ORIGINAL ARTICLE

INCIDENCE MICROBIOLOGICAL PROFILE AND DRUG RESISTANCE PATTERN OF UROPATHOGENS CAUSING ASYMPTOMATIC BACTERIURIA AMONG BELOW POVERTY LINE DIABETIC MALE PATIENTS

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ABSTRACT

Introduction: With the prevalence of DM increasing among rural population in developing countries, factors associated with diabetes and its complications also becomes more important. More than half of diabetic patients with ASB have upper urinary tract involvement and the frequency of symptomatic UTI had been significantly higher. Symptomatic UTIs tends to be more common in diabetic subjects with ASB than in those without ASB. Although ASB is of major concern in diabetic population, the long-term consequences of ASB in patients with DM are poorly documented, Almost all studies were performed among elderly women with type 2 diabetes and there is very little information on the occurrence of ASB among BPL diabetic males in our local setting. Hence in the present study the incidence and etiology of ASB among BPL diabetic male patients was monitored along with the resistance pattern of bacterial isolates to antimicrobial agents.

Materials and methods: Clean catch voided midstream urine samples were collected from 1131 BPL Diabetic male patients enrolled for the study. Wet film of centrifuged urine was performed to detect the presence of pus cells, epithelial cells, erythrocytes, microorganisms, cast. Culture was performed using standard loop method and antimicrobial susceptibility of the isolates was studied using Kirby Bauer disc diffusion method following CLSI guidelines.

Results: Out of 1131 BPL diabetic male patients screened for ASB, 155 (13.7%) were culture positive. Among the uropathogens Gram negative bacilli was the most commonest type (72.7%) and the most prevalent organisms isolated was *Klebsiella spp* (35.2%), *Enterococcus spp* (22.4%), followed by E. coli (19.4 %) ,Pseudomonas aeruginosa (7.3%), etc.,. 87.5% of *E.coli* isolated were ESBL, followed by 77.6 % of *Klebsilla spp* and 11.1 % *Enteroabacter spp. Pseudomonas aeruginosa* reported in this study were 100% ESBL and 16.6% Metallo β lactamase (MBL) producers.8.1 % of Vancomycin resistant Enterococcus (VRE) was also found in this study.

Conclusion: This study demonstrated a high occurrence of ASB in BPL diabetic males (13.7%). Klebsiella was the most commonest uropathogen found in our study followed by Enterococcus , E.coli and Pseudomonas. E.coli and Pseudomonas showed high rates of drug resistance. Nitrofurantoin and Amikacin was the most effective drugs for majority of the isolates. Hence routine monitoring and screening for ASB in this population is essential. Moreover patients in rural parts of developing countries with diabetes has to be sensitized about the complications of ASB and regarding maintenance of their glycemic control which is of major importance in prevention of the condition.

PROFIL MICROBIOLOGIQUE DE L'INCIDENCE ET LA RÉSISTANCE DES UROPATHOGÈNES CAUSANT LA BACTÉRIURIE ASYMPTOMATIQUE CHEZ LES DIABÉTIQUES SOUS LE SEUIL DE PAUVRETÉ CHEZ L'HOMME

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RÉSUMÉ

Introduction: Avec la prévalence de DM en hausse chez les populations rurales dans les pays en développement, les facteurs associés au diabète et à ses complications devient aussi plus important. Plus de la moitié des patients atteints de diabète, à l'ASB ont voies urinaires et la fréquence de l'infection urinaire symptomatique a été sensiblement plus élevé. Infection urinaire

symptomatique a tendance à être plus fréquente chez les sujets diabétiques avec CNA que dans ceux sans BSA. Bien que l'ASB est une préoccupation majeure dans la population diabétique, les conséquences à long terme de l'ASB chez les patients atteints de DM sont mal documentés, presque toutes les études ont été effectuées chez les femmes âgées atteintes de diabète de type 2 et qu'il y a très peu de renseignements sur l'incidence du CNA entre les hommes diabétiques BPL dans notre contexte local. Par conséquent, dans la présente étude, l'incidence et l'étiologie de l'ASB chez les patients hommes diabétiques BPL a été suivie avec le patron de résistance des isolats bactériens aux agents antimicrobiens.

Matériels et méthodes : Nettoyer la route barrée de capture des échantillons d'urine ont été recueillis à partir de 1131 hommes diabétiques BPL patients recrutés pour l'étude. Urine centrifugé de film humide a été effectuée pour détecter la présence de pus, les cellules épithéliales, érythrocytes, micro-organismes, exprimés. La culture a été réalisée à l'aide d'une méthode de la boucle et à la sensibilité aux antimicrobiens des isolats a été étudiée à l'aide de méthode de diffusion disque Bauer Kirby qui suit les lignes directrices du CLSI.

Résultats: sur 1131 patients hommes diabétiques BPL de dépistage de l'ASB, 155 (13,7 %) étaient positifs à la culture. Parmi les uropathogènes bacilles Gram négatif a été la plus commune la plupart type (72,7 %) et le plus souvent organismes isolés a été Klebsiella spp (35,2 %), Enterococcus spp (22,4 %), suivi par E. coli (19,4 %), Pseudomonas aeruginosa (7,3 %), etc.,. 87,5 % d'E.coli BLSE ont été isolés, suivie par 77,6 % des Klebsilla Enteroabacter spp et 11,1 % spp. Pseudomonas aeruginosa rapportés dans cette étude ont été de 100 % et 16,6 % de BLSE Métallo β lactamase (MBL) les producteurs.8,1 % d'entérocoque résistant à la vancomycine (ERV) a également été constaté dans cette étude.

Conclusion: Cette étude a montré une fréquence élevée de l'ASB dans le BPL les hommes diabétiques (13,7 %). Klebsiella a été le plus plus commun uropathogen trouvés dans notre étude suivie d'E.coli et Enterococcus, Pseudomonas. E.coli et Pseudomonas ont montré des taux élevés de résistance aux médicaments. La nitrofurantoïne et l'amikacine a été les médicaments les plus efficaces pour la majorité des isolats. Par conséquent, la surveillance de routine et de dépistage de l'ASB dans cette population est essentielle. De plus les patients dans les régions rurales des pays en développement souffrant de diabète doit être sensibilisés sur les complications de l'ASB et concernant l'entretien de leur contrôle glycémique qui est d'une importance majeure dans la prévention de l'état.

INTRODUCTION

Diabetes, a silent epidemic has been diagnosed in about 31.7 million people in the world which comprises 10% of the world's population, where India stands as the "Diabetic Capital" of the world (1). With the prevalence of both Type I and Type II diabetes increasing worldwide, factors associated with diabetes and its complications also become more important (2). In 2030 the estimated amount of Diabetes in India is 79.4 million (3, 4) and the prevalence among rural areas of India ranges from 2.4% to 2.7% (5, 6). Poverty is found to be a major risk factor for kidney disease (7), hypertension (8), diabetes (9), UTI (10),etc., Diabetes to little knowledge is just an acute metabolic threat to life, but it actually leads to complications that are life threatening and one such complications is Urinary Tract Infection (UTI) (11). Reports on the association of diabetes mellitus (DM) and urinary tract infections (UTI's) has been increasingly found (12) and UTI being the most important cause of morbidity in these patients (11). UTI's generally commence asymptomatically which leads to the symptomatic phase and may lead to serious complications if not properly managed that requires treatment with antibiotics (13). Upper urinary tract infections and the frequency of symptomatic UTI has been significantly higher in half of diabetic patients with asymptomatic bacteriuria (ASB) (14). Diabetic patients have an increased risk of certain symptomatic UTIs such as pyelonephritis, acute cystitis, emphysematous infections, *Candidal* infections, renal and perinephric

abscess (15). The important clinical concerns of ASB in diabetic individuals are its contribution to morbidity, either the short-term risk of developing a symptomatic UTI and its more serious complications or the longer-term risks of developing serious diabetic complications such as nephropathy (16). Complications of ASB include emphysematous cystitis, pyelonephritis and renal papillary necrosis which occurs more commonly in subjects with type II DM (17). The rate of 30% of ASB is a risk factor for development of pyelonephritis (18) and Symptomatic UTIs tended to be more common i.e., 2.8 % higher in diabetic subjects with ASB than in those without ASB (19). The incidence of ASB in diabetic women varied from 9% - 29% and 0.7% -11% in diabetic men (20). Prevalence of ASB is usually 3 times higher in diabetic population compared to non-diabetic population. This is because of the fact that there is metabolic derangement, impaired granulocyte function, neuropathic bladder, increased adherence of bacterial organism to bladder epithelial cells and increased glucose content of urine (21). Moderate and severe glycosuria enhances bacterial growth in-vivo, thereby glycosuria may be one factor contributing to the increased prevalence of the bacteriuria in patients with DM (22) .Uropathogenic bacteria possess specific virulence factors that enhance both invasion and colonization of UTI i.e P-fimbriae of certain strains of *E.coli* (23, 24). The higher prevalence of UTI in diabetic patients does not appear to be based on the difference in virulence of the causative microorganism but due to differences in host

response (24). *E.coli* being the most common pathogen in ASB with 80% of isolates (25). Infections with other Gramnegative bacilli such as *Klebsiella*, *Pseudomonas aeruginosa a*nd *Proteus mirabilis*, *Enterococcus* species, coagulase-negative *Staphylococci* and fungi like *Candida spp*, are also common organisms causing UTI in men (26, 27). Antibiotic resistance of uropathogens is increasingly being reported in Diabetic patients with high occurrence of multiple drug resistant strains (28). Higher percentage of resistance to the most commonly prescribed antimicrobials such as Amoxicillin, Nitrofurantoin, Trimethoprim/Sulfamethoxazole and Ciprofloxacin are reported in isolates from diabetic patients (29). Multi-Drug Resistant (MDR) *E. coli* has also been increasingly reported in UTI (30). Keeping in view the estimated prevalence of DM worldwide, with the increasing burden of DM in the rural areas and the emergence of MDR strains escalating in the developing countries. The only way to thoroughly clarify the significance of ASB in patients with diabetes is to perform high-quality prospective studies on screening and treating ASB (31). Moreover the long-term consequences of ASB in diabetic male patients are poorly documented and there is little data on the occurrence of ASB among Below Poverty Line (BPL) diabetic males in our local setting. Hence with this perspective the present study was undertaken with the objective to determine the incidence and etiology of ASB among BPL diabetic male patients along with the resistance pattern of the bacterial isolates.

MATERIALS & METHODS
A prospective study conducted over a period of 1 year from March 2015 to April 2016 in the Department of Microbiology and Diabetic Outpatient departmentSri Lakshmi Narayana Medical College & Hospital Pondicherry, India. This study was approved by the Institutional Human Ethics Committee and Informed consent was obtained from all participants included in the study. Accordingly all men included in this study were diabetic, BPL card holders of age > 35 years and had not been on any antimicrobials (oral or topical) within the previous 4 weeks. Diabetic male patients with any indwelling urinary tract catheters, history of UTI symptoms dysuria, frequency and urgency, hypertension, known congenital anomalies of urinary tract were excluded from the study. A total of 1131 BPL Diabetic men who attended the diabetic clinic were enrolled in this study. 1131 Clean catch voided midstream urine samples were collected in a sterile wide mouthed culture container from all participants enrolled in this study and it was processed in the microbiology laboratory within 1hr (IDSA 2005) following collection. Microscopic examination of wet film of centrifuged urine was performed to detect the presence of pus cells, epithelial cells, erythrocytes, microorganisms, cast, etc. Urine samples were cultured using standard loop method on to 5%sheep blood agar, MacConkey agar & CLED medium and incubated at 37° C for 24hrs and prolonged incubation was done for 48 hrs if there is no growth after 24 hrs. The growth was interpreted as sterile if no growth after 48 hrs, significant if the number of colonies corresponded to 10^5 Colony forming Units (CFU)/ mL, insignificant growth if colony count was less than 10^5 CFU/ mL and Mixed growth if > 2 types of colonies were present (32) The growth was identified based on Gram staining , Motility , Catalase test, Oxidase test & other routine biochemical tests like Indole, Methyl red test, Vougesproskauer test, Citrate , Urease , Triple sugar iron agar test & Coagulase test as per Cowan and Steels Manual.9. Antimicrobial susceptibility of the isolates was studied using Kirby Bauer disc diffusion method following CLSI guidelines (2012) on Muller Hinton agar plate, the antibiotics tested were Amikacin 30 mcg, Gentamycin 10 mcg , Nitrofurantoin 300 mcg, Ceftazidime 30 mcg, Amoxyclav 30/10 mcg, Cefepime 30 mcg, Co-trimoxazole 25 mcg, Ceftazidime-clavulanicacid 30/10 mcg, Norfloxacin 10 mcg, Clindamycin 2 mcg, Vancomycin 30 mcg, Cefoxitin 30 mcg, Imipenem 10 mcg, Meropenem 10mcg , Imipenem with EDTA , Aztreonam 50 mcg,Gentamycin 120 mcg and Erythromycin 15 mcg (33).

RESULTS
A total of 1131 BPL diabetic male patients were screened for ASB. Among 1131 patients tested 155 (13.7%) were culture positive and reported to have ASB. Out of 1131 urine samples screened 166 (14.7%) of urine samples showed insignificant bacteriuria, 78 (6.9%) samples showed mixed growth & about 732 (64.7%) samples showed No growth. (Table : 1) .

TABLE 1: RESULTS OF URINE CULTURE

Results of culture	No. of cases n = 1131	Percentage (%)
Significant bacteriuria	155	13.7
Insignificant bacteriuria	166	14.7
Mixed Growth	78	6.9
Sterile	732	64.7

TABLE 2: AGE DISTRIBUTION OF CULTURE POSITIVE CASES

Age(yrs)	No. of culture positive cases n = 155	Percentage (%)
36 – 45	22	14.2
46 – 55	13	8.4
56 – 65	70	45.2
66- 75	44	28.4
> 76	06	3.9

(The youngest among the cases studied was 36 years old and oldest was 86 years old)

Of the 155 cases reported to have ASB, the majority of culture positive cases were in the age group 56 - 65 years (45.2%) followed by 66 - 75 years (28.4%) and 36 – 45 years (14.2 %) while the least (3.9 %) was seen in the age group above 76 years (Table : 2).   The distribution of uropathogens isolated from ASB positive cases is listed in (Table :3) .

TABLE 3: DISTRIBUTION OF UROPATHOGENS IN ASB POSITIVE CASES

S.No	Urine isolates	% (Percentage)
1.	Gram negative bacilli	72.7%
2.	Gram positive cocci	22.4%
3.	Yeast	4.8%

Gram negative bacilli was the most commonest type (72.7%) isolated, followed by Gram positive cocci (22.4%) and then yeasts (4.8%). In the present study, 10 cases showed double growth and the most prevalent organisms isolated was *Klebsiella* spp (35.2%), *Enterococcus spp* (22.4%), *followed by E. coli* (19.4   %), *Pseudomonas aeruginosa* (7.3%), *Enterobacter spp* (5.5%), *Proteus mirabilis* (5.5%) and *Candida spp* (4.8%) (Table: 4).

The antibiotic susceptibility pattern of gram negative bacilli revealed, majority of the isolates were sensitive to nitrofurantoin & amikacin except 6 (50%) isolates of *Pseudomonas aeruginosa* and 1 (3.1%) isolate of *E.coli* which was found resistant to nitrofurantoin (Chart :5). 87.5% of *E.coli* strains isolated were Extended spectrum β lactamase (ESBL), followed by 77.6 % of *Klebsillaspp*& 11.1% of *Enterobacter spp* isolated in this study were ESBL.

TABLE 4: MICROBIOLOGICAL PROFILE OF UROPATHOGENS IN CULTURE POSITIVE CASES

Organism Isolated	No. of isolates n = 165	Percentage (%)
E.coli	32	19.4
Klebesillaspp	58	35.2
Enterobacter spp	09	5.5
Pseudomonas aeurigonosa	12	7.3
Proteus mirabilis	09	5.5
Enterococcus	37	22.4
Candida albicans	08	4.8

All the 12 isolates of *Pseudomonas aeruginosa* were found resistant to ceftazidime, ceftazidime - clavulanic acid & gentamicin. *Pseudomonas aeruginosa* reported in this study were 100% ESBL and 16.6% Metallo β lactamase (MBL) producing strains (Table: 6). *Klebsiella spp.* being the most prevalent organism in this study, showed maximum resistance to ampicillin (94.8%), norfloxacin (82.7%), followed by gentamycin (79.3%), ceftazidime (77.6%) and ciprofloxacin (75.9%) (Chart :5). There was 1 (3.1%) multidrug resistant *E.coli* found in this study. Among the gram positive organisms, 3/37 (8.1%) of *Enterococcus spp*isolates were resistant to vancomycin (Table: 6) and the highest percentage of resistance was seen to ampicillin   (40.5%),   erythromycin   (29.7%), ciprofloxacin (27.0%) followed by low level resistance to clindamycin (10.8%).
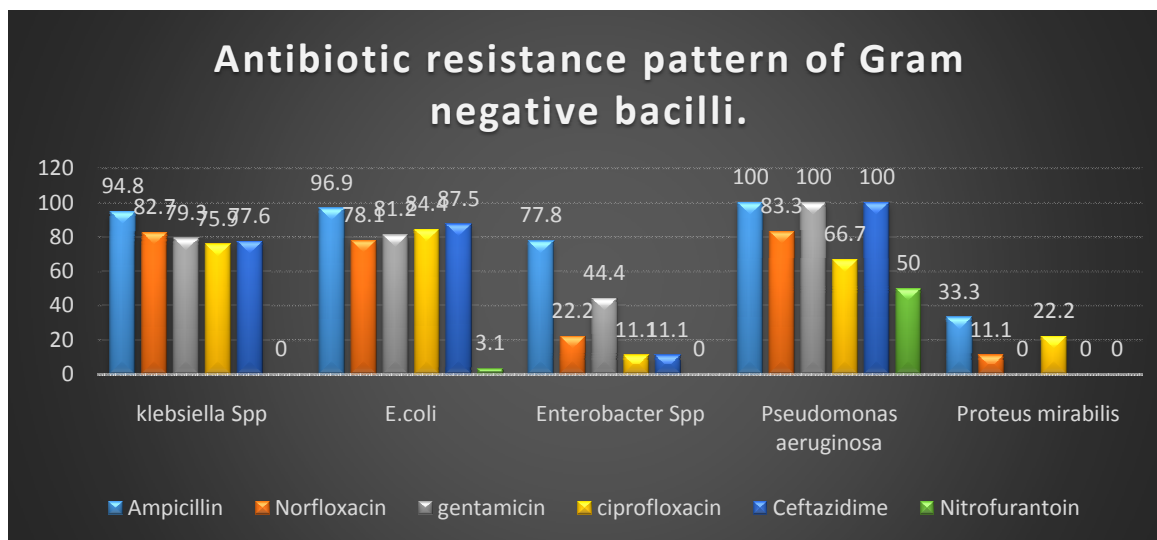
CHART 5: ANTIBIOTIC RESISTANCE PATTERN OF GRAM NEGATIVE BACILLI.

TABLE 6: DRUG RESISTANCE PATTERN OF THE ISOLATED STRAINS

Organism Isolated	Total no. of isolates	Resistant strains (%)
Enterococcus sps	37	3 VRE (8.1%)
Pseudomonas aeurigonosa	12	12 ESBL (100%) 2 MBL (16.7%)
E.coli	32	28 ESBL (87.5%) 1 MDR (3.1 %)
Enterobacter spp	09	01 ESBL (11.1%)
Klebsillaspp	58	45 ESBL (77.6%)
Proteus mirabilis	09	Nil

Foot Notes: VRE: vancomycin resistance Enterococci, ESBL: Extended spectrum β lactamases, MBL: Metallo β lactamase, MDR: Multi drug resistance.

DISCUSSION

The present study was undertaken to determine the incidence rate and etiology of ASB among BPL Diabetic male patients. This study demonstrated a high occurrence of ASB in BPL diabetic males with an overall incidence of (13.7%). This is in concurrence with many other studies as well (34,35, 36). In a study from North Indian Type 2 Diabetic Patients the prevalence of ASB in males was 17.3% (37). Whereas in Bharatpur the prevalence of ASB among diabetic

males patients was reported to be 5.08% (38). Variations in prevalence have been attributed to factors such as geographical variations, ethnicity of the study participants and variation in the screening tests used (1, 34). Studies consistently state that Patients with DM have a higher prevalence of ASB and incidence of UTIs compared to patients without DM (39). Patients with DM had 8.7 % bacteremia and urinary tract was the commonest focus for these infections hence UTI in men should be considered complicated (40). It is well understood that lack of awareness about diabetics and its complications, their financial status and lack of time impedes their regular visit to heath care centers which contributes to the higher incidence in this population. Unfortunately, there is very poor awareness about the real dimension of the problem among the BPL male patients. Moreover the risk of end stage renal disease (ESRD) has been found to be increased in individuals with low income and in low income communities (41) and multiple studies have documented an association of poverty and diabetes with UTI and kidney disease (42, 43,44,45,46). Hence routine monitoring & screening for ASB in this population is essential.

Klebsiella spp. was the most prevalent pathogen 35.2 % in our study which correlated with earlier published reports of Alebiosu et al., were 42.4% was reported (47, 48). However this result was in contrast to majority of published reports where among the gram negative bacilli *Escherichia coli* was the most prevalent uropathogen isolated in diabetic patients with ASB and UTI (21,31,49,50,51). *Enterococcus and Pseudomonas* was also found to be higher in this study. The predominance of bacteria other than *E. coli* in the urinary tract is increasingly being reported (28,52).

The recent study in Nigeria has reported *Staphylococus aureus* to be the most common uropathogen in patients with DM (53) .The occurrence of ASB in BPL diabetic male was highest in the age group 56 – 65 years, but studies consistently document that the prevalence of ASB is not influenced by the age or type or duration of diabetes (20,54). Earlier studies show that symptomatic UTI occurred in 69.2 % of diabetic male patients out of 76.5% of diabetic males with ASB (20). The presence of ASB was found to be the major risk factor for developing symptomatic UTI in diabetic male patients, other risk factors include prostatic syndrome in men (20, 54)**.** Hence further follow up studies are essential to prove or to assess the true incidence of ASB among BPL diabetic males across various age groups and their clinical progression into symptomatic UTI. Moreover there is also inadequate awareness about existing intervention for the prevention of disease in this population.

The antimicrobial sensitivity and resistance pattern differs from each community and each hospital. In our study nitrofurantoin and amikacin was the most effective drugs for the majority of isolates, except 6 isolates of *Pseudomonas aeruginosa* and 1 isolate of *E.coli*, which was found resistant to nitrofurantoin. High rates of drug resistance was found in our study with increased percentage of drug resistance shown by *Pseudomonas aeruginosa, E.coli &Klebsiella spp.* This is in accordance with other studies from developing countries (31, 47, 50, 55, 56). This may be due to indiscriminate use of antibiotics or previous exposure of these patients to antibiotics. Treatment of ASB is still an open issue with no clear guidelines. In U.S., the treatment of ASB is recommended, even though specific screening recommendations do not exist whereas in Europe, ASB is not treated (57). However, many of the patients with ASB can progress to symptomatic UTI (34, 58) and UTI in diabetic patients

is more likely to cause complications than in non-diabetic patients (59). Hence screening and treatment of ASB in diabetics may be warranted. However more studies and Meta-analysis needs to be done before formulating guidelines and for more successful outcome it is essential to educate this population on ASB, its long term complications and importance of treatment adherence once diagnosed. Early diagnosis and prompt treatment of ASB will definitely pave way to reduce health care related expenditure and morbidity.

Conclusion: The incidence of ASB was found to be higher in BPL diabetic male patients. This is one of the major public health importance. Diabetic patients with ASB have a tendency to progress to symptomatic UTI and develop complications from UTI. Hence screening, monitoring and if needed treatment of these patients on a routine basis may be beneficial in such cases. Majority of the isolates in this study showed increased drug resistance. Therefore there is need to create awareness against antibiotic abuse in this population. Proper glycemic control is also of major importance in prevention of the condition. Moreover patients in rural parts of developing countries with DM has to be sensitized about the complications of ASB & UTI which can lead to dreadful consequences in terms of mortality and morbidity.

REFERENCES

1.   Mehta SR, Kashyap AS, Das S. Diabetes mellitus in India: The modern scourge. Medical journal armed forces India. 2009 Jan 31;65(1):50-4.https://doi.org/10.1016/S0377-1237(09)80056-7

2.   Deshpande AD, Harris-Hayes M, Schootman M. Epidemiology of diabetes and diabetes-related complications. Physical therapy. 2008 Nov 1;88(11):1254.http://doi.org/10.2522/ptj.20080020

3.   Mohan D, Raj D, Shanthirani CS, Datta M, Unwin NC, Kapur A, Mohan V. Awareness and knowledge of diabetes in Chennai-The Chennai urban rural epidemiology study [CURES-9]. Japi. 2005   Apr   1;53:283-7. https://www.ncbi.nlm.nih.gov/pubmed/15987011

4.   Kaveeshwar SA, Cornwall J. The current state of diabetes mellitus in India. The Australasian medical   journal. 2014;7(1):45.https://www.ncbi.nlm.nih.gov/pubmed/24567766

5.   Sadikot SM, Nigam A, Das S, Bajaj S, Zargar AH, Prasannakumar KM, Sosale A, Munichoodappa C, Seshiah V, Singh SK, Jamal A. The burden of diabetes and impaired glucose tolerance in India using the WHO 1999 criteria: prevalence of diabetes in India study (PODIS). Diabetes research and clinical practice. 2004 Dec 31;66(3):301-7. https://www.ncbi.nlm.nih.gov/pubmed/15536027

6.   Ramachandran A. Epidemiology of diabetes in India—three decades of research. J Assoc Physicians India. 2005 Jan 29;53(34):8. https://www.ncbi.nlm.nih.gov/pubmed/15857011

7. Nicholas SB, Kalantar-Zadeh K, Norris KC. Socioeconomic Disparities in Chronic Kidney Disease. *Advances in chronic kidney disease.* 2015;22(1):6-15.http://doi.org/10.1053/j.ackd.2014.07.002

8. Coresh J, Wei GL, McQuillan G, Brancati FL, Levey AS, Jones C, Klag MJ. Prevalence of high blood pressure and elevated serum creatinine level in the United States: findings from the third National Health and Nutrition Examination Survey (1988-1994). Archives of internal medicine. 2001 May 14;161(9):1207-16.https://www.ncbi.nlm.nih.gov/pubmed/11343443

9. Robbins JM, Vaccarino V, Zhang H, Kasl SV. Socioeconomic status and type 2 diabetes in African American and non-Hispanic white women and men: evidence from the Third National Health and Nutrition Examination Survey. American Journal of Public Health. 2001 Jan;91(1):76.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1446485/

10. Saleem M, Daniel B. Prevalence of urinary tract infection among patients with diabetes in Bangalore city. International Journal of Emerging Sciences. 2011 Jun 1;1(2):133.https://pdfs.semanticscholar.org/0a41/9741a50cdc637d3230f658cb6d40d2f63039.pdf

11. Viswanath S, Sarda R, D'Souza AO, Mukhopadhyay C. Asymptomatic Bacteriuria among patients with Diabetes mellitus at a tertiary care center. National Journal of Laboratory Medicine. 2013;2:16-19.

12. Jha BK, Singh YI, Khanal LK, Yadab VC, Sanjana RK. Prevalence of asymptomatic bacteriuria among elderly diabetic patients residing in Chitwan. Kathmandu University Medical Journal. 2009;7(2):157-61.

13. BD Sharma, Rohit Bansal, B Gupta , Asymptomatic bacteriuria in diabetics. JIACM 2011; 13(1): 55-59. http://medind.nic.in/jac/t12/i1/jact12i1p55.pdf

14. Najar MS, Saldanha CL, Banday KA. Approach to urinary tract infections. Indian journal of nephrology. 2009 Oct 1;19(4):129.https://www.ncbi.nlm.nih.gov/pubmed/20535247

15. Geerlings SE. Urinary tract infections in patients with diabetes mellitus: epidemiology, pathogenesis and treatment. International journal of antimicrobial agents. 2008 Feb 29;31:54-7.http://dx.doi.org/10.1016/j.ijantimicag.2007.07.042

16. Nicolle LE. Asymptomatic bacteriuria in diabetic women. Diabetes care. 2000 Jun 1;23(6):722-.723.http://care.diabetesjournals.org/content/diacare/23/6/722.full.pdf

17. Ellenberg MA. Development of urinary bladder dysfunction in diabetes mellitus. Annals of internal medicine. 1980 Feb 1;92(2_Part_2):321-3.http://annals.org/aim/article/693787/development-urinary-bladder-dysfunction-diabetes-mellitus

18. Meiland R, Geerlings SE, Stolk RP, Netten PM, Schneeberger PM, Hoepelman AI. Asymptomatic bacteriuria in women with diabetes mellitus: effect on renal function after 6 years of follow-up. Archives of internal medicine. 2006 Nov 13;166(20):2222-7.http://jamanetwork.com/journals/jamainternalmedicine/fullarticle/411234

19. Karunajeewa H, McGechie D, Stuccio G, Stingemore N, Davis WA, Davis TM. Asymptomatic bacteriuria as a predictor of subsequent hospitalisation with urinary tract infection in diabetic adults: The Fremantle Diabetes Study. Diabetologia. 2005 Jul 1;48(7):1288-91.https://www.ncbi.nlm.nih.gov/pubmed/15918016

20. Zhanel GG, Harding GK, Nicolle LE. Asymptomatic bacteriuria in patients with diabetes mellitus. Review of Infectious Diseases. 1991 Jan 1;13(1):150-4.https://www.ncbi.nlm.nih.gov/pubmed/2017615

21. Bonadio M, Boldrini E, Forotti G, Matteucci E, Vigna A, Mori S, Giampietro O. Asymptomatic bacteriuria in women with diabetes: influence of metabolic control. Clinical Infectious Diseases. 2004 Mar 15;38(6):e41-5. http://dx.doi.org/10.1086/381755

22. Geerlings SE, Brouwer EC, Gaastra W, Verhoef J, Hoepelman AI. Effect of glucose and pH on uropathogenic and non-uropathogenic Escherichia coli: studies with urine from diabetic and non-diabetic individuals. Journal of medical microbiology. 1999 Jun 1;48(6):535-9.https://www.ncbi.nlm.nih.gov/pubmed/10359302

23. Johnson JR. Virulence factors in Escherichia coli urinary tract infection. Clinical microbiology reviews. 1991 Jan 1;4(1):80-128.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC358180.

24. Ghenghesh KS, Elkateb E, Berbash N, Nada RA, Ahmed SF, Rahouma A, Seif-Enasser N, Elkhabroun MA, Belresh T, Klena JD. Uropathogens from diabetic patients in Libya: virulence factors and phylogenetic groups of Escherichia coli isolates. Journal of medical microbiology. 2009Aug1;58(8):100614.http://jmm.microbiologyresearch.org/content/journal/jmm/10.1099/jmm.0.007146-0

25. Nicolle LE. Asymptomatic bacteriuria in the elderly. Infectious disease clinics of North America. 1997 Sep 1;11(3):647-62.https://www.ncbi.nlm.nih.gov/pubmed/9378928

26. Mims AD, Norman DC, Yamamura RH, Yoshikawa TT. Clinically inapparent (asymptomatic) bacteriuria in ambulatory elderly men: epidemiological, clinical, and microbiological findings. Journal of the American Geriatrics Society. 1990 Nov 1;38(11):1209-14.https://www.ncbi.nlm.nih.gov/pubmed/2246458

27. Lye WC, Chan RKT, Lee EJ, Kumarasinghe G. Urinary tract infections in patients with diabetes mellitus. J Infect 1992; 24: 169-74. https://www.ncbi.nlm.nih.gov/pubmed/1569307

28. Bonadio M, Costarelli S, Morelli G, Tartaglia T. The influence of diabetes mellitus on the spectrum of uropathogens and the antimicrobial resistance in elderly adult patients with urinary tract infection. BMC infectious diseases. 2006 Mar 17;6(1):54. http://www.biomedcentral.com/1471-2334/6/54.

29. Meiland R, Geerlings SE, De Neeling AJ, Hoepelman AI. Diabetes mellitus in itself is not a risk factor for antibiotic resistance in Escherichia coli isolated from patients with bacteriuria. Diabetic medicine. 2004 Sep 1;21(9):1032-4.https://www.ncbi.nlm.nih.gov/pubmed/15317610

30. Aswani SM, Chandrashekar UK, Shivashankara KN, Pruthvi BC. Clinical profile of urinary tract infections in diabetics and non-diabetics. Australasian Medical Journal. 2014 Jan 1;7(1). http://doi.org/10.4066/AMJ.2014.1906

31. Venkatesan KD, Chander S, Loganathan K, Victor K. Study on Asymptomatic Bacteriuria in Diabetic Patients. International Journal of Contemporary Medical Research.|February 2017 Volume 4: Issue 2 Proteus.;33(4):60.

32. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. Clinical Infectious Diseases. 2005 Mar 1:643-54. http://www.jstor.org/stable/4463100

33. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing. Twenty-first informational supplement. M100-S21, 2011, Wayne, Pennsylvania ,USA : Clinical and Laboratory Standards Institute.

34. Renko M, Tapanainen P, Tossavainen P, Pokka T, Uhari M. Meta-analysis of the significance of asymptomatic bacteriuria in diabetes. Diabetes Care. 2011 Jan 1;34(1):230-5.https://doi.org/10.2337/dc10-0421

35. Colgan R., Nicolle L. E., McGlone A., Hooton T. M. (2006). Asymptomatic bacteriuria in adults. Am. Fam. Physician 74, 985–990.https://www.ncbi.nlm.nih.gov/pubmed/17002033.

36. Hari A. Asymptomatic Bacteriuria in Patients with Diabetes Attending a Tertiary Care Level–A Descriptive Study. International Journal of Preventive and Therapeutic Medicine. 2013 Jan 3;1(1).http://ijptm.com/index.php/ijptm/article/view/176.

37, Hiamanshu DSinghal S, Vaish AK, Singh M, Rana H, Agrawal A. A study of asymptomatic bacteriuria in North Indian type 2 diabetic patients. International journal of diabetes in developing countries. 2017;37(1):42-5.https://link.springer.com/article/10.1007/s13410-015-0430-0

38. Senthamarai S, Sivasankari S, Anitha C, Vasumathi A, Venugopal V, Thenmozhivalli PR, Amsavathani SK. A study on clinical presentation, bacterial profile and its antibiotic sensitivity pattern in urinary tract infections among diabetic patients attending tertiary care hospital, Tamilnadu. infection.International Journal of Applied Research 2016;2(3): 157-159.http://www.allresearchjournal.com/archives/2016/vol2issue3/PartC/2-2-79.pdf

39. Carton JA, Maradona JA, Nuno FJ, Fernandez-Alvarez R, Perez-Gonzalez F, Asensi V. Diabetes mellitus and bacteraemia: a comparative study between diabetic and non-diabetic patients. The European journal of medicine. 1992 Sep;1(5):281-7.https://www.ncbi.nlm.nih.gov/pubmed/1341610

40. Joshi N, Caputo GM, Weitekamp MR, Karchmer AW, Hugoson A, Thorstensson H, Falk H, Kuylenstierna J, Oliver RC, Periodontitis TT, Seppala B. Infections associated with diabetes mellitus. N Engl J Med. 2000 Mar 23; 2000(342):895-6.http://www.nejm.org/doi/full/10.1056/NEJM200003233421215

41. Patzer RE, McClellan WM. Influence of race, ethnicity and socioeconomic status on kidney disease. Nature Reviews Nephrology. 2012 Sep 1;8(9):533-41.http://www.nature.com/nrneph/journal/v8/n9/abs/nrneph.2012.117

42. Martins D, Tareen N, Zadshir A, Pan D, Vargas R, Nissenson A, Norris K. The association of poverty with the prevalence of albuminuria: data from the Third National Health and Nutrition Examination Survey (NHANES III). American journal of kidney diseases. 2006 Jun 30;47(6):965-71.http://doi.org/10.1053/j.ajkd.2006.02.179

43. Crews DC, Charles RF, Evans MK, Zonderman AB, Powe NR. Poverty, race, and CKD in a racially and socioeconomically diverse urban population. American journal of kidney diseases. 2010 Jun 30;55(6):992-1000.https://www.ncbi.nlm.nih.gov/pubmed/20207457

44. McClellan WM, Newsome BB, McClure LA, Howard G, Volkova N, Audhya P, Warnock DG. Poverty and racial disparities in kidney disease: the Regards study. American journal of nephrology. 2010 May 31;32(1):38-46.https://www.ncbi.nlm.nih.gov/pubmed/20516678

45. Volkova N, McClellan W, Klein M, Flanders D, Kleinbaum D, Soucie JM, Presley R. Neighborhood poverty and racial differences in ESRD incidence. Journal of the American Society of Nephrology. 2008 Feb 1;19(2):356-64.https://www.ncbi.nlm.nih.gov/pubmed/18057219

46. Crews DC, McClellan WM, Shoham DA, Gao L, Warnock DG, Judd S, Muntner P, Miller ER, Powe NR. Low income and albuminuria among REGARDS (Reasons for Geographic and Racial Differences in Stroke) study participants. American Journal of Kidney Diseases. 2012 Nov 30;60(5):779-86.https://www.ncbi.nlm.nih.gov/pubmed/22694949

47. Alebiosu CO, Osinupebi OA, Olajubu FA. Significant asymptomatic bacteriuria among Nigerian type 2 diabetics. Journal of the National Medical Association. 2003 May;95(5):344.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2594521/

48. Trautner Barbara W, Gupta Kalpana (2008) Urinary Tract Infections, Pyelonephritis, and Prostatitis In: chapter 288: Harrisons Principles of Internal Medicine p.18.http://accessmedicine.mhmedical.com/content.aspx?bookid=331&sectionid=40727077

49. Papazafiropoulou A, Daniil I, Sotiropoulos A, Balampani E, Kokolaki A, Bousboulas S, Konstantopoulou S, Skliros E, Petropoulou D, Pappas S. Prevalence of asymptomatic bacteriuria in type 2 diabetic subjects with and without microalbuminuria. BMC research notes. 2010 Jun 17;3(1):169.https://bmcresnotes.biomedcentral.com/articles/10.1186/1756-0500-3-169

50. Shill MC, Huda NH, Moain FB, Karmakar UK. Prevalence of uropathogens in diabetic patients and their corresponding resistance pattern: results of a survey conducted at diagnostic centers in Dhaka, Bangladesh. Oman medical journal. 2010 Oct;25(4):282.https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3191656/

51. Boroumand MA, Sam L, Abbasi SH, Salarifar M, Kassaian E, Forghani S. Asymptomatic bacteriuria in type 2 Iranian diabetic women: a cross sectional study. BMC women's health. 2006 Feb 23;6(1):4.https://www.ncbi.nlm.nih.gov/pubmed/16504076

52. Bissong ME, Fon PN, Tabe-Besong FO, Akenji TN. Asymptomatic bacteriuria in diabetes mellitus patients in Southwest Cameroon. African health sciences. 2013;13(3):661-6.https://www.ncbi.nlm.nih.gov/pubmed/24250304

53. Omoregie R, Erebor JO, Ahonkhai I, Isibor JO, Ogefere HO. Observed changes in the prevalence of uropathogens in Benin City, Nigeria. NZJ Med Lab Sci. 2008 Aug;62(2):29-31.http://www.nzimls.org.nz/user/file/147/Uropathogens

54. Nitzan O, Elias M, Chazan B, Saliba W. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. Diabetes, metabolic syndrome and obesity: targets and therapy. 2015;8:129.https://www.ncbi.nlm.nih.gov/pubmed/25759592

55. Lyamuya EF, Moyo SJ, Komba EV, Haule M. Prevalence, antimicrobial resistance and associated risk factors for bacteriuria in diabetic women in Dar es Salaam, Tanzania. African Journal of Microbiology Research. 2011 Mar 18;5(6):683-9. http://www.academicjournals.org/journal/AJMR/article-abstract/B3ACE5940166

56. Nigussie D, Amsalu A. Prevalence of uropathogen and their antibiotic resistance pattern among diabetic patients. Turkish Journal of Urology. 2017 Mar;43(1):85.http://doi.org/10.5152/tud.2016.86155

57. Geerlings SE, Stolk RP, Camps MJ, Netten PM, Hoekstra JB, Bouter PK, Braveboer B, Collet TJ, Jansz AR, Hoepelman AM. Asymptomatic bacteriuria can be considered a diabetic complication in women with diabetes mellitus. InGenes and Proteins Underlying Microbial Urinary Tract Virulence 2002 (pp. 309-314). Springer US.https://www.ncbi.nlm.nih.gov/pubmed/11386891

58. Yacoub R, Akl NK. Urinary tract infections and asymptomatic bacteriuria in renal transplant recipients. Journal of global infectious diseases. 2011 Oct 1;3(4):383.http://doi.org/10.4103/0974-777X.91064

59. Hoepelman AI, Meiland R, Geerlings SE. Pathogenesis and management of bacterial urinary tract infections in adult patients with diabetes mellitus. International journal of antimicrobial agents. 2003 Oct 31;22:35-43.https://doi.org/10.1016/S0924-8579(03)00234-6