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Significance of pathogen identification for urinary tract infection and *Helicobacter pylori* infection in type 1 and type 2 diabetes mellitus patients

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Abstract

Objective. The aim of this study was to understand the significance of pathogen identification for Urinary tract infection and Helicobacter pylori infection in Diabetes Mellitus Type 1 and Diabetes Mellitus Type 2 patients.

Materials and methods. The study was conducted among 1749 patients with Type 1 and Type 2 Diabetes Mellitus. Using microbiological techniques, the frequency of urinary tract infection was identified and the aetiology and sensitivity of microorganisms to antibacterial drugs were assessed. Data collected on Helicobacter pylori infection were verified through PCR tests on biopsies collected from the gastric mucosa.

Results. The study showed that urinary tract infection has a high incidence rate with 58.3% of cases from Type 1 diabetes mellitus, and in 47.2% of cases from Type 2 diabetes. Pathogens such as Escherichia coli, Staphylococcus saprophyticus, Enterococcus faecalis and Klebsiella pneumoniae were the main causative agents of urinary tract infections. Helicobacter pylori infection was common in DM and more in cases of Type 2 Diabetes Mellitus at 27.1%, compared to cases in Type 1 Diabetes Mellitus at 22.8%. Also 5.9 % cases of Type 2 Diabetes Mellitus had combined Helicobacter pylori and urinary tract infections.

Conclusion. The study showed the significance in identification of urinary tract infections and Helicobacter pylori infections in patients with Type 1 and Type 2 Diabetes Mellitus, and especially significant for Type 2 Diabetes Mellitus patients.

Keywords: *diabetes mellitus, urinary tract infection, Helicobacter pylori, antibiotic resistance*

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Значимость идентификации патогена для инфекции мочевыводящих путей и *Helicobacter pylori* инфекции у пациентов с сахарным диабетом 1 и 2 типа

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Резюме

Цель исследования. Изучить значимость идентификации патогена инфекции мочевыводящих путей и *Helicobacter pylori* инфекции у пациентов с сахарным диабетом 1 и 2 типа.

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Материалы и методы. Изучены данные 1749 пациентов с сахарным диабетом 1 и 2 типа. Проведена оценка распространенности инфекции мочевыводящих путей, идентификации патогенов и их чувствительности к антибактериальным средствам с использованием микробиологического метода. Изучены данные верификации *Helicobacter pylori* инфекции методом ПЦР в биоптате слизистой желудка.

Результаты. Установлено, что инфекция мочевыводящих путей имеет высокую распространенность у пациентов с сахарным диабетом: 58,3 % — при сахарном диабете 1 типа и 47,2 % — при сахарном диабете 2 типа. Выделены основные возбудители инфекции мочевыводящих путей: *Escherichia coli*, *Staphylococcus saprophyticus*, *Enterococcus faecalis* и *Klebsiella pneumoniae*. Выявлена более высокая распространенность *Helicobacter pylori* инфекции при сахарном диабете 2 типа (27,1 %), чем при сахарном диабете 1 типа (22,8 %). 5,9 % пациентов с сахарным диабетом 2 типа имели сочетанную инфекцию мочевыводящих путей и *Helicobacter pylori* инфекцию.

Заключение. Исследование продемонстрировало высокую клиническую значимость идентификации патогена инфекции мочевыводящих путей и *Helicobacter pylori* инфекции при сахарном диабете, особенно у пациентов с сахарным диабетом 2 типа.

Ключевые слова: *сахарный диабет, инфекция мочевых путей, Helicobacter pylori, антибиотикорезистентность*

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Introduction

Diabetes mellitus (DM) is a defined risk factor for the development of urinary tract infections (UTIs) and glucosuria creates favorable conditions for the reproduction of opportunistic micro flora and the development of asymptomatic bacteriuria [1]. UTIs against the background of DM are also noted with multidrug-resistant infections, often resulting in lower efficacy of empirically prescribed antimicrobial treatment [2].

Another challenge is management of Helicobacter pylori (H. pylori) infections co-morbid with DM. According to a 2017 meta-analysis summarizing the results of 79 studies (57,397 individuals); the prevalence of H. pylori infection with DM is significantly higher than without DM (OR 2.05, $p < 0.01$) [3, 4].

H. pylori is a gram-negative pathogen transmitted by oral-oral or fecal-oral route, with good mobility and adhesion abilities and have a high incidence of gastroduodenal and extra-gastroduodenal complications. Researches on the role of H. pylori in the developing DM shows that H. pylori infections are associated with increased levels of glycated hemoglobin HbA1c and microalbuminuria [5, 6]. It also showed that patients with DM had an increased seropositivity of the H. pylori strain, as well as higher risk of eradication failure and Body mass index (BMI) influences the effectiveness of H. pylori eradication in DM, and better glycemic control was noted after successful eradication [7].

The aim of this study was to understand the significance of pathogen identification for Urinary tract infection and Helicobacter pylori infection in Diabetes Mellitus Type 1 (Type 1 DM) and Diabetes Mellitus Type 2 (Type 2 DM) patients.

Materials and methods

The data for the study was collected from patients with DM hospitalized in the department of endocrinology of Republican Research Center for Radiation Medicine and Human Ecology (RRCRM &HE).

A total of 1749 cases were studied, of which 602 were patients with Type 1 DM and with 1147 Type 2 DM. The mean age of the subjects was 58.0 (51.0; 63.0) years, with Type 1 DM 37.6 (31.0; 46.0) and Type 2 DM 66.4 (54.0; 68,0) years. The duration of DM did not differ statistically with Type 1 DM, 14.5 (4.0; 23.5) years; Type 2 DM, 12 (7.0; 16.5) years, $p=0.631$.

To establish the etiology of infectious complications, a complex of molecular genetics, bacteriological and mycological methods were used. To detect H. pylori genome, PCR testing was used in a multi-primer format with real-time detection. To verify gastritis and detect H. pylori infections, endoscopic esophagogastroduodenoscopy (EFGS) with biopsy was performed in accordance with operating standards. The effectiveness of the earlier eradication of H. pylori infection was assessed by antigen of

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H. pylori in feces, or with microscopic detection in the biopsy of the gastric mucosa [8].

Screening for the presence of bacteria and leukocytes were performed by microscopy of non-centrifuged urine, the results were recorded taking into account WHO recommendations on primary microscopy and bacteriuria. Urine inoculation to isolate pure cultures of microorganisms were performed by quantitative methods using classical nutrient media. Subsequent identification of microorganisms and determination of their antibiotic susceptibility were performed on a VITEK 2 Compact automated analyzer (BioMerieux, France) [9]. Amounts that constitute more than 105 CFU/ml were considered etiologically significant.

Past history of patients were obtained from electronic patient database of RRCRM & HE. Also, relevant information was obtained from the diagnosing and treatment processes of UTIs and H. Pylori cases.

Statistical data processing was carried out using non-parametric statistics, since the distribution within the groups was not normal. Data is presented in Me (q^{25}; q^{75}) format. Correlation analysis was performed using the Spearman test (r_s). The frequency of occurrence of differences was estimated using $\chi 2$, using Fisher's method for small groups.

Results and discussion

Urinary Tract infections

The study data showed that leukocyturia was confirmed in 31.6% of cases of Type 1 DM and in 37.6% of cases of Type 2 DM. Statistical significance of the occurrence of leukocyturia in patients with different types of DM was not obtained ($\chi 2$=0.40; p=0.52). The main causative agents of UTI in DM were Escherichia coli (31% in Type 1 DM and 25% in Type 2 DM) and Enterococcus faecalis (15.8% in Type 1 DM and 17.9% in Type 2 DM). Staphylococcus aureus alone or in combination with Escherichia coli accounted for 26.3% of cases in Type 1 DM and 28.6% in Type 2 DM. Another common pathogen in the study was Staphylococcus saprophyticus, the frequency of which, alone or in combination with Escherichia coli, Candida albicans, and Streptococcus species was 13.7% in Type 1 DM and 19.4% in Type 2 DM (Table 1). Klebsiella pneumonia was identified in 9.5% of cases of Type 1 DM and 6.3% in Type 2 DM.

Table 1. The spectrum of isolated microflora from the urine samples of patients with diabetes mellitus

Pathogen	Type 1 DM (n=190), %	Type 2 DM (n=431), %	p
	Case Detection		
Escherichia coli	23 (12,1%)	61 (14,2%)	>0,05
Escherichia coli + Staphylococcus aureus	18 (9,5%)	27 (6,3%)	>0,05
Escherichia coli + Staphylococcus saprophyticus	12 (6,3%)	39 (9%)	>0,05
Staphylococcus Saprophyticus	7 (3,7%)	19 (4,4%)	>0,05
Enterococcus faecalis	30 (15,8%)	77 (17,9%)	>0,05
Klebsiella pneumoniae	27 (14,2%)	62 (14,4%)	>0,05
Staphylococcus aureus	59 (31%)	108 (25%)	>0,05
Staphylococcus saprophyticus + Candida albicans	4 (2,1)	10 (2,3%)	>0,05
Staphylococcus saprophyticus + Streptococcus species	3 (1,6%)	16 (3,7%)	>0,05
Streptococcus species	7 (3,7%)	12 (2,8%)	>0,05

A retrospective analysis of patient's medical records showed that, from the initial consultations, UTI was confirmed in 57.9% of patients with Type 1 DM and 31.8% of patients with Type 2 DM (Table 2). It also showed that UTI's treated without identification of the pathogens were 37.5% of cases with Type 1 DM and in 17.1% with Type 2 DM. Follow-up data from these patients showed that treatment of UTI after identification of the pathogen was effective in 75% of T1DM and 52% of T2DM.

Evaluation of the effectiveness of previous antimicrobial therapy for UTIs demonstrated the high effectiveness of treatment after preliminary identification of the pathogen and determination of its sensitivity to antimicrobial drugs (75% & 37.5%; $\chi 2$=3.26; p=0.07 in Type 1 DM and 52% & 17.1%; $\chi 2$=13.98; p<0.001 in Type 2 DM).

Table 2. Results of treatment of urinary tract infection with and without verification of the pathogen

Type of DM	Retrospective analysis of UTI n (%)	
Type 1 DM 110 (57,9%)	Treated without pathogen identification	Treated with pathogen identification
	80 (21,3%)	62 (16,5%)
	Successful treatment for UTIs	
	30 out of 80 (37,5% effective)	46 out of 62 (75%)
	χ^2=3,26; p=0,07	
Type 2 DM 137 (31,8%)	99 (26,5%)	133 (35,7 %)
	Successful treatment for UTIs	
	17 out of 99 (17,1% effective)	69 out of 133 (52% effective)
	χ^2=13,98; p<0,001	

Helicobacter pylori Infections

Among all 1749 examined complaints of a dyspeptic nature (problems with swallowing, nausea and/or vomiting, belching, heartburn, bloating, constipation, diarrhea) were presented by 22 (3,7%) patients with Type 1 DM and 342 (29,8%) patients with Type 2 DM. Stool disorders (flatulence, discomfort before or after defecation, diarrhea, constipation, heterogeneous stools, mucus excretion with feces) were noted in 49 (8,1%) patients with Type 1 DM and 369 patients (32,2%) with Type 2 DM. In order to verify gastritis and detect H. Pylori infections, endoscopic esophagogastroduodenoscopy (EFGS) was performed in 114 (18,9%) patients with Type 1 DM and 436 (38%) with Type 2 DM.

The results of biopsies of the gastric mucosa showed that chronic gastritis with mild atrophy or without atrophy, are more common in Type 2 DM compared to Type 1 DM patients (Table 3). Metaplasia, dysplasia or H. Pylori infections were identified more often in Type 2 DM patients (25.9% and 27.1%) than in Type 1 DM patients (11.4%; χ2=21.76; p<0.001 and 22.8% χ2=9.07; p=0.003).

Table 3. The results of the study of biopsy of the gastric mucosa

Biopsy Results	Type 1 DM n (%)	Type 2 DM n (%)	χ^2; p
Gastritis Inflammation 0	39 (34,2%)	183 (41,8%)	χ^2=14,03; p<0,001
Gastritis Inflammation 1	59 (51,8%)	166 (38,1%)	χ^2=1,52; p=0,22
Gastritis Inflammation 2	16 (14%)	75 (17,1%)	χ^2=6,54; p=0,01
Gastritis Inflammation 3	–	13 (3%)	–
Atrophy 0	55 (48,2%)	135 (31%)	χ^2=0,19; p=0,67
Atrophy 1	59 (51,8%)	244 (55,9%)	χ^2=12,8; p<0,001
Atrophy 2	–	44 (10,1%)	–
Atrophy 3	–	13 (3%)	–
Metaplasia/Dysplasia	13 (11,4%)	113 (25,9%)	χ^2=21,76; p<0,001
H. pylori infection	26 (22,8%)	118 (27,1%)	χ^2=9,07; p=0,003
All Cases	114	436	

The data also shows that H. pylori infections were significantly more frequent in Type 2 DM than in Type 1 DM (4.3%; χ2=16.07; p<0.001). Simultaneous and combination of two diseases (UTI + H. Pylori infection) was recorded in 68 (5.9%) patients in Type 2 DM, which was significantly higher than in Type 1 DM patients. (3.5%; χ2=4.43; p=0.04) (Table 4).

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Table 4. The frequency of urinary tract infections, H. Pylori infections and their combination in diabetes mellitus

Biopsy Results	Type 1 DM n=602	Type 2 DM n=1147	χ^2; p
UTI	190 (31,6%)	431 (37,6%)	χ^2=3,01; p=0,08
H. Pylori Infection	26 (4,3%)	118 (10,3%)	χ^2=16,07; p<0,001
UTI + H. Pylori Infection	21 (3,5%)	68 (5,9%)	χ^2=4,43; p=0,04

Discussion

The results of this study have demonstrated that 31.6% of cases of Type 1 DM and in 37.6% of cases of Type 2 DM were positive for urinary tract infections. Escherichia coli and Enterococcus faecalis were the causative agents of UTIs in about 40% of cases, and Staphylococcus aureus was 25%. The results of this study showed that there were no significant variances in pathogens based on the Types of DM. The treatment efficacy of Type 2 DM with pathogen verification showed an increase from 17.1% to 52% and in Type 1 DM patients, the data showed an increase in efficacy from 37.5% to 75%. The study data also showed a notable significance in successful treatment outcomes for DM patients being treated after pathogen verification and pathogen sensitivity based antibiotic treatment.

Asymptomatic bacterial infections are more common in DM in the presence of autonomic neuropathy due to chronic hyperglycemia [10, 11]. Due to the effectiveness of sensitive specific antimicrobial treatment for UTI, determining the sensitivity of the pathogens and selection of antibacterial agents based on the results of microbiological studies and local data on resistance can be an important treatment strategy [12, 13]. According to our previously published data, the highest sensitivity for enterobacteria (E. coli, K. pneumoniae) was noted to imipenem, amikacin and levofloxacin. S. saprophyticus and E. faecalis are more sensitive to levofloxacin, and vancomycin [14].

The study also revealed the high incidence rate of dyspeptic symptoms in Type 2 DM patients compared to Type 1 DM patients. And among the cases of for H. pylori, 22.8% were Type 1 DM and 27.1% were Type 2 DM. Combined infections of UTI and H. Pylori in Type 2 DM patients were 5.9 % of cases and was higher in Type 2 DM compared to Type 1 DM.

The findings of this study indicated that about 22% to 27% of cases of the DM patients tested had H. pylori infection. Based on the available data on the relationship between metaplasia of the gastric mucosa and the presence of H. Pylori infections, the importance of effective eradication to reduce the risk of progression of precancerous lesions of the gastric mucosa are significant based on researches such as Hang Liu et. et al. [15].

Antibiotic resistance of H. pylori infection is also an important factor in the ineffectiveness of therapy. According to the recent studies, H. pylori resistance to major antimicrobials are noted in the global population as clarithromycin (19.71%), metronidazole (47.22%), amoxicillin (14.67%), tetracycline (11.7%), levofloxacin (18.94%) [16]. Also, a meta-analysis of 12 studies showed that individual selection of drugs based on the results of H. pylori resistance testing is more effective than the empirical prescription of 7-10-day courses of classical triple therapy (OR 1.16, 95% CI 1.10 to 1,23) [17, 18]. Thus, considering that H. Pylori infections are positive in almost 1 in 5 cases with DM, and also due to a significant amount of cases identified with combined UTI and H. Pylori infections, pathogen identification and culture sensitivity should be considered for better outcomes of treatments.

Conclusion

Based on the study, analyzed data has shown that verification of the causative pathogens of urinary tract infections, as well as the detection of H. pylori infection in Type 1 DM and Type 2 DM patients, are of significant relevance, especially in patients with Type 2 DM.

The results also point to the need for a more in-depth study of the issues of determining the tactics of diagnosing UTIs and H. pylori infection during routine examinations of patients with Type 1 and Type 2 DM, taking into account the characteristics of clinical manifestations against the background of complications of DM.

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