

Clinical Profile of Asymptomatic Bacteriuria in Type 2 Diabetes Mellitus: An Eastern India Perspective

Mainak Banerjee, Manidipa Majumdar¹, Prabir K. Kundu¹, Indira Maisnam², Apurba K. Mukherjee¹

Department of Endocrinology and Metabolism, Institute of Post Graduate Medical Education and Research, ¹Department of General Medicine, R.G. Kar Medical College and Hospital, ²Department of Endocrinology and Metabolism, R.G. Kar Medical College and Hospital, Kolkata, West Bengal, India

Abstract

Introduction: Asymptomatic bacteriuria (ASB), believed to precede symptomatic urinary tract infection (UTI) in diabetes mellitus, has geographical variation in microbial pattern and risk factors. However, data from the Eastern part of India are still lacking. **Materials and Methods:** A prospective longitudinal study was performed over 80 otherwise healthy type 2 diabetes patients with a follow-up for one year to (1) estimate the prevalence of ASB and its association with age, gender, duration of diabetes, and renal and glycemic status; and (2) identify the antibiotic sensitivity pattern of uropathogens as well as evaluate the usefulness of microbial pattern as a predictor of symptomatic UTI. **Results:** ASB was prevalent in 21.25% of type 2 diabetes population in our study. *Klebsiella sp* emerged as the commonest cause among males. The only risk factor for ASB was found to be long-standing type 2 diabetes. There was no association with age, gender, or recent glycemic status. Bacteriuric patients with worse baseline HbA1C values were at greater risk of UTI. Female diabetic patients with ASB due to *Escherichia coli* had significantly greater risk of developing UTI within one year. **Conclusion:** A large-scale prospective study reproducing similar findings will genuinely obviate the need to review recommendations on screening of ASB due to *E. coli* in females with long-standing diabetes and poor glycemic control. Early adoption of stringent HbA1C lowering strategy and measures to improve genital hygiene can help prevent symptomatic UTI in these patients.

Keywords: Asymptomatic bacteriuria, asymptomatic bacteriuria, type 2 diabetes mellitus, urinary tract infection

INTRODUCTION

The permissive definition of asymptomatic bacteriuria (ASB) used in many studies, refers to the presence of a freshly voided midstream urine specimen yielding positive cultures ($\geq 10^5$ CFU/ml) of the same bacterium in a patient without symptoms of urinary tract infection (UTI); for example, dysuria, urinary frequency, urgency or fever. On contrary, some studies use two positive urine culture samples for defining ASB in females.^[1] It is not well understood why same uropathogens, responsible for UTI, are less virulent in these patients. Decreased uroepithelial adherence and mostly decreased host responsiveness in diabetes can explain this lack of symptoms.^[2] Since ASB is believed to precede symptomatic urinary tract infection (UTI; relative risk [RR] 1.65, 95 percent confidence interval [CI] 1.02–2.67); it is necessary to identify the risk factors to prevent UTI because of its adverse effect on glycemic control and general well-being of patients.^[3,4] The existing Infectious Disease

Society of America (IDSA) guideline does not recommend screening for ASB in type 2 diabetes patients in general. However, this recommendation may not be entirely relevant in Indian context where poor genital hygiene continues to be an issue, especially among female patients coming from lower socioeconomic status. Although two recent studies were conducted on ASB in patients with diabetes from North^[5] and South India,^[6] there is still lack of such studies from Eastern India. In view of the changing prevalence of ASB, emerging drug resistance, and geographical variation in the drug susceptibility pattern of uropathogens, this study attempts to fill up that lacuna in data.

Address for correspondence: Dr. Indira Maisnam,
Department of Endocrinology, RGKMCH,
Kolkata - 700 004, West Bengal, India.
E-mail: i.maisnam@gmail.com

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MATERIALS AND METHODS

Aims and Objectives

This study aimed to study the clinical profile of ASB in patients with type 2 diabetes mellitus. The specific objectives of this study were to: (1) estimate the prevalence of ASB in patients with type 2 diabetes mellitus patients in Eastern India; (2) study the association of ASB with age, gender, renal and glycemic status, and duration of diabetes; (3) identify the microorganisms and their sensitivity pattern in ASB in patients with diabetes mellitus, and (4) evaluate the usefulness of microbiological pattern on urine culture as a predictor of symptomatic UTI.

Sample size

Assuming 80% power and 5% significance level with 95% confidence interval, the total sample size (n) came out to be 76 according to the formula [$n = 4pq/e^2$], where p = prevalence (5%)^[7], $q = (1 - p)$, and e = precision.

Study population and setting

We studied 100 patients who were above 18 years of age, had type 2 diabetes mellitus, and attended the diabetes clinic of R. G. Kar Medical College and Hospital Kolkata. Pregnant females, patients on indwelling urinary catheter and having symptoms of UTI, patients with recent history of antibiotic treatment and history of antiseptic use before urine sample collection were excluded from the study. Patients with contaminated sample, suggested by presence of at least three different microorganisms in one urine sample, were also excluded.

Study design

After excluding 20 patients according to the exclusion criteria, a prospective longitudinal study was performed among 80 patients with a follow-up period of one year. Patients were enrolled via systemic random sampling after choosing the first patient randomly using a two-digit random number table [Figure 1].

Method of data collection

Clinical examination and relevant investigations were done after obtaining informed consent from each individual. Fasting

and postprandial blood glucose, urea, creatinine, and HbA1c were measured. The renal status of the patient was assessed using estimated GFR (eGFR), calculated from Modification of Diet in Renal disease Study (MDRD) equation. Asymptomatic patients with diabetes mellitus selected according to sample design were screened for bacteriuria. One random clean-catch midstream urine specimen was collected after proper cleaning of glans penis in men and labia in women with swabs soaked in clean tap water. The collected samples were inoculated onto blood agar, MacConkey agar, and nutrient agar and incubated at 37 degree celcius aerobically for 18–24 hours. The organisms were identified by colony morphology, gram staining, and biochemical reactions.^[8] The antibiotic sensitivity test for positive organisms was performed using the Kerby–Bauer disc diffusion method according to the CLSI guidelines.^[9] Asymptomatic patients with diabetes mellitus were then divided into two groups for comparative analysis: Group 1 (ASB Positive patients) and Group 2 (ASB Negative patients) [Figure 1].

Outcomes

Every individual was followed up for 12 months to observe for an episode of UTI. They were on oral antidiabetic drugs and/or insulin as part of their standard treatment. UTI is a broad term used to describe simple cystitis as well as complicated upper UTIs where systemic symptoms like fever, chill, rigor, malaise, or flank pain appear. UTI was defined in our study by presence of any classic symptom, for example, dysuria, urinary frequency, urinary urgency, and suprapubic pain with or without systemic symptoms supported by presence of urine pus cells more than 5 per high power field.

Statistical analysis

At the end of the study, the data were compiled, tabulated, and analyzed with appropriate standard statistical method using SPSSv22. Mean of the continuous variables were analyzed using student's t test between both ASB and non-ASB population as well as UTI and non-UTI subgroups. Contingency tables were made for groupwise distributed data which was analyzed using Chi-Square test or Fisher's exact test for small sample size. The P value < 0.05 was considered significant.

RESULTS

Study population

Out of 80 participants, 52.5% of study population fell in the 40–59 years age group and 2.5% were above 80 years. Majority (53.75%) of the study population were females.

Prevalence

A total of 21.25% of the study population had ASB. Majority of ASB occurred over 40 years of age. However there was no statistical significance between age and the presence of ASB in type 2 diabetes [Table 1]. A total of 23.25% of females had ASB as compared to 18.91% out of 37 male participants. Female gender was not found to be significantly associated

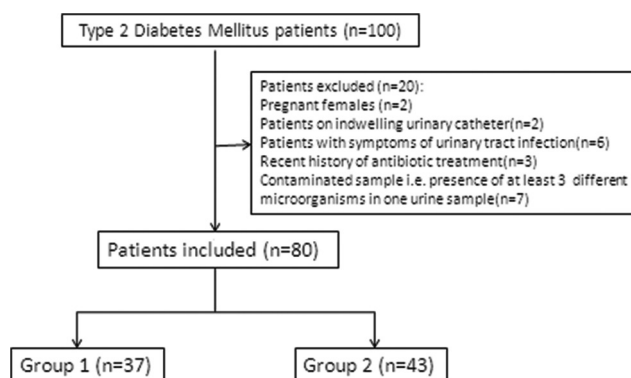


Figure 1: Method of Selection of subjects (N = 80)

with occurrence of ASB in type 2 diabetes in our study [Table 1].

Bacterial spectrum

The most common causative organism of ASB in the study population was *E. coli* (47%) followed by *Klebsiella sp.* (35.3%). Two cases of *Enterococcus sp.* and one case of *coagulase negative staphylococcus* were also found. *Klebsiella sp.* was the commonest organism among male population.

Sensitivity and resistance pattern

Among this study population, resistance was highest toward amoxicillin and ciprofloxacin (76.455 and 70.5%, respectively). Intermediate resistance was seen toward ampicillin (52.94%) and cotrimoxazole (41.17%). There was no resistance toward imipenem; low resistance towards cefepime (5.88%), piperacillin-tazobactam, amikacin (both 11.7%) as well as levofloxacin and nitrofurantoin (both 17.6%).

Association with HbA1C and duration of diabetes

The prevalence of ASB was highest among the patients who had diabetes for more than 15 years (50%), followed by those with 11–15 years (33.33%) and 6–10 years (26.31%). Only 5.5% of ASB was present in patients with less than 5 years of diabetes. ASB was highest among patients with HbA1c level 6.5–7.4, but was not higher among patients with HbA1c greater than 8. The mean duration of diabetes was significantly higher among patients with ASB as compared to non-ASB population but there was no significant difference in the mean HbA1C level between the two groups [Table 1].

Association with renal status

The majority of the patients with ASB had an eGFR of 30–59 ml/min/m². There was no significant difference in mean eGFR between ASB and non-ASB population [Table 1].

Significance with respect to future symptomatic UTI

In our study, type 2 diabetes patients with ASB were found to carry a significantly higher risk of developing UTI in future [Table 1]. Patients with ASB and worse baseline HbA1C values were at a significant greater risk of UTI. Notably, duration of diabetes had no significant effect in this scenario [Table 2]. Compliance to treatment was ensured in both ASB and non-ASB groups to eliminate the confounding bias. There was no statistically significant difference of baseline and follow-up HbA1C values between two groups either [Table 2].

E. coli was the causative organism of all cases of UTI on follow-up. Around 29% of diabetic patients with ASB, who developed UTI on follow-up within 12 months, were all females. None of the male patients with ASB had developed UTI in the follow-up period. ASB due to *E. coli*, was observed to have a greater risk of UTI on follow-up, which was statistically significant when compared to second most common cause *Klebsiella*. (Fisher's exact statistic value 0.031, $P < 0.05$).

DISCUSSION

Prevalence of ASB (21.25%) in this study population was similar to many studies reporting prevalence estimates ranging from 8–26%,^[10,11] which was more than the 12.5% prevalence rate reported in the meta-analysis done by Renko *et al.*^[7] and less than 28–32% prevalence rate reported in recent Indian studies.^[5,6,12] Majority of ASB occurring over 40 years of age was consistent with the finding in several studies on otherwise healthy people.^[13-15] Female predilection of ASB (23.25% vs 18.91%), as evidenced in several studies,^[14,15] is due to their short urethra located close to the warm, moist, vulvar, and perianal areas that are colonized with enteric bacteria.

Table 1: Association of Asymptomatic bacteriuria (ASB) with baseline characteristics and Urinary tract infection (UTI)

Characteristics	Total (n=80)	ASB (n=17)	Non-ASB (n=63)	Statistic value	P
Age	54.91±11.4	55.29±10.37	54.65±12.5	-	0.846
Male	37 (46%)	7 (41%)	30 (48%)	0.223*	p>0.05
Female	43 (54%)	10 (59%)	33 (52%)		
Duration of diabetes (years)	9.70±5.64	11.76±4.89	7.65±6.53	-	0.018
HbA1C (%)	7.62±1.12	7.65±1.11	7.6±1.14	-	0.880
eGFR (ml/min/m ²)	79.1±33.42	73.41±33.62	84.62±33.22	-	0.267
UTI on follow up	10 (13%)	5 (29%)	5 (8%)	0.031**	p<0.05
No UTI on follow up	70 (87%)	12 (71%)	58 (92%)		

Data are presented in n (%) or mean±standard deviation. (*) denotes Chi square statistic value. (**) denotes Fisher's exact test statistic value

Table 2: Association of Urinary tract infection (UTI) with Diabetes duration and HbA1C in study population with and without Asymptomatic bacteriuria (ASB)

	ASB (n=17)			Non-ASB (n=63)			P*
	UTI (n1=5)	No UTI (n2=12)	P	UTI (n3=5)	No UTI (n4=58)	P	
Duration of diabetes (years)	10±6.68	11.53±5.56	0.650	8.5±7.85	7.61±6.48	0.796	>0.05
Baseline HbA1C (%)	8.57±0.73	7.3±0.83	0.015	8.2±0.84	7.32±0.39	0.311	>0.05
HbA1C on follow up (%)	7.8±0.18	7±0.3	0.001	7.32±0.39	7.19±0.59	0.659	>0.05

Data are presented in mean±standard deviation. (*) denotes P values for difference between means of study populations n1 and n3

Similar to previous studies, the most common causative organism of ASB in the study population was *E. coli*.^[16,17] *Klebsiella sp.* was interestingly more common among male population. A study by Janda *et al.* similarly showed that adult males were more susceptible to infection by *Klebsiella sp.*^[18] This may be explained by the higher prevalence of several other risk factors like chronic alcoholism, phimosis etc. in males.

Our study showed good sensitivity toward cephalosporin, despite the increasing reports of resistance, particularly in *Klebsiella sp.*^[19-21] In this study, sensitivity for levofloxacin was better than ciprofloxacin, pointing toward escalating ciprofloxacin resistance reported in one study.^[22] In the context of reported prevalence of pan drug-resistant *Enterobacteriaceae* by Kumarasamy *et al.*,^[23] our study, however, reported excellent sensitivity to imipenem among enterobacteriaceae in Eastern India.

Our study found significant association between duration of diabetes and the prevalence of bacteriuria similar to study by Bahl *et al.*^[24] The lack of association with HbA1c was consistent with studies by Renko *et al.*^[7] and Zhanel *et al.*^[10] This suggests that glycosuria is not an important determinant for occurrence of ASB.

During the 12 months follow-up, ASB has been found to be significantly associated with UTI and all of these episodes occurred in females. Some prospective cohort studies conducted among diabetic females reported no difference in the rates of symptomatic urinary infection between initially bacteriuric and nonbacteriuric women during their 18 months or 14 years of follow-up.^[25,26] However, in one prospective observational study, ASB was found to be associated with increased risk of hospitalization for urosepsis.^[27]

The substantial greater ability of *E. coli* to produce symptomatic UTI than *Klebsiella sp.* in our study points toward a separate pathogenetic mechanism in causing UTI. The reason behind lesser incidence of UTI in ASB with *Klebsiella sp.* may be because they are nonmotile and do not have flagella like other coliforms. Flagellin or FliC, the major subunit of bacterial flagellum, not only plays a role in innate immunity but also acts as a dominant antigen of adaptive immune response. In various pathogens, for example, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Clostridium difficile*, flagellin has been reported to function as adhesins. Recently, FliC of Shiga-toxicogenic *E. coli* was found to be involved in cellular invasion via lipid rafts.^[28]

A landmark randomized controlled trial on ASB by Harding *et al.* showed that treatment of ASB did not reduce the risk of symptomatic UTI.^[29] Since the trial was not carried out on a specific high-risk group, we speculated that preemptive antibiotic therapy might be beneficial in ASB patients due to *E. coli* with poor glycemic control. However, considering the risk of recurrent bacteriuria and drug resistance, we emphasize the need for stringent HbA1C lowering for this group of patients along with hygiene education. A large-scale

prospective study reproducing similar findings will genuinely obviate the need to review recommendations on screening of ASB in females with long-standing diabetes and poor glycemic control.

CONCLUSION

Prevalence of ASB was found to be 21.25% in type 2 diabetes with majority in females over 40 yrs of age. *Klebsiella sp.* emerged as commonest uropathogen among male population. In view of significantly higher occurrence of UTI in female patients with ASB due to *E. coli*, we suggest the need for ASB screening in female patients of our population with long duration of diabetes. Early adoption of strict glycemic control and measures to improve genital hygiene can prevent UTI in these patients.

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Conflicts of interest

There are no conflicts of interest.

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