



## Evaluating Association between Glycosylated Hemoglobin and the Spectrum and Antibiotic Resistance of Uropathogens: A Cross Sectional Study

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### ABSTRACT

**Background:** Antimicrobial resistance among uropathogens causing community-acquired urinary tract infections (UTIs) is a worldwide concern. It has been suggested that diabetes could be a possible cause of antibiotic resistance. This study was undertaken to identify the responsible microbial culprits for UTI in patients with different range of glycosylated hemoglobin (HbA1C) and evaluate their corresponding resistance pattern.

**Methods:** In a cross-sectional study between 2013 to 2018, data related to the urine culture and sensitivity of patients who had bacteriuria were gathered. For patients with positive urine culture, HbA1C was requested and correlations between HbA1C level with microorganism and its susceptibility were evaluated.

**Results:** In total, 121 patients were recruited. All study participants were female. The mean age of the patients was  $50.2 \pm 22.5$  (range 19-96). All study participants were of the same race. Fifteen (12.4%) out of 121 patients were diabetics. There were no difference between bacteriology of UTIs in diabetic and nondiabetic patients with the preponderance being caused by *E. coli* and other gram-negative organisms but, there were positive association between HbA1C and resistance to Nalidixic acid and Gentamicin.

**Conclusion:** Our study supports the findings that diabetes in itself could be a possible cause of antibiotic resistance to some antimicrobial agents.

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### Introduction

Antibiotic resistance is a worldwide problem. There are high proportions of antibiotic resistance in bacteria that cause common infections (e.g. urinary tract infections, pneumonia, sepsis) in all regions of the world. Antibiotic-resistant infections add considerable and avoidable costs to the already overburdened Iran healthcare system (1, 2). Infections caused by resistant bacteria often fail to respond to the standard and first line treatment, resulting in prolonged illness, higher health care expenditures, and a greater risk

of death. New forms of antibiotic resistance can cross international boundaries and spread between continents with ease.

Antimicrobial resistance among uropathogens causing community-acquired urinary tract infections (UTIs) is a worldwide concern. However, little information is available on the factors associated with the risk of having a UTI with a resistant uropathogen. The use of antibiotics is the single most important factor leading to antibiotic resistance around the world.

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Although many studies report that the rates of antibiotic resistant infections have increased dramatically in the diabetes mellitus (DM) population over the last decade, to our knowledge there have been no reports directly comparing the rates of antibiotic resistant infections in DM versus non-DM urinary tract infection.

Urinary tract infection (UTI) is the most common hospital infection, accounting for more than 40 percent of all hospital infections (3). Even though the exact mechanisms for the predilection of pathogens to cause UTI in diabetics remains unclear, a few studies have revealed that the reasons could be immunological defects such as impaired migration of neutrophils, intracellular killing, phagocytosis, defects in the local urinary cytokine secretions (IL-8, IL-6), and chemotaxis of polymorphonuclear leukocytes from diabetic patients and neuropathic complications such as impaired bladder emptying. In addition, a higher glucose concentration in the urine acts as a favorable culture medium for pathogenic bacteria and promotes rapid bacterial colonization and growth (4, 5).

The information regarding the prevalence of different microorganisms and antibiotics susceptibility is very important for the treating physician so that the proper antibiotics can be prescribed.

It has been suggested that diabetes in itself is a possible cause of antibiotic resistance (6). Factors such as frequent hospitalization, urological instrumentation, and antimicrobial treatment, could contribute to resistant uropathogens (7). Some authors (7), but not all (8, 9), have demonstrated an association between the presence of a TMP-SMX or quinolone resistant uropathogen and diabetes.

Owing to the fact that the incidence of UTI is increasing worldwide, the aim of this study was to define any association between glycosylated hemoglobin and the spectrum of uropathogens and their corresponding resistance pattern in patients with symptomatic and asymptomatic bacteriuria. To our knowledge, this is the first study in which the relationship between glycosylated hemoglobin and the spectrum of uropathogens and their corresponding resistance pattern was evaluated in individuals who referred for screening to a private laboratory in Tehran, Iran.

## Methods

This was a prospective study done from 2013 to 2018 where the urine culture assay data from patients who suffered from both symptomatic and asymptomatic bacteriuria were studied. The study protocol was in accordance with the ethical guidelines of the 1975 Declaration of Helsinki.

Urinary isolates and their patterns of susceptibility to the antimicrobials were evaluated in diabetics and non diabetics who were screened for significant bacteriuria.

The exclusion criteria were: pregnancy, chronic renal failure (creatinine clearance test < 30 ml/min), HIV, HBV And HCV infection, connective tissue diseases, spinal

cord injury, permanent urinary catheter, urinary tract stent, nephrostomy tube, urinary incontinence, history of vesicoureteral reflux, neurogenic bladder, kidney malformations, kidney stones, gynecological problems, organ transplant, chronic use of corticosteroid or any immunosuppressive therapy, antibiotic use within the last 3 months, and substance abuse.

Clean voided midstream urine samples were collected in sterile containers after giving proper instructions and samples were processed in the laboratory within 2 hours of collection. Samples were streaked on MacConkey and EMB agar and the agar plates were incubated at 37°C for 24 hrs. The identification of the bacterium was carried out with the help of colony morphology, staining characters and biochemical properties.

For patients with positive urine samples the patterns of susceptibility to the antimicrobials were recorded and patients HbA1C was measured. Diabetes mellitus was defined as HbA1C equal or greater than 6.5 percent. Antimicrobial susceptibility testing was performed using Kirby-Bauer disc diffusion method employing Mueller-Hinton Agar plate as described by the Clinical and Laboratory Standards Institute (CLSI).

Data were analysed using SPSS software package version 20 (IBM, New York, USA). Kolmogorov-Smirnov test was performed to evaluate the normality of distribution. Data are presented as mean  $\pm$  SD if normally distributed and otherwise as median (range). Independent sample T-test was used to investigate the difference between groups.

## Results

We evaluated HbA1C level in positive urine samples and analyzed their antimicrobial susceptibility patterns accordingly. Within the 5 years period from 2013 to 2018, two hundred patients were evaluated and 121 of them were recruited based on exclusion criteria.

All study participants were female. The mean age of patients enrolled in our study was 50.2 $\pm$ 22.5 (range 19-96). All study participants were of the same race. Fifteen (12.4%) out of 121 patients were diabetics (defined as HbA1C  $\geq$  6.5).

*E. coli* was found to be the major pathogen responsible for the infections and accounted for 62.8% of infections (62.3% in non diabetic and 66.7% in diabetic patients). The proportion of *klebsiella* and enterococcus were 8.3% and 4.1% respectively and for staphylococcus was 7.4% while of the other pathogens accounted for 17.4% of infections (Figure 1).

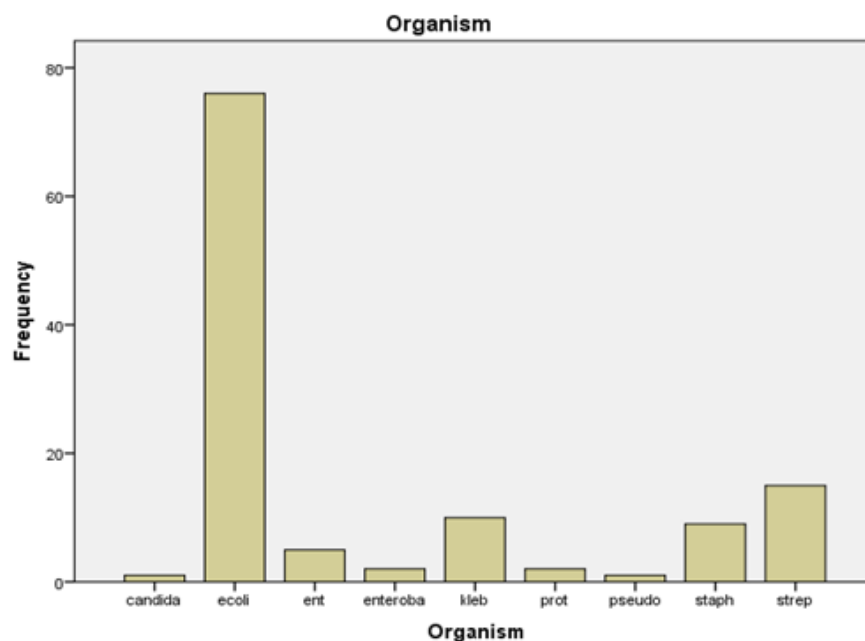
Among the population infected with *E. coli*, the mean level of glycosylated hemoglobin was 5.5 while that of other organisms was 5.4 which did not showed any significant correlation between HbA1C level and type of uropathogen (P=0.86).

Mean HbA1C level in co-trimoxazole resistant and

co-trimoxazole sensitive infections were  $5.7 \pm 0.8$  and  $5.5 \pm 0.6$ , respectively ( $P=0.4$ ). The mean level of HbA1C was  $5.7 \pm 0.8$  in nalidixic resistant group while it was  $5.4 \pm 0.5$  in nalidixic sensitive group ( $P=0.03$ ). Also the mean level of HbA1C was  $5.8 \pm 0.8$  in cefixime resistant

group while it was  $5.5 \pm 0.6$  in cefixime sensitive group ( $P=0.04$ ). Mean HbA1C level in ciprofloxacin, gentamicin and nitrofurantoin resistance and sensitive groups were  $5.9 \pm 0.8$  vs  $5.5 \pm 0.7$  ( $P=0.03$ ),  $6.02 \pm 0.9$  vs  $5.5 \pm 0.6$  ( $P=0.008$ ) and  $5.8 \pm 0.8$  vs  $5.6 \pm 0.8$  ( $P=0.23$ )

**Figure 1.** Frequency of isolated microorganism from urine culture of patients.



Again, in patients with symptomatic and asymptomatic bacteriuria, the mean level of HbA1C in ciprofloxacin resistant and ciprofloxacin sensitive infections were 5.9 and 5.5 respectively ( $P=0.8$ ). The mean level of HbA1C in gentamicin resistant and gentamicin sensitive infections

were 6 and 5.4 respectively. ( $P=0.05$ ) The mean level of HbA1C was 5.7 in nitrofurantoin resistant group while it was 5.5 in nitrofurantoin sensitive group ( $P=0.9$ ). Data related to frequency and sensitivity and resistance pattern of isolated microorganisms are summarized in Table 1.

**Table 1.** Antibigram data of isolated microorganisms from urine sample of the patients

Antibiotics		Non-diabetic		Diabetic		P-Value
		Count	Percent	Count	Percent	
Ciprofloxacin	Resistant	26	35.1	7	46.7	0.29
	Sensitive	48	64.9	8	53.3	
Nalidixic acid	Resistant	40	61.5	10	83.3	0.13
	Sensitive	25	31.5	2	16.7	
Gentamicin	Resistant	13	18.6	5	41.7	0.08
	Sensitive	57	81.4	7	58.3	
Sulfamethoxazole	Resistant	38	46.9	6	60	0.33
	Sensitive	43	53.1	4	40	
Nitrofurantoin	Resistant	20	23.5	5	33.3	0.31
	Sensitive	65	76.5	10	66.7	
Cefixim	Resistant	28	40	6	54.5	0.23
	Sensitive	42	60	5	45.5	

## Discussion

Our study revealed that there was no significant difference in uropathogens isolated from urine samples of diabetic and non diabetic patients. Also the antibiogram results did not showed any significant difference in sensitivity pattern between diabetic and non-diabetic patients but, the mean HbA1C levels were significantly higher in patients with microorganisms which were resistant to cefixime, gentamicin, ciprofloxacin and nalidixic acid.

Diabetics are more prone to infections than their nondiabetic counterparts. Since screening for the presence of microalbuminuria is recommended in diabetic patients, these routine evaluations often lead to the incidental discovery of asymptomatic bacteriuria. Bacteriuria is more common in diabetics than in non-diabetics due to a combination of host and local risk factors (10). Some observations reveal that there is an approximately three- to fourfold increase in risk of bacteriuria in diabetic women (11, 12).

A large cohort of diabetic women in the Netherlands was studied to determine the incidence of symptomatic UTIs (13). In women with type 2 diabetes (but not with type 1), the presence of asymptomatic bacteriuria at baseline increased the risk of subsequent symptomatic UTI in the 18 month follow-up period from 19 to 34 percent. The rate of asymptomatic bacteriuria in this population was approximately 28 percent. By contrast, incidence of asymptomatic UTI was 6 percent in women who were not diabetic but attended other clinics in the same institution (14).

Higher antibiotic resistance rates in diabetic patients compared with those without DM have been reported in some studies. In Indian outpatients with chronic wounds, most (70%) antibiotic-resistant bacteria were isolated from diabetic patients (15). In Cameroon, in diabetic patients with asymptomatic bacteriuria, the causative agents were *E. coli*, *S. pyogenes*, *S. aureus*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *P. aeruginosa* (13). The isolates exhibited very high resistance rates to amoxicillin (96.2%), ceftriaxone (70.1%) and ciprofloxacin (61.3%) (16). The problem of increased antibiotic resistance in the causative agents of infections in patients with DM is especially important in countries, districts or hospitals with low adherence to national antibiotic policy.

The successful management of urinary tract infection in diabetics depends on the proper identification of the responsible bacteria and the selection of effective antibiotics based on the patterns of susceptibility.

In our study, the bacteriology of UTIs was similar in diabetic and nondiabetic patients with the preponderance being caused by *E. coli* and other gram-negative organisms. However, as in the subgroups described above, antimicrobial susceptibility patterns were different in diabetic and nondiabetic patients.

There was a significant association between glycosylated

hemoglobin and Nalidixic and Gentamicin resistant organisms. The HbA1C was significantly greater in patients with symptomatic and asymptomatic bacteriuria with Nalidixic and Gentamicin resistant organisms.

Despite the results of some studies (7) which demonstrated an association between the presence of a TMP-SMX or quinolone resistant uropathogen and diabetes, we found that there was no significant association between these agents and glycosylated hemoglobin while the level of HbA1C was greater in patients with symptomatic and asymptomatic bacteriuria with TMP-SMX or quinolone resistant organisms. Also, there was no significant association between cefixime and nitrofurantoin resistance and glycosylated hemoglobin while the level of HbA1C was greater in patients with symptomatic and asymptomatic bacteriuria with cefixime and nitrofurantoin resistant organisms.

In conclusion, higher antibiotic resistance rates in diabetic patients compared with those without DM have been reported in some studies. Our study supports the findings that diabetes in itself is a possible cause of antibiotic resistance in some antimicrobial agents.

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