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Helicobacter pylori and urinary system stones: Endoluminal damage as sub-hypothesis to support the current stone theory

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ABSTRACT

Helicobacter pylori (*H. pylori*) is a atypical gram-negative bacteria preferring gastric mucosa which also have bizarre multisystem effects extended to some malignancies, hematologic and vascular disorders through some not well defined pathophysiologic pathways. Our pioneer data was pointing that the urinary system stone existence was seemed to be high in the group of *H. pylori* + cases. While the explanation of the reason of the coincidence of renal-gall bladder stones, it was previously suggested that there may be a shift mechanism of intestinal microbial flora, from *Oxalobacter formigenes* that may reduce the risk of renal stone by consuming intestinal oxalate, to *H. pylori* which is known to induce gallstone by unknown mechanism. This hypothesis is an indirect one and highly controversial for the effect of *H. pylori* in the renal stone formation because intestinal absorption of oxalate is not significant when it is compared with the endogen oxalate. The present preliminary unique data in connection with our hypothesis claimed that a possible relation between *H. pylori* and renal stones. We think that this detrimental effect is due to the possible systemic influence such as vascular and/or endoluminal sickness due to the *H. pylori* other than directs bacteriologic colonization. There is strong evidence that *H. pylori* have some role in the atherosclerotic procedure. The *vascular theory of Randall plaque* formation at renal papilla and subsequent calcium oxalate stone development that suggests microvascular injury of renal papilla in an atherosclerotic-like fashion results in calcification near vessel walls that eventually erodes as a calculus format into the urinary system. Briefly, theories of stone and atherosclerosis seemed to be overlap and *H. pylori* is one of the factor of both processes. In addition to our hypothesis, we claimed that *H. pylori* might have same detrimental effect on endoluminal surfaces of urinary and genital systems and resulting in some special pathologies as *Hunner's* ulcers in interstitial cystitis and even posttesticular infertility. The accumulating knowledge about extragastric sequelae of *H. pylori* may open new aspects on therapeutic and the prevention strategies of urolithiasis and even this progress may reach to chronic pelvic pain syndromes and idiopathic infertility.

Introduction

Helicobacter pylori (*H. pylori*) is a gram-negative aerophilic spiral shaped bacteria that selectively colonizes the gastric mucosa and focus of attention because of its link in extragastric gastrointestinal disorders such as gallstones and colonic polyps [1]. Furthermore, this extraordinary association extends to some extra-intestinal and systemic pathologies such as malignant neoplasms, some hematologic disorders, atherosclerosis and even Alzheimer's disease [2–6]. *H. pylori* positivity reached to more than 2 in every 3 especially in developing countries [7]. Due to the present knowledge, the association of *H. pylori* and most of these pathologic status attributed to their genes, mainly the cytotoxin-associated (CagA) and the vacuolating cytotoxin (VacA) genes other than the direct bacteriologic effect [7,8]. Many strains of *H. pylori* have a genomic fragment of Cag-PAI containing CagA which is the one of the most important virulence factors is synthesized by Cag Gene Island. CagA is protein molecule related with the production of cytokine that induce cellular transformation directly by its mutagenic and/or immunosuppressor impact [9]. Moreover, VacA and Cag-PAI have been known to be associated with apoptosis and growth factors [10]. In the gastric fluids secretions of the gastric cancer patient, *H. pylori* had shown to be promote P53 expression and mutations which is a well known cancer suppressor protein that have a main role in cell cycle control and apoptosis

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[11]. On the other hand, Cyclooxygenase (COX) is an overexpressed enzyme during *H. pylori* that converts arachidonic acids to prostaglandins, acting a major role in physiological and pathological pathways. COX-2 is active form that expressed in response to inflammation and carcinogenesis [12].

H. pylori was considered in some urogenital system diseases. In the limited studies, *H. pylori* was searched in the Urologic chronic inflammatuar diseases such as interstitial cystitis but any trace of it had been found as a direct atypical bacteriologic agent and chronic prostatitis that showed a significant high seropositivity [13,14]. Aforementioned, *H. pylori* selectively preferred gastric mucosa but not urothelium. Nevertheless, the authors resulted in that any unknown antigens including the present one may lead a secondary inflammation that causes these pelvic painful syndromes. Similarly, Kurotsuchi et al. found out a detrimental effect on male infertility of *H. pylori*, by suggesting similarity between bacterial flagella of *H. pylori* and spermatozoa as the unique flagellated human cells, and that the immune response against *H. pylori* flagella may cross-react with spermatozoon flagella [15]. Another study confirm the same conclusion in another way, reporting the high level of TNF-alpha that is a significant cytokine that rise up during Cag + *H. pylori* infection, in systemic circulation of idiopathic infertiles, induces apoptosis in a group of human cells including spermatozoa [16]. Last of all, there have been some suspicions that *H. pylori* may have ability to induce – as for the all lymphomas – bladder lymphoma and prostate cancer through a mechanism of triggering inflammatory process [17].

In our simple and retrospective investigation, we found out that the urinary system stone existence for the groups with *H. pylori* + (*n*:110) and *H. pylori* – (*n*:45) were 9 and 1 respectively, in a group of patients who underwent gastric biopsy for any reason in certain period in a single center of a stone endemic region. This simple determination was pointing a possible positive association between *H. pylori* infection and urolithiasis that was not previously described. However, in a unique study that was trying to find valid hypotheses for the answer of the question that why patients with gallstones have also high incidence of renal stones, one of the hypotheses was that there might be a shift of intestinal microbial flora from *Oxalobacter formigenes* (*O. formigenes*) that metabolizes intestinal oxalate may reduce the risk of renal stone to *H. pylori* which induce gallstone [18]. Nevertheless, the overall risk of *O. formigenes* on renal stone formation is not clear, actually the role of intestinal oxalate itself because, the contribution of dietary oxalate to urinary one was presumed to be less than 20% [19]. On the contrary, we hypothesis that the induction of urinary stones by *H. pylori* due to its systemic chronic influence such as endoluminal damage other than direct bacteriologic colonization either in gastrointestinal or urinary system.

The hypothesis

A wide variety of systemic diseases such as obesity, hypertension, diabetes and metabolic syndrome are associated with urinary stones and thus urolithiasis can be mentioned as a systemic disorder that locally appears. Reiner et al., in their community based study, suggested that kidney stones are associated with subclinical atherosclerotic disease in young to middle-aged adults and they hypothesize that kidney stones and atherosclerosis act together through the same pathogenic mechanisms as in vascular injury, inflammation and calcification [20]. As an indirect deduction, both atherosclerosis and nephrolithiasis are uncommon diseases in Eskimo people and this result was attributed to the consumption of high amount eicosapentaenoic acid that is one of the main composites of fish oil [21].

In the current stone theory; the calcium apatite deposits (Randall's Plaque) in the basement membrane of the thin limbs of Henle (the tip of the papilla) demonstrate a plaque formation that this composition subsequently extends subepithelial location. Then, Randall's Plaque erodes through the urothelial epithelium and falls into the collecting tubules – act as nidus for calcium oxalate stone – and the stone story continues via nucleation on death cells, fibrin, etc. just before the crystallization period [19]. This scenario evolved into the vascular theory of Randall plaque formation and subsequent calcium oxalate stone development that suggests microvascular injury of renal papilla in an atherosclerotic-like fashion results in calcification near vessel walls that eventually erodes as a tiny calculus into the papilla [22]. In other words, this story analogously overlap an atherosclerotic procedure even subsequent additive atheroembolism event; Atherosclerotic plaque is located subendothelial inner layer of the artery and composed of fatty substances, cholesterol, waste products from the cells, fibrin and calcium, furthermore this formation can rupture and crack open through the vessel resulted in thromboembolism.

Bagga et al. suggested this vascular theory of Randall plaque formation depending on the special physiological properties of the renal papilla that promoting an atherosclerotic like response to inflammation with perivascular calcification; (i) the turbulent flow at the tip of the renal papilla caused by arterial plaques at the locations such as the bifurcation of large arteries of the pelvis. (ii) The hyperosmolar microenvironment of the location that harboring inflammatory cytokines can accumulate and promote plaque aggregation in response to vascular injury. (iii) The limited oxygen-carrying capacity of the renal papilla [22].

If we construct our hypothesis, *H. pylori* accused of detrimentally effects vascular well being especially in microcirculatory level. Briefly, the collecting venules of the *H. pylori* suffered gastric mucosa shows initially platelet–endothelial and shortly after leukocyte–endothelial interactions, such as leukocyte adhesion. The platelet thrombi occurs microvascular blood flow occlusions that inevitably results in local ischemia. At the final step, white cell migration through the endothelial cell layer harboring extravasation, limited oxygen supply to the gastric epithelium and neutralizing the toxic gastric acid and thus, all these leads to gastric micro mucosal injury enlarged with effect of gastric acids [23]. We think this model of endoluminal micro epithelial injury adapts the Randall plaque theory. In regard to structure of our hypothesis, the limitation is that *H. pylori* do not seem to colonize in kidney apart from some limited evidence of it in glomerulonephritis diagnosed by renal biopsy specimens [24]. Nevertheless, this microcircular pathologic status attributed to *H. pylori* was not thought to be restricted in the capillary level. *H. pylori* were defined in the scenarios of the atherosclerotic plaques of the larger arteries [25]. Some certain infectious pathogens including *H. pylori* supposed to be contribute the atherosclerotic plaques depending on studies using polymerase chain reaction (PCR) method, however someone bear in mind that PCR studies may give rise false positive results [25]. In another suggestion, chronic *H. pylori* may induce coronary atherosclerosis in the development phase other than plaque formation through systemic effect by causing lipid alterations via cytokines [26]. Furthermore, it is thought that *H. pylori* infection stimulate the alterations of the acid-base environment of the gastric fluid that resulted in elevated serum homocysteine concentrations which is harmful for the endoluminal surfaces of the arterial and/or endoluminal walls. The cross immunologic reaction against *H. pylori* and endovascular proteins is another possible explanation. Nevertheless, *H. pylori* increase the risk of atherosclerosis