Prevalence of asymptomatic bacteriuria in patients with diabetes mellitus- a distribution analysis.

Running title: A study on prevalence of asymptomatic bacteriuria among diabetes patients.

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Abstract:

Diabetes Mellitus is a metabolic disorder in which there is an impairment of the metabolism of carbohydrates, fats, and proteins. The conditions are caused either by a lack of insulin secretion in the case of Type 1 DM / insulin dependent diabetes mellitus (IDDM) or by decreased sensitivity of tissues to insulin in the case of Type 2 DM / non-insulin dependent diabetes mellitus (NIDDM). Uropathogenic E coli (UPEC) is one of the most common causes of urinary tract infections.Among patients with diabetes mellitus, we aimed to determine the prevalence of ASB.164 diabetes mellitus patients were included in this study with proper demographic data. Urine culture was done to isolate the predominant organisms among the study population. The results were tabulated and analysed.The mean age of asymptomatic bacteriuria was 48 years, with a preponderance of females. If fasting blood glucose is above 230mg/dl, postprandial blood glucose is above 260mg/dl, and HbA1c is 7%, caution is advised.Escherichia coli is the most common cause of asymptomatic bacteriuria, which can also be caused by other gram-negative organisms. Staphylococcus aureus was the least commonly isolated organism in ASB.

Keywords: Diabetes, ASB, Bacteriuria, Asymptomatic, E.Coli

INTRODUCTION:

Diabetes Mellitus is a series of metabolic disturbances caused by impaired metabolism of carbohydrates, fats, and proteins. The conditions are caused either by a lack of insulin secretion in the case of Type 1 DM / insulin dependent diabetes mellitus (IDDM) or by decreased sensitivity of tissues to insulin in the case of Type 2 DM / non-insulin dependent diabetes mellitus (NIDDM). Currently, there are several factors leading to the development of type 1 diabetes, including viral infections (which destroy insulin-producing cells), autoimmune disorders and hereditary tendencies towards the degeneration of insulin-producing beta cells. The cause of type 2 diabetes is due to an inadequate level of insulin receptors on the surfaces of target cells in the body. Basically, insulin resistance is characterized by a reduced sensitivity of insulin to the body's own cells, which are responsible for metabolizing glucose in the body. Common symptoms of diabetes are polyuria, which is frequent urination, polydipsia, which is excessive thirst, and polyphagia, which is excessive hunger.Type 1 diabetes is treated with the administration of exogenous insulin, whereas type 2 diabetes is treated with drugs such as thiazolidinedione and metformin to increase insulin sensitivity in patients suffering from type 2 diabetes(1,2). There is a high risk of urinary tract infection (UTI) in diabetics.There are a number of reasons for this, but it is mainly due to the high glucose content in their urine. According to the National Centre for Biotechnology Information (NCBI), patients with type 2 diabetes are more likely to experience urinary tract infections (UTIs) that are more frequent and severe.Complicated urinary tract infections associated with diabetes include renal and perirenal abscess, the gas-forming infections, such as emphysematous,pyelonephritis and emphysematous cystitis, fungal infections, xanthogranulomatous pyelonephritis, and renal papillary necrosis(2).

The gram-negative bacteria E. coli, commonly known as Escherichia coli, is anaerobic and rod-shaped; it's common in the lower intestine because it's anaerobic. Most strains of E. coliare harmless. Human food poisoning can be caused by some serotypes of this bacteria (EPEC, ETEC, etc). It produces vitamin K2 that prevents colonization by pathogenic bacteria in the intestine, thus they enjoy a mutually beneficial relationship. Along with other bacteria, E.coli is expelled into the environment in faeces. After being introduced into fresh faeces, the bacterium grows rapidly in air for three days, but then slowly declines(3). Facultative anaerobes, such as E.coli, comprise about 0.1% of gut microbiota, and the majority of these strains cause disease through faecal-oral transmission, their most common route of spread. The presence of faecal contamination in an environment can be detected by testing environmental samples for cells that can survive outside the body for a limited time. Increasing amounts of research have examined E.coli's environmental persistence, which can survive outside its host for up to several days and grow for a very long time. Growth of E.coli requires carbon and energy sources in chemoheterotrophic medium. Biotechnology and microbiology have extensively used E.coli to create recombinant DNA. When conditions are favourable, replication can be completed in just 20 minutes(4).

Although most E coli strains require the gut to live, virulent strains may cause gastroenteritis, urinary tract infections, meningitis in neonates, hemorrhagic colitis, and Crohn's disease. Common signs and symptoms include severe abdominal cramps, diarrhoea, hemorrhagic colitis, vomiting, and sometimes fever. Viral strains may also cause bowel necrosis (death of tissue) and perforation in rare cases without progressing to hemolytic-uremic syndrome, peritonitis, mastitis, sepsis, or Gram-negative pneumonia. It is more likely for very young children to develop serious illnesses, such as hemolytic uremic syndrome, but people of all ages are susceptible to severe consequences from infections with E. coli(5).

Uropathogenic E. coli (UPEC) is a leading cause of urinary tract infections. A normal microbiota in the gut can introduce it in many ways. Faecal contamination of urogenital orifices can occur as a result of wiping backwards after defecation, especially for females. UPEC can also be introduced into the male urethra during anal intercourse, and when switching from anal to vaginal intercourse, UPEC can also enter the female urogenital system (6).

Escherichia coli asymptomatic bacteriuria (ASB) is common among people with diabetes mellitus, but the duration and the rates of recolonization of this infection are unknown.E.coli colonization durations and rates of recolonization have been estimated in the past among diabetic women with ASB, as well as the difference between uropathogenic and commensal strains(7). Compared with women without diabetes mellitus (DM), women with ASB and symptomatic urinary tract infections (UTIs) are more likely to experience these conditions(8). In addition to differences between diabetics and non-diabetics in their immune responses to infection, diabetics also have different infecting organisms(9). Based on studies in the past, it has been shown that the increased prevalence of ASB in diabetic women is not due to a difference in the bacteria that cause ASB, since the same number of virulence factors were found in the Escherichia coli microorganisms (the species that most commonly causes ASB) in our diabetic patients with ASB, which were also found in the literature for nondiabetic patients with ASB(10). According to studies conducted in vitro, there is an increase in the growth of bacteria when glucose concentrations are altered, and this increase was also found in urine from poorly controlled patients. The researchers, however, were unable to confirm that glycosuria was a risk factor for ASB in vivo(11). The researchers also showed that women who had both diabetes mellitus and ASB had lower levels of urinary cytokines and leukocytes than women who did not have diabetes mellitus but had ASB (12). Diabetes women are more likely to be infected with E.coli that expresses type 1 fimbriae than women without diabetes who do not express type 1 fimbriae.

Diabetes mellitus patients often develop asymptomatic Escherichia coli bacteriuria (ASB), but there is no information on the duration and rate of recolonization. The authors in a research estimated the duration of colonization and the rate of recolonization among successively isolated E. coli from diabetic women with ASB and compared the virulence profiles with uropathogenic and commensal E. coli (7). Women with diabetes mellitus (DM) have asymptomatic bacteriuria (ASB) and symptomatic urinary tract infections (UTIs) more often than women without DM. Diabetic patients are more likely to develop bacteriuria than nondiabetic patients because of differences in host responses or differences in the bacteria that cause it(9). It was shown that the increased prevalence of ASB in diabetic women is not the result of a difference in bacteria, because the same number of virulence factors was found in the infecting Escherichia coli (most common causative microorganism of ASB) in our diabetic women with ASB, as listed in the literature for nondiabetic patients with ASB. Different glucose concentrations increased bacterial growth in vitro, as observed in poorly controlled patients. Glycosuria, however, was not a risk factor for ASB in vivo. The urine cytokine and leukocyte concentrations of women with both DM and ASB are lower than those without DM (12). The type 1 fimbriae of E coli (the virulence factor responsible for UTI pathogenesis) adhere better to uroepithelial cells of women with diabetes than to those without diabetes. Our study aimed to know the prevalence of ASB among patients with diabetes mellitus.

MATERIALS AND METHODS:

The study was carried out in the central lab, Madha medical college and Research institute between March 2022 to October 2022. After a proper informed consent, a clean catch midstream urine collected in sterile container from 164asymptomatic diabetic patients confirmed with fasting and postprandial blood sugar values and HbA1c. Person will be educated how to collect clean catch midstream urine. Urine collected is transported immediately to the central lab and processing will be done. The bacterial flora causing UTI in diabetic patients is identified and the antibiotic susceptibility patterns of the isolates are obtained. The prevalence of ESBL among those bacterial isolates are identified.**Inclusion criteria** considered were,1) Patients with history of diabetes mellitus,2)Patients should not be on antibiotic course for 15 days before study,3) Age group- 30years to 60 years,4) Both males and females,5) Patients without any complication like retinopathy, nephropathy, polyneuropathy due to diabetes mellitus and 6) Diabetics without any other debilitate/co-morbid condition. **Exclusion criteria were**, 1)Diabetic patients with UTI symptoms,2) Diabetic patients with complications and 3) Diabetic patients with debilitate co-morbid condition.

Methodology:
About 5ml of urine was collected from each study population. CCMSU was collected in sterile universal containers in the central lab from patients who were attending diabetic Out Patient Department (OPD).After centrifugation, urine sample was examined under high power objective (40x) for presence of pus cells and bacteria.A semi quantitative calibrated loop technique was done. A loop which delivers 0.01ml of urine was used. Sample from well mixed uncentrifuged urine was streaked on to the surface of MacConkey agar and standard loop technique of streaking was used for nutrient agar and CLED agar medium. The plates were then incubated at 37^{o}C overnight in an incubator. Cultures grown on the media were counted using hand lens and sample showing colony count less than 10^{5}/ml were excluded from the study. The organism thus isolated were characterized based on Gram’s Staining, motility and standard biochemical reactions such as slide and tube catalase test, slide and tube coagulase test, indole test, MR test, VP test, citrate utilisation test, urease test, nitrate reduction, oxidase test, triple sugar iron (TSI) test, carbohydrate fermentation tests. Plates used for the study are nutrient agar and MacConkey agar and special media CLED agar was used.The antibiotic storage container was refrigerated at 4 – 8^{o}C or kept frozen at -14^{o}C. β- Lactam antibiotics were stored frozen. Some unstable antibiotics like cefpodoxime and clavulanic acid retained greater stability when stored frozen till the day of use. Disc containers were brought to room temperature before use. Cartridge of discs placed in a tightly sealed container.

16-18 hrs of incubation after the inoculation with the sample, plates were examined. The plates which were satisfactorily streaked with proper inoculum showed uniformly circular zones of inhibition and a confluent lawn of growth was seen. The test was repeated when individual colonies were apparent, the probable reason could be too light inoculum. The diameter of the zones of complete inhibition were measured using a sliding caliper which was held on the back of the inverted Petri dish, including the diameter of the disc. The Petri plate was held a few inches above a black, non-reflecting background and illuminated with reflected light. The area which showed no obvious visible growth with the naked eye was taken as zone margin. The tiny colonies which were detected only with the magnifying lens was ignored. Discrete colonies that grew within a clear zone of inhibition were sub-cultured, re-identified and retested. The sizes of the zones of inhibition were interpreted by referring to the Clinical and Laboratory Standards Institute (CLSI) standards and reported as susceptible, intermediate, or resistant to the agents that have been tested. Commercially obtained, Escherichia coli ATCC 25922, Staphylococcus aureus ATCC 25923 were used as control samples. The descriptive data of gender distribution,fasting blood sugar (FBS), Post prandial blood sugar (PPBS), HbA1C, urine culture sensitivity were recorded.

Statistical analysis of data

Descriptive statistics were computed by arithmetic mean and standard deviation. Pearson Chi Square test was used to quantify the extent of relationship between the ESBL producers and other quantitative variables. SPSS version 23.0 was used for statistical analysis. All the statistical tests used for analysis were two tailed. $P<0.05$ was considered as statistically significant.

Results:

Bacterial isolates obtained from one hundred and sixty-four diabetic patients without symptoms of UTI to find the prevalence of most common organisms out of all isolates. Study included patients of both sexes between 30 and 60 years of age. Specimen included was urine. Out of one hundred and sixty-four specimens collected, in 81 specimens organisms were isolated. Seventy isolates were identified as gram negative bacilli which included E.coli, K.pneumoniae, K.oxytoca, Proteus mirabilis by biochemical reactions. Six out of them were gram positive cocci.

The results were analysed as follows.

Table 1: Gender and age distribution:

Gender	Total Number	Minimum age	Maximum age	Mean Age	SD
Diabetic Male	108	31	59	48.26	8.06
Diabetic Female	56	31	59	48.23	7.89

Table 2: Fasting and Post Prandial Blood Glucose and HbA1C values of study population

Blood glucose level	Minimum	Maximum	Mean	SD
FBS	86	393	234.92	84.08275
PPBS	111	421	262.7622	79.20664
HbA1C	5	11	7.018293	1.614629

Table 3: Distribution of Culture positive samples.

Number of culture positive in female	Number of culture positive in males	Total culture positive samples
43(52.43%)	38(46.34%)	81(49.3%)

Table 4: Distribution of the organisms cultured from the urine samples.

Samples	Total isolates	E.coli	K.pneumoniae	K.oxytoca	P.mirabilis	Candida	S.aureus	No Gro
Female urine sample	43	23	11	2	2	3	2	39
Male urine sample	38	20	9	4	4	1	0	44
Total	81	43(26.2%)	20(12.2%)	6(3.7%)	6(3.7%)	4(2.4%)	2(1.2%)	83(5

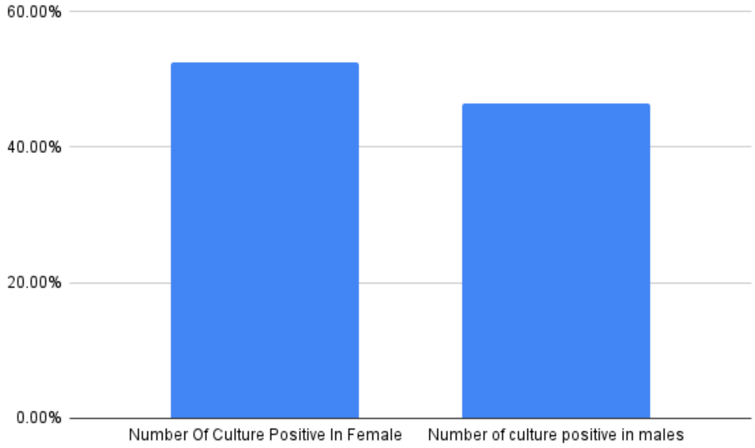

Figure 1: Gender distribution of the culture positive samples.

DISCUSSION:

This study was aimed to analyse the prevalence of asymptomatic bacteriuria in Diabetes mellitus individuals. Out of 164 study population in our study showed that most of the diabetic population were of males(n=108) than the females(n=56) as shown in Table 1. The predominance of the males in case of diabetes mellitus was also documented in many researches especially the study by Yeshitela et al mentioned that prevalence of diabetes mellitus is more in males. This is well correlated with over study.(13).The age distribution was shown in Table 1, our study population has a mean age of 48 years for both males and females. The similar report was obtained by a previous literature that most of diabetes mellitus were prevalent at an range of 40-50 years of age, which was correlating with our study. (14)

As tabulated in table 2, the study population showed a mean fasting blood sugar value of 234.92 mg/dl, mean postprandial blood sugar value of 262.76 mg/dl, HbA1C mean value of 7%. The treatment for diabetes mellitus has not considered as the standard values will not fall in a particular range. These findings were obtained in many previous studies and one such evidence was the research done by Woldemariam in 2019 stated the average fasting and post prandial blood sugar levels in diabetes mellitus patients under treatment. (15)

Out of 164 study population, 81(49.3%) samples showed culture positivity, in that the bacteriuria was found to be higher in females (n=43(52.43%)) than males (n=38(46.34%)) as shown in the table 3 and figure 1. Many of the previous literature highlighted that asymptomatic bacteriuria is more common in females than males. One such evidence is the study done by Dalal et al in 2009.(7). Distribution of the organisms cultured from the urine samples of asymptomatic diabetic patients was shown in table 4.Escherichia Coli is the most prevalent organism which is isolated in many of the diabetes mellitus patients without having symptoms and patients undergoing antidiabetic treatment. In many literatures it was highlighted in symptomatic patients except a study from Hamdam et al in 2015 found the similar results of our study that we isolated E.Coli in 43 out of 81(53%) culture positive patients among the 164 study population(16). Followed by E.Coli, other gram negative organisms like, K.pneumoniae, K.oxytoca and P.mirabilis also isolated from the study population in an average of 20(24%),6(7%), 6(7%) out of 81 culture positive study population(17). Candida, yeast like fungal organisms were isolated in 4 out of 81(5%) patients followed by least gram positive organism which isolated in our study was Staphylococcus aureus in 2 out of 81 (2%)culture positive samples(18,19).

While analysing the risks, persons with diabetes are at an increased risk of developing an UTI if they have a history of UTI and recently engaged in sexual activity. UTI risk is twice as high for those with diabetes as for those without diabetes, but the reason why this is true is unknown. There is a hypothesized link between bladder dysfunction and low control of diabetes, resulting in glycosuria(20). Epidemiological data, however, do not consistently support these hypotheses(21). Diabetes-related impaired voiding function increases the risk of recurrent UTIs among postmenopausal women with diabetes.Postmenopausal women with diabetes are more likely to get UTIs than those without diabetes(22). As in our study with females with average age of 48years has asymptomatic bacteriuria. As a marker of diabetic-induced nephropathy, proteinuria is more common in patients with diabetes and ASB. Proteinuria does not necessarily predict an increased risk of UTI(23). There is an association between increased post residual urinary volume and ASB among men, as well as prostate hypertrophy and UTIs, which are not specific to diabetes(24). Glycosuria or poor diabetic control may contribute to UTI risk among diabetics, but the evidence is similarly weak. Washington State researchers found no association between diabetes duration, HbA1C levels, and specific diabetic complications (retinopathy, neuropathy, or nephropathy) and the risk of cystitis or pyelonephritis(25). Postmenopausal women were not found to be at greater risk of UTI due to either diabetes duration or HbA1c level. Nevertheless, women taking insulin and those who have had diabetes for a longer period are at greater risk for UTIs than nondiabetic women(26). In a 2013 study conducted in Taiwan, the level of HbA1C, among other factors, was associated with urosepsis caused by E. coli, as compared with ASB or noncomplicated UTI. In contrast, this was not the case with ASB(27).As compared with diabetic subjects without ASB, mean HbA1C did not differ for diabetics with ASB in 10 phase 3 antidiabetic clinical trials(28). It was well correlating with our study with a range of 5-11% HbA1c and mean of 7%.

To determine the prevalence of E. coli versus other organisms in our study, no comparison was made between diabetics and non-diabetics. In addition to antibiotic sensitivity results, it may be better to include the treatment protocol for patients with asymptomatic bacteriuria. Future studies with elaborative data will take this into consideration.

CONCLUSION:

Within the limitations of our study, we found the mean age of asymptomatic bacteriuria to be 48 years, with a preponderance of females. It is prudent to be cautious if the average fasting blood glucose level is over 230mg/dl and postprandial blood glucose levels are over 260mg/dl and the average HbA1c is 7%. The most common cause of asymptomatic bacteriuria is Escherichia coli, which may also be caused by other gram-negative organisms. The least commonly isolated organism was Staphylococcus aureus. In the future, we hope to compare asymptomatic bacteriuria among diabetics and non-diabetics as well as antibiotic sensitivity and treatment protocols for asymptomatic bacteriuria among diabetic patients.

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