Is There a Role for Helicobacter Pylori Infection in Urological Diseases?

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Introduction: *Helicobacter pylori* (*H pylori*) infection is a focus of attention nowadays. It has been found to cause gastrointestinal disorders and also extra-intestinal disorders. The aim of this paper is to explore the role of *H pylori* in urological diseases and to keep urologists up to date in this subject.

Materials and Methods: Medline and PubMed were searched from 1950 to December 2007 for the following combined terms: *Helicobater pylori* together with *urology*, *urological diseases*, *kidney*, *kidney cancer*, *ureter*, *bladder*, *bladder cancer*, *prostate*, *prostate cancer*, *benign prostatic hyperplasia*, *urethra*, *seminal vesicle*, *testis*, and *testicular cancer*.

Results: Accumulating evidence is appearing in the literature relating *H pylori* infection to urological diseases. The most obvious is the implication of *H pylori* in inducing chronic cystitis leading to bladder lymphoma. In addition, some epidemiological studies have shown significant associations between infective chronic prostatitis and prostatic carcinoma.

Conclusion: A simple hypothetical model relating *H pylori* infection to prostate and bladder diseases is proposed to stimulate the collaborative work between the urologists and scientists to explore this field which is underinvestigated to date. If *H pylori* is found to have a significant role in urological diseases, prevention of bladder and prostate cancers by eradication of *H pylori* infection may become a reality like what happened in the treatment of peptic ulcer disease and gastric cancer.

Keywords: Helicobacter pylori, prostatic neoplasms, urinary bladder neoplasms, lymphoma, prostatitis

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INTRODUCTION

Today, *Helicobacter pylori* (*H pylori*) infection is a focus of attention. It has been found to cause gastrointestinal disorders and extra-intestinal disorders, too. The gastrointestinal disorders include gastric adenocarcinoma, gastric lymphoma, duodenal ulcer, and chronic atrophic gastritis.[1-4] Whereas, the extra-intestinal disorders include vascular, respiratory, liver, skin, and kidney diseases.[5-9]

The possibility that a bacterium could cause gastritis, peptic ulcer, and cancer was a difficult concept to accept, especially as it would change the whole concept of the pathophysiology of ulcer disease which was based on acid etiology. It is now clear that infection with *H pylori* is associated with peptic ulcer disease and gastric cancer. *Helicobacter pylori* has been designated a group 1 (definitive) carcinogen by the World Health Organization.[10] The pathways by which *H pylori* leads to gastric cancer have been shown by models of gastric carcinogenesis. Correa's multistep model[11] showed that *H pylori* infection is a triggering

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factor in the process of increasingly severe gastric lesions progressing from chronic active gastritis to atrophy, intestinal metasplasia, dysplasia, and gastric cancer. Earlier, we proposed a model indicating the initial changes induced by *H pylori* infection that play a role in protecting the organism and enhancing its colonization in the stomach that may lead to gastric cancer.[12] The aim of this paper is to explore the role of *H pylori* in urological diseases through a review of published articles and to keep the urologists up to date on this subject. New discoveries about the role of bacteria in urological neoplasms and other diseases may change the concepts of treatment in urology like what happened in the treatment of peptic ulcer disease and gastric cancer.

MATERIALS AND METHODS

Medline and PubMed were searched from 1950 to December 2007 for the following combined terms: *Helicobater pylori* together with *urology*, *urological diseases*, *kidney*, *kidney cancer*, *ureter*, *bladder*, *bladder cancer*, *prostate*, *prostate cancer*, *benign prostatic hyperplasia*, *urethra*, *seminal vesicle*, *testis*, and *testicular cancer*. A total of 124 articles were found, of which 27 that were relevant to our subject were reviewed. There were 6, 16, and 5 articles on *H pylori* related to the kidneys, bladder, and prostate, respectively. No title was found on the subject in relation to the ureters, seminal vesicles, urethra, or testes.

HELICOBACTER PYLORI

Helicobacter pylori is a spiral gram-negative rod. It has 2 important strains based on their genetic characteristics: vacuolating toxin gene (*vacA*) and cytotoxin associated gene (*cagA*). The cagA strains are more virulent than vacA strains.[13] *Helicobacter pylori* infection triggers local and systemic inflammatory response. It may cause chronic inflammation and stimulate chronic systemic inflammatory response through the production of various inflammatory metabolites, such as tumor necrosis factor-α (TNF-α), interferon-γ (IFN-γ), interleukin 1β (IL-1β), interleukin 6 (IL-6), interleukin 8 (IL-8), and interleukin 10 (IL-10).[14,15] These mechanisms and the latest findings on *H pylori* infection and its relation with urinary tract and urological diseases are discussed below.

Prostatitis

It has long been known that certain infectious agents that affect specific areas of the body can also have systemic sequelae. A typical example of this is infection with beta-hemolytic *Streptococcus* group A. These bacteria frequently cause acute or chronic tonsillitis, which can also lead to glomerulonephritis. *Helicobacter pylori* might also be a cause of infections distant from the stomach. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is the most common form of the prostatitis syndromes.[16] The etiology of CP/CPPS is unknown in most of the cases, although some of the microorganisms including *Escherichia coli*, *Mycoplasma genitalium*, or *Chlamidya trachomatis* are accused as the etiology of CP/CPPS.[17] Chronic prostatitis might have been triggered by secondary inflammatory reactions to an unknown antigen. In CP/CPPS, no organism could be exactly found by conventional methods of microbiology. There are many measurable proinflammatory cytokines and chemokines in human semen such as IL-1β, IL-6, IL-8, IL-10, IFN-γ, and TNF-α that show high levels in seminal, plasma, and/or expressed prostatic secretion of men with CP/CPPS.[18] One could hypothesize that chronic infection with *H pylori* may be an occult etiological factor in the pathogenesis of CP/CPPS by inducing the secretion of IL-1β, IL-6, IL-8, IL-10, IFN-γ, and TNF-α. Thus, finding a relationship between *H pylori* infection and chronic prostatitis may help in finding new approaches for the diagnosis and treatment of CP/CPPS.

It has been demonstrated that the prostate does not harbor normal bacterial flora by the absence of bacterial genomes in histologically normal prostates.[19] The etiology of the chronic prostatitis/pelvic pain syndrome remains controversial, some believing that bacteria are present but do not appear on conventional aerobic cultures. A molecular technique to detect bacteria that do not grow in such cultures is to use polymerase chain reaction assay for bacterial 16S rDNA. Bacterial DNA sequences were

found to be present in prostate biopsy specimens in 77% of men with chronic prostatitis/pelvic pain syndrome.[20] Also, 78% of prostatectomy specimens from men who had prostate cancer or benign prostatic hyperplasia (BPH) were positive for bacterial DNA.[19]

Prostate Cancer

In 1999, a case of the association of prostatic adenocarcinoma with adenocarcinoid of the ileum and gastric mucosa-associated lymphoid tissue (MALT) lymphoma with *H pylori* infection was reported in the literature.[21] Carcinoma of the prostate is the most frequently diagnosed malignancy of men in the western countries.[22] It has been hypothesized that prostatic infection and inflammation might be a cause of prostatic carcinoma. Epidemiological studies show significant associations between infection and prostatic carcinoma.[23,24] Proliferative inflammatory atrophy could be a connection between prostatitis and prostatic carcinoma in a progressive process from proliferative inflammatory atrophy to prostatic intraepithelial neoplasm,[23,25,26] induced by infection and inflammation causing cellular damage by free radicals or genetic alterations.[27,28] The findings associating infection with prostatic carcinoma include detection of bacteria in prostatic specimens and experimental studies in mice.[29-31] Bacterial DNA sequences of urogenital pathogens and bacterial sequences not reported previously were detected in 19.6% of patients with prostate cancer and 46.4% of those with CPPS.[30] On the other hand, in an experimental study on a mouse model of chronic bacterial prostatitis induced by *Escherichia coli*, it was shown that chronic inflammation leads to severe dysplasia and atypical hyperplasia in the prostate.[31]

Benign Prostatic Hyperplasia

Prostatitis and BPH are the most common benign diseases of the prostate gland.[32] It is also well recognized by both urologists and pathologists that BPH and prostatitis can coexist.[33] The *National Institute of Health*'s classification of prostatitis includes the following categories: category I is acute bacterial prostatitis; category II, symptomatic chronic bacterial prostatitis; category III, chronic pelvic pain syndrome (chronic nonbacterial prostatitis/prostatodynia); and category IV, asymptomatic prostatitis (bacterial or nonbacterial). The association between prostatic inflammation and BPH and the bacterial presence in association with BPH has been documented.[35] The clinical significance of asymptomatic Category IV chronic prostatitis associated with BPH has yet to be determined.[36]

Interstitial cystitis

To date, most of the studies have not supported any role for *H pylori* in the pathogenesis of interstitial cystitis.[37,38]

Bladder Cancer

There are some reports of MALT lymphoma arising in the bladder.[39,40] Since a history of chronic cystitis is common among patients with MALT lymphoma of the bladder,[41] a relation between chronic antigenic stimulation with infectious agents and the occurrence of this malignancy has been postulated. A large body of data have implicated *H pylori* in the pathogenesis of bladder MALT lymphoma, and regression of MALT lymphoma by eradication of *H pylori* has been reported.[42] Since the success of eradication by antibiotic therapy is hampered by the occurrence of antibiotic-resistant strains, it has been hypothesized that intravesical vacA-based vaccines against *H pylori* may protect against the development of bladder MALT lymphoma in patients with chronic cystitis, who are at high risk of developing this tumor.[43] On the other hand, in an animal study, researchers transurethrally inoculated *H pylori* into the mouse urinary tract and observed that the organism established infection and induced inflammation in the urinary bladder and the pelvis.[44]

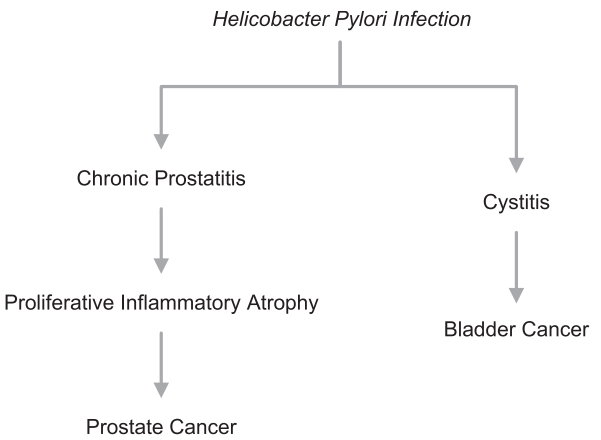
Kidney Diseases

The prevalence of *H Pylori* infection in kidney transplant recipients is quite variable. Some authors have found it to be quite low (38%),[45] while others have reported its incidence rate up to 80%.[46] In uremic patients who are known to be infected with *H pylori*, it has been recommended

to eradicate *H pylori* infection prior to kidney transplantation to avoid a long-term significant increase of gastric and/or duodenal peptic ulcer disease.[47] A primary MALT lymphoma of the kidney was reported in a 50-year-old man who was infected with *H pylori*.[48]

CONCLUSION

Based on the above summary of the literature, a model relating *H pylori* infection to prostate and bladder diseases can be hypothesized (Figure). However this proposed model has many gaps to be proved and investigated. This model has been proposed to stimulate the collaborative work between the urologists and other scientists to explore this field which is underinvestigated and full of knowledge gaps. If *H pylori* is found to have a significant role in urological diseases, prevention of bladder and prostate cancers by eradication of *H pylori* infection may become a reality like what happened in the treatment of peptic ulcer disease and gastric cancer.



Hypothetical model for the relation of *Helicobacter pylori* infection to urological diseases.

CONFLICT OF INTEREST

None declared.

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