Original Article

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Infectious Diseases Section

Asymptomatic Bacteriuria among Patients with Diabetes Mellitus at a Tertiary Care Center

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ABSTRACT

Objective: Patients with diabetes mellitus have a higher prevalence of asymptomatic bacteriuria and incidence of urinary tract infections compared to patients without diabetes mellitus. A prospective pilot study was conducted to determine the frequency of association of asymptomatic bacteriuria among patients with diabetes mellitus in comparison to control group without diabetes mellitus.

Methods: Urine specimens were processed by microscopy and culture following standard guidelines. The spectrum of uro-pathogens causing asymptomatic bacteriuria and their antibiotic susceptibility profile were noted.

Results: Asymptomatic bacteriuria was seen more commonly in patients with diabetes mellitus (4%) than in healthy control subjects. Asymptomatic bacteriuria was not seen in the non-diabetic individuals under control group. Three out of the four patients with asymptomatic bacteriuria had associated complications of diabetes mellitus. *Enterococcus faecalis* (2,50%), *Staphylococcus saprophyticus* (1, 25%) and *Escherichia coli* (1, 25%) were the organisms isolated from patients with asymptomatic bacteriuria. *Staphylococcus saprophyticus* isolate was mostly sensitive to antimicrobials tested. *Enterococcus faecalis* was sensitive to ampicillin. *Escherichia coli* isolate was multi-drug resistant.

Conclusion: Asymptomatic bacteriuria was more common among patients with diabetes mellitus than in healthy control subjects. Further, long term studies investigating the occurrence of complications secondary to asymptomatic bacteriuria in patients with diabetes mellitus and randomized control studies for studying the efficacy of antimicrobial therapy in preventing further complications in diabetes mellitus patients in Indian setups are needed.

Key Words: Bacteriuria, Diabetes Mellitus, *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus saprophyticus*

INTRODUCTION

Diabetes mellitus has become a major health challenge worldwide. In India alone, the prevalence of diabetes is expected to increase from 31.7 million in 2000 to 79.4 million in 2030 [1]. As the prevalence of diabetes mellitus increases worldwide, complications associated with it also assume equal importance. Patients with diabetes mellitus have a higher prevalence of asymptomatic bacteriuria (ASB) and incidence of urinary tract infections (UTIs) compared with patients without diabetes mellitus [2]. Presence of ASB in patients with Type 2 diabetes is a predictor of subsequent development of a symptomatic UTI [3]. Complications of UTIs such as emphysematous cystitis, pyelonephritis and renal papillary necrosis occur more commonly in subjects with Type 2 diabetes mellitus [4].

The reported prevalence rate of ASB in diabetic patients are 9-29% among females and 0.7-11% among males [5]. There are reports of symptomatic UTI in patients with diabetes mellitus and ASB in pregnant women from Indian setups. However, reports on the incidence of ASB among diabetes mellitus patients from India are scarce. Hence, there is a need for studying the impact of ASB in patients with diabetes mellitus in Indian setups. A prospective pilot study was conducted to assess the frequency of occurrence of ASB among patients with diabetes mellitus.

MATERIAL & METHODS

A prospective case-control study was conducted, in a tertiary care hospital attached to a teaching Institution, to study the frequency of occurrence of ASB among patients with diabetes mellitus. This study was approved by our Institutional Ethical Committee. Following informed consent, one hundred randomly selected adult patients (18-65 years) diagnosed with diabetes mellitus and presenting to hospital with ailments other than urinary tract infection were included in the present study. Pregnant females, individuals who had received antimicrobial drugs during the previous 2 weeks, those with urinary catheterization, symptomatic urinary tract

infection and renal failure were excluded from the study. One hundred healthy, non-diabetic age and sex matched controls were included in the control group.

Sample Collection & Processing: Clean-voided, mid-stream urine samples were collected in wide mouth sterile containers from both case and control groups. All specimens were transported within 2 hours to the microbiology laboratory for immediate processing. The specimens were processed following standard guidelines [6]. Urine wet mount and gram stain examination were done for presence of pus cells and bacteria. Presence of >5 polymorphonuclear leukocytes/ high power field (which correlates with WBC excretion rate of >400,000 WBC/hr) indicated pyuria which is evidence of an inflammatory response in the urinary tract [6,7] and; one organism per oil-immersion field in gram stain of uncentrifuged urine would suggest bacteriuria with a colony count of ≥ 105 CFU/ml of urine [6]. Specimens were inoculated onto blood agar and MacConkey agar by standard loop method for semi-quantitative culture [8]. The inoculated media were incubated aerobically for 24 hrs at 37°C. A diagnosis of asymptomatic bacteriuria in female patients was made, if two consecutive clean-voided midstream urine specimens yielded the same bacterial strain in quantitative counts of ≥105 CFU/mL in the absence of symptoms referable to urinary infection. In male patients, asymptomatic bacteriuria was diagnosed if one bacterial species was isolated from a single, clean-voided midstream urine specimen in a quantitative count ≥105 CFU/ mL in the absence of symptoms referable to urinary infection [9]. In those cases with significant bacteriuria, the isolates were identified by biochemical reactions using standard methods [8]. Antibiotic susceptibility testing of the isolated strains was done by Kirby-Bauer's disc diffusion method following Clinical Laboratory Standards Institute (CLSI) guidelines [10].

Asymptomatic Bacteriuria	Patients with Diabetes mellitus	Control group
Yes	4	0
No	96	100
Total	100	100

[Table/Fig-1]: Showing the occurrence of asymptomatic bacteriuria among patients with diabetes mellitus and control group
Fisher's exact - p: 0.121

RESULTS

Of the 100 patients with diabetes mellitus, 62 were males and 38 were females (M:F::1.6:1; Range 35 – 65 years). Majority of the individuals were between the age group of 51 - 60 years (50%). All patients (100%) in the study group had diabetes mellitus – Type 2. Of the 100 patients with diabetes mellitus in study group, four (4%) had asymptomatic bacteriuria (males – 3.2% and females – 5.3%). Of the four patients with ASB, two (50%) were males and two (50%) were females. All patients with ASB had uncontrolled diabetes mellitus status. None of the healthy controls without diabetes mellitus had ASB. Presence of other complications of diabetes mellitus (diabetic retinopathy, neuropathy, nephropathy) was seen in three (75%) out of the four patients with ASB [Table/Fig-2].

Enterococcus faecalis (2, 50%), *Escherichia coli* (1, 25%) and *Staphylococcus saprophyticus* (1, 25%) were the organisms isolated. *S. saprophyticus* was sensitive to most of the antibiotics tested. However CLSI does not recommend routine sensitivity testing of urine isolates of *S. saprophyticus* because infections respond to concentrations achieved in urine of antimicrobial agents commonly used to treat acute, non-complicated urinary tract infections [10]. Both isolates of *Enterococcus spp.* were sensitive to Ampicillin (100%). *E. coli* isolate was multi-drug resistant, resistant to most of first line drugs except for the aminoglycoside, Gentamicin. The isolate was sensitive to Meropenem and Beta lactam-Beta lactamase inhibitor (BL-BLIs) drugs, Ticarcillin-clavulanate and Piperacillin-tazobactam. Quinolones, the commonly used antibiotics for urinary tract infections were found to be ineffective against all the four isolates [Table/Fig-3].

DISCUSSION

A prospective case-control study was done to detect the presence of asymptomatic bacteriuria in patients with diabetes mellitus. The present study showed that, ASB was present in four (4%) out of 100 patients with type-2 diabetes mellitus. This is lower compared to the reported rates of 36.15% (Ophori EA et al., Nigeria, 2010) [11], 26% (Geerlings SE et al., Utrecht, 2001) [12], 17.5% (Bonadio M et al., Italy, 2004) [13] and 17% (Meiland R et al., Utrecht, 2006) [14]. However, Karunajeewa H et al. [15], (2005, Australia) found a lower rate of 7.3% of

Sl. No.	Age (years)	Sex	Duration of DM* (Years)	Current Treatment	Diabetes status	Presence of other complications of DM	Micro albuminuria
1	56	Male	6-10	Oral Hypoglycemics	Uncontrolled	Neuropathy	No
2	53	Female	1-5	Insulin	Uncontrolled	No	No
3	48	Female	6-10	Oral Hypoglycemics	Uncontrolled	Retinopathy	No
4	47	Male	> 10	Insulin	Uncontrolled	Retinopathy	Yes

[Table/Fig-2]: Showing the clinical profile of patients with asymptomatic bacteriuria among the study group
*DM: Diabetes mellitus

Organisms (No.)	Antibiotics (% ge sensitive)														
	Ap	Ac	Cf	Cr	Fr	Nf	Ct	Er	Cm	Te	Gm	Ak	Tim	Tzp	Ipm
Escherichia coli (01)	0	0	0	0	0	0	0	NT	NT	NT	100	0	100	100	100
Enterococcus faecalis (02)	100	NT	NT	NT	NT	0	NT	NT	NT	0	50	NT	NT	NT	NT
Staphylococcus saprophyticus (01)	100	100	100	100	NT	0	100	100	100	0	0	NT	NT	NT	NT

[Table/Fig-3]: Showing the sensitivity pattern of organisms isolated from asymptomatic bacteriuria

Ap: Ampicillin (10 µg), Ac: Amoxicillin–Clavulanic acid (20/10 µg), Cf: Cefazolin (30 µg), Cr: Cefuroxime (30 µg), Fr: Ceftriaxone (30 µg), Nf: Norfloxacin (10 µg), Ct: Trimethoprim-Sulfomethaxazole (23.75/1.25 µg), Er: Erythromycin (15 µg), Cm: Clindamycin (2 µg), Te: Tetracycline (30 µg), Ak: Amikacin (30 µg), Gm: Gentamicin (10 µg), Tim: Ticarcillin-Clavulanate (75/10µg), Tzp: Piperacillin-Tazobactum: (100/10 µg), Ipm: Imipenem (10 µg), NT: Not tested

diabetic patients having ASB. Low incidence of ASB (4%) in the present study is probably due to more number of male subjects (62%) in the present study.

Various risk factors for ASB in women with diabetes have been suggested including age, disease duration, renal microangiopathy (proteinuria, albuminuria), UTI in the previous year, sexual activity, lower body mass index and status of diabetic complications (retinopathy, nephropathy and neuropathy) [3, 5, 13]. There are differences of opinion by different investigators regarding these predisposing factors. [5] Three patients with ASB in the present study had associated complications of diabetes mellitus [Table/Fig-2]. None of the four patients with ASB had prior history of UTI, urinary catherization or genito-urinary surgery. Poor metabolic control though not a risk factor for developing ASB, was seen in most of the study subjects. [5] Considering the small number of patients with ASB among diabetic individuals, statistical analysis of significance of presence of risk factors could not be performed.

E. coli, *E. faecalis* and *S. saprophyticus* were the organisms isolated in the present study. These are among the most common organisms isolated from diabetic subjects with ASB and those with symptomatic UTI in other studies [11, 16]. *E. coli* was the most common organism isolated in the studies of Nicolle LE et al. [17] and Ophori EA et al. [11] In the present study, *E. faecalis* was the most commonly isolated bacteria. Quinolones, the commonly used antibiotics for urinary tract infections were found to be ineffective against all the four isolates. Janifer J et al., [16] have reported 62% of gram-negative bacilli and 33% of gram-positive cocci in their study to be sensitive to Ciprofloxacin. Rising rates of drug resistance among both gram-positive & gram-negative pathogens is a cause for concern.

Only two (50%) of the four patients with ASB had pyuria. Nicolle LE [18] in their study found that the prevalence of pyuria among diabetic women with ASB was relatively low (68% of women with Type 2 diabetes and with positive cultures). It has been speculated that the low leukocyte count is a marker for a dampened inflammatory response that promotes persistence of bacteriuria and contributes to the observed increased prevalence of bacteriuria in diabetic patients [18].

None of the control subjects with normal glucose tolerance had ASB. It is reported that ASB is found in 2-5% of healthy adult women and is quite unusual in healthy men [19]. Renko M et al., [19] in their meta-analysis of 22 studies found that ASB was present in 12.2% of patients with diabetes and in 4.5% of healthy controls. Point prevalence of ASB was higher in both women (14.2% vs 5.1%) and men (2.3% vs 0.8%) with diabetes than in health control subjects [19].

However, the important clinical concerns of ASB in diabetic individuals are its contribution to morbidity, either the short-term risk of developing a symptomatic urinary infection and its more serious complications or the longer-term risks of developing serious diabetic complications (e.g, nephropathy) [18]. In the present study, the patients with ASB were not treated with any antibiotics. The identification and treatment of ASB would be appropriate if doing so prevents symptomatic infection, especially pyelonephritis or complications of urinary tract infection in diabetes. Antimicrobial therapy for ASB is also beneficial in some patient populations like pregnant women and individuals undergoing traumatic genitourinary interventions [3]. Not many randomized control studies are performed to determine the efficacy of treating ASB in diabetic individuals to prevent the occurrence of complications and the dilemma of treatment versus not treating patients with ASB persists. Harding GKM et al., [20] (2002) in their study on 55 patients with ASB found that treatment does not reduce complications. They recommended against treatment of ASB. Also, in the absence of valid reason to treat, unnecessary antibiotic exposure risks the development of resistance to antimicrobial agents.

The limitation of the present study was the lack of follow-up of patients with ASB. This need has to be addressed in future studies. Further, studies in Indian setups including larger population based study group to assess the true incidence of ASB among diabetic individuals across various age groups and in both sexes; clinical progression of ASB cases into symptomatic UTI, pyelonephritis and; other long term complications of ASB in diabetic patients are needed. Also randomized control studies for studying the efficacy of antimicrobial therapy in preventing further complications in diabetes mellitus patients may be planned. This would provide

guidelines for screening or treating ASB among patients with diabetes mellitus in Indian setups.

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