Klinik Araştırma

Helicobacter Pylori and Urinary System Stones: Any Relation and How? *

Helikobakter Pilori ve Üriner Sistem Taşları Arasında Nasıl Bir İlişki Vardır?

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ABSTRACT

Introduction: *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. 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 Oxalabacterformigenesthat may reduce the risk of renal stone by consuming intestinal oxalate, to H. pylori which is known to induce gallstone by unknown mechanism. In this study we aimed to investigate the relation between H. pylori and urinary system disease.*

Material and Method: *We retrospectively evaluated the data of the 155 patients who underwent gastric biopsy for any reason in Fatih Sultan Mehmet Research & Training Hospitalbetween 2008 and 2013.Patients divided into two groups according to the H. pylori positivity.*

Results: *It was found out that the urinary system stone coincidence for the groups with H. pylori+ (n:110) and H. pylori - (n:45) were 9 and 1 respectively.*

Conclusion: *We think that this coincidence of stone and H. Pylori positivity 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 factors of both processes.*

Keywords: *Helicobacter pylori, urolithiasis, atherosclerosis.*

ÖZET

Giriş: *Helicobacterpylori (H. pylori) mide mukozasına yerleşen, patofizyolojik mekanizması tam olarak aydınlatılamamış yollarla bazı kanserlerin, hematolojik ve damarsal hastalıkların oluşumunda rol aldığı düşünülen, atipik bir gram-negatif bakteridir. Üriner sistem ve safra kesesi taşları birlikteliği açıklanırken intestinalmikrobiyalflorada oksalatı tüketerek böbrek taşı oluşum riskini azaltan 'Oxalabacterformigenes'in, safra kesesi taşları için uyarıcı olan H. pylori ile bilinmeyen bir mekanizma doğrultusunda yer değiştirdiği düşünülmüştür. Biz bu çalışmada üriner sistem taş hastalığı ile H. pyloriarasındaki ilişkiyi araştırmayı amaçladık.*

Materyal ve Metod: *Biz burada İstanbul Fatih Sultan Mehmet Eğitim ve Araştırma Hastanesi'nde, 2008 -2013 tarihleri arasında, herhangi bir nedenle mide biyopsisi yapılan 155 hastanın bilgilerini H. pylori-pozitifliği yönünden iki gruba ayırarak retrospektif bir çalışma yaptık.*

Bulgular: *Geriye dönük baktığımızda H. pylori (+) olan 110 hastanın 9'unda ve H. pylori (-) olan 45 hastanın birinde koinsidental olarak üriner sistem taş hastalığı varlığını saptadık.*

Sonuç: *Biz üriner sistem taş hastalığı ve H. Pylori-pozitifliği birlikteliğinin, bakterinin direkt kolonizasyonunun oluşturduğu vasküler ve-veya endolüminal hasarın olası sistemik etkisinden kaynaklandığını düşünüyoruz. H. pylori'nin aterosklerozis oluşumunda rolünün olduğuna dair güçlü kanıtlar mevcuttur. Renalpapillada Randall plak formasyonu oluşumu ve sonrasında gelişen kalsiyum oksalat birikimi, aterosklerozis benzeri mikrovasküler hasar oluşumuyla; bu da papilla duvarında erozyon ve kalsifikasyonla sonlanan üriner sistem taş hastalığı ile sonuçlanır. Kısaca, üriner sistem taş oluşumu ve aterosklerozis gelişimi teorileri benzerdir ve H. pylori her iki süreçte de rol alan faktörlerden birisidir.*

Anahtar Kelimeler: *Helicobakter pylori, ürolitiazis, aterosklerozis.*

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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 extra-gastric 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 (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 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 Oxalabacter 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. In this study we aimed to documented the possible relation between H. pylori and urinary system disease and discuss the possible mechanisms.

MATERIAL AND METHOD

We retrospectively evaluated the data of the 155 patients who underwent gastric biopsy for any reason in Fatih Sultan Mehmet Research & Training Hospital between 2008 and 2013. The study was approved by the Institutional review board of the mentioned center. Patients divided into two groups according to the H. pylori positivity. Chi-square test was used for statistical analysis.

RESULTS

The mean age of the patients male and female were 62,1 and 60,2 (Range 17 and 88) respectively. 86 of them were male and rema-

ining 69 were female. It was found out that the urinary system stone coincidence for the groups with H. pylori+ (n:110) and H. pylori- (n:45) were 9 and 1 respectively (Table 1). Chi-square test was used for statistical analysis (p=0,12).

Table 1: Urinary system stone coincidence for the groups with H. pylori (+) and H. pylori (-).

	urinary system stone (+)	urinary system stone (-)
H. pylori (+)	9	101
H. pylori (-)	1	44

DISCUSSION

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 AP 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 urethelial 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 tromboembolism. 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).

In regard to aim of this study, H. pylori accused of detrimentally effects vascular well being especially in microcirculatory level. Briefly, the collecting venules of the H. pyloris uffered 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, chro-

nic 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 and serebrovascular events (27). On the contrary, some rare studies did not share the idea of H. pylori detrimental effect on vascular wall (28).

The property of endoluminal erosion due to the H. pylori was confirmed at the gastric mucosa and has strong evidence at endovascular endothelium. Thus, we introduce the question: Might H. pylori have same detrimental effect on endoluminal surfaces of urinary and genital systems? At the proximal side of urinary system, this may appeared as urolithiasis via Randall plaque theory and at the distal side of endoluminal surface of the bladder, Hunner's ulcers of interstitial cystitis may be the answer of the question. Besides, the detrimental impact of H. pylori on male fertility might be through the defective endolumina of the sperm transport system.

The bacteriological relation with urinary stone disease had been defined via urease positive bacteria mostly Proteus strains and E. Coli in especially the Struvite stones and extends to some atypic microorganisms such as Mycobacterium family and yeasts but not H. pylori (19). The most interesting view on these topics that presence of nano-bacteriums/particules at kidney stone and calcified aneurysm etiology, however even the existence of nanobacters is highly suspicious (29-30). For supporting the idea of their self replicating living organisms; these particles have morphologic similarities to bacteria, fragments of DNA, RNA, and bacterial proteins and susceptibility to antibiotics. On the contrary; they have extremely small size, no sequenced genome, morphologic similarities to other mineralo-protein structures and especially have resistance to DNase and RNase activity. However, these organic particles have some associations in some pathologies such as cholelithiasis, prostatitis, atherosclerotic disease, cardiovascular calcification and particularly, urinary stone disease with a high occurrence rate 62-100% (22). Nevertheless, a part from the nano-organisms that harboring science fiction point of view, micro-organisms cooperation with urinary stones seemed to be at the later growing period but not at the initiation scenario such as the present hypothesis. All in all, the direct relation between H. pylori and urinary stones does not seemed to be classical coincidence of microorganism and stone, but may be result of systemic effect of H. pylori via possible several ways such as antigen-antibody relation, toxic-ischemic effects on endoluminal surfaces and apoptotic-cancerogenic pathways or distant effect of larger atherosclerotic plaques of possible H. pylori contribution.

CONCLUSION

In some unconfirmed theories to explain the direct coincidence between gallstone and urinary stone disease; the shift of intestinal microbial flora from Oxalabacter formigenes that may reduce the risk of renal stone to H. pylori which induce gallstone was mentioned. 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. In addition, oxalate as a substrate is only one factor among the remaining many inhibitors and promoters of stone formation. However, H. pylori supposed to have some extragastrointestinal system effects via inducing atherosclerotic and apoptosis pathways. The most popular urolithiasis theory includes the subepithelial Randall plaque in Henle loop system as analogously similar with atherosclerosis. The present preliminary data and hypothesis was pointing a possible positive correlation between H. pylori and renal stones. However, at the next milestone, we think that this effect is due to the possible systemic influence such as vascular and/or endoluminal sickness due to the H. pylori other than directs bacteriologic effect. Besides, further studies at extragastric sequelae of H. pylori may lead new aspects on therapeutic and especially the prevention strategies of urolithiasis and even this progress may open new horizons in understanding of chronic pelvic pain syndromes and idiopathic infertility. Further well designed prospective studies are needed to confirm the results of this study.

Conflict of interest statement

There is no conflict of interest.

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