OUTCOMES OF ASYMPTOMATIC BACTERIURIA IN PATIENTS WITH DIABETES MELLITUS IN A YEAR-LONG FOLLOW UP STUDY

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ABSTRACT

BACKGROUND
Diabetes mellitus is a major public health problem worldwide today. It affects the genitourinary system. It predisposes patients to a variety of urinary tract infections and has long term effects on patient health. Asymptomatic bacteriuria (ASB) in diabetic patients, its effects on renal function, microalbuminuria, hypertension are not clearly defined. This study was carried out to determine the prevalence of asymptomatic bacteriuria, its clinical and microbiological outcomes in Indian diabetic patients.

METHODS
Two hundred and fifty type-2 diabetics (100 males and 150 females) without genitourinary symptoms or abnormalities were included in the study. Midstream urine samples were collected from the study participants after getting informed consent. Urine samples were examined and processed for the culture using the standard microbiological procedures. The spectrum of uropathogens causing asymptomatic bacteriuria was noted. Follow up after one year was done to evaluate clinical and microbiological outcomes.

RESULTS
Among the 250 diabetic patients, 43 (17.2%) had asymptomatic bacteriuria of which 31 (72.1%) were females and 12 (27.9%) were males. Escherichia coli (37.2%) was the most prevalent organism followed by Klebsiella (13.9%), Enterococcus faecalis (9.3%), Pseudomonas aeruginosa (6.9%), Staphylococcus aureus (6.9%), Candida species (6.9%), Proteus species (4.7%) and Coagulase Negative Staphylococcus (4.7%). On follow up it was found that incidence of symptomatic UTI in the study duration was 10 (23.26%) in the group with ASB and 39 (18.84%) in patients not having ASB at baseline. Prevalence of hypertension was also similar at the end of one year in both the groups. eGFR, prevalence of microalbuminuria and macroalbuminuria was also similar in both the groups at one year of follow up.

CONCLUSIONS
The overall prevalence of ASB in the diabetic patients was 17.2%. It was more common in females. Post-menopausal females have higher prevalence of ASB. E. coli was the most prevalent organism. Risk of symptomatic UTI appears to be comparable to general diabetic population. Hypertension, renal function and microalbuminuria do not appear to be affected by presence of ASB.

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involve upper urinary tract compared to general population. Upper urinary tract infections in diabetes can present in a variety of pattern like pyelonephritis, emphysematous pyelonephritis, xanthogranulomatous pyelonephritis, renal abscess, perinephric abscess, and papillary necrosis. Infections cause considerable morbidity and mortality in patients with diabetes mellitus and urinary tract infections are among the most common infections seen in diabetes. Studies have reported varying prevalence of ASB in diabetic patients, with estimates ranging from 8%–26%. ASB is more prevalent in women, due to a short urethra and shorter distance between rectum and vulva. Effect of ASB on renal function, microalbuminuria, and its effect in causation of hypertension is not clearly defined. There is little information available regarding natural history and outcome of ASB in diabetes in North western India. In an era where drug resistance is emerging as major global challenge it is important to define outcomes of ASB and better define need of antibiotics in their management.

METHODS
Present follow up study on asymptomatic bacteriuria in type 2 diabetic patients was conducted in Mahatma Gandhi hospital Jaipur from March 2016 to February 2018. Patients for the study were recruited from Medicine and Endocrinology outpatient department of the hospital. Patients were recruited from April 2016 to December 2016. Patients aged more than 18 years with Type 2 Diabetes Mellitus (diagnosed by treating physician based on WHO definition of Diabetes Mellitus) were eligible to participate. They were included if they had two positive urine culture in females (more than $10^5$ cfu/ml of urine in a midstream clean catch sample) or one positive culture in males (more than $10^5$ cfu/ml of urine in a midstream clean catch sample), done as per definition and had no symptoms related to urinary tract.

Exclusion Criteria
Patients having pregnancy or planning pregnancy, lower urinary tract anomalies, prior urogenital problems requiring instrumentation, surgery or per urethral/supra pubic catheterization, recent hospitalization (within last 90 days), using antimicrobial drugs like anti tuberculosis drugs or on immunosuppressant were excluded from the study.

Data Collection
Detailed clinical history with emphasis on symptoms pertaining to Diabetes, microvascular and macrovascular complications of Diabetes Mellitus and lower urinary tract was taken, general and systemic physical examination and relevant laboratory work up (Haemoglobin, glycated haemoglobin levels, serum creatinine, urine complete examination, urinary microalbuminuria, urinary proteinuria and urine culture and sensitivity) was done.

Mid-stream urine sample was collected in sterile wide mouthed container and the samples were processed using standard microbiological procedures. The specimens were inoculated on to Cystine Lactose Electrolyte Deficient agar, by standard loop method for semi quantitative culture and incubated at 37°C for 24 hours. After 24 hours of incubation, the plates were examined.

At one year of follow up again detailed clinical history and examination was done for all patients. Laboratory work up was done (Haemoglobin, glycated haemoglobin levels, serum creatinine, urine complete examination, urinary microalbuminuria, urinary proteinuria) for all the patients. Urine culture was done for patients having ASB at enrolment.

Definitions
1. **Asymptomatic Bacteriuria**
   - The definition of ASB in mid-stream clean catch urinary sample is growth of equal to or more than 100, 000 colony-forming units (CFU)/mL of urine without signs or symptoms attributable to urinary tract infection. In women, it is preferable to take two urinary samples within a period of 2 weeks.

2. **Diabetes Mellitus**
   - Criteria used for the diagnosis of diabetes as recommended by American Diabetes Association. Presence of any one of the following.
     - Glycated haemoglobin level equal to or more than 6.5%(48 mmol/mmol).
     - Fasting plasma glucose levels equal to or more than 126 mg/dl (7.0 mmol/l).
     - 2-h plasma glucose levels equal to or more than 200 mg/dl (11.1 mmol/l) during an OGTT.
     - In a patients having symptoms of hyperglycaemia, random plasma glucose equal to or more than 200 mg/dl (11.1 mmol/l).

3. **Microalbuminuria**
   - Microalbuminuria is defined as levels of albumin ranging from 30 to 300 mg in a 24-h urine collection. It can also be diagnosed on spot urine sample with excretion rate of albumin in the urine in the range of 30-299 mg/g creatinine.

RESULTS
A total of 275 patients of type 2 diabetes mellitus with female to male in ratio of 2: 1 were selected and screened, of these 250 patients completed one year follow up and provided sufficient information to be included in the study. Of the included patients, 150 were females and 100 were males. Out of the selected 250 patients 43(17.2%) were found to have asymptomatic bacteria at baseline. Among these 43 patients, 31 (72.1%) were females and 12 (27.9%) males. In the present study, prevalence of asymptomatic bacteriuria among female diabetic patients was 20.6% as opposed to 12% in males. Prevalence of ASB was 24.14% in post-menopausal females compared to 18.46% in pre-menopausal females. The age and gender distribution as well as baseline important characteristics of study population are shown in Table-1. Patients with or without ASB were...
comparable in baseline characteristics including age, BMI, hypertension, renal function, complications of diabetes and control of diabetes as shown in Table 1.

Table-2 shows the microorganisms isolated from the urine specimens of the study population at baseline. Among the organisms isolated, Gram negative bacilli 31(72.1%) were the predominant organisms followed by Gram positive cocci 9 (20.9%) and Candida albicans 3(6.9%). E. coli was found to be the most prevalent isolate in diabetic patients with asymptomatic bacteriuria (37.2%) followed by Klebsiella pneumoniae (13.9%), Enterococcus faecalis (9.3%), Staphylococcus aureus (6.9%), and Candida species (6.9%).

On follow up it was found that incidence of symptomatic UTI in the study duration was comparable in both groups, 10(23.26%) in the group with ASB and 39(18.84%) in patients not having ASB. Prevalence of hypertension was also similar at the end of one year in both the groups. eGFR, prevalence of microalbuminuria and macroalbuminuria was also similar in both the groups at one year of follow up.

Out of 43 patients with ASB at beginning 15 patients received antibiotics for various reasons (10 for symptomatic UTI, 3 for upper respiratory tract infection and 2 for fever) within one year. Of these 15 patients 6(40%) patients were found to have persistent bacteriuria at one year follow up. Among 28 patients who were not exposed to antibiotics during the study period 19(67.8%) continued to have persistent ASB at the end of study period.

| Organism                        | Prevalence |
|---------------------------------|------------|
| Escherichia coli                | 16 (37.2%) |
| Klebsiella pneumoniae           | 6 (13.9%)  |
| Enterococcus sp.                | 4 (9.3%)   |
| Pseudomonas aeruginosa          | 3 (6.9%)   |
| Staph aureus                    | 3 (6.9%)   |
| Candida sp.                     | 3 (6.9%)   |
| Coagulase negative staphylococci| 2 (4.7%)   |
| Proteus sp.                     | 2 (4.7%)   |
| Other Gram-negative bacteria     | 4 (9.3%)   |

**Table 2. Urine Isolates Among Diabetic Patients with ASB**

| Abbreviations: ASB- Asymptomatic Bacteriuria; Staph- Staphylococcus; sp- Species.

| Variable                          | Total Patients N=250 | Asymptomatic Bacteriuria N=43 | Non Bacteriuric Patients N=207 | p Value |
|-----------------------------------|----------------------|-------------------------------|-------------------------------|---------|
| **Age (years)**                   | 54.6±9.4             | 56.3±6.9                      | 53.7±11.2                    | 0.34    |
| M:F                               | 1.5:1                | 4:4:1                         | 1.25:1                       | <0.01   |
| Females                           | 150 (60%)            | 31 (72.1%)                    | 119 (57.48%)                 | <0.01   |
| Pre-menopausal                    | 92 (61.34%)          | 17 (54.8%)                    | 75 (63.0%)                   | <0.01   |
| Post-menopausal                   | 58 (38.67%)          | 14 (45.2%)                    | 44 (36.98%)                  | <0.01   |
| Males                             | 100 (40%)            | 12 (27.9%)                    | 88 (42.5%)                   | <0.01   |
| BMI (kg/m²)                       | 24.6±2.6             | 23.9±3.2                      | 25.4±1.9                     | 0.23    |
| Hypertension                      | 96 (38.4%)           | 18 (41.86%)                   | 78 (37.68%)                  | 0.51    |
| eGFR (ml/min./1.73m²)             | 96.1±12.5            | 98.3±18.7                     | 95.4±10.8                    | 0.49    |
| HbA1c                             | 8.6±1.4              | 8.2±1.1                       | 8.6±1.5                      | 0.84    |
| Autonomic Neuropathy              | 56 (22.4%)           | 11 (25.6%)                    | 45 (21.7%)                   | 0.62    |
| Micro-                            | 38                   | 7                              | 31                            | 0.76    |

**Table 3. Outcomes at One Year of Follow up**

| Abbreviations: eGFR- Estimated Glomerular Filtration Rate; HbA1c- Glycated Haemoglobin; UTI- Urinary Tract Infection.

| Outcome                        | Asymptomatic Bacteriuria N=43 | Non Bacteriuric Patients N=207 | p Value |
|--------------------------------|-------------------------------|-------------------------------|---------|
| Symptomatic UTI                | 10 (23.26%)                  | 39 (18.84%)                  | 0.07    |
| Hypertension                   | 16 (37.3%)                   | 75 (36.2%)                   | 0.39    |
| eGFR (ml/min./1.73m²)          | 94.7±13.2                    | 96.5±11.6                    | 0.42    |
| HbA1c                          | 8.4±1.2                      | 8.2±1.4                      | 0.57    |
| Microalbuminuria               | 7 (16.28%)                   | 30 (14.9%)                   | 0.31    |
| Macroalbuminuria               | 3 (6.98%)                    | 14 (6.76%)                   | 0.24    |

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Asymptomatic bacteriuria is more commonly found in females compared to males. Previously done studies also found similarly higher prevalence of ASB in females compared to males. A study done by Venkatesan et al, found a prevalence of ASB of 40% among females as opposed to 24% in males. Similarly study done by Bissong M E A et al, showed a prevalence of ASB in 34% of females compared to 7% in males in their study group.

Earlier studies have shown a prevalence of 8 to 26% in female diabetic patients. In this study prevalence of ASB was 17.2% in study group, 20.6% in female patients and 12% in male patients which is in agreement with results shown by earlier studies. Girish Babu et al. showed a prevalence of 12% in their study. While a meta-analysis involving studies with total 3539 patients showed a prevalence of 12.2%. Slightly higher prevalence was reported by Venkatesan et al, with total 3539 patients showed a prevalence of 12.2%.

Similarly follow up studies have also shown persistent bacteriuria at 1 year (n=43) of patients which was significantly higher than in previous studies. Girish Babu et al. showed a prevalence of ASB in 34% of females compared to males. A study done by Venkatesan et al, found a prevalence of ASB to be 32% of their study population while earlier studies have shown equal incidence of symptomatic UTI in diabetic patients with or without ASB. A study involving follow up of 3 years of group of diabetic patients with ASB did not found any beneficial effects of antibiotic treatment. Geerlings SE et al, followed up 636 diabetic patients for 18 months and found a higher incidence of symptomatic UTI in patients with type 2 diabetes mellitus and ASB compared to those without ASB at baseline. Although study by Ribera M.C. et al had shown increased incidence of symptomatic UTI in diabetic patients with ASB (69.2%) compared to those not having ASB(9.8%). Metanalysis done by Koves B et al found that for most people, treatment was not beneficial and may be harmful.

We also found that presence of ASB does not affect renal function, rate of renal function decline, presence of microalbuminuria or hypertension. Microalbuminuria and renal dysfunction has not demonstrated any correlation with ASB in recent studies. Study by Meiland R et al included 644 female patients with diabetes mellitus with ASB did not found an increased risk for development of hypertension or worsening of renal function at 6 years of follow up. A population-based screening study in Sweden done by Bengtsson C et al enrolled women with ASB were treated for bacteriuria at time of initial diagnosis. At 2 years of follow-up after treatment of bacteriuria it recurred in 52%. These women were further followed up and evaluated at 15 and 28 years follow-up, an increased frequency of bacteriuria was found in women with initial ASB, incidence of kidney disease and hypertension was not increased in patients with ASB at recruitment.

We found that most patients who had ASB at enrolment continued to have bacteriuria even at follow up of one year. Similarly follow up studies have also shown persistent bacteriuria in diabetic females initially detected to have ASB. Study conducted by Nicolle, L.E. et al found the prevalence of bacteriuria to be 50% in diabetic female patients observed that E. coli (37.5%) was the most prevalent organism isolated from urine cultures in their study. In contrast to these studies few have shown other organisms being more common. Bissong et al, in their study found Coagulase-negative staphylococci were the predominant organisms (36.3%) isolated, Klebsiella pneumonia (seen in 42.4%) was the most common organism isolated in the study done by Alebiosu et al. The other commonly isolated organisms included Klebsiella pneumoniae (13.9%), Enterococcus faecalis (9.3%), Staphylococcus aureus (6.9%), and Candida spp. (6.9%) which is in concordance with findings of various studies.

Incidence of symptomatic UTI was similar in both the groups at one year of follow up. Other studies have also shown equal incidence of symptomatic UTI in diabetic patients with or without ASB. A study involving follow up of 3 years of group of diabetic patients with ASB did not found any beneficial effects of antibiotic treatment. Geerlings SE et al, followed up 636 diabetic patients for 18 months and found a higher incidence of symptomatic UTI in patients with type 2 diabetes mellitus and ASB compared to those without ASB at baseline. Although study by Ribera M.C. et al had shown increased incidence of symptomatic UTI in diabetic patients with ASB (69.2%) compared to those not having ASB(9.8%). Metanalysis done by Koves B et al found that for most people, treatment was not beneficial and may be harmful.

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patients at about 9 months of follow up and this persisted throughout their 3 years of follow-up.37

CONCLUSIONS
Asymptomatic bacteriuria is common in diabetic patients and it is more common in females. Post-menopausal females have higher prevalence of ASB. Risk of symptomatic UTI appears to be comparable to general diabetic population. Gram negative organisms are most common causative organism of ASB, E.coli being most common. Hypertension, renal function and microalbuminuria do not appear to be affected by presence of ASB.

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