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Full Length Research Paper

Antimicrobial Resistance and Risk Factors Associated with Bacteriuria in Diabetic Women: A Study from Dar es Salaam, Tanzania

Eligius F. Lyamuya[1], Sabrina John Moyo [1]*, Ewaldo V. Komba[2] and Martin Haule[1]

[1]Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania.

[2]Department of Internal medicine, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania.

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Urinary tract infections (UTIs) occur frequently among women with diabetes. The present study aimed at determining prevalence and risk factors of bacteriuria in diabetic women and antimicrobial resistance pattern of the isolates at Muhimbili National Hospital (MNH), Dar es Salaam. Three hundred diabetic women attending clinic at MNH from June to November 2010 were included in the study. Demographic and clinical information were collected using a structured questionnaire. Urine specimens were collected for urinalysis, microscopy, culture and antimicrobial susceptibility testing. Significant, asymptomatic and symptomatic bacteriuria was found in 13.7% (41/300), 13.4% (31/231), and 14.5% (10/69) diabetic women, respectively. The isolated pathogens were *Escherichia coli* (39.0%), *Klebsiella pneumoniae* (22.0%), coagulase negative Staphylococci (14.65) and *Proteus spp.* (12.2%). Both Gram positive and negative bacteria showed high rate of resistance towards co-trimoxazole (55.6% and 50.0%, respectively). Gram negative bacteria showed high rate of resistance to ampicillin (62.55%), penicillin (53.1%) and moderate resistance to cefotaxime (18.8%). Advanced age and glycosuria were significantly associated with bacteriuria (P < 0.05). *E. coli* was the commonest aetiological agent for both symptomatic and asymptomatic bacteriuria among diabetic women, especially those with advanced age and glycosuria. Most uropathogens were resistant to co-trimoxazole, ampicillin and ciprofloxacin.

Key words: Diabetes mellitus, bacteriuria, antimicrobial resistance.

INTRODUCTION

The urinary tract is the most common site of infection and a common problem in patients with diabetes mellitus (MacFarlane et al., 1986; Wheat, 1980). The prevalence of asymptomatic bacteriuria is 2 to 3 times higher among women with diabetes compared to women without diabetes (Patterson et al., 1997; Zhanel et al., 1995). Various risk factors for bacteriuria in women with diabetes have been suggested including sexual intercourse, age and degree of glycosuria, duration of metabolic control, complications of diabetes, macro albuminuria and high body mass index (BMI) (Andriole, 2002; Zhanel et al., 1995). The exact pathogenesis of this problem has not been clearly delineated (Zhanel et al., 1995). One possible explanation is high glucose concentration in urine among these patients which may provide nutritional support for the proliferation of pathogenic microorganisms. A variety of other factors may also contribute, especially urinary bladder dysfunction as a complication of diabetic neuropathy and cystopathy. Impaired sensation in the bladder causes bladder distention and increased residual volume, which results in a physiological obstruction of the urinary tract, which, in turn, increases the susceptibility to infection and allows infection to be initiated by much smaller numbers of uropathogens (Andriole, 2002). Women with diabetes probably have a higher frequency and serious

*Corresponding author. E-mail: sabmoyo26@yahoo.com. Tel: +255714 627995.

complications of urinary tract infections (UTIs) such as emphysematous cystitis, pyelonephritis, renal or perinephric abscess, bacteraemia and renal papillary necrosis (Nicolle, 2000; Harding et al., 2002). In most cases, UTIs are asymptomatic and whether the symptomatic UTIs are preceded by asymptomatic bacteriuria (ASB) is not known. The prevalence of ASB in women with type 2 diabetes is reported to be 29% (Geerlings et al., 2000).

The most common aetiological species for bacteriuria in diabetic women include ***Escherichia coli, Proteus mirabilis*** and ***Klebsiella pneumoniae*** (Papazafiropoulou et al., 2010). Gram-positive organisms such as group B streptococcus and ***Staphylococcus saprophyticus*** are less common causes of bacteriuria (Ghenghesh et al., 2009; Warren et al., 1999). Antimicrobial resistance among uropathogens causing community and hospital acquired UTIs is increasing (Bonadio et al., 2001). Moyo and coworkers also reported high prevalence of antimicrobial resistance among urinary isolates including ESBL producers in Dar es Salaam (Moyo et al., 2010a). The extent to which UTIs occur among diabetic women in Tanzania, the spectrum of pathogens involved and their antimicrobial susceptibility pattern is little known.

Many tests are available for the diagnosis of bacteriuria. So far, semi- quantitative culture of a urine specimen is the only method that can provide confirmatory determination of urinary tract bacterial infection. However, performing a culture is costly and takes at least 24 h to generate results. An ideal test for UTIs is one that requires limited technical expertise, is cheap and has a high accuracy, enabling a quick diagnosis in high-risk patients including diabetic patients (Brooks, 1990; Cochat et al., 1998). An example is the dipstick test, where only nitrites and leukocyte esterase can be accurately determined, in contrast to quantitative culture where the bacterial load is demonstrated (Lohr et al., 1991). There is limited data on prevalence of bacteriuria in diabetic women in our set up.

The current study therefore, is aimed at filling this gap by investigating the prevalence of bacteriuria among diabetic women, establishing the antimicrobial resistance pattern of the causative agents, and identifying the associated risk factors. In addition, dipstick test was performed and results were compared with those of culture.

MATERIALS AND METHODS

Study design and study settings

This was a cross sectional study conducted at Muhimbili National Hospital (MNH) during June to November 2010. The study included 300 female adult diabetic patients attending diabetic clinic at MNH. Special designed questionnaire was used to collect demographic and clinical information including age, sex, weight, address, occupation and antibiotic use. The criterion used for defining asymptomatic bacteriuria was the presence of at least 10^5 colony forming units/ml (cfu/ml) in one culture of clean-voided mid-stream urine specimen. According to the WHO criteria (1998), diabetes mellitus was defined as fasting glucose concentration of at least 6.1 mmol/L (110 mg/dl) or a 2 h post prandial glucose concentration of at least 10.0 mmol/L (180 mg/dl) or the use of glucose-lowering medication (tablets or insulin) (Wahl et al., 1998).

Urine collection and processing

About 20 ml of clean voided midstream urinary specimens were collected for urinalysis, microscopical examination, culture and sensitivity test. Urine thus collected was immediately transported to the MUHAS microbiology laboratory and processed within 1 h. A drop of uncentrifuged well mixed urine was put on a clean grease-free slide, stained by Gram's staining method and examined under the oil immersion objective of the microscope (examining 20 fields). Presence of ≥1 bacteria per oil immersion field correlates with significant bacteriuria of $\geq 10^5$ cfu/ml of urine. Urinalysis was done using urine dipstick following manufacturer's instructions (Mannheim GmbH, Germany).

Urine culture

A semi- quantitative calibrated loop technique was adopted for the primary isolation of the organism. A loopful of well-mixed uncentrifuged urine was streaked onto the surface of blood agar and CLED agar medium (OXOID, UK). After incubating aerobically for 24 to 48 h at 37°C, the colony forming units per milliliter of urine was determined. The bacteria isolated were identified by standard procedures (Murray et al., 1999**)**. Significant bacteriuria was defined as the presence of at least 10^5 cfu/ml of one bacterial species in a culture of clean-voided midstream urine. Presence of at least two different microorganisms in a urine specimen was considered as contamination.

Antimicrobial susceptibility testing

Kirby Bauer's disc diffusion agar method was used for antimicrobial susceptibility testing according to Clinical and Laboratory Standards Institute (CLSI) guidelines. Antibiotic discs of common drugs used for treatment of suspected Gram negative and positive bacterial infection in our hospital were tested, plus other reserve drugs for Gram negative bacteria commercially available in our setting. Antibiotics tested were ampicillin 10 µg, amoxicillin/clavulanic acid 20/10 µg, ciprofloxacin 100 µg, gentamicin 10 µg, cefotaxime 30 µg, cotrimoxazole 25 µg, amikacin 30 µg, nitrofurantoin (Oxoid, UK). Individual colonies were suspended in normal saline to 0.5 McFarland standards and using sterile swabs, the suspensions were inoculated on Muller Hinton agar for 18 to 24 h.

According to the sizes of the zones of inhibition around the antibiotic discs, the organisms were classified as sensitive, intermediate or resistant to a specific antibiotic (CLSI 2000). ***E. coli*** ATCC 25922 was used as a reference strain for quality control. The isolates were screened for extended spectrum beta – lactamases (ESBLs) production using MacConkey agar plates with 30 µg/ml cefotaxime and confirmed using disc approximation method. Ceftazidime (30 µg) and cefotaxime (30 µg) discs were placed equidistant from the amoxicillin/clavunate (20/10 µg) disc; enhanced zone of inhibition towards amoxicillin/clavunate (20/10 µg) disc was considered as positive result for ESBLs production (De gheldre et al., 2003; M'Zali et al., 2000).

Statistical analysis

The Statistical Package for the Social Sciences (SPSS) 17.0 for

Table 1. Distribution of diabetic women by demographic characteristics

Demographic characteristic	Frequency (%)
Age groups in years	
8-35	57 (19.0)
36-49	90 (30.0)
50-64	120 (40.0)
≥ 64	33 (11.0)
District	
Ilala	79 (26.4)
Temeke	74 (24.7)
Kinondoni	147 (49.0)
Job (occupation)	
Peasants	19 (6.3)
Employed	51 (17.0)
Business	70 (23.3)
House wife	137 (45.7)
Students	23 (7.7)
Level of education	
No formal education or Incomplete primary education	44 (14.7)
Complete primary education	169 (56.3)
Secondary education and above	87 (29.0)

windows version was used for statistical analysis. The Chi square test and Fisher's exact tests were used to establish any statistical difference. Univariate analysis was used to determine the association. Probability values (P) of < 0.05 were considered as statistically significant.

Ethical consideration

The study was carried out in accordance with ethical guidelines. Ethical clearance was obtained from the Senate Research and Publications Committee of the Muhimbili University of Health and Allied Sciences, Dar es Salaam. Permission was sought from MNH authority. An informed consent was obtained before collection of urine specimens and results were used in the management of patients.

RESULTS

Demographic characteristics of patients

The study participants were 300 diabetic women with ages ranging from 18 to 89 years, (mean of 48 years). Table 1 shows demographic data of these participants. Patients included were from all the three districts of Dar es Salaam region and most patients were residents of

Table 2. Distribution of isolated bacteria.

Isolated pathogen	Frequency (%)
Escherichia coli	16 (39.0)
Klebsiella pneumoniae	9 (22.0)
Proteus mirabilis	5 (12.2)
CoN Staphylococcus	6 (14.6)
Staphylococcus aureus	2 (4.9)
Salmonella typhi	1 (2.4)
Enterococcus faecalis	1 (2.4)
Pseuodomonas aureginosa	1 (2.4)
Total	41(100%)

Kinondoni district 147 (49.0%) followed by Ilala and Temeke districts 26.4 and 24.7%, respectively. Most of the study participants were housewives 137/300 (45.7%), others were business women 70/300 (23.3%), employed 51/300 (17.0%), peasants 19/300 (6.3%) and students 23/300 (7.7%).

Bacteriuria and isolated microorganisms

Of the 300 women, 69 had symptoms but significant bacteriuria was detected in only 10 (14.5%). The remaining 231 had no symptoms of UTIs but 31 (13.4%) of them had significant bacteriuria. Overall significant bacteriuria was found in 13.7% (41/300) diabetic women. Of the diabetic women with UTI symptoms, 85.5% (59/69) did not show significant bacteriuria. Table 2 summarizes the isolated microorganisms whereby Gram negative bacteria were more prevalent 78.0% (32/41) than Gram positive bacteria 22.0% (9/41). ***E. coli*** was the most common pathogen (39.0%) followed by ***K. pneumoniae*** (22.0%), coagulase negative Staphylococci (CoNS) (14.65%) and ***Proteus*** spp. (12.2%).

Antimicrobial resistance pattern

Tables 3 and 4 show antimicrobial resistance pattern of isolated bacteria. Overall, both Gram positive and negative bacteria showed high rate of resistance towards co-trimoxazole (55.6 and 50.0%, respectively) and amikacin (66.7 and 50.0%, respectively). Gram positive bacteria showed high rate of resistance towards nalidixic acid (55.6%) but no resistance was seen against the third generation cephalosporin cefotaxime. Gram negative bacteria showed high rate of resistance to ampicillin (62.55%), penicillin (53.1%) and moderate rate of resistance to cefotaxime (18.8%).

Bacteriuria and associated risk factors

Risk factors for ASB in the studied diabetic women are

Table 3. Resistance pattern of isolated bacteria

Antibiotic	*E. coli* (n=16)	Klebsiella (n=9)	Proteus (n=5)	*S. typhi* (n=1)	Pseudomonas (n=1)	*CoNS* (n=6)	*S. aureus* (n=2)	Enterococcus (n=1)
amp	11(68.7)	5(55.6)	3(60.0)	0(0.0)	1(100)	1(16.7)	1(50.0)	1(100)
amc	6(37.5)	1(11.1)	0(0.0)	0(0.0)	0(100)	2(33.3)	1(50.0)	0(0.0)
cip	2(12.5)	4(44.4)	3(60.0)	0(0.0)	1(100)	3(50.0)	0(0.0)	0(0.0)
gen	7(43.7)	1(11.1)	2(40.0)	0(0.0)	0(100)	1(16.7)	1(50.0)	0(0.0)
sxt	8(50.0)	5(55.6)	3(60.0)	1(100)	1(100)	3(50.0)	1(50.0)	1(100)
amk	11(68.7)	5(55.6)	1(20.0)	0(0.0)	1(100)	5(83.3)	1(50.0)	0(0.0)
nf	5(31.2)	2(22.2)	2(40.0)	0(0.0)	1(100)	1(16.7)	0(0.0)	1(100)
nal	6(37.5)	1(11.1)	3(60.0)	1(100)	1(100)	4(66.7)	1(50.0)	0(0.0)
p	6(37.5)	5(55.6)	4(80.0)	1(100)	1(100)	1(16.7)	1(50.0)	0(0.0)
ctx	3(18.8)	3(33.3)	0(0.0)	0(0.0)	0(100)	0(0.0)	0(0.0)	0(0.0)

amp, ampicillin:amc, amoxicillin/clavulanic acid; cip, ciprofloxacin; gen, gentamicin; sxt, co-trimoxazole; amk,amikacin; nf, nitrofurantoin; nal, nalidixic acid, p, penicillin and ctx, cefotaxime

Table 4. Resistance pattern of gram positive and gram negative bacteria

Antimicrobial agent	Gram positive bacteria (n=9) (%)	Gram negative bacteria (n=32) (%)
Ampicillin	3 (33.3)	20 (62.5)
Amoxicillin/clavunate	3 (33.3)	7 (21.9)
Ciprofloxacin	3 (33.3)	9 (28.1)
Gentamicin	2 (22.2)	10 (31.2)
Co-trimoxazole	5 (55.6)	16 (50.0)
Amikacin	6 (66.7)	16 (50.0)
Nitrofurantoin	2 (22.2)	10 (31.2)
Nalidixic acid	5 (55.6)	12 (37.5)
Penicillin	2 (22.2)	17 (53.1)
Cefotaxime	0 (0.0)	6 (18.8)

shown in Table 5. Age of the patients (≥50 years) and presence of glucose in urine were the only factors which were significantly associated with bacteriuria ($P< 0.05$). BMI, blood glucose level, level of education and occupation did not influence the risk for bacteriuria.

Sensitivity and specificity of urine dipstick

The prevalence of UTIs among diabetic women determined by dipstick and urine culture was 14.3% (43/300) and 13.7% (41/300), respectively. The sensitivity and specificity of urine dipstick was 58.5 and 92.7%, respectively. False positives and false negatives by dipsticks were 44.2 and 6.6%, respectively (Table 6).

DISCUSSION

Diabetes mellitus has long been considered to be a predisposing factor for UTI. In several instances, UTIs are asymptomatic, especially in women. Furthermore, it has been shown that the bacteria isolated from diabetic patients with a UTI are similar to those found in non diabetic patients with a complicated UTI (Nicolle, 2001). Diabetes mellitus is one of the non communicable diseases whose incidence and prevalence are rapidly increasing in developing countries including Tanzania, almost to epidemic proportions. However, limited information is available regarding the extent to which UTI occur, among diabetic patients in our setting. It was considered of interest, therefore, to investigate the prevalence of bacteriuria among diabetic women and determine the antimicrobial susceptibility profile of the responsible pathogens.

In the present study, significant bacteriuria was found in 13.7% of diabetic women. Asymptomatic bacteriuria was found in 13.4% whereas symptomatic bacteriuria was found in 14.5%. These findings are comparable to those observed in other studies with reported range of ASB between 6 to 26% (Zhanel et al., 1995; Geerlings et al., 2000). As observed in most other previous studies, ***E. coli*** was the most prevalent microorganism (39.0%) isolated from urine cultures of the study participants. Other uropathogens found in this study were Klebsiella, Proteus, Enterococcus, etc. These results compare with those reported by other studies (Zhanel et al., 1991; Zhanel et al., 1995; Nicolle, 2001) suggesting that, the aetiological pattern of UTIs with respect to bacterial pathogens is apparently similar worldwide. Antibiogram results of our study showed that, most isolated microorganisms are resistant to co-trimoxazole, ampicillin and penicillin. This observation may be a consequence of wide and uncontrolled use of these drugs in the study population leading to high selection pressure for resistant bacteria. The extensive use of these drugs could be explained because they are relatively cheap, easy to administer and often used for empiric treatment of

Table 5. Association between bacteriuria and risk factors.

Risk factors	Prevalence of significant bacteriuria (%)	P value
Age		
18-49 years (n=147)	14 (9.5)	0.04
≥ 50 years (n=153)	27 (17.6)	
Level of education		
No formal education or incomplete primary education (n=44)	5 (11.4)	>0.05
Primary education (n=169)	29 (17.2)	
Secondary education and above (n=87)	7 (8.0)	
Glucose level		
Normal blood glucose (n=56)	9 (16.1)	>0.05
Increased Blood Glucose(n=244)	32 (13.1)	
Urine glucose		
Presence of glucosuria (n=199)	33 (16.6)	0.039
Absence of glucosuria (n=101)	8 (7.9)	
BMI		
Thin (n=7)	0 (0.0)	>0.05
Normal BMI (n=64)	5 (7.8)	
Fat-abnormal BMI (n=229)	36 (15.7)	

Table 6. Sensitivity and specificity of urine dipstick test using culture as gold standard.

	Culture positive (%)	Culture negative (%)	Total (%)
Urine dipstick positive	24 (55.8)	19 (44.2)	43 (100)
Urine dipstick negative	17 (6.6)	240 (93.4)	257 (100)
Total	41 (13.7)	259 (86.3)	300 (100)

Sensitivity = 58.5%; Specificity = 92.7%; False positive = 44.2%; False negative = 6.6%

suspected infection.

In addition, resistance to cotrimoxazole may be due to the fact that this drug is widely used for prophylaxis against opportunistic infections associated with HIV. Use of these drugs (co-trimoxazole, ampicillin and penicillin) to treat bacteriuria in diabetic women should be done with caution and patients should be closely monitored for both clinical and microbiological response. Ciprofloxacin is another antibiotic that is used routinely for treatment of UTIs in symptomatic diabetic patients in our setting. Microorganisms isolated from the present study displayed a moderate rate of resistance (28.1 to 33.3%) towards this drug. Resistance to ciprofloxacin is a great concern because fluoroquinolones are reasonable agents for empirical treatment of both uncomplicated and complicated UTIs in areas where resistance to cotrimoxazole is over 20% as seen in our setting, and they have become more commonly prescribed as first-line antibiotic therapy in the last few years (Goettsch et al., 2000; Hooton, 2003). A study done by Alos and co-workers reported 8.5 and 19.5% resistance rates for the uncomplicated and complicated UTI strains, respectively (Alos et al., 2005) . Our rate of resistance is much higher and this may be due to frequent use of ciprofloxacin, since it is considered the drug of choice in UTIs. The association between ciprofloxacin use and the emergence of resistance has been reported previously (Alos et al., 2005; Ena et al., 1995; Goettsch et al., 2000).

Gram negative bacteria showed 18.8% resistance to third generation cephalosporin (cefotaxime) which was due to ESBLs production. This finding is remarkably lower than the recently reported ESBL rates of 45.2% from urinary isolates (Moyo et al., 2010a) and 31.2% among pregnant women (Moyo et al., 2010b) in Dar es

Salaam. ESBLs producing strains are resistant to all beta - lactamic antibiotics and this explains the high rate of resistance of Gram negative bacteria to ampicillin and penicillin. Some studies have reported increased co-resistance in ESBLs producers than in non-ESBLs producers. The observed high rate of resistance to different antimicrobial agents which augurs with the increasing problem of resistant uropathogens worldwide (Gupta et al., 1999) calls for additional non-antimicrobial strategies for the prevention of UTIs such as sufficient fluid intake, complete emptying of the bladder during voiding, less use of spermicides and restrictive catheter use.

Furthermore, studies should be done to compare the antibiograms of uropathogens isolated from diabetic and non-diabetic patients. Age is a well-known risk factor for bacteriuria in women without diabetes (Nordenstam et al., 1986). Advanced age was also the most important risk factor for bacteriuria in diabetic patients in the present study which concurs with the findings shown by others who have reported age as an increased risk factor for ASB in type two diabetic women (Geerlings et al., 2000). The present study also found a significant relationship between glucosuria and bacteriuria as reported by other studies (Boroumand et al., 2006). ***In vitro*** studies have also demonstrated that glucosuria increased growth of ***E. coli*** (Geerlings et al., 2000). This has been attributed to decreased antibacterial activity that is associated with presence of glucose in urine leading to enhanced growth rate of bacteria (Geerlings et al., 2000).

We observed a significant difference between dipstick and culture in determining bacteriuria among diabetic women. While it is desirable to have a test that provides quick results to guide decision-making in the management of patients, it is essential to also consider other important attributes especially accuracy and reliability. In the present study, the dipstick demonstrated a low sensitivity of 58.5% and a high false positive rate of 44.2% when compared to urine culture. These performance characteristics indicate that, dipstick has a limited role in predicting bacteriuria among diabetic women.

In conclusion, symptomatic and asymptomatic bacteriuria is prevalent among diabetic women in our setting and ***E. coli*** is the commonest aetiological agent. Most bacterial isolates are resistant to co-trimoxazole, ampicillin and ciprofloxacin. Gram negative bacteria showed resistance to cefotaxime due to ESBLs production. Glucosuria and advanced age of the patient increases the risk of bacteriuria in diabetic women, observations that call for rigorous measures for control of sugar levels among diabetic women especially with advanced age. The dipstick test has limited use in screening for asymptomatic bacteriuria because of its low sensitivity, compared with the urine culture.

Finally, we recommend periodic screening, by urine culture, for diabetic patients older than 50 years to detect ASB early. Further studies need to be done on wider population samples in health facility as well as community settings, to assess the magnitude of asymptomatic bacteriuria in diabetic women in the country. It would also be interesting to assess the antimicrobial sensitivity pattern of the offending pathogens for the purpose of formulating evidence-informed treatment guidelines.

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