Asymptomatic Urinary Tract Infection In Diabetic Patients In Ago –Iwoye, Ogun State, Nigeria.

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Abstract: Diabetes is problem of worldwide dimension. Urinary Tract Infection (UTIS) are a common burden in patients with diabetes mellitus .This study was done to determine the prevalence of UTI among diabetic patients, causative pathogens and their antimicrobial pattern. Three –Hundred and fifty -two (352) patients were given sterile wide-mouth universal containers into which a clean - catch midstream urine samples were collected with symptoms or no signs of urinary tract infection. *Uropathogens* were isolated and identified by using conventional standard micro biological methods. Samples were cultured on blood agar, MacConkey agar and Cysteine Lactose Electrolyte Deficient (CLED) Media and Incubated at 37^0c aerobically for 24 hrs. Antibacterial resistance pattern was determined by standard Kirby –Bauers disc diffusion method .A total of 61 (17.3%) bacterial *uropathogens* were isolated. Out of bacterial isolate, *Escherichia* coli has the highest isolation rate (45.5%), followed by *Klebsiella spp* (26.2%), *Enterococcus spp* (10.0%), *Staphylococcus aureus* (10.0%) while *Enterobacter spp* (6.6%) and (3.2%) for *Pseudomonas aeruginosa* and *Proteus spp* each respectively. The Gram Positive and Gram Negative bacterial accounted for (20.0%) and (80.0%) of the bacterial isolates respectively. Significant *bacteriuria* was strongly associated with history of previous UTI, antibiotic treatment, types of diabetes and blood glucose level ($p<0.05$). Both Gram positive and Gram negative bacterial show significant level of resistance to two or more antimicrobial agents tested. Treatment of *Asymptomatic* and *Symptomatic bacteriuria* in patient with diabetes must be by drug prescribed by physicians after proper laboratory analysis. The misuse of antibiotic, is a major factor responsible for bacterial resistance.

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1. Introduction:

Diabetes mellitus is the most common endocrine disease and is associated with organ complications due to micro vascular and macro-vascular disease. People with diabetes also suffer from simple and complicated infections, although the association between diabetes mellitus and increased susceptibility to infection has been questioned (Wheat et al, 1980 and St. Thornton 1971).

Diabetes mellitus has a number of long term effects on the genitourinary system. This effect pre-disposes to bacterial urinary tract infection (UTI) in the patient with diabetes (Nicolle, 2003). Diabetes Mellitus is a major health problem in Nigeria. The prevalence of asymptomatic bacteriuria (ASB) in women has been reported as in school children (6-7%), during pregnancy (6% asymptomatic) and 10-12% among elderly women (Meiland et al, 2006). Development of asymptomatic UTI in diabetes women has been reported to be much more common than in non-diabetic women, men, and from diabetic out-patients with urinary tract infections (Geerling et al, 2001; Stapleton, 2002; Nicolle, 2005).

Asymptomatic bacteruria is a major risk factor for the development of UTI in pregnancy due to physiological changes (Assel et al., 2009). Other factors include low socio-economic status, sickle cell trait, and grand multiparty. The term bacteriuria means the presence of bacteria in urine and it is taken to be significant if 10^5 organisms per millitre of a fresh "clean catch" urine specimen are present any patient (Alebiosu et al., 2003; Kaasi, 1956). Asymptomatic bacteriuria is established if the diagnostic methods used do not detect presence of pus cell in urine, but the culture of same urine shows at least 10^5 colony forming units (CFU) per unit millitre of urine in subject without clinical symptoms of bacteriuria (Goswami et al., 2001). While symptomatic bacteriuria is the isolation of at least, 10^4 CFUm1 in subject already presenting with the clinical symptoms of bacteriuria studies are limited, but many experts believe that asymptomatic bacteriuria in diabetes should be treated because of the frequency and

severity of upper urinary tract infections in these patients.

Urinary tract is the principle site of infection in diabetic patients. Changes in host defense mechanisms, the presence of diabetes cystopathy and of microvascular disease in the kidneys may play a role in the higher incidence of UTI in diabetic patients (Sridhar et al., 2002). Worldwide about 150 million people are diagnosed with UTI each year UTI continues to be an important and frequent cause of morbidity and mortality in our community and mainly women are predisposed. An association between UTI and diabetes was noted in an autopsy series reported in the 1940 (Bryan et al., 1985). Urinary tract infections are the most commonly found bacterial infections, accounting for nearly seven million OPD visits and one million emergency department visits, resulting in 100,000 hospitalization of women, the elderly and patients with spinal cord injuries and or catheters multiple sclerosis`, HIV and also diabetes (Foxman, 2003).

The urinary infection is the common bacterial infection in human being and urinary tract is the second commonest site after the respiratory tract, for bacterial infection. During last 25 years, two discoveries in particularly, there is high prevalence of UTI in apparently healthy populations all over the world and the second is that the morbidity and mortality of UTI have remained static even though there are many powerful and effective antimicrobial drugs (Delamaire et al., 1997).

The incidence of diabetes mellitus (DM) throughout the world is increasing strikingly and is becoming a serious public health problem especially in the developing countries. It has a long term effect on the incidence of UTI and it has been reported to be around four times higher in diabetics compared to non-diabetic patients (Adeyeba et al., 2007). The exact reasons for this trend remains unclear, a few studies have shown that the reason could be the presence of static pools of urine due to dysfunctional bladders contracting poorly, which serves a favourable media for bacterial growth while others suggest that hyperglygemic urine promotes rapid bacterial growth and colonization (King et al.,1993 and Andriole, 2002). This study was done to determine the prevalence of UTI among diabetes patients, causative pathogens and their antimicrobial pattern.

2. Materials and Methods

This study was done at health centre and other clinics in Ago-Iwoye, Ogun State. Ago-Iwoye is located between $6^0 21^1$N latitudes, and $3^0 55^1$ E longitudes, is situated in Ijebu-North, Ogun State Nigeria.

A cross sectional study was conducted at difference clinic of Ago-Iwoye, during the period from November, 2012 to August, 2013. Informed and consented adult diabetic patients with symptoms and without symptoms of UTI coming for their diabetic clinic check-up at diabetic clinic date at Ago-Iwoye, Ogun State were investigated for UTI's.

Three hundred and fifty-two patients were given sterile wide-mouth universal containers into which a clean catch (Midstream Urine) of about 10-20ml urine was collected on the morning of test. Urine samples were stored at 2-8^0C in the refrigerator until culture time (Cheesbrough, 2000). Urinalysis was carried out using a dip stick (Ref:20150124/20130125). Fasting blood sugar and two-hour post prandial blood sugar were estimated as reported (Alebiosu et al; 2003).Diagnosis of diabetes was made based on the WHO criteria (WHO;1999).

Urine specimen were directly inoculated on to blood agar, Cysteine Lactose Electrolyte Deficient (CLED) media, and Mac Conkey agar (Oxoid Ltd, Basing stroke, Hamsphire, England) using a standard calibrated wire loop (0.002ml) streaked culture plates were incubated at 37^0C overnight. On the next day, the bacterial growth on the respective media was observed, and total colony count was done on blood agar and checked for significant bacteriuria.

Plates were observed under the microscope for bacterial growth after 24-48hours. Colonies greater than 30 or 10^4 colony forming units per millimeters were considered significant. Isolated colonies after purification were initially Gram stained. By using Bergey's Manual of determinative bacteriology, the isolates were biochemically characterized and identified. Biochemical tests including coagulase test, oxidase test, indole, Grams stains as elucidated by Cheerbrough (2000) were carried out on the colonies to ascertain organisms isolated. All the bacterial isolates were preserved on nutrient agar slants at 4^0C and sub-cultured periodically.

Muller Hinton agar was used to determine the sensitivity of isolates to antimicrobial agents using the disc diffusion technique of *Bauer* et al; (1966). The antibiotics used were Ampicillin (AMP), Amoxicillin-clavulanicc acid (AMC), Ceftriaxone (CRO), Chloramphenicol (C), Ciprofloxacin (CIP), Erythromycin (E), Gentamicin (CN), Penicillin (P), Trimethopin-Sulphamethoxazole (SXT) and Tetracycline (TTC). Briefly, colonies of each isolates were emulsified in Bioju bottles containing already prepared normal saline.

A sterile cotton swab was the dipped into the suspension and the excess was removed by gentle rotation of the swab against the surface of the tube. The swab was the used to distribute the bacteria suspension evenly over the entire surface of Mueller

Hinton agar (oxoid). Using a sterile forceps the antibiotic discs were placed on the inoculated plates and incubated at 37^0C for 24hours. Diameter of the zone of inhibition around the disc was measured to the nearest millimeter using a metal caliper and the isolates were classified as sensitive, intermediate and resistance according to NCCLS (2002).

3. Results

A total of 352 mid stream urine samples from patients were collected between the range of 20-70-years which consists 188 female (53.4%) and 164 male (46.6%). A total of 61 bacterial uropathogens were isolated from the patients investigated for UTIs. Of these, 44/61 (72%) were from asymptomatic patients and the remaining 17/61 (28%) were from symptomatic diabetic patients (p= 0.000) (Table 2).

Out of the 61 bacterial isolates, E. coli (45.5%), Klebsiella spp. (26.2%), Enterococcus spp(10.0%),. Staphyloccus aureus (10.0%) while Enterobacter spp (6.6%) and (3.2%) for Pseudomonas aeruginosa and Proteus spp each respectively (table 3). The gram positive and negative bacteria accounted for 12/61, (19.7%) and 49/61 (80.3%) of the bacteria isolates, respectively.

In general statistically significant differences were observed in the isolation frequency of each pathogen in the two groups (P<o. 05).

Antimicrobial susceptibility:

Gram Negative Bacteria.

The antimicrobial susceptibility pattern of gram-negative bacteria (n = 49) is presented in Table 4. All isolates showed intermediate level of resistance (60 - 80%) against ampicillin and chloramphenicol. Low level of resistance (< 60 %) was observed against amoxicillin –clavulanicacid, ciprofloxacin, ceftriaxone, gentamicin and trimethoprim – sulphamethoxazole. High level of resistance (>80%) was observed against tetracycline.

Gram Positive Bacteria

The antimicrobial susceptibility pattern of gram positive bacteria (n = 12) is presented in Table 5. Gram – positive bacteria showed low level of resistance (< 60%) to all anti – microbials tested except for tetracycline.

Discussions

In this study, the overall prevalence of significant bacteriuria (SB) in both symptomatic and asymptomatic diabetic patients was 17.3%. Similar findings have been reported in previous study conducted in Kenya (17.8%) Gizachew et al, (2012), and other countries e.g. in Ethiopia (14%) Feleke et al (2007), Pakistan (21%) Rakhshanda et al, (2008) and Germany (22.5%) Alimohammidiasi et al (2007). Diabetes mellitus has been considered a predisposing factor for UTI, especially in women, in whom the prevalence of asymptomatic bacteriuria is four fold higher when compared to women without diabetes Geerlings et al; (20006). This is not true for men with diabetes, in whom the prevalence of SB is similar to that in the general population. In this study, SB was more common in females (20,2%) than males (14.0%) (p = 0.05) (Table 1 & 2). This is in agreement with previous studies done in Ethiopa, with women (21.0%) while men (14.0%) Tessema et al. (2007). The high prevelance of UTI among female population may be due to decrease of normal vaginal flora (Lactobacilli) prone to infection, less acidic pH of vaginal surface, poor hygienic conditions, short and wide urthra and proximity to anus.

Diabetes mellitus is a major health problem in Nigeria. DM has for a long time been associated with increase in prevalence of bacteriuria compared with patients without diabetes (Harding et al, 2002). In this study, a total of 61 bacterial uropathogens were isoloated. Out of bacterial isolates, Escherichia coli has the highest isolation rate (45.5%), followed by Klebsiella spp (26.2%, Enterococcus spp (10.0%). staphylococcus aurous (10.0%), while Enterobacter spp. (6.6%) and (3.2%) for pseudomonas aeruginosa and protus spp. each respectively. E. coli was the most common pathogen isolated in this study. This is contrast to the report of (Alebiosu et al; 2003) in Nigeria where K. pneumonia was the most common isolate from ASB.

However, the result is consistent with the majority of reports where E. coli had been reported to be the major pathogen in ASB (Olaitan, 2006, Hajeri, 2008, Baqai et al, 2008 and Assel et at; 2009). This is why in general practice most work on pathogenesis of UTI focuses on E. coli because of its high prevalence in UTI (Johnson, 2003). In chronic UTI, a slow growing E. coli with atyphical colony morphology and multi –drug resistance has been reported (Trilzsch et al; 2003).

In general, the present study confirmed that almost no difference in the type and frequency of bacteria isolated in diabestic and non. diabetic patients investigated for UTIs when compared with the findings from the general population observed in Ethiophia (Moges et al, (2002), Tessema et al, (2007), and Asefa et al; (2008). In the present study, significant bacteriuria (SB) was detected in (13.7%) of asymptomatic daibetic patients; similar finding have been reported from diabetes pateins in Nigeria by (Alebiosu et al 2003 and Adeyeba et al 2007) a higher prevalence of (26.6%) and (21.%) respectively. But this study is in line with previous study reported from diabetic patients in Iran (11.1%) Boroumand et al;(2006).

Table 1: Social demographic characteristics of diabetic patients investigated for UTIs in Ago-Iwoye

Age	Total = 352 Sex		City Blood Glucose		Types of Diabetic		Past History of Antibiotic		Duration of Diabatic		Past UTI		Blood Glucose level mg / dL	
	M	F	U	R	1	2	Yes	No	<5yrs	>5yrs	Yes	No	<120	>120
20 - 30	28	32	42	24	28	15	38	27	68	16	31	28	21	30
31 - 40	42	48	47	33	21	49	43	25	49	17	28	65	38	59
41 - 50	29	35	45	23	19	57	32	39	51	24	18	57	25	56
51 - 60	36	40	36	30	20	58	29	46	40	31	9	52	15	51
61 - 70	29	33	34	38	15	69	18	55	19	36	10	54	6	50
Total	**164**	**188**	**204**	**148**	**103**	**249**	**160**	**192**	**228**	**124**	**96**	**256**	**106**	**246**

Key:
U = Urban
R = Rural
M = Male
F = Female

Table 2: The age and sex distribution of diabetes with asymptomatic bacteriuria (ASB) and symptomatic (SB)

Age Years	Male number with ASB/%	SB/%	Female number with ASB/%	SB/%	Total number with ASB/%	SB/%
20-30	2 (16.7)	--	3 (9.4)	1(16.7)	5 (11.4)	1(5.9)
31-40	2 (16.7)	2(18.0)	6 (18.8)	1(16.7)	8 (18.2)	3(17.6)
41-50	3(25.0)	3(27.3)	11(43.7)	2(33.3)	14(40.9)	5(29.4)
51 – 60	3(25.0)	3(27.3)	8 (25.0)	1(16.0)	11(27.3)	4(23.5)
61 – 70	2 (16.7)	3(27.3)	4(12.1)	1(16.7)	6(13.6)	4(23.5)
TOTAL	**12(27.27)**	**11(64.7)**	**32(72.73)**	**6(35.3)**	**44(100)**	**17(100)**

SB – Symptomatic bacteriuria
ASB – Asymptomatic significant bacteriuria

Table 3: Frequency and types of bacteria species isolated from asymptomatic and symptomatic diabetes patients

Types of bacteria Spp	Asymptomatic(%) diabetes patients	Symptomatic (%) diabetes patients	Total (%)
Escheichia coli	20(45.5)	5(29.4)	25(41.0)
Klebsiella spp	9(20.5)	7(41.2)	16(26.0)
Enterococcus spp	4(9.1)	2(1.8)	6(10.0)
Staphylococcus aureus	4(9.1)	2(1.8)	6(10.0)
Enterobacter spp	3(6.8)	1(5.9)	4(6.6)
Pseudomonas aeruginosa	2(4.5)	-	2(3.2)
Proteus spp	2(4.5)	-	2(3.2)
Total	*44(72.1)*	*17(27.9)*	*61(100)*

Table 4 Antimicrobial susceptibility pattern of Gram negative bacteria isolated from urine culture of diabetic patients.

Bacteria isolated	Total No	S/R	AMP No.%	AMC No.%	CRO No.%	CIP No.%	C No.%	CN No.%	SXT No.%	TTC No.%
E. Coli	25	S	10(40,00)	16(64.0)	20(80.0)	23(92.0)	11(44.0)	22(88.0)	19(76.0)	5(20.0)
		R	15(60.0)	9(36.0)	5(20.0)	2(8.0)	14(56.0)	3(12.0)	6(24.0)	20(80.0)
Klebsiella	16	S	-	6(37.5)	7(43.7)	12(75.0)	3(18.6)	3(18.6)	3(18.6)	3(18.6)
SPP.		R	16(100)	10(62,5)	9(56.3)	4(25.0)	13(81.4)	13(81.4)	13(81.4)	13(81.4)
P. aeruginosa	2	S	-	1(50.0)	1(50.0)	2(100)	1(50.0)	-	1(50.0)	-
		R	2(100)	1(50)	1(50)	-	1(50)	2(100)	1(50)	2(100)S
Proteus	2	S	-	-	2(100)	2(100)	-	2(100)	2(100)	-
SPP		R	2(100)	2(100)	-	-	2(100)	-	-	2(100)
Enterobacter										
SPP	4	S	3(75.0)	4(100)	4(100)	4(100)	1(25.0)	3(75.0)	2(50.0)	-
		R	1(25.0)	-	-	-	3(75.0)	1(25.0)	2(50.0)	4(100)
TOTAL	49	S	13(26.5)	(27(55.1)	34(69.4)	41(83.7)	16(32.7)	30(61.2)	27(55.1)	8(16.3)
		R	36(73.5)	22(44.9)	15(30.6)	8(16.3)	33(67.3)	19(38.8)	22(44.9)	41(83.7)

AMP = Ampicillin Amc = Amoxicillin – clavulonic acid SXT = Trimethoprim - sulphomethoxazole
CRO = Ceftriaxone; CIP = Ciprofloxacin TTC = Tetracycline

Table 5 Antimicrobial susceptibility pattern of Gram positive bacteria isolated from urine culture of diabetic patients.

Bacteria isolated	Total No	S/R	AMP No.%	AMC No.%	CRO No.%	CIP No.%	E No.%	C No.%	P	CN No.%	SXT No.%	TTC NO.%
S.aureus	6	S	2(33.3)	4(66.7)	4(66.7)	-	2(33.3)	2(33.3)	-	4(66.7)	-	-
		R	4(66.7)	2(33.3)	2(33.3)	6(100)	4(66.7)	4(66.7)	6(100)	2(33.3)	6(100)	
6(100)												
Enterococcus	6	S	5(83.3)	6(100)	4(66.7)	5(83.3)	5(83.3)	5(83.3)	2(33.3)	4(66.7)	2(33.3)	
SPP		R	1(16.7)	-	2(33.3)	1(16.7)	1(16.7)	(16.7)	4(66.7)	2(33.3)	4(66.7)	
Total	12	S	7(58.3)	10(83.3)	8(66.7)	5(41.7)	7(58.3)	7(58.3)	2(16.7)	8(66.7)	2(16.7)	
		R	5(41.7)	2(16.7)	4(33.3)	7(58.3)	5(41.7)	5(41.7)	10(83.3)	4(33.3)	10(83.3)	(83.3)

E = Erthromycin P= Penicillin TTC = Tetracycline CRO = Cefriaxome CIP = Ciprofloxacin CN = Gentamicin
SXT = Trimethoprim –sulphamethoxazole AMC = Amoxicillin – clavulanic acid. AMP = Ampicillin.

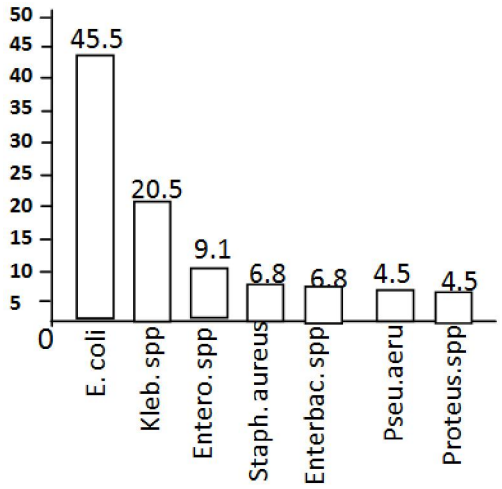

Fig 1: percentage of infection in UTI.

Morphological and biochemical characterization of urinary isolates

In the present investigation significant bacteriuria (SB) was detected in (56.7%) of symptomatic diabetic patients, which is in line with the previous study in Addis Ababa, Ethiopia (51. 4%) reported by Gizacheh et al (2012). The finding of this study shows that diabetic patients are more prone to UTIs than others. In this study, history of previous UTI, previous antbiotic treatment, type II diabetes and blood sugar level have strong association with significant bacteriuria in both symptomatic and asymptomatic diabetes patients (Table I). Previous UTI as a risk factor for ASB indicates that bacteriuria can be present with or without symptoms of UTI. In some reports the presence of UTI during past year, has also been postulated as important risk factor for ASB in diabetics (Hoepelman et al; 2003).

It can be concluded that, the colonization of uropathogens in urinary tract of diabetes after episodes of UTI, decrease local secretion of cytokines and increased adherence of bacteria to uroepithelial cells

can accelerate the prolonged release of bacteria from urinary tract resulting in bacteriuria.

In this study both gram negative and positive bacteria showed intermediate to low level of resistance to one or more antimicrobial agents except for tetracycline (Tables 4 and 5). Similar findings have been reported in previous studies conducted in Ethiopia (Moge et al, 2002 and Tessema et al, 2007) and also in Nigeria (Olaitan; 2006). The high level resistance to tetracycline may be due to easy availability and low cost of the antibiotic. These factors are common in Nigeria, where some patients buy drugs without prescription.

In the present study, gram negative bacteria were relatively susceptible to ciprofloxacin (83.7%) and gentamicine (61.2%) as shown in Table 4. But compare to previous studies conducted in Nigeria where Ciprofloxacin susceptibility among the isolates was 89.9% (Alebiosu et al; 2003) In contrast to the present study, 98.3%) and (97.3%) gram negative bacteria isolated from pregnant women in Addi Ababa, Ethiopia were susceptible to ciprofloxacin and gentamicine respectively (Assefa et al; 2008).

The result also showed that most of the gram negatives isolates (55. 1%) were susceptible to amoxicillin - clavulanic acid. This is a contrast to 70% susceptibility observed to this drug in a previous study from Ethiopia (Assefa et al 2008). Decrease susceptibility to this drug in the present study may be due to self –medication and indiscriminate use like any other antibiotics in the study area.

In this study, S. aureus was resistant to penicillin (100%) as shown in Table 5. It is an established fact, most S. aureus strains produce penicillinase and alternative penicillin binding proteins produce (PBP - 2A) helps the organisms to become resistant to most beta lactam antibiotics to (Moreillon P; 1995). Klebsiella species showed high level of resistance to most antimicrobial agents tested except for ciprofloxacin in the present study (Table 4). It is a well –known fact that Klebsiella spp is inherently resistant to ampicillin, cephalosporins and aminoglycosides due to increasing acquisition of R-plasmids (Rennie R and Duncab I, 1978). Klebsiella spp also produces SHV, a chromosomally mediated penicillinase which can hydrolyze ampicillin and first generaltion cephalosporin's (Barker, 1999).

Amoxicillin clavulanic acid is recommended for treatment of urinary tract infection as it acts on all urinary isolates of E. coli instead of using other broad spectrum antibiotics. The susceptibility of E. coli to amoxicillin clavulanic (64..0%) in this study was not as high as expected.

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