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URINARY TRACT INFECTION AMONG DIABETIC PATIENTS WITH REGARD TO THE RISK FACTORS, CAUSATIVE ORGANISMS AND THEIR ANTIMICROBIAL SUSCEPTIBILITY PROFILES

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ABSTRACT

Diabetes Mellitus(DM) is of the world's biggest health problems .Human behavioral changes and lifestyle over the last century have resulted in a dramatic increase in incidences of diabetes worldwide. In the world, about420 million people have diabetes. This number is expected to double by 2025, disproportionately affecting working-age people. The present study was conducted to determine the risk factors, causative organisms and antimicrobial susceptibility of urinary tract infection (UTI) in diabetics and non-diabetics seeking treatment at ,Firoozgar hospital. Iran University of Medical Sciences, Tehran, Iran. This research designed based on a Prospective, descriptive and analytical study. Two hundreds samples:100 samples of urine and blood from diabetic subjects and 100 from control subjects were collected and urinalysis, culture and antimicrobial sensitivity done,during a period of 3 months (Jan 2015 to March 2015).Data obtained from urinalysis, culture and sensitivity was performed for detection of the infective etiology of UTI and antimicrobial susceptibility,to determine prevalence of UTI among both groups. Prevalence of UTI in diabetics was 32.0% and in non-diabetics 22.0% (P=0.111). The most commonly isolated pathogens for both groups were E. coli (48.1%), Enterobacter (24.1%), Klebsiella spp (13%), Candida albicans (9.3%), and S. aureus (3.7%).Isolates in both groups had similar antibiotic sensitivity patterns. The present study identified older age, female gender, hyperglycemia, elevated HbA1c, glycosuria, albuminuria as risk factors of UTI in diabetics. Aminoglycosides, nitrofurantoin,gatifloxacin had excellent activity against the isolates, and could be used for empirical treatment.

Key words: Diabetes mellitus, UTI,Glycosuria, Antibiotic sensitivity.

INTRODUCTION

Diabetes Mellitus(DM) is set to become one of the world's biggest health problems owing to the projected increase in new cases [1]. Human behavioral changes and lifestyle over the last century have resulted in a dramatic increase in incidences of diabetes worldwide[2]. In the world, about 420 million people have diabetes. This number is expected to double by 2025, disproportionately affecting working-age people[3]. Prevalence of diabetes has increased in Iran between 1996 and 2004[4].It is thus clear that the diabetes epidemic experienced in Iran may be due to strong genetic factors coupled with urbanization and lifestyle changes leading to insulin resistance[5,6]. It is estimated that 150 million Urinary Tract Infections (UTI) occur yearly on a global basis, resulting in more than 6 billion dollars in direct health care expenditures[7].Nearly 1 in 3 women will have had at least 1 episode of UTI requiring antimicrobial therapy by the age of 24 years. UTIs infections are often asymptomatic, although on occasion they produce discomfort for selective older patients[8].UTIs are one of the most important community-acquired, more common among women than men[9-11]. The urinary tract is the principle site of infection in diabetics[12].Most studies agree that diabetic women have a 2-4 times higher incidence of bacteriuria compared to those without diabetes. Diabetes mellitus constitutes a risk factor for the development of UTIs from fungi[13]. UTI is a major disease burden for many patients with diabetes[14].Several types of UTIs occur more commonly in diabetic patients. These include, in increasing clinical severity, cystitis, emphysematous cystitis, pyelonephritis, emphysematous pyelonephritis, and perinephric abscess[15]. Infections associated with fungus are vulvovaginal candidiasis,invasive candidiasis,andrenal actinomycosis[16]. Most studies have shown that there is significant relation or increased rate of UTI between diabetics and non-diabetics,while some studies had shown increased prevalence among diabetic women in contrast to diabetic men[17-20]. Studies have also shown that diabetes by itself does not seem to influence the isolation rate of different uropathogens and their susceptibility patterns to antimicrobials[21]. The main objective of the study would be to determine the risk factors, causative organisms and antimicrobial susceptibility of UTI in diabetics and non-diabetics seeking treatment at Firoozgar hospital. This study aims: 1:To determine the prevalence of bacterial UTIs among diabetics and non-diabetics. 2:To identify the common etiologic agents causing UTI in both groups. 3: To determine the susceptibility pattern of reported isolates.

MATERIAL AND METHODS

The present study was undertaken over a period of 3 months from (Jan 2015 to March 2015), at Firoozgar hospital. Hundred (M: F, 44: 56) consecutive diabetic subjects and hundred non-diabetic subject (M: F, 59:41) patients attending the outpatient of Firoozgar hospital were studied during a period of 3 months. The patients were detected to be diabetic or non-diabetic by blood glucose and HbA1c estimation at the time of their visit to the diagnostic center. A detailed history of the patient regarding age and sex were collected. A written consent was obtained prior to collection of specimens. All significant results were exchanged with patient's physician at regular intervals.A non-diabetic normal range for HbA1c was taken as below 6%. Values above 6% were regarded as diabetic range irrespective of treatment [22]. Diagnosis of diabetes was made based on the WHO criteria [23].

Inclusion Criteria

(1) Diabetic group: Proven diabetics (Type 1 or Type 2) whose FPG is >126 mg/dl plasma or 2 hour glucose is > 11.1 mmol/L, (200 mg/dl), HbA1c > 6.1% and using oral anti-diabetic medication with or without insulin or who were referred to a dietician with or without any medication will be classified as diabetics.
(2) Control group: Non-diabetics with no family history of diabetes having same age and sex match.
(3) Age: Adult population above 18-75 years.
(4) Sex: Female & Male

Exclusion Criteria

To avoid compounding factors, we excluded; traumatic urinary tract, abnormalities and other diseases of the urinary tract.Malignanciesof the urinary tract,leukemia, and HIVinfection.Subjects diabetic ornon-diabetic on antibiotic therapy for last 14 days,pregnant women.

Sample Collection and Microscopy

A random mid-stream urine sample was collected in a sterile container and examined within 45-60 minutes of voiding. If delay for culture was inevitable, the urine specimen was immediately refrigerated at 4^{O}C. A volume of 15 cm^3 of urine

was centrifuged 3,000 r.p.m. for 5 minutes, after which the supernatant fluid was drained off, the deposit resuspended and the last drop or two examined under a cover slip. Urinalysis was considered abnormal according to the criteria of Kroenke et al24.

Culture and Inoculation

The urine samples were inoculated on Urechrom II media (composition and preparation given in Annexure I), with calibrated loop (0.001 ml of sample), incubated aerobically at 37^{O}C 24 to 48 hours, and examined. The isolated microorganism was identified to the species level as per standard protocols.An inoculating loop of standard dimensions (holding 0.001 ml of urine) was used to take up uncentrifuged well-mixed urine and spread it over a plate of culture medium, in a dimensional stroke across the middle of a culture plate. The plate is incubated, the number of colonies counted or estimated, and this number used to calculate the number of viable bacteria/ml of urine. The growth of 100 colonies by this method indicates the presence of 10^5 bacteria/ml of urine. Cultural media plates were examined under magnifying lens and identified using the standard microbiological procedures like colony morphology, provided the manufacturer[25, 26]. All isolates were subjected to further identification by conventional biochemical profiles as per urechrom II manufacturer's recommendations and standard protocols [25, 27-30]. Antibiotic susceptibility testing was done by Kirby Bauer method of disk diffusion[31].

ANTIBIOTIC SUSCEPTIBILITY TESTING

In the treatment of control of infectious disease, especially when caused by pathogens that are often drug resistant, sensitivity testing is used to select effective antimicrobial drugs. They are not indicated if sensitivity reactions of a pathogen can be predicted. Sensitivity testing must not be performed on commensal organisms and contaminants, which may mislead the clinicians resulting in unnecessary drug therapy, causing possible side effects and resistance to other potential pathogenic organisms. The disc diffusion method currently recommended by the NCCLS is also known as the Kirby-Bauer test and widely used in the clinical laboratories since 1966. In the disc diffusion test, a McFarland 0.5 standardized suspensions of bacteria are swabbed over the surface of an agar plate, and then paper discs containing single concentrations of each antimicrobial agent is placed on to the inoculated agar surface. The plates are incubated at 35^{O}C, the zones of inhibition are examined the following day, and the isolate is interpreted as susceptible, intermediate or resistant to a particular drug according to preset criteria.

Disk susceptibility test- Kirby-Bauer Test
Inoculation of Agar Plates

A 150 mm plate must be used. To inoculate the plate, dip a sterile swab into standardized inoculums and rotate on side of tube to remove the excess liquid. Swab entire plate 60^{O}, swab again, and repeat once more.

Application of antimicrobial disks

Antimicrobial disc are applied with a commercially available dispenser and tapped gently to ensure contact with agar surface.

Incubation

The plates are inverted and incubated agar side up for 16 to 18 hours at 35^{O}C. Plates should be incubated within 15 minutes after discs are applied.

Measurement of inhibition zones

After 24 hours of incubation plates are examined to see if there is a lawn of growth and zones are even and circular. The diameters of the inhibitory zone are measured to the nearest millimeter using either a ruler or calipers.

Interpretation

The zone size around each antimicrobial disc is interpreted as susceptible, intermediate or resistant based on the criteria indicated in tables provided by the manufacturer.

Table 1
Discs of antimicrobial agents, potencies and zone size in mm.

Antibiotics	Resistant	Intermediate	Sensitive
Ceftriaxone-30mcg	13	14-20	21
Ceftazidime-30mcg	14	15-17	18
Cefaperazone-75mcg	15	16-20	21
Cephalexin-10mcg	14	15-17	18
Cefuroxime-5mcg	13	14-22	21
Ciprofloxacin-5mcg	15	16-20	21
Amikacin-30mcg	14	15-16	17
Gentamicin-10mcg	12	13-14	15
Norfloxacin-10mcg	12	13-16	17
Nalidixic acid-30mcg	13	14-18	19
Gatifloxacin-5mcg	14	15-17	18
Nitrofurantoin-300mcg	14	15-16	17

STATISTICAL METHODS

Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance. Chi-square/Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups. The Statistical software namely SPSS 15.0, Stata 8.0, MedCalc 9.0.1 and Systat 11.0 were used for the analysis of the data.

RESULTS

The mean age group for the non-diabetics was (39.53±15.76) and for the diabetics was (52.19±12.43).100 Non-diabetics (44 males and 56 females) and 100 diabetics with (59 males and 41 females) were studied.Diabetic females had higher incidence of UTI compared to diabetic males. Twenty-nine of diabetics had HbA1c levels >8.0%, while thirty also had glycosuria(Table2).The predominantly isolated uropathogens for diabetics was E. coli (43.8%), followed by Enterobacter (21.9%), C. albicans (15.6%), Klebsiella spp. (12.5%), S. aureus (6.2%), and for non-diabetics, E. coli (54.5%), Enterobacter (27.3%), Klebsiella spp. (13.6%), and Pseudomonas spp. (4.5%), respectively. Significant correlation of HbA1c was seen with hyperglycemia and glycosuria ($P < 0.001$**). Poor glycemic control and hyperglycemia was significantly associated with UTI ($P < 0.001$**). Glycosuria and albuminuria also had significant association (P=0.072+ vs P = 0.083+) with UTI, whereas pyuria had no significant association with UTI (P =0.783). The prevalence of UTI was not very marked until the age of 41 years. The highest incidence (22.7%) of UTI in non-diabetics was seen in the age groups of (31-40) (Table 3). The gender wise incidence of UTI in diabetic women (56.3%) vs non-diabetic women (40.9%), diabetic males (43.8%) vs non-diabetic males (59.1%) had a statistically similar distribution of UTI, (P =0.406). Diabetic females (56.3%) had higher incidence of UTI compared to diabetic males (43.8%). Hyperglycemia was found in (28.1%) of the diabetic UTI cases. Similarly glycosuria was present in (15.6%) of diabetic (Table 4). Isolates in both groups had similar antibiotic sensitivity patterns with sensitivity to aminoglycosides, nitrofurantoin, gatifloxacin and resistance to cephalosporins, norfloxacin, and nalidixic acid(Table5 and 6).Most isolates from diabetics were found to be sensitive to, amikacin, gentamicin, nitrofurantoin, and gatifloxacin while they were resistant to ceftriaxone, ceftazidime, cefaperazone, ciprofloxacin, norfloxacin, nalidixic acid, cefuroxime and cephalexin. Although isolates from non-diabetics showed a higherpercentage of sensitivity to ciprofloxacin. Although E. coli has been the predominant organism causing UTI, it has not displayed high level of resistance to antibiotics.

Table 2

Comparison of hyperglycemia, HbA1c, glycosuria, urine albumin, urine WBC, pyuria, and SB in two groups of patients studied

Variables	Status	Non-Diabetic (n=100)		Diabetic (n=100)		P vaule
		No	%	No	%	
Hyperglycemia	Present	0	0.0	22	22.0	<0.001**
	Absent	100	100.0	78	78.0	
HbA1c %	<6.9%	100	100.0	30	30.0	<0.001**
	7.0-7.9%	0	0.0	29	29.0	
	>8.0%	0	0.0	41	41.0	
Glycosuria	Present	0	0.0	30	30.0	<0.001**
	Absent	100	100.0	70	70.0	
Urine albumin	Present	26	26.0	27	27.0	0.873
	Absent	74	74.0	73	73.0	
Urine WBC/HPF	10 or less	84	84.0	75	75.0	0.011*
	11-15	4	4.0	14	14.0	
	16-25	1	1.0	5	5.0	
	26-50	3	3.0	4	4.0	
	Plenty	8	8.0	2	2.0	
Pyuria	Present	16	16.0	25	25.0	0.165
	Absent	84	84.0	75	75.0	
Significant bacteriuria	Present	22	22.0	32	32.0	0.111
	Absent	78	78.0	68	68.0	

Note: ** strongly significant, * moderately significant

Table 3

Incidence of UTI infection according to age distributionof patients studied

Variables	Status	UTI infection				P value
		Non-Diabetic (n=22)		Diabetic (n=32)		
		No	%	No	%	
Hyperglycemia	Present	0	0.0	9	28.1	0.007**
	Absent	22	100.0	23	71.9	
HbA1c %	<6.9%	22	100.0	11	34.4	<0.001**
	7.0-7.9%	0	0.0	9	28.1	
	>8.0%	0	0.0	12	37.5	
Glycosuria	Present	0	0.0	5	15.6	0.072+
	Absent	22	100.0	27	84.4	
Urine albumin	Present	11	50.0	8	25.0	0.083+
	Absent	11	50.0	24	75.0	
Urine WBC/HPF	10 or less	12	54.5	14	43.8	0.006**
	11-15	2	9.1	8	25.0	
	16-25	0	0.0	5	15.6	
	26-50	0	0.0	3	9.4	
	Plenty	8	36.4	2	6.3	
Pyuria	Present	11	50.0	18	56.3	0.783
	Absent	11	50.0	14	43.8	
Significant bacteriuria	Present	22	100.0	32	100.0	NS
	Absent	0	0.0	0	0.0	

Table 4
Comparison *of incidence of UTI infection in hyperglycemia, glycosuria , urine albumin, urine WBC, pyuria, significant bacteriuria in two groups of patients studied.*

Age in years	Incidence of UTI infection			
	Non-diabetic		Diabetic	
	No	%	No	%
18-20	4	18.2	0	0.0
21-30	3	13.6	3	9.4
31-40	5	22.7	3	9.4
41-50	2	9.1	8	25.0
51-60	4	18.2	7	21.9
61-70	2	9.1	7	21.9
71-75	2	9.1	4	12.5
Total	22	100.0	32	100.0
Inference	Incidence of UTI is positively associated with higher age in Diabetic group with P=0.241			

Note: ** strongly significant, * moderately significant, + Suggestive significance, NS- Not significan

Table 5
Sensitive and resistance of drug in Group A (Non-Diabetic)

Drug Table 2: Discs of antimicrobial agents, potencies and zone size in mm.	Sensitive (n=100)	Resistance (n=100)
1.Ceftriaxone	9(9.0%)	13(13.0%)
2.Ceftazidime	0	22(22.0%)
3.Cefaperazone	1(1.0%)	21(21.0%)
4.Ciprofloxacin	13(13.0%)	9(9.0%)
5.Amikacin	13(13.0%)	9(9.0%)
6.Gentamicin	19(19.0%)	3(3.0%)
7.Norfloxacin	10(10.0%)	12(12.0%)
8.Nalidixic acid	4(4.0%)	18(18.0%)
9.Gatifloxacin	16(16.0%)	6(6.0%)
10.Nitrofurantoin	17(17.0%)	5(5.0%)
11.Cefuroxime	5(5.0%)	17(17.0%)
12.Cephalexin	7(7.0%)	15(15.0%)

Table 6
Sensitive and resistance of drug in Group B (Diabetic)

Drug	Sensitive (n=100)	Resistance (n=100)
1.Ceftriaxone	13 (13.0%)	14(14.0%)
2.Ceftazidime	0	27(27.0%)
3.Cefaperazone	3(3.0%)	24(24.0%)
4.Ciprofloxacin	9(9.0%)	18(18.0%)
5.Amikacin	16(16.0%)	11(11.0%)
6.Gentamicin	18(18.0%)	9(9.0%)
7.Norfloxacin	12(12.0%)	15(15.0%)
8.Nalidixic acid	5(5.0%)	22(22.0%)
9.Gatifloxacin	14(14.0%)	13(13.0%)
10.Nitrofurantoin	21(21.0%)	6(6.0%)
11.Cefuroxime	9(9.0%)	18(18.0%)
12.Cephalexin	12(12.0%)	15(15.0%)

DISCUSSION

Higher frequency of bacteriuria among females than men were reported[32,33].Janifer J and et al reported that in type 2 diabetes mellitus(T2DM) subjects, gender wise prevalence of UTI in women (47.9%) having a significantly higher prevalence of UTI than men (34.1%)[34]. In a related study in a tertiary Indian hospital have shown UTI to occur more frequently in females (70.5%) as compared to males (29.5%)[35]. .In this study, we found that the prevalence of lower UTI was significantly higher in females than in male diabetic patients. In our study diabetic females with UTI was (56.3%), a higher incidence of UTI compared to diabetic males with UTI having (43.8%).Results of this study was comparable to another studies [10, 34-36]. The current study showedrate of bacteriuria was (18% vs 9%) respectively in diabetic and non-diabetic women. The rate of bacteriuria was (14% vs 13%) in diabetic and non-diabetic men respectively. Our results are comparable with the observations made by the other authors[16,21,37]. Some studies has postulated age being an important risk factor in development of ASB in young women due factors such as sexual activity and menstrual periods[38].The mean age of patients in our study, male and female was (50.8 vs 40.9) years respectively. The result of our study is comparable to other studies, which also has shown a lower age for women[18, 21, 39-40]. Increasing age has increased the incidence of UTI in diabetics in our study, which is similar Adeyeba A (2007)[18], findings. Ourstudy have found significant relation with UTI and HbA1c levels and is supported by previous studies[37-41]. In a study reported the prevalence of pyuria among diabetic women with ASB was relatively low. Only (33% vs 68%) respectively, ofT1DM and T2DM women with positive urine cultures had pyuria[42]. The current study shows that 11 (50%) of non-diabetics and 14 (43.8%) of diabetics with culture proven UTI did not have significant pyuria. Hence, presence of pyuria had no significant association with UTI in our study, which supports by other studies[43-45]. Our study also showed that prevalence of pyuria is higher in diabetics (25%) vs non-diabetics (17%), which is comparable with another study[46]. Etiologic pathogens associated with UTI among patients with diabetes include E. coli, Klebsiella spp, S. aureus, Group B streptococci,beta-hemolytic streptococci, Citrobacter spp, Pseudomonas spp, proteus and Enterococcus spp, as well as Candida albicans[15,21,41,47-56]. In the present study 54 cases yielded microbial growth (32 vs 22) in diabetic and non-diabetic respectively. E. coli was the commonest organism isolated in 26 cases, (48.1%). Followed by Enterobacter 13 (24.1%), Klebsiella spp. 7 (13%), Candida albicans 5 (9.3%), S. aureus in 2 (3.7%) and Pseudomonas spp. in 1 case. Our study is comparable with many studies who reported E. coli as the predominant etiologic agent ofUTI[20,21,57-71]. Our study shows that antimicrobial susceptibility pattern was not significantly different for isolates irrespective of presence or absence of diabetes. Most isolates from diabetics were found to be sensitive to, amikacin, gentamicin, and nitrofurantoin,gatifloxacin, while they were resistant to cephalosporins, ciprofloxacin, norfloxacin, andnalidixic acid. Our study confirms other reports that showed similar sensitivity and resistance to the drugs[18,55,58,59].

CONCLUSION

Our data reveal that E. coli was the predominant bacterial isolate followed by Enterobacter, Klebsiella spp, Pseudomonas spp, and S. aureus. Candiduria is common in diabetics with UTI and the most commonly isolated is Candida albicans. Antibiotic susceptibility patterns do not differ significantly between diabetics and non-diabetics. Aminoglycoside, nitrofurantoin, and gatifloxacin can be used to treat UTI in diabetics and non-diabetics.

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