Original Article

Diversity of uropathogens and their resistogram in diabetic and non-diabetic patients in sub Himalayan region of Uttarakhand, India: A case control study

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Access this article online

Website: www.ijmedph.org

DOI: 10.4103/2230-8598.127171

Quick response code:

Abstract

Background: Both symptomatic and asymptomatic urinary tract infections (UTIs) are thought to occur more frequently in diabetic patients. Local data about the antimicrobial resistance of Uropathogens should be available for proper therapeutic interventions of UTI. **Objective:** To evaluate the spectrum of the Uropathogens and their profiles of antimicrobial resistance on a series of diabetic and non-diabetic patients. **Materials and Methods:** A Case-Control study with 100 participants was conducted targeting the Diabetic and Non-diabetic population, symptomatic or asymptomatic for UTI. Antibiotic sensitivity test was done on each of the isolates and the results of the antibiogram were compared with that of control group (nondiabetic group). The statistical analysis was done by Chi-Square Test, Fisher exact test using statistical product and service solutions formerly known as Statistical Package for the Social Sciences (SPSS) 16.0 Version. **Results:** Most common isolate responsible for UTI was *Escherichia coli* followed by *Klebsiella, Enterobacter, Proteus, Citrobacter, Acinetobacter and Candida*. 93.3% and 86.6% of the isolates were sensitive to Amikacin and Amoxycillin-clavulanic acid respectively for Non Diabetics. Whereas isolates from diabetic group were 77.7 and 50% sensitive to Amikacin and Amoxycillin-clavulanic acid respectively. Highest resistance was seen for Cefuroxime for the isolates from both diabetic and non-diabetic group with 53.3 and 72.2% respectively. Significant difference in resistance pattern was observed in Amoxycillin-clavulanic acid, cefazolin, piperacillin- tazobactam and ticarcillin-clavulanic acid. **Conclusion:** Culture of urine and susceptibility testing of isolated organisms is strongly advocated in the clinical management of impending complication in diabetic individuals.

Key words: Diabetes, resistance pattern, symptomatic and asymptomatic, urinary pathogens

INTRODUCTION

Urinary tract infections are the most commonly found bacterial infections, accounting for nearly seven million hospital visits and one million emergency department visits, resulting in 100,000 hospitalizations of women, the elderly and patients with spinal cord injuries, catheters, multiple sclerosis, HIV and also diabetes.[1]

Several severe and less commonly encountered urinary tract infections (UTIs) are thought to occur more frequently in diabetic patients.[2] In a recent study from Europe, asymptomatic bacteriuria was more prevalent among women with diabetes (26%) than in women without diabetes (6%).[3] Diabetic patients are at a high risk of development of UTIs, so it is recommended that special attention is paid to them, especially for the management of bacterial UTIs.[4] Various risk factors such as sexual intercourse, age, duration of diabetes, poor glycemic control, and complications of diabetes are associated with UTI.[5]

A high incidence of urinary tract infections has been observed among patients with comorbid illness such as diabetes than non-diabetic,[6] probably due to alteration in genitourinary system, debilitated

immune system, altered bacterial adhesion to the uroepithelium, due to abnormality of Tammhorsfal protein, granulocyte dysfunction, the presence of diabetic cystopathy and microvascular disease in kidneys.[7] Moreover, among the diabetic patients, females (42.8%) are prone to UTI than males (34.1%)[8] along with high prevalence of asymptomatic bacteriuria.[9] Treatment of UTI cases is often started empirically and a large proportion of unrestrained antibiotic usage results in upsurge of resistance among the uropathogens in both community and health care settings.[10] The local data about the antimicrobial resistance of Uropathogens should be available for proper therapeutic interventions of UTI. For this purpose the study had been designed to evaluate the spectrum of the uropathogens and their profiles of antimicrobial resistance on a series of diabetic and non-diabetic patients.

MATERIALS AND METHODS

A Case-Control study with 100 participants was conducted from august 2012 to January 2013 in Department of Microbiology and Immunology at Veer Chandra Singh Garhwali Government Medical Science And Research Institute and attached HNB Base Hospital, Srinagar, Pauri-Garhwal, Uttarakhand, targeting the Diabetic and Non-diabetic population, symptomatic or asymptomatic for UTI.

Patients attending/admitted to HNB base hospital with fasting blood glucose level above (Diabetic) and below 110 mg/dl (Non-diabetic) and no prior history of UTI for past three months and without any medication for past one month were included in the study. Patients with on-going medication for urinary tract infection and Patients with any intubation or catheterization were excluded from the study. Clean catch mid stream urine sample were collected in a pre- sterilized universal container after educating the patient. Specimens were transported within 30min of collection to the laboratory for processing. Routine wet-mount, of the properly mixed un-centrifuged urine sample, was performed along with Gram Staining. Aerobic Culture was done on 5% Sheep blood agar and MacConkey agar. Kass Concept of Semi Quantitation was employed for the determination of bacterial load. Un-centrifuged specimen was inoculated on Blood Agar and MacConkey Agar. Antibiotic sensitivity test was done according to CLSI guidelines, on Mueller Hinton agar by Kirby-Bauer method. Concept of significant bacteriuria was followed while considering the patient's information (age, sex) and any past history. The statistical analysis was done by Chi-Square Test, Fisher exact test using Statistical Package for the Social Sciences (SPSS) 16.0 Version.

RESULT

Fifty each urine samples of both diabetic and non-diabetic patients were screened for symptomatic and asymptomatic bacteriuria. Out of 50 diabetic patients 26 were males and 24 were females.[Table 1] In this study, all the patients were above 30 years of age. In diabetic group 6 (12%) patients were between 31 and 40 years of age and remaining were above 41 years, whereas 7 (14%) were between 31 and 40 years of age and remaining were above 41 years among nondiabetic group [Table 2]. Rate of asymptomatic bacteriuria among diabetic and non-diabetic males was 58.8% and 41.2% respectively followed by 57.1% diabetic and 42.9% non-diabetic females respectively [Table 3].

Escherichia coli was the most common isolate responsible for asymptomatic UTI in 45% of diabetic and 63% of non-diabetic patients followed by *Klebsiella spp.* of which isolation rate was 14% in diabetic and 13% in non-diabetic. *Enterobacter* and *Proteus spp.* constituted 9% of infection among diabetic and 6% in non-diabetic. *Citrobacter* was isolated only in non-diabetic group. *Acinetobacter* (4.5%) was isolated only in diabetic group. Candida species constitute the major part of infectious etiology ranging between 4 (18.2%) among diabetic and 1 (6.3%) in non-diabetic study population. Out of total Candida species *Candida albicans* was isolated in 3 (75%) and 1 (25%) in diabetic and non-diabetics respectively, whereas Non albicans Candida was isolated only in 1 (4.5%) of total diabetic isolates [Table 5]. Among the first line drug used for treating UTI, Amikacin and Amoxycillin-clavulanic acid was found to be most sensitive for the uropathogens isolated in our study. 93.3% and 86.6% of the isolates were sensitive to Amikacin and Amoxycillin-clavulanic acid respectively for Non Diabetics. Whereas isolates from diabetic group were 77.7 and 50% sensitive to Amikacin and Amoxycillin-clavulanic acid respectively. Highest resistance was seen

Table 1: Gender wise distribution of diabetics and controls

Gender	Diabetics	Non-diabetics	Total
Male	26	23	49
Female	24	27	51
Total	50	50	100

Table 2: Age wise distribution of bacterial isolates in diabetics and controls

Age	Diabetics (Number of Isolates)	Non-Diabetics (Number of Isolates)	Total
0-10	0	0	0
11-20	0	0	0
21-30	0	0	0
31-40	4	3	7
41 and Above	18	13	31
Total	22	16	38

Table 3: Gender wise distribution of significant bacterial isolates in diabetic and controls

Isolate	Diabetic		Non-Diabetic	
	Male	Female	Male	Female
Escherichia coli	5	5	4	6
Klebsiella species	1	2	1	1
Proteus species	0	2	0	1
Candida albicans	0	3	0	1
Non-albicans Candida	1	0	0	0
Enterobacter species	2	0	1	0
Citrobacter species	0	0	1	0
Acinetobacter species	1	0	0	0
Total	10	12	7	9

for Cefuroxime for the isolates from both diabetic and non diabetic group with 53.3 and 72.2% respectively. Though the resistance pattern of most of the isolates from both the study group were not significant ($P > 0.05$), except for Amoxycillin-clavulanic acid, cefazolin, piperacillin-tazobactam and ticarcillin-clavulanic acid which displayed significant difference between resistogram of the two study groups [Table 6].

DISCUSSION

Over the years, evidences from many epidemiological studies have suggested that asymptomatic bacteriuria and UTI is a common occurrence in women with diabetes than in those without diabetes.[11] Long term cohort studies have also reported no negative outcomes attributable to asymptomatic bacteriuria, although women with asymptomatic bacteriuria do have an increased frequency of symptomatic infection.[12,13] Although uropathologic complications are common in men and women with diabetes, data to define expected prevalence, incidence and risk factors as well as interventions to reduce the risk of developing complications are limited. Furthermore, the majority of data has been collected in patients with type 2 diabetes and in females; therefore data regarding these relationships in type one diabetes and in men are less available. Recent study has focused in the association of Asymptomatic bacteriuria ASB to diabetes.[12,14,15] Both symptomatic and asymptomatic urinary tract infection are reported to occur with increased frequency in women with diabetes.[16,17] In women without diabetes, ASB is relatively uncommon and increases risk of UTI but does not lead to serious sequelae[18] Diabetic women have a two to three fold higher prevalence of ASB and are at risk of developing more serious consequences.[14,15] Women with type two diabetes and ASB, have an increased risk for development of a symptomatic UTI[19] and women with type one diabetes are at increased risk for pyelonephritis and subsequent impairment of renal function. Uropathogens were isolated more in diabetics than in nondiabetic [Table 4].

The prospective cohort of present study illustrates the prevalence of ASB more among diabetic females (57.1%) than non-diabetic females (42.9%) followed by 58.8% diabetic and 41.2% non-diabetic males respectively [Table 3]. This corroborate the reports of Raz and Stomm (1992)[1,29] that females are more commonly affected with UTI than males[25] and with that of Geerlings, Stolk and Camp (2001)[12] that women with Diabetes mellitus DM are about 2-3 times more likely to have bacteria in their bladder than women without DM.[12,28]

E. coli was the most commonly isolated Uropathogens in the urine of DM and non DM patients in our study. However, we found that there was a trend towards a lower proportion of UTI caused by the E. coli in DM compared with non- DM patients (45 versus 63 respectively) [Table 5]. Other investigators have reported similar findings.[20,39]

Next to E. coli we isolated Klebsiella spp. of which isolation rate was 14% in diabetics and 13% in nondiabetics. This corroborates the findings of other researchers who isolated klebsiella and Proteus in 12.7 and 6.3% respectively.[21] Geerlings *et al.*,[22] isolated Klebsiella in 14.3%, Janifer *et al.,* isolated Klebsiella in 13.5%.[23]

Subsequent isolated organisms were Proteus spp. and Enterobacter which constituted 9% of the infection among diabetic and 6% in nondiabetic. This finding is in total disagreement to the findings of B pargavi *et al.*, which isolated Proteus in 85% of diabetic patients.[24]

DM is a common predisposing factor for UTI caused by fungi, particularly Candida spp.[20,22] This is because diabetes affects much system that protect against general infections and against UTI specifically.[26] Poor circulation in diabetes reduces the ability of macrophages and polymorph nuclear (PMN) cells to get away where they are required and even when they do, they are less able to phagocytize the offending bacteria and kill them than normal PMNs. It may also be due to bladder dysfunction caused by diabetic neuropathy which allows urine to remain in static pools for long period of time, providing luxurious ponds for bacteria to thrive in.[27]

Changes in host defence mechanism, the presence of diabetic cystopathy and of microvascular disease in the kidneys may play a role in the higher incidence of UTI in diabetic patients.[32]

Age appeared to play major role in prevalence of bacterial pathogens among DM as those between30 and 41 years and above age had more isolates [Table 2]. This can be derived from the fact that people in this age group are more prone to diabetes and therefore their urine provides conducive condition for bacteria to thrive.[26] Although urologic complications are common and major health problems in men and women with diabetes, data to define expected prevalence, incidence and risk factors as well as

Table 4: Prevalence of bacteriuria in diabetic patients as compared to controls

	Diabetic		Non-Diabetic	
	No. of Isolates	Percentage	No. of Isolates	Percentage
With bacteriuria	22	44	16	32
Without bacteriuria	28	66	34	68
Total	50	100	50	100

Table 5: Percentage distribution of bacterial Isolates in Diabetic and Controls

Isolate	Diabetic		Non-Diabetic	
	No. of Isolates	Percentage	No. of Isolates	Percentage
Escherichia coli	10	45	10	63
Klebsiella species	3	14	2	13
Proteus species	2	09	1	6
Candida albicans	3	14	1	6
Non-albicans Candida	1	4.5	0	0
Enterobacter species	2	9	1	6
Citrobacter species	0	0	1	6
Acinetobacter species	1	4.5	0	0
Total	22	100	16	100

Table 6: Sensitivity Pattern of significant isolates in Diabetics and Controls

Drugs	Non-Diabetic		Diabetic		*P* value
	Sensitive (%)	Resistance (%)	Sensitive (%)	Resistance (%)	
Amikacin	28 (93.33)	2 (6.67)	28 (77.78)	8 (22.22)	x^2=1.989; *P*=0.1585
Ampicillin	16 (53.33)	14 (46.67)	12 (33.33)	24 (66.67)	x^2=1.923; *P*=0.1655
Amoxycillin-clavulanic acid	26 (86.67)	4 (13.33)	18 (50)	18 (50)	x^2=8.319; *P*=0.0039
Cefazolin	18 (60)	12 (40)	10 (27.78)	26 (72.22)	x^2=5.699; *P*=0.0170
Cefuroxime	14 (46.67)	16 (53.33)	14 (38.89)	22 (61.11)	x^2=0.149; *P*=0.699
Cefotaxime	18 (60)	12 (40)	20 (55.56)	16 (44.44)	x^2=0.013; *P*=0.909
CiProfloxacin	18 (60)	18 (40)	20 (55.56)	16 (44.44)	x^2=0.056; *P*=0.8134
Cotrimoxazole	18 (60)	12 (40)	16 (44.44)	20 (55.56)	x^2=1.024; *P*=0.3117
Aztreonam	16 (53.33)	14 (46.67)	14 (66.11)	22 (38.89)	x^2=0.856; *P*=0.355
Gentamicin	18 (60)	12 (40)	14 (38.89)	22 (66.11)	x^2=1.412; *P*=0.2347
Nitrofurantoin	28 (93.33)	2 (6.67)	26 (72.22)	10 (27.78)	x^2=3.586; *P*=0.058
CefoPerazone-sulbactam	28 (93.33)	2 (6.67)	26 (72.22)	10 (27.78)	x^2=3.586; *P*=0.058
Piperacillin-tazobactam	28 (93.33)	2 (6.67)	24 (66.67)	12 (33.33)	x^2=5.458; *P*=0.019
Ticarcillin-clavulanate	28(93.33)	2 (6.67)	24 (66.67)	12 (33.33)	x^2=5.458; *P*=0.019
Meropenem	28 (93.33)	2 (6.67)	26 (72.22)	10 (27.78)	x^2=3.586; *P*=0.058

interventions to reduce the risk of developing these complications are limited. Intensive glycemic control delays the onset and progression of micro vascular complications of diabetes in both type one and type two diabetes.[30,31]

Increasing antimicrobial resistance among bacteria is a major concern. The most important variable promoting resistance is the indiscriminate use of antimicrobial agents. Rational use of these agents requires the identification of clinical situations in which antimicrobial therapy is not indicated.

Regarding antimicrobial resistance profile, we observed no significant difference ($P > 0.05$) between the two groups for ampicillin, cotrimoxazole, ciprofloxacin and nitrofurantoin [Table 6]. Although the resistance pattern of the antibiotics summarized in [Table 6], exhibited significant difference for Amoxycillin-clavulanic acid ($P = 0.0039$), cefazolin ($P = 0.0170$), Piperacillin-tazobactam($P = 0.019$) and ticarcillin-clavulanic acid ($P = 0.019$) in diabetic and nondiabetic group. This requires special attention as most authors prefer antimicrobial agents which achieve high levels not only in the urine but also in the urinary tract tissue eg. Fluoroquinolones, Trimethoprim-sulfamethoxazole TMP-SMX, Amoxicillin-clavulanic acid.[35,36] Although some authors state that choice of antimicrobial remains the same as that of nondiabetic otherwise healthy subjects.[25,33,34,37,38] The eradication of microorganisms that cause UTI has been reported to be more difficult in diabetic patients than in nondiabetic patients because of an increased frequency of multidrug resistance.[40,41] The outcomes of the results become more prominent in the clinical management of impending complication in diabetic individuals. Our findings strongly advocate culture of urine and susceptibility testing of isolated organisms in order to formulate antibiotic policy of the concerned clinical setup.

These data indicate that routine mechanisms must be established in communities to assess antimicrobial susceptibility of uropathogens and that standard regimen for empirical therapy must be reassessed periodically in light of changing susceptibility patterns. Additional types of studies would enhance our understanding of optimal management of uncomplicated UTIs. Antimicrobial resistance patterns will continue to change, implying that properly designed studies performed in a timely fashion will be necessary to maintain the affectivity of the existing antibiotics. These trials should include not only newly introduced agents but also extant antimicrobials, to gauge their relative importance.

The paucity of knowledge has been a barrier to develop the best strategy to combat the further complications of ASB and to decide the best therapeutic management with special emphasis on type of antimicrobial agent and optimal treatment duration. However, new research initiatives with bigger sample size are solicited to validate the outcome of the study.

ACKNOWLEDGEMENTS

The authors thankfully acknowledge the support of ICMR-Studentship programme & Dr. Amit Mittal for carrying out statistical analysis of the article.

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How to cite this article: Prakash R, Pal S, Sharma N, Adekhandi S, Juyal D, Gaurav V. Diversity of uropathogens and their resistogram in diabetic and non-diabetic patients in sub Himalayan region of Uttarakhand, India: A case control study. Int J Med Public Health 2014;4:115-9.

Source of Support: Nil, **Conflict of Interest:** None declared.