14). Still, these differences are only correlative, and to date causative mechanistic relationships between alterations in the microbiome, also known a microbial dysbiosis, and human pathology have yet to be discovered.

Many of the human tissues or bodily fluids studied had previously been considered sterile per conventional culture methods. With the advent of polymerase chain reaction (PCR) technology, it is possible to selectively amplify the 16S ribosomal RNA found only in bacteria allowing identification of differences in all of the genera and species present in a specimen without the need for culture-selective media and microbial replication. These differences may be reflected at the ecological level (alpha diversity) and at the individual genus and species level.

The microbiome is not static, but responds and evolves in response to environmental factors. As may be expected, the gut microbiome is molded by oral intake of both food and medications. Variation in diet between cultures and dietary lifestyles lead to rapid and reproducible changes in the human gut microbiome (15). Similarly, antibiotics, both oral and parenteral, can have significant effects on the microbial ecosystem of the human gastrointestinal tract. The susceptibilities of the majority of the bacteria that comprise the microbiome are rarely taken into consideration when prescribing because they are often thought to be of little clinical significance, until patients subsequently develop antibiotic-associated diarrhea or contract an opportunistic infection by *Clostridium difficile* and even develop pseudomembranous colitis, a life-threatening condition (16,17). The effects of antibiotics on the gut microbiome have been well documented, and may persist for a period up to many months after a treatment course has been completed, typically resulting in a decrease in both abundance and diversity of bacterial genera (18,19).

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS)

CP/CPPS is characterized by a variety of symptoms, and has been shown to have a significant impact on quality of life (20). While most typically associated with pain in the pelvic region, patients may have varying degrees of obstructive and/or irritative voiding symptoms, pain with ejaculation, sexual dysfunction, depression and/or psychosocial dysfunction that may be concomitant or related to the other symptoms. Chronic pelvic or genitourinary pain is a primary component of the condition and is typically present for at least three of the preceding 6 months. As much as 10–15% of the male population may be affected at some point in their lives, and affects men of all ages. Prostatitis is responsible for up to 2 million outpatient clinic visits per year, including 8% of all male visits to a urologist and 1% of men presenting to primary care physicians (21).

Patients are often initially diagnosed as having a primary infection and treated empirically with or without culture-proven infection. They often receive prolonged doses of unnecessary antibiotics, as the disease entity is often incorrectly diagnosed as chronic bacterial prostatitis. One of the key diagnostic steps is separating the two entities with traditional mid-stream urine culture and/or properly collected prostatic localization cultures, which are up to 90% accurate in localizing a bacterial source if one is present within the lower urinary tract (22). If culture results are negative and no other clear etiology can be identified, then the patient is presumed to have CP/CPPS.

While a primary infectious agent may not be the cause of ongoing symptoms, it has been suggested that infection may be a precipitating factor. Many organisms have been implicated has possible sources of undocumented infection, including *Mycoplasma hominis*, *Trichomonas vaginalis*, *Candida* species, *Ureaplasma urealyticum*, *Chlamydia trachomatis*, herpes simplex virus, and even parasites (23-29). Such an infection may actually be an inciting incident rather than an ongoing cause that leads to development of the clinical syndrome. Other possible inciting factors may include a history of trauma, autoimmune reaction, or dysfunctional voiding. Subsequently patients develop localized inflammation or neurological damage in the pelvic region or the peri-prostatic area, and the unresolved inflammation and chemokine expression further potentiate tissue injury. Patients may even develop pelvic floor dysfunction as a result (30). Sensitization is thought to occur at a CNS level, resulting in an altered visceral pain response and chronic neuropathic state (22). A number of risk factors have been suggested in the pathophysiology of CP/CPPS, including intra-prostatic urinary reflux, hormonal imbalances, psychological factors, autoimmune disease, musculoskeletal dysfunction, voiding dysfunction, and cytokine imbalances (31-37). However none of these have revealed a definitive pathway for the development of CP/CPPS, and unfortunately no validated biomarkers exist to aid in the diagnosis or clinical severity of CP/CPPS.

In order to distinguish CP/CPPS from other similar

clinical entities, the National Institutes of Health (NIH) delineates it as one of four sub-categories of prostatitis. Acute bacterial prostatitis is classified as category I, and antibiotics targeted towards a specific uropathogen are a mainstay of treatment. Category II is chronic bacterial prostatitis, with recurrent urinary tract infections with the same uropathogen that may be recovered from prostate fluid in between symptomatic episodes. Again, targeted antibiotics based on localization cultures are a mainstay of treatment. Category IV represents asymptomatic inflammatory prostatitis, which by definition is in the absence of pain or urinary symptoms, and is most often found incidentally during an evaluation for other indications, such as prostate biopsy for prostate cancer. The clinical significance of category IV prostatitis is unknown. CP/CPPS comprises category III prostatitis, which is further subdivided into inflammatory (IIIA) and non-inflammatory (IIIB) sub-types, as differentiated by the presence of leukocytes in extraprostatic secretions, post-prostate massage urine specimens (VB3), or semen (38,39). The distinction between IIIA and IIIB prostatitis, however, has not been shown to have an impact on symptoms (40). As a result CP/CPPS is often a diagnosis of exclusion, as it is considered the most likely diagnosis in the absence of other identifiable causative factors such as growth of known uropathogens on standard culture media. Unlike its counterparts, CP/CPPS presents unique difficulties in diagnosis and management as the etiology and mechanisms by which it occurs are not well understood.

In order to begin addressing this ambiguity, the NIH Chronic Prostatitis Clinical Research Network recognized the need for a universally accepted, properly validated outcome measure for both clinical and research applications. The consensus panel developed a nine-item questionnaire, dubbed the NIH Chronic Prostatitis Symptom Index (NIH-CPSI), which addresses four major domains of symptoms: pain/discomfort, urination, impact and quality of life (39). This tool has been validated and is used as a standard measure of disease severity in CP/CPPS (41). In practice a threshold 6-point decline in NIH-CPSI score is considered necessary for patients to say they are significantly better (42).

Treatment approaches to CP/CPPS

Antibiotics are largely ineffective in the treatment of CP/CPPS as the chronic nature of the syndrome is thought not to be completely attributable to an ongoing active or latent bacterial infection (43-45). Despite this, up to almost 80% of CP/CPPS patients receive antibiotics as treatment at some point during their disease course, more than 7 times that of non-CP/CPPS patients, and many receive multiple rounds of antibiotics despite lack of efficacy (46). Many other monotherapies have been applied in prospective, randomized, placebo-controlled clinical trials, including anti-inflammatory drugs, finasteride, phytotherapies, alpha-receptor blockers, antianxiolytics, and the interstitial cystitis drug pentosan polysulfate. No single drug has been able to show consistent, significant benefit in CP/CPPS patients (47).

The goal of treatment for CP/CPPS is primarily symptom relief. CP/CPPS patients often present with a constellation of symptoms despite their singular categorization; the failure of monotherapy is thought to be due to this heterogeneity. One of the early studies that was undertaken after recognition of this problem took a step-wise approach to prostatitis treatment. Of 54 patients with either category II or III prostatitis, patients were treated with antibiotic therapy initially. If this failed they were moved on to quercetin for its anti-inflammatory properties; if this failed they were then treated with neuromuscular-acting drugs such as amitriptyline or gabapentin. Patients with concomitant urinary symptoms or elevated post-void residual volumes were treated with the alpha-blocker tamsulosin. Adjunctive therapies such as finasteride or sodium pentosan polysulfate were incorporated into the treatment algorithm in select patients. Following the outlined treatment algorithm the investigators saw significant (≥6 point) mean decreases in NIH-CPSI in all three domains (pain, urinary, quality of life). While the authors note that the NIH-CPSI was not designed as a diagnostic tool to evaluate treatment response, they do conclude that a step-wise, multimodal approach to therapy for long-standing CP/CPPS may be more effective than monotherapy protocols (48). A subsequent study involving the use of step-wise monotherapy strategy confirmed that patients with refractory CP/CPPS did show modest benefit as compared to monotherapy alone, but that the responses to this approach were still suboptimal, and instead multimodal, concurrent therapy would potentially be more appropriate (49).

UPOINT: clinical phenotyping and targeted multimodal treatment

Given the multifactorial etiology of CP/CPPS and a lack of specific biomarkers available to characterize it, the practitioner and patient are more likely to benefit from a more systematic approach to classification based

on phenotype. By doing so the variable presentation and symptom severity with which CP/CPPS presents can be taken into account. A number of large multicenter trials have failed to show significant benefit of many different treatment options as compared to placebo, which in part may be due to the heterogeneity of the patients classified as having CP/CPPS. In response to this dilemma, a multimodal approach to classifying urologic chronic pelvic pain [both CP/CPPS and interstitial cystitis/bladder pain syndrome (IC/BPS)] into qualitative clinical domains was created (50). The system, known as UPOINT, is an acronym derived from the six clinically defined areas being addressed: urinary symptoms, psychosocial dysfunction, organ-specific findings, infection, neurologic/systemic, and tenderness of muscles. Intentionally, each of these domains is associated with a specific approach to therapy. As a result, UPOINT confers unto the practitioner the ability to not only diagnose and classify chronic pelvic pain syndromes, but to develop a tailored, multi-modal treatment plan for each patient (41,51). The number of positive UPOINT domains has been shown to correlate with the NIH-CPSI in a study of 90 patients diagnosed with CP/CPPS at the Cleveland Clinic. As expected, the inter-individual variability in the diversity of positive domains between patients reflected the heterogeneity in symptoms. The authors also found a correlation between symptom duration and the number of positive UPOINT domains, which is consistent with the understanding that ongoing, unresolved inflammatory processes propagate the magnitude of the syndrome (52).

The use of UPOINT classification to direct treatment was demonstrated in a prospective study of 100 patients with CP/CPPS seen at a single institution. Treatment was directed based on UPOINT clinical phenotyping, and treatment response was measured using NIH-CPSI score after a median follow-up of 50 weeks. Each UPOINT domain was interpreted as binary input, with the most common being organ-specific (positive in 70% of patients) as determined by the presence of prostatic tenderness on examination, leukocytosis in prostatic fluid or VB3 or hematospermia. Each UPOINT domain was assigned a specific treatment targeted to the specific symptoms characteristic of that domain. Of the 100 patients enrolled in the study, 84% achieved an improvement in NIH-CPSI score of 6 points or greater. Over half of patients had a greater than 50% improvement and 84% had a greater than 25% improvement. The total number of positive UPOINT domains, initial CPSI, symptom duration and number of previous therapies did not have statistically significant relationships with treatment response (53). A more recent retrospective observational study of 914 patients validated the use of UPOINT to direct multimodal therapy. Patients were sub-categorized patients as having inflammatory (NIH category IIIA) versus non-inflammatory (NIH category IIIB) CP/CPPS, clinically phenotyped according to UPOINTS (a modification of UPOINT with the addition of a sexual dysfunction domain), and compared NIH-CPSI and International Index of Erectile Function (IIEF) before and after treatment. A combination pharmacological treatment targeted to the urinary, organ-specific and infection domains of UPOINTS included alfuzosin and *Serenoa repens* (saw palmetto berry extract), the latter of which was administered alone or in combination with lycopene and selenium. Oral antimicrobial therapy was added for patients with culture-confirmed prostate-specific microorganisms. At a total of 18 months follow-up, 77.5% of patients saw improvements in NIH-CPSI of six points or greater, with improvements in both total CPSI and voiding symptoms in patients who received antibiotics over those who did not receive antibiotics regardless of whether they were initially classified as category IIIA or IIIB prostatitis (54).

Quercetin

As the scientific method is applied to what are traditionally considered "complementary and alternative" medical therapies, the discovery of potentially bioactive properties in naturally-occurring biological compounds is receiving wide spread recognition in the peer-reviewed literature (55-59).

The bioflavonoid quercetin has been identified as a compound with effects on both gut microbiota composition and CP/CPPS, though the mechanism by which it exerts its effects, particularly in the latter, is not well known. In a prospective, double-blind, randomized placebo-controlled trial, Shoskes and colleagues investigated the use of the quercetin-containing commercial drug, Prost-Q, as a treatment option for men with category III chronic prostatitis (60). A prior study had shown that quercetin intake resulted in significant symptomatic improvement in 59% of men with chronic prostatitis (61). Thirty patients who met criteria for CP/CPPS and had never taken quercetin before were enrolled in the study. Half were randomized to quercetin capsules 500 mg orally twice daily while the other half ingested an identical-appearing placebo. In the treatment arm, NIH-CPSI scores showed a mean improvement of 35% as compared to 7.2% in the placebo group. The greatest changes were seen in patients'

pain and quality-of-life scores, but quercetin did not appear to significantly affect the urinary score, further supporting the need to assess and treat CP/CPPS as a syndrome with a constellation of symptoms rather than by attempting to address it through monotherapy.

While quercetin has previously been cited to exercise both anti-inflammatory and anti-obesity effects, the mechanism by which these properties exist is largely unknown (62,63). *In vitro*, quercetin has been shown to increase PTEN expression and downregulate the AKT pathway (64). As has been recently shown, PTEN plays a role in development of the immune system (65,66). Similarly, diet and obesity have been shown to be associated with imbalances in the gut microbiome (67,68). Owing to the fact that quercetin is known to be poorly absorbed in the gastrointestinal tract and the majority of the dosage reaches the colon intact (69,70), Etxeberria and colleagues postulated that oral administration of quercetin might exert some of its anti-obesity effects through alterations in the gut microbial ecosystem (71). The study authors induced dysbiosis of the gut microbiome by feeding Wistar rats a high-fat sucrose diet, and subsequently treating them with quercetin, trans-resveratol, or a combination of the two. The combination treatment group trended towards a decrease in body weight gain as compared to controls, and supplementation of either compound led to significant decreases in serum insulin levels and insulin resistance. Analysis of fecal matter revealed that rats treated with quercetin mitigated the increases in *Firmicutes* levels, which have previously been described in diet-induced rat models of obesity, and significantly decreased the *Firmicutes/Bacteroidetes* ratio. The expected growth of bacterial species associated with diet-induced obesity (*Erysipelotrichaeceae*, *Bacillus*, *Eubacterium cylindroides*) was also inhibited in quercetin-fed rats. Conversely, these rats also showed increases in certain bacteria (*Bacteroides vulgatus*, *Akkermansia muciniphila*) that have been shown to be inversely related to obesity (72). The administration of trans-resveratol did not show similar effects on the gut microbiome. The authors concluded that quercetin can significantly alter the expected dysbiosis of the gut microbiome, that otherwise can be induced by a high-fat "Western-style" diet (71).

The microbiome in urologic chronic pain syndromes

Long considered to be a sterile environment, more recent studies have shown that urinary tract harbors its own unique microbiome. Comparison of urine specimens to healthy controls have shown that the microbiota differ in varying urologic diseases, including urge urinary incontinence, neurogenic bladder dysfunction, and urologic chronic pain syndromes such as interstitial cystitis and chronic nonbacterial prostatitis. In addition, alterations in the normal stool microbiome have shown correlations with the presence of urologic diseases as with many other areas of the body that are thought to be physically distinct from the gut (73). For example, patients with renal calcium oxalate stones have been shown to have decreased *Oxalobacter formigenes* in the gut microbiome, a bacterial known to degrade dietary oxalate and thus is thought to at least be partially irresponsible for lower levels of urinary oxalate (74-76). Unfortunately a mechanistic relationship between the gut microbiome and urologic disease is not always so straightforward to discern.

As discussed previously, the absence of any identifiable bacterial infection is a hallmark of CP/CPPS. The current definition relies upon the use of *in vitro* bacterial detection techniques facilitated by culture media optimized for the growth and replication of specific microorganisms. The microbiomic approach to bacterial detection instead uses a culture-independent method of isolating the 16S ribosomal RNA from existing bacteria present in the collected specimen and amplifies this genomic material, without relying on amplification/replication of the whole microorganism itself (77).

Early studies applying these culture-independent PCR-based methods of detecting uropathogens in expressed prostatic secretions prostatitis patients demonstrated the presence of detectable bacterial ribosomal RNA in both chronic bacterial prostatitis and chronic non-bacterial prostatitis (78). Higher levels of 16S ribosomal RNA have been detected in prostate tissue or prostatic fluid of patients with prostate cancer, benign prostatic hyperplasia and CP/CPPS (78,79). Many previous studies have attempted to evaluate the bacterial flora present within the prostate using prostate tissue either from biopsies or whole-gland sections (80). However, there also has been variability in how patients were categorized as having CP/CPPS (81). In one study of men with CP/CPPS, it was hypothesized that the local microbiota of the prostate in CP/CPPS patients would be different than that of controls, either due to or being the cause of an inflammatory process within the tissue. The study authors found that there was a larger abundance of 16S ribosomal RNA in CP/CPPS patients as opposed to

prostate cancer, however further characterization of the microbial dysbiosis at the taxonomic level or correlation with clinical phenotype were not explored (80).

No definitive targetable pathogen or pattern of microbial dysbiosis within prostate tissue has been identified that was clearly correlated with CP/CPPS in the absence of other confounding variables such as prostate cancer or other proper controls (82-84). A recent study by Nickel *et al.* compared urethral and bladder urine specimens from CP/CPPS patients in the Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Network Study, and found differences in the CP/CPPS urinary microbiome as compared to control patients, more specifically an increase in *Burkholderia cenocepacia* in urethral specimens. Interestingly this study used mass spectrometry techniques to identify bacterial genera than more conventional sequencing and OTU-picking protocols, and like many prior studies the incorporation of a quality control screen was not included in the study protocol (85). Furthermore the role of the gut microbiome in CP/CPPS has remained unexplored until recently.

CP/CPPS patients often have received multiple, sometimes long courses of oral antibiotics in order to treat possible infectious causes prior to presenting to the practitioner who take a phenotypic approach to treatment (46). Ciprofloxacin for example, a fluoroquinolone antibiotic that is very commonly used to treat genitourinary infections and is often prescribed for CP/CPPS patients at initial presentation prior to the proper diagnosis being made, has been shown to alter the microbiome. In a small study of three individuals, each received a 5-day course of twice daily oral ciprofloxacin, which is a typical treatment for an uncomplicated urinary tract infection. Stool samples were subsequently collected and processed. Analysis revealed alterations to both the abundance and diversity of the gut microbiome, with changes persisting until about 4 weeks after treatment ended (86).

In a comprehensive approach to evaluating changes in the gut microbiome in men with category III prostatitis, Shoskes and colleagues attempted to correlate findings with clinical measurements such as symptom severity using the NIH-CPSI and phenotype using UPOINT (87). CP/CPPS patients showed a pattern of clustering distinct from demographically similar controls, and analysis revealed lower mean alpha diversity of the gut microbiome in the CP/CPPS group, with significantly different gut microbial taxa between the two groups, the most significant of which was underrepresentation of *Prevotella* (genus), known to colonize the gastrointestinal tract and suspected to play a role in mitigating inflammation, as compared to controls. Correlations with measures of symptom severity, including CPSI, UPOINT score, symptom duration, gastrointestinal or neurological symptoms did not reveal significant differences in the gut microbiome of patients versus controls, however there were non-statistically significant trends towards tighter OTU clustering in those patients with neurological symptoms and CPSI less than 26 (87). In a contrasting parallel study of the urinary microbiome of these patients, the authors found a higher alpha diversity as compared to controls (88). There does exist precedent for findings of higher bacterial diversity in correlation with urinary symptoms, as in a study of women with urge urinary incontinence in whom response to the anticholinergic medication solifenacin was inversely related to microbial diversity as well (89). In another study of women with an oft-equated pain syndrome, interstitial cystitis, urinary microbiome showed lower alpha diversity. However this was thought to be due to overabundance of lactobacilli, a common contaminant from the vagina. It is currently unclear why patients with CP/CPPS would have a greater alpha diversity of their urinary microbiome, as after receiving multiple rounds of antibiotics it would have seemed intuitive that alpha diversity would be lower if anything as compared to controls. Unlike the gut microbiome, significant differences in the urinary microbiome were found to be related to symptom severity, symptom duration and UPOINT phenotypic domains for psychosocial and neurologic symptoms. In the urinary microbiome findings *Porphyromas* genera were most overrepresented, a more common component of oral cavity flora. While it may have been suspected that increases symptom severity and symptom duration would be due to a similar pattern of microbial dysbiosis, LEfSe analysis revealed that different sets of bacterial taxa were overrepresented in the psychosocial-predominant and neurologic-predominant groups (88). The authors conclude that the observed differences in the gut or urinary microbiome may present potential objective biomarkers for clearly identifying CP/CPPS in patients with pelvic pain rather than relying on purely clinical or phenotypic variables for classification, however further study is needed.

Microbiome differences have likewise been discovered in another poorly understood urologic pelvic pain syndrome, IC/BPS in women. Whereas bacterial pain phenotypes have been identified in murine models of urinary tract infection, a group from Northwestern University hypothesized that the microbiome of adjacent organs, namely the gut and

reproductive tract, might modulate pelvic pain through organ crosstalk visceral sensory pathways (90,91). While analysis of the vaginal microbiome did not yield significant differences between IC/BPS patients and controls, analysis of the stool (gut) microbiome revealed differential representation of specific bacterial species, suggesting that these characteristic changes in the microbiome may lead to use as potential biomarkers for the disease state (92). In an earlier study by the same group, female patients classified as having urologic CPPS were classified by self-report as currently having symptom "flares" (acute worsening of symptoms) versus no flares, and initial and mid-stream urine specimens were collected and microbiomes of urethral and mid-stream urine were analyzed. Comparison of microbial species between the two groups did not show significant differences between the two groups. However, after controlling for antibiotic use and menstrual phase, univariate analysis showed a greater prevalence of Candida and Saccharomyces fungal species in midstream urine specimens, indicating a potential difference in the mycobiome rather than the microbiome of patients experiencing a flare (93).

Summary

The interplay between the human body and our microbiomes is complex and our understanding of these relationships continues to evolve rapidly. Whether detectable changes in the bacterial ecology of the gastrointestinal tract of patients with CP/CPPS are causative or resultant of the syndrome is unclear. At this time these differences are correlation. Given what we know currently about the role of microbiome and how it may affect systemic inflammation, modulate pain response and its putative role in psychosocial stress, it is not impossible that the gut microbiome may play a role in the etiology of CP/CPPS. Perhaps initially this information may be used as a diagnostic tool to confirm a suspected case of CP/CPPS. Future investigation of changes in the gut microbiome over time may be used to correlate with changes in symptoms and even aid in prognosticative (or phenotypically-driven) treatment approach. At the least, knowing these relationships exist lays the groundwork for further study in a novel and rapidly developing area at the cross-section of laboratory science and clinical medicine.

Acknowledgements

None.

Footnote

Conflicts of Interest: Charis Eng is a member of the external strategic advisory board of N-of-One; Daniel A. Shoskes is a consultant to Farr Labs and stock ownership in Triurol. Hans C. Arora has no conflicts of interest to declare.

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Cite this article as: Arora HC, Eng C, Shoskes DA. Gut microbiome and chronic prostatitis/chronic pelvic pain syndrome. Ann Transl Med 2017;5(2):30. doi: 10.21037/atm.2016.12.32

