Are Helicobacter Pylori and Benign Prostatic Hyperplasia Related, and If So, How?

Ayhan Verit,* Özgür Haki Yüksel, Mithat Kivrak, Hanife Aydin Yazicilar, Nurver Özbay, Fatih Uruç

**Purpose:** Although many virulence factors have been defined for Helicobacter pylori (HP), vacuolating cytotoxin A (VacA) is known to be associated with apoptosis, the Cag pathogenicity island protein (Cag-PAI), and growth factors. Both apoptosis and growth factors are thought to be related to the etiology of benign prostatic hyperplasia (BPH). Additionally, the relation between atherosclerosis-BPH and atherosclerosis-HP has also been reported in a limited number of studies. The aim of this pioneering study was to investigate the presence of HP in BPH patients who had undergone transurethral resection of prostate (TURP) and to discuss the potential pathophysiologic effects of HP on BPH.

**Materials and Methods:** A total of 113 cases who underwent TURP due to infravesical obstruction due to BPH were included in the study. Preoperatively, parameters including, age, height, body weight, body mass index (BMI), prostate specific antigen (PSA), prostate volume (PVo), maximum urinary flow rate (Qmax), fasting plasma insulin, and International Prostate Symptom Score (IPSS) values were evaluated. The presence of HP was investigated in the prostate specimens with real-time polymerase chain reaction (RT-PCR) method. Postoperatively, histopathological evidence of chronic prostatitis (CP) was also analyzed.

**Results:** HP was detected in 1.8% (n = 2) of the participants. Additionally, hCP was observed in 58.4% (n = 66) of the 113 patients. The demographic and clinical parameters confirmed the presence of BPH disease.

**Conclusion:** Although BPH is a common disease, its physiologic etiology mechanisms are not clear. Based on our pilot study, despite its gastric location, we believe that HP should be considered in cases with clinical BPH because HP induces apoptosis and alterations in the equilibrium between apoptosis and local growth factors in addition to its recently demonstrated extragastric effects mediated via the atherosclerotic pathway. Although our uncontrolled pioneer study was not designed to investigate the pathophysiologic mechanism, the isolation of HP from prostatic adenoma suggests the need for further well-designed studies on this topic.

**Keywords:** helicobacter infections; complications; epidemiology; humans; male; prostatic hyperplasia; etiology; physiopathology; risk factors.

**INTRODUCTION**

Benign prostatic hyperplasia (BPH) is the most common benign adenoma in men. BPH obstructs the bladder outflow, which leads to significant clinical symptoms, and nearly 40% of men are at risk of suffering from BPH during their lifetimes. Although alterations in the levels of estrogens and androgens have been demonstrated to be etiologic factors that result in muscular growth in BPH, it is thought to be multifactorial and include the involvement of stromal growth factors induced by hypoxia secondary to abnormal blood flow. The incidence and lifelong prevalence of Helicobacter pylori (HP) infection are similar to those of BPH (> 80%) and also increase similarly with age. HP is a relatively recently discovered microorganism. In 1997, Tomb and colleagues decoded and described complete genomic structure of HP. Analyses performed with the recently developed repetitive sequence-based polymerase chain reaction (rep-PCR) method have identified two main groups of HP. Researchers have observed that the first group predominantly causes simple gastritis, while the second group primarily induces duodenal ulcers. Thus, the idea of the presence of various disease-specific HP strains has been proposed. Strains carrying the HP JHP947 gene have primarily been detected in association with duodenal ulcers and gastric carcinomas, which suggests that this gene is an important marker of pathogenicity. HP has recently been considered in terms of its extragastric effects. Indeed, potential associations have been proposed between some malignant neoplasms, atherosclerosis, and even Alzheimer’s disease. Among the many HP-related virulence factors, vacuolating cytotoxin A (VacA) and Cag pathogenicity island (Cag-PAI) are known to be associated with apoptosis and growth factors, respectively. Based on a hypothesis similar pathophysiologies and considering the concomitancy of atherosclerosis with both BPH and HP in addition to the potential influence of HP on apoptosis, we...
Table 1. Demographic and clinical characteristics of patients who underwent transurethral resection of prostate.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Min-Max</th>
<th>Mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, (year)</td>
<td>50-83</td>
<td>65.95 ± 7.67</td>
</tr>
<tr>
<td>Height, (m)</td>
<td>1.50-1.86</td>
<td>1.71 ± 0.07</td>
</tr>
<tr>
<td>Body weight, (kg)</td>
<td>55-106</td>
<td>78.65 ± 11.26</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>18.94-36.68</td>
<td>27.04 ± 3.62</td>
</tr>
<tr>
<td>Insulin, (n = 46)</td>
<td>1.20-25.00</td>
<td>6.04 ± 4.25</td>
</tr>
<tr>
<td>PVo, (mL)</td>
<td>15-140</td>
<td>60.63 ± 21.22</td>
</tr>
<tr>
<td>Qmax, (mL/s)</td>
<td>0-19</td>
<td>7.22 ± 3.53</td>
</tr>
<tr>
<td>IPSS</td>
<td>12-25</td>
<td>21.29 ± 2.21</td>
</tr>
<tr>
<td>PSA, (ng/mL)</td>
<td>0.2-22.0</td>
<td>3.88 ± 3.43</td>
</tr>
<tr>
<td>Duration of treatment, (year)</td>
<td>1.15</td>
<td>4.33 ± 3.03</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; BMI, body mass index; PVo, prostate volume; IPSS, international prostate symptom score; PSA, prostate specific antigen.

Table 2. Frequencies of comorbidities and prostatitis in study patients.

<table>
<thead>
<tr>
<th>Variables</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>42</td>
<td>37.2</td>
</tr>
<tr>
<td>CAD</td>
<td>23</td>
<td>20.4</td>
</tr>
<tr>
<td>COPD</td>
<td>3</td>
<td>2.7</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>22</td>
<td>19.5</td>
</tr>
<tr>
<td>Other comorbidities</td>
<td>58</td>
<td>51.3</td>
</tr>
<tr>
<td>AUR</td>
<td>25</td>
<td>22.1</td>
</tr>
<tr>
<td>Chronic prostatitis</td>
<td>66</td>
<td>58.4</td>
</tr>
</tbody>
</table>

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; AUR, acute urinary retention.

RESULTS

After the exclusions, 113 cases who underwent TURP operations in our department were included in the study. The mean age of the group was 65.95 ± 7.67 years (range 50-83). Demographic pre-and postoperative data and the comorbidities of the patients are given in Tables 1 and 2. HP positivity was detected in the specimens from 2 (1.8%) patients.

DISCUSSION

BPH is a chronic condition and generally exhibits a progressive course. Lower urinary tract symptoms (LUTS) have been thought to be associated with both prostatic apoptosis and prostatic hyperplasia. In contrast, HP exerts long-term unexpected effects on human beings. The prevalence of HP infection is similar to that of BPH, and both increase with age. In our study, we used a real-time PCR method to perform HP screening tests on the prostatic specimens of 113 patients with clinical BPH that was refractory to medical treatment and thus necessitated TURP operations. HP was detected in 1.8% (n = 2) of the cases who participated in the study. No significant differences were observed between the patients with and without HP in the pre- or postoperative data. Associations of LUTS with prostatic apoptosis and hyperplasia have been recognized. It is well known that LUTS can be very severe in cases with normal or small prostate volumes. Literature reviews have demonstrated that this phenomenon can be explained by prostatic elastosis (i.e., elastic tissue loss). In a study (n = 65) of prostatic elastosis, associations of elastosis with increased age, prostatic atrophy, and local atherosclerosis were observed, but no significant associations were detected with histologically confirmed cancer, higher grades of prostatic intraepithelial neoplasia, systemic atherosclerosis, nodular prostatic neoplasia, or acute inflammation.(12) However, the association with local atherosclerosis indicates that ischemia has a possible role in the etiopathogenesis.(12) In our study, prostatic elastosis was not separately evaluated. The prostate volumes of the cases with HP were not different from the mean prostate volume (60 mL) of the study group. Additionally, local atherosclerotic foci have been observed in histopathological samples in which HP has been detected. Atherosclerosis decreases blood flow through tissues, which leads to atrophy. Additionally,
atherosclerosis increases the release of hypoxia-inducible factor and secondary growth factors, which results in potential stromal hyperplasia. Impairment of the prostatic stromal cells has been demonstrated to be an important factor in the pathogenesis of BPH and is the most prevalent etiological factor of BPH in older men. Although estrogens and androgens have been confirmed as causes of increased numbers of prostatic stromal and epithelial cells, fibromuscular growth in BPH is thought to be multifactorial. However, some of these factors have been suggested to be stromal growth factors that are induced by hypoxia secondary to abnormal blood flow. Interactions between growth factors and steroid hormones might tilt the balance to stimulate cellular proliferation in BPH, which also corresponds to programmed cell genesis of BPH and is the most prevalent etiological factor and secondary growth factors, which results in potential stromal hyperplasia. Some of the growth factors have been characterized in normal, hyperplastic, and neoplastic prostatic tissues. These factors include basic fibroblast growth factor (FGF-β), transforming growth factor β (TGF-β), epidermal growth factor (EGF), and heparin-binding growth factor-alpha (α-FGF and others). TGF-β is potentially an inhibitor of normal epithelial cell proliferation in many tissues. In recent in vitro studies that utilized human prostatic stromal cell culture models, increases in growth factor secretions secondary to hypoxia have been detected. This phenomenon might indicate that hypoxia triggers prostatic enlargement. Hypoxia of the prostatic tissue might occur due to generalized or localized vascular damage. Various studies have disclosed an association between diabetes mellitus (DM) and coronary artery disease (CAD) that causes vascular damage and BPH. In our study, 51.3% (n = 58) of the cases also had comorbid diseases, such as hypertension (HT) (37.2%; n = 42), CAD (20.4%; n = 23), and DM (19.5%; n = 22).

LUTS might be induced by various conditions that affect the nervous system. Nearly half of diabetes somatic neuropathy patients develop LUTS, and many symptoms resembling LUTS can be observed in this population. The impairment of the perfusion of the prostatic transitional zone (TZ) has also been demonstrated. If vascular damage is important in the pathogenesis of BPH, then patients with peripheral arterial occlusive disease (PAD) and severe atherosclerotic entities, such as CAD, who lack any DM-related neuropathic component should exhibit worse prostatic symptom scores and prostatic perfusion compared with controls. Resistive index is the most reliable criterion for demonstrating blood flow in small prostatic vessels. In the necropsy specimens of 100 patients, atherosclerotic processes were evaluated based on decreases in the intima/media thickness. A total of 119 arterial specimens of 20 patients with diagnoses of BPH were examined histopathologically, and atherosclerosis was detected in nearly 20% of these arteries. In the same study, an association between PCa, and atherosclerosis was also observed. Overall, it seems reasonable to suggest that atherosclerosis might be a factor that affects the progression of BPH but probably not its onset. As mentioned previously, the incidence and prevalence of HP infection and BPH are similar and exhibit similar increases with age. Although HP infection is a globally prevalent disease, its incidence differs between regions and between different groups residing in the same region. The incidence of HP is strongly linked to socioeconomic status. In developing countries, the incidence of HP in middle-aged individuals is over 80%, however, its incidence in the same age group in developed countries varies between 20% and 50%. When HP-positive and -negative patients have been compared, increases in carotid artery intima-media thickness, total oxidative status, total antioxidative capacity, oxidative stress index, and triglyceride values have been observed in the HP-positive patients. In contrast, associations of carotid atherosclerosis with severe clinical symptoms and CagA-positive HP infection have been observed. Thus, a role of HP infection in atherosclerosis has been suggested.

Among the many virulence factors related to HP, CagAand Cag-PAI have been reported to be associated with apoptosis and growth factors, respectively. As indicated above, associations of LUTS with both prostatic apoptosis and hyperplasia have previously been defined. One of the most important virulence factors related to HP is VacA. VacA also affects mitochondrial membranes and leads to the secretion of cytochrome C and the consequent formation of acidic vacuoles and cellular apoptosis. Many strains of HP (60-80% in Western and > 90% in Asian countries) contain a 37-kb genomic fragment termed Cag-PAI that contains 29 different virulence genes. CagA is the one of the most important virulence factors and is synthesized by the Cag gene, which is located in this gene island. CagA has a molecular weight of 120 kD and is translocated into a host cell after its synthesis. This protein molecule is phosphorylated after its intracellular inclusion and bound to SHP-2 tyrosine phosphatase, which results in the production of cytokines in response to a cellular response that resembles that elicited by intracellular growth factors.

There is no doubt that HP has important roles in the pathogenesis of gastric cancer and lymphoma. In pilot studies, possible associations between HP and other gastrointestinal system neoplasms [i.e., liver, pancreas, oropharyngeal cancers (in the tonsillar and adenoid tissue), etc.] have been suggested. Interestingly, an association between HP and extragastrintestinal neoplasms (i.e., pulmonary and ocular adenoidal lymphomas) has been reported. The mechanism of the carcinogenic effect of HP has not yet been defined. However, HP might induce cellular transformations directly via its mutagenic and/or immunosuppressor affects or via increments in the productions of cytokines and regulatory molecules. Although BPH does not possess the trait of malignancy, from the pathophysiologic perspective, it nearly defines a group of neoplasms.

Actually, chronic inflammatory effects of HP on the gastric and duodenal mucosa have previously been recognized. Additionally, many studies have provided evidence supporting the apoptotic and growth factor-stimulating effects of HP and its association with atherosclerosis. These conditions can induce the development of neoplasias or hyperplasias. Several investigations have indicated that prostatic hyperplasia and/or chronic infection can result in LUTS. The associations between HP and chronic urologic pathologies, such as interstitial cystitis (IC) and chronic prostatitis have rarely been investigated, and a direct link between HP and urologic infections has not been demonstrated. HP has been suggested to be a possible unidentified etiological factor in the development of hCP and IC via...
its triggering of the release of interleukin 1β (IL-1β), IL-6, IL-8, IL-10, IFN-γ, and TNF-α. We believe that an investigation of the potential association between HP and CP in a well-designed, large-scale series might aid in the discovery of more effective diagnostic and therapeutic methods for the management of CP. It is well known that the presence of clinical CP necessitates the rapid management of BPH due to its disturbing symptoms; however, in an autopsy series, a significant correlation between BPH and CP was not detected. Indeed, in our study, the percentage (58%) of specimens in which CP was detected during the histopathological examinations resembled that of a previous autopsy series in a patient population without BPH. It is known that all microorganisms exert deleterious effects on tissues via bacterial or autoimmune pathways. The effects of the substantially greater incidence of HP-BPH concomitancy on the etiology of the apparently multifactorial BPH should be investigated. Direct or indirect interactions between BPH and many microorganisms have been investigated; however, these authors failed to detect any significant correlations between these factors. Nevertheless, the direct and indirect correlations between BPH and HP have not yet been analyzed.

The main limitation of our study was that it was an uncontrolled study that did not allow for satisfactory statistical analyses to achieve a high scientific value. However, the inclusion of a control group was nearly impossible for ethical reasons because there is no indication to extract normal prostate specimens. Furthermore, it is well known that the majority of men in this age group exhibit histological BPH, prostatitis and/or prostate cancer in postmortem studies; thus, it would have been nearly impossible to include males with “normal” prostates. Our pioneering study is an indirect cause-effect study that did not investigate the underlying pathophysiological mechanisms. The limited numbers of study patients and specimens that were sent to the histopathology laboratory, the inability to perform serologic tests, and the evaluations related to prostatic perfusion constitute limitations of our study. However, we revealed that HP can be detected in prostatic tissue specimens. In 2% of our cases (best referred to as random specimens), HP DNA was detected. However, it must not be forgotten that this small percentage was based on a limited number of specimens. Notably, if all of the TUR materials and whole prostate volumes were considered, this percentage might have been much higher. Additionally, previous PCR studies have revealed that the prostate rarely harbors a normal bacterial flora and thus contamination was a likely possibility. Although HP was detected in a limited number of cases and at a low percentage, we believe that HP localized inside the prostate does not play a role in the clinical manifestations or hCP but might be involved in the etiopathology of BPH mediated by atherosclerosis, apoptosis and/or growth factors.

To confirm the results of our pioneering study, multidisciplinary studies analyzing a large number of parameters with the possible support of gastroendoscopy and necropsy examinations of the prostate are needed. Although the scientific value of the present study is not satisfactory, this pioneering manuscript may elicit future well-designed studies with multiple groups that potentially include cadaveric samples or animal models that evaluate the relationships of HP with prostatic diseases, such as BPH, prostate cancer and prostatitis.

CONCLUSIONS
Although BPH is a very frequently encountered disease, its etiopathologic mechanisms are not clear. Based on our pilot study, despite its use of gastric samples, we believe that HP should not be overlooked in cases of clinical BPH based on the fact that HP induces apoptosis and alterations in the equilibrium between apoptosis and local growth factors in addition to its recently discerned extragastric effects via the atherosclerotic pathway. Although our pioneering study was not designed with the intention of elucidating the relevant pathophysiological mechanism, the isolation of HP from prostatic adenomas indicates the necessity of further investigations in this field.

ACKNOWLEDGEMENTS
This study was financial supported by the administration of the Istanbul Fatih Sultan Mehmet Research and Training Hospital.

CONFLICT OF INTEREST
None declared.

REFERENCES


