"ASSESSMENT OF ASYMPTOMATIC BACTERIURIA IN ADULT FEMALES WITH TYPE 2 DIABETES MELLITUS IN TERTIARY CARE HOSPITAL, KOLAR"

By

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IN

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Under the guidance of

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I hereby declare that this dissertation entitled **"ASSESSMENT OF ASYMPTOMATIC BACTERIURIA IN ADULT FEMALES WITH TYPE 2 DIABETES MELLITUS IN TERTIARY CARE HOSPITAL, KOLAR"** is a bonafide and genuine research work carried out by me under the guidance of Dr**. LAKSHMAIAH V.** MD, Professor**,** Department of General Medicine. SDUMC, Kolar.

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ABBREVATIONS

ADA	American Diabetic Association
ASB	Asymptomatic Bacteriuria
CFU	Colony Forming Unit
DM	Diabetes Mellitus
E.coli	Eschericia Coli
FBS	Fasting Blood Sugar
HbA1c	Glycated Haemoglobin
PPBS	Post Prandial Blood Sugar
UTI	Urinary Tract Infection
WHO	World Health Organization

ABSTRACT

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The prevalence of type 2 diabetes is increasing all over the world particularly in the developing countries. The WHO estimated that there were 31.7 million persons with diabetes in India in 2000 and this number is likely to be 71.4 million in 2030. India has the distinction of having the largest number of patients with diabetes in the world with increasing incidence worldwide, diabetes mellitus will likely continue to be a leading cause of morbidity and mortality

Asymptomatic Bacteriuria (ASB) is common in neonates, pre school children, pregnant women, elderly people and patients with diabetes.[4] Asymptomatic bacteriuria occurring in diabetes mellitus can cause serious complications like emphysematous pyelonephritis, renal papillary necrosis and renal abscess

OBJECTIVES AND METHODOLOGY

- To estimate the prevalence of asymptomatic bacteriuria among females with diabetes mellitus.
- To identify the causative organisms responsible for asymptomatic bacteriuria in female with diabetes mellitus.
- To determine the antibiotic susceptibility of the isolated organisms
- To correlate asymptomatic bacteriuria with plasma glucose level, macroalbuminuria and glycosuria

A predesigned and pretested proforma/questionnaire was used to collect data regarding personal details, treatment history, duration of diabetes and symptomatology. 100 females with diabetes mellitus are randomly enrolled in the study. These females are the patients of medical wards of department of Internal Medicine, R L Jalappa hospital, Tamaka, Kolar. A randomly selected controlled group of 100 healthy females without diabetes are evaluated in the same period. Fasting blood sugar, post prandial blood sugar, urine routine, glycated haemoglobin, urine culture and sensitivity by Kirby Bauer method of every subject enrolled in the study is done.

RESULTS

29% among cases tested positive for ASB. The most common micro organism isolated was E.coli (23%) among cases followed by Proteus (3%), Coagulase negative staphylococci (2%) and Klebsiella (1%). Most of the bacterial isolate were sensitive to conventional antibiotics.

CONCLUSION

Prevalence of ASB and UTI are more common in diabetics compared to general population. Most common bacterial isolate identified was E.coli. The ASB had significant association with glucosuria, macroalbuminuria and poor glycemic index. The treatment of ASB in diabetics is still debated.

KEYWORDS

Diabetes Mellitus, Asymptomatic bacteriuria, Urinary tract infection, E.coli.

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INTRODUCTION

Diabetes mellitus (DM) is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. The prevalence of type 2 diabetes is increasing all over the world particularly in the developing countries. The WHO estimated that there were 31.7 million persons with diabetes in India in 2000 and this number is likely to be 71.4 million in 2030. India has the distinction of having the largest number of patients with diabetes in the world with increasing incidence worldwide, diabetes mellitus will likely continue to be a leading cause of morbidity and mortality.

The complication of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality associated with the disease. The complication due to acute hyperglycemia may occur at any stage of the disease whereas those related to microvascular complications begin to appear during the second decade of diabetes. Individuals with previously undetected diabetes mellitus may present with macrovascular complications of diabetes mellitus at the time of diagnosis.[1,2]

The incidence of infection in diabetes is estimated to be around 30%. Infections are common because of impaired cell mediated immunity and phagocyte function. Reduced vascularity and hyperglycemia aids colonization of a variety of organisms. Though introduction of insulin in the treatment of diabetes mellitus has decreased the mortality in diabetes due to infection to great extent, the morbidity due to infection still remains high. Poorly controlled diabetics are susceptible to infections of skin, soft tissue, respiratory tract and urinary tract.

Urinary tract infection (UTI) is classically assumed to be a clinically relevant problem for patients with diabetes mellitus. Symptomatic urinary infections are frequent precipitants of

ketoacidosis. Bacteremia may be associated with worsening of diabetic nephropathy.[3] Some individuals with diabetes may present with a distressed picture showing progression of pyelonephritis characterized by evidence of systemic infection, local extension of infection eg. Renal papillary necrosis, perinephric abscess, septicemia and severe impairment of metabolic control which may be difficult to manage.

Urinary tract infection usually present with dysuria, urgency, frequency and suprapubic pain. Many urinary tract infections are asymptomatic especially in women. Most of symptomatic urinary tract infections are preceded by asymptomatic bacteriuria

Asymptomatic Bacteriuria (ASB) is common in neonates, pre school children, pregnant women, elderly people and patients with diabetes.[4] Asymptomatic bacteriuria occurring in diabetes mellitus can cause serious complications like emphysematous pyelonephritis, renal papillary necrosis and renal abscess.

Various studies have studied the risk factors for asymptomatic bacteriuria in diabetic patients. Risk factors are age, duration of diabetes, glycemic status, and other complications of diabetes. Many studies have recommended screening patients with diabetes to detect and treat asymptomatic bacteriuria because of increased frequency of upper urinary tract infection in such patients.

AIMS AND OBJECTIVES

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REVIEW OF LITERATURE

Diabetes mellitus (DM) refers to a group of metabolic disorders that share the phenotype of hyperglycemia. Factors contributing to hyperglycemia are reduced insulin secretion, decreased glucose utilization and increased glucose production. The metabolic dysregulation associated with diabetes causes secondary pathological changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on health care systems. Diabetes is the leading cause of end stage renal disease in adult population in the United States. India has the distinction of having the largest number of diabetics in the world.

The management of diabetes aims to achieve a good control of several metabolic parameter and a euglycemic state to avoid acute and chronic complications of diabetes mellitus. These includes diabetic ketoacidosis, hyperglycemia, hyperosmolar state, neuropathy, erectile dysfunction, retinopathy, cerebro-vascular diseases, coronary artery disease, peripheral vascular disease and infections. Despite the introduction of insulin, diabetic patients still have a considerably reduced life expectancy, good metabolic control can definitely help to delay the onset of complications as well as slow down their progression to a large extent.

Individuals with diabetes mellitus exhibit a greater frequency and severity of infections. The reasons for this include incompletely defined abnormalities in cell mediated immunity and phagocyte function associated with hyperglycemia as well as diminished vascularity. Hyperglycemia aids colonization and growth of a variety of organisms especially Candida and other bacteria. Many common infections are more frequent and severe in diabetic population where as several rare infections are seen almost exclusively in diabetic

population. Examples are rhinocerebral mucormycosis, emphysematous infections of urinary tract, malignant invasive otitis externa.

Asymptomatic bacteriuria was defined by the finding of at least 10^5 CFU of the same organism per milliliter in cultures of two consecutive urine specimens in the absence of symptoms referable to the urinary tract.[5]

A study conducted by **Suzanel E Geerlings et al,** the prevalence of ASB was 29% in women with type 2 diabetes. Risk factors for ASB in type 2 diabetic women included age, macroalbuminuria, lower BMI, and UTI during previous year. No association was evident between current HbA1C level and the presence of ASB[6]

A study conducted by Boroumand in Iranian Diabetic women has shown, the prevalence of ASB was 10.9% among diabetic women. E.coli was the most prevalent microorganism responsible for positive urine culture. Most of the isolated microorganisms were resistant to Co-trimoxazole, Nalidixic acid and Ciprofloxacin. Pyuria ($P<0.001$) and glucosuria ($P<0.05$) had a meaningful relationship with bacteriuria but no association was evident between age ($P<0.45$), duration ($P<0.09$), macroalbuminuria ($P<0.01$) and HbA1C level ($P<0.75$), and presence of ASB. The prevalence of ASB is higher in women with type 2 diabetes, for which pyuria and glucosuria can be considered as associates. Glycosuria predisposes to various urinary infections and hence Routine urine culture can be recommended for diabetic women even when there is no urinary symptoms [7]

A similar study conducted in an urban black population Central Africa has shown the prevalence of asymptomatic bacteriuria was 32%in the diabetics and 11% in nondiabetic participants. The commonest bacterial organism isolated in participants afflicted by diabetes mellitus was Escherichia coli (26%) followed by Staphylococcus aureus (21%), Streptococcus group B (14%), Streptococcus group D and non lactose fermenting coliforms

(7% respectively) . Other isolates were micrococcus and Pseudomonas (5% respectively), Klebsiella and Proteus (2% respectively). Gentamicin, nitrofurantoin, ampicillin were the most effective antimicrobials in the majority of the isolates. Certain isolates exhibited some bacterial resistance to conventional antibiotics. An association was found between bacteriuria and glucosuria and between bacteriuria and leucocyturia[8] .

Isolation of candida species from the urinary tract of diabetic women without symptoms of UTI is not uncommon[9]

A similar study in South India type 2 diabetic subjects by J.Janifer et al published in Indian Journal of Nehprology pointed out the causative pathogens, their antimicrobial pattern, and the recurrence of infection in type 2 diabetic subjects. A total of 1157 (M:F 428:729) type 2 diabetic subjects were selected for his study. midstream urine specimens were collected and the culture tests were done by a quantitative method whereas antimicrobial sensitivity was determined by using the KirbyBauer method. A significant colony count was seen 495 (42.8%) subjects and an insignificant in 350 (30.3%) subjects; there were a few cases of recurrent UTI. Women (47.9) had a significantly higher prevalence of UTI than men (34.1%) (x^2=20.3,P<0.0001).Except for BMI, UTI was significantly associated with age, duration of diabetes, and poor glycemic control in both sexes. About 533 pathogens of gram positive and gram negative bacilli were isolated from 495 subjects in this study. Escherishia coli (E.coli) was the most commonly found organism. Gram negative pathogens were found to be highly sensitive to salbactum/ cefoperazone and pipericillin/tazobactum. The prevalence of UTI was significantly higher in women than men with E.coli being he major isolated pathogen. Gram negative pathogens were highly sensitive to salbactum/cefoperazone and piperacillin/ tazobactum[10]

Urinary tract infections either lower urinary tract or pyelonephritis are result of common bacterial agents such as Escherichia coli, though several yeast like species like Candida may be involved. Complications of urinary tract infections include emphysematous pyelonephritis and emphysematous cystitis. Poor glycemic control is common in these individuals with infections.[11]

Strict glycemic control reduces post operative infections in diabetic individuals undergoing CABG and should be the goal in all diabetic patients with an infection. Trivial infections may progress rapidly due to lowered immunological resistance. Insulin is needed for normal metabolism of glucose to provide energy for phagocytosis and to destroy microorganisms. Hence the consequences of insulin lack are defective enzyme activity and defective bactericidal activity. Micro angiopathy results in impaired tissue perfusion which delays healing. The antibiotics fail to reach the site of infection. Autonomic neuropathy results in bladder dysfunction and stasis which predisposes to urinary tract infections.

Treatment of ASB in different population groups is still debated. A study by Lin et al suggests the need for greater focus on optimizing the use of antibiotics in patients with enterococcal bacteriuria; overtreatment of ABU is common, especially among patients with pyuria.[12] Another randomized, controlled trial found that treatment of asymptomatic bacteriuria in women with diabetes does not appear to reduce complications. These investigators concluded that diabetes itself should not be an indication for screening for or treatment of ASB[13]

Microbiology:

Urinary tract infection, from a micro biologic perspective exists when pathogenic micro organisms are detected in the urine, urethra, bladder, kidney, or prostate. Bacteriological diagnosis of urinary tract infection has undergone a marked change following the development by Kass concept of 'significant bacteriuria'. In most instances, growth of more than 10^5 organisms per milliliter from a properly collected midstream clean catch urine sample indicates infection. For symptomatic patients , a small number of bacteria like 10^2 to 10^4 per milliliter may signify infection. In urine specimens collected by suprapubic aspiration or in and out catheterization and in samples from a patient with an indwelling catheter colony counts of 10^2 to 10^4 per milliliter generally indicate infection. Examination of the urine for leukocytosis is the final validation test that can be applied in the evaluation patients with possible UTI. When a randomly collected urine sample is examined in a hemocytometer and at least 10 leucocytes/$mm^3$are found, there is a high probability of clinical infection.[14]

1. More than 96% of symptomatic men and women with significant bacteriuria have at least this level of pyuira: fewer than 1% of asymptomatic, non bacteriuria individuals have this level of pyuria.
2. Most symptomatic women with pyuria but without significant bacteriuria have an inflammatory process.

Bacteriology:

Escherichia coli is the most common gram negative micro organism isolated from urinary tract of affected individuals. Other gram negative rods especially Proteus, Klebsiella and Enterobacter are responsible for a smaller proportion of urinary tract infections. Serratia and Pseudomonos assume increasing importance in recurrent infections and in infections associated with urologic manipulation, calculi or obstruction. This test detects E.coli,

Klebsiella, Proteus, Staphylococcus and Pseudomonas species. False negative test occurs in the presence of some yeast, some gram positive cocci and urinary ascorbic acid.

Catalase test

This test depends on the generation of oxygen bubbles by catalase produced by the bacteria when hydrogen peroxide is added to the infected urine. False positive results occur in the presence of hematuria.

Triphenyl tetrazolium chloride test

The respiratory activity of growing bacteria reduce 2,3,5 triphenyl tetrazolium chloride to pink red insoluble precipitate.

Glucose oxidase test

This test depends on the bacterial metabolism of glucose normally present in urine. In the presence of infection, glucose is not detected. False positive results occur in glycosuric patients.

Leucocyte esterase test

The leucocyte esterase test detects esterases released from degraded white blood cells. This is an indirect test for bacteriuria. This test is rapid and requires little expertise

Dipsulphide culture methods

Agar coated slides are immersed in urine or even exposed to the stream of urine during voiding, incubated and the growth estimated by colony counting or by colour change of indicators

Bac T screen bacteriuria detection device

In this method urine is forced through a filter paper, which retains microorganisms, somatic cells and other particles. A dye is then added to the filter paper to visualize the particulate matter that has adhered. The intensity of the colour relates to the number of particles. This procedure is very rapid and has been shown to detect even 10^2 organisms per ml.

None of the screening methods are reliable as urine culture.

QUANTITATIVE URINE CULTURE

Pour plate dilution technique:

This is an extremely accurate method but time consuming. It is used as a standard of comparison for other methods. Here double dilution series of urine are spread over the culture plate. The number of colonies in each plate is read in 24 hours and 48 hours and colonies are calculated.

Surface culture methods:

Serial 10 fold dilution of urine are plated by surface culture method. Number of colonies is calculated at the end of 24 hours and 48 hours. These methods are too complicated for routine diagnosis

Bacteriological loop technique:

This is the most commonly employed method. In this standard platinum loops or disposable sterile loops designed to deliver either 0.01ml or 0.001ml of urine are used. The urine should be mixed thoroughly before I-plating. Flame an inoculating loop and allow it to cool without touching any surface. Insert the loop vertically into the urine to allow urine to adhere to the loop. Spread the loopful of urine to the surface of blood agar. The loop is touched to the center of the plate from which the inoculum is spread in line across the diameter of the plate. Without flaming insert the loop vertically into the urine again for transfer of a loopful to an indicator medium. Incubate plates for atleast 24 hours at 350 to 370C in air. The colonies are counted on each plate. The number of colonies are multiplied by 1000 (if a 0.01ml loop is used) or by 100 (if a 0.01ml loop is used) to determine the number of microorganisms per milliliter in the original specimen. The former medium gives quantitative measurement of bacteriuria and the latter a presumptive diagnosis of the bacterium. The isolates are identified by their properties. Reincubate plates with no growth or scanty growth for an additional 24 hours before discarding the plate.[15]

Pathogenesis:

The risk of infection is higher and urinary tract infections are serious clinical problem in patients with diabetes mellitus[16,17]

Urinary tract infections are much more common in females. In the age group of 15 to 40 years, the ratio of females to males affected being 8:1. This is due to

1. Shorter urethra in females
2. Absence of antibacterial properties which are found in prostate gland
3. Hormonal changes affecting adherence of bacteria to the mucosa

4. Urethral trauma during sexual intercourse

The vaginal introitus and distal urethra are normally colonized by Diphtheroids, Streptococcal species, Lactobacilli and Staphylococci species but not by the enteric gram negative bacilli that commonly cause urinary tract infection.

The factors that predispose to periurethral colonization with gram negative bacilli remain poorly understood. But alteration of normal vaginal flora by antibiotics, other genital infections or use of contraceptives especially spermicides appear to play an important role. Loss of the normally dominant H_2O_2 producing Lactobacilli in the vaginal flora appears to facilitate colonization by E.coli

Under normal circumstances, bacteria placed in bladder are rapidly cleared partly through the flushing and dilutional effects of voiding but also as a result of the antibacterial properties of urine and the bladder mucosa. Owing mostly to a high urea concentration and high osmolarity, the bladder urine of many normal persons inhibits or kills bacteria. Polymorphonuclear leukocytes enter the bladder epithelium and the urine soon after infection sets in and play a role in clearing the bacteria.

Predisposing factors of UTI

1. Female gender and sexual activity

Female urethra appears to be prone to colonization with colonic gram negative bacilli because of its proximity to the anus, its short length, its termination beneath the labia. Sexual intercourse causes introduction of bacteria into bladder and is associated with onset of cystitis. Patients may even develop pyelonephritis

2. Pregnancy:

In pregnancy, predisposition to upper tract infection is due to decreased urethral tone, decreased urethral peristalsis and temporary incompetence of vesicourethral valves due to hormone influence. Urinary tract infection are detected in 2 to 8% of pregnant women

3. Vesicoureteral reflex:

An anatomically impaired vesico ureteral junction facilitates reflux of bacteria and upper tract infection. Vesicoureteral reflux occurs during voiding or with elevation of pressure in the bladder.

4. Neurogenic bladder dysfunction

Interference in nerve supply to the bladder as in spinal cord injury, diabetes mellitus, tabes dorsalis and other diseases are associated with frequent urinary tract infections. The infection is favored by prolonged stasis of urine in the bladder obstruction.

Any obstruction to the free flow of urine like tumour, stricture, congenital posterior urethral valves or stone results in hydronephrosis and greatly increases the frequency of urinary tract infections. Obstruction may lead to rapid destruction of renal tissue

Hypothesis of a higher prevalence of UTI in diabetes, goes back to the studies of Vejlsguard who noted a higher frequency of bacteriuria that is greater than 10^5 colony forming units per millimeters urine in female (18.8% vs 7.9% in control) but not in male diabetics. Such UTI was mostly asymptomatic (33%). A higher prevalence of UTI was also found in pregnant diabetic patients and was related to the presence of retinopathy, presumably as a surrogate maker for autonomic polyneuropathy. [18]

Results of prospective studies remained controversial. A higher prevalence of UTI in diabetic women was noted by Balasour and Zhanel and their associates but not by Brauner

and coworkers. A recent 4 year prospective study in a cohort of diabetics and noon diabetics showed however, that the incidence of UTI's as well as ASB was as high in diabetic compared to non diabetic women. The risk was higher in women on insulin and with longer duration of diabetes.

One of the study on ASB shows that the increased prevalence of asymptomatic bacteriuria 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 in diabetic women with asymptomatic bacteriuria, and non diabetic patients with asymptomatic bacteriuria. The study found that bacterial growth in vitro was increased after the addition of different glucose concentrations, as found in urine of poorly controlled patients. The study also found that E.coli expressing type 1 fimbriae adhere better to uroepithelial cells of women with diabetes mellitus compared with the cells of women without diabetes mellitus .[19]

Eighty percent of women with diabetes and bacteriuria have been shown to have renal parenchymal infection by seven weeks after initial testing. A variety of factors may contribute to the increased frequency of urinary tract infection in diabetic women. Bladder dysfunction as a result of diabetic neuropathy and cystopathy are the most important.

It was hypothesized that E coli adhere more to the uroepithelial cells of diabetic women, either because of substances excreted in the urine (e.g albumin, glucose and Tamm Horsfall protein) or because of a difference in the uroepithelial cells. A T24 bladder cell line and uroepithelial cells of 25 diabetic women and 19 control subjects were incubated with 3 different E.coli strains. They were Type-1 fimbriated E.coli, P-fimbriated Ecoli and non fimbriated E.coli. Type -1 fimbriated E.coli adhere more to diabetic than to control uroepithelial cells.[20]

Virulence factors in E.coli isolated from diabetic women with asymptomatic bacteriuira did not differ from those in non diabetic women and the spectrum of bacterial

isolates as well as the resistance to antibiotics did not differ between diabetic and non diabetic individuals.

Symptomatic UTI run a more aggressive course in diabetic patients. UTI in diabetics may also lead to complications such as prostatic abscess, emphysematous cystitis and pyelonephritis. In community acquired UTI, the predominant microbe is E.coli, but Klebsiella is more frequently found in diabetic patients than in control subjects.[21] Exotic microbials such as Pasteurella and Staphylococci may also be found.

Among diabetic subjects, prevalence of bacteriuria increased with longer duration but was not affected by measures of glucose control. One of the study concludes that NIDDM increases the prevalence of bacterial colonization of the urine and, therefore, probably also increases the risk of symptomatic urinary tract infection.[22]

SERIOUS COMPLICATIONS

Diabetic patients with asymptomatic bacteriuira are at high risk of developing serious complications of urinary infection such as emphysematous cystitis, pyelonephritis and a two fold increased risk for the development of renal corticomedullary abscess among diabetic patients.[23]

PAPILLARY NECROSIS

When infection of the renal pyramids develop in association with vascular diseases of the kidney or with urinary tract obstruction, renal papillary necrosis is likely to result. Patients with diabetes seem peculiarly susceptible to this complication. Hematuria, flank pain, chills and fever are the most common presenting symptoms. Renal papillary necrosis is often bilateral. Acute renal failure with oliguria or anuria sometimes develops. Rarely, sloughing of a pyramid may take place without symptoms in a patient with chronic urinary

tract infection, and the diagnosis is made when the necrotic tissue is passed in the urine or identified as a ring shadow on pyelography. If renal function deteriorates suddenly in a diabetic individual, the diagnosis of renal papillary necrosis should be suspected even in the absence of fever or pain.

EMPHYSEMATOUS PYELONEPHRITIS

Emphysematous pyelonephritis is an unusual complication that almost always occurs in diabetic patients. Emphysematous pyelonephritis is usually characterized by a rapidly progressive clinical course, with high fever, leukocytosis, renal parenchymal necrosis, and accumulation of fermentative gases in the kidney and perinephric tissues. Most patients have pyuria and glycosuria. Escherichia coli causes most of the infections, but occasionally Enterobacteriaceae are isolated, gas in tissues can often be seen on plain films and can be confirmed by computed tomography. Surgical resection of the involved tissue in addition to systemic antimicrobial therapy is usually needed to prevent mortality in emphysematous pyelonephritis.

EMPHYSEMATOUS CYSTITIS

Emphysematous cystitis occurs primarily in diabetic patients, usually in association with Escherichia coli or facultative gram negative rods and often in relation to bladder neck obstruction. Patients with this condition are less severely ill and have less rapidly progressive disease than those with emphysematous pyelonephritis. The patient typically reports abdominal pain, dysuria, frequency and in some pneumaturia. Computed tomography shows gas within both the bladder lumen and bladder wall. Conservative therapy with systemic antimicrobial agents and relief of outlet obstruction are effective.

PERINEPHRIC AND RENAL ABSCESS

Perinephric and renal abscesses are quite uncommon now. Before the advent of antibiotics, most renal and perinephric abscesses were hematogenous in origin, with Staphylococcus aureus most commonly responsible. Nowadays, >75% of perinephric and renal abscesses arise from an initial urinary tract infection. Infection ascends from the bladder to the kidney, with pyelonephritis occurring first.

Bacteria may directly invade the renal parenchyma from medulla to cortex. Local vascular channels within the kidney may also facilitate the transport of organisms. Areas of abscess developing within the parenchyma may rupture into the perinephric space.

Many patients with perinephric abscess have concomitant nephrolithiasis producing local obstruction to urinary flow. The organisms most commonly encountered in perinephric and renal abscess are Escherichia coli, Proteus species and Klebsiella species. Escherichia coli have unique virulence properties in the urinary tract which promote adherence to uroepithelial cells. The urease of Proteus species splits urea thereby creating a more alkaline and hostile environment for bacterial proliferation.

The presentation of perinephric and renal abscesses is quite nonspecific. Flank pain and abdominal pain are common. Fever is usually present. The diagnosis is usually made by renal ultrasonography or abdominal computed tomography.

TREATMENT PRINCIPLES

The following principles underlie the treatment of urinary tract infections:

1. Except in uncomplicated cystitis in women, a quantitative urine culture or a gram stain should be performed to confirm infection before treatment is begun. When culture results become available, antimicrobial sensitivity should be used to direct therapy.

2. Factors predisposing to infection such as obstruction and calculi should be identified and corrected if possible
3. Relief of clinical symptoms does not always indicate bacteriological cure
4. Each course of treatment should be classified as a failure or a cure. Recurrent infections should be classified as same strain or different strain and as early (occurring within 2 weeks of the end of therapy) or late
5. Uncomplicated infections confined to the lower urinary tract respond to short courses of therapy while upper tract infections require longer treatment.
6. Despite increasing resistance, community-acquired infections, especially initial infections are usually due to more antibiotic sensitive strains
7. In patients with repeated infections, instrumentation or recent hospitalization, the presence of antibiotic-resistant strains should be suspected.

MATERIALS AND METHODS

SOURCE OF DATA:

- **Study design**- Comparative study conducted in Internal Medicine Department on women with and without type 2 diabetes mellitus at R L Jalappa Hospital, Tamaka, Kolar
- **Sample size** – 100 diabetic female patients and 100 non- diabetic females

METHOD OF COLLECTION OF DATA

A predesigned and pretested proforma/questionnaire was used to collect data regarding personal details, treatment history, duration of diabetes and symptomatology. 100 females with diabetes mellitus are randomly enrolled in the study. These females are the patients of medical wards of department of Internal Medicine, R L Jalappa hospital, Tamaka, Kolar. A randomly selected controlled group of 100 healthy females without diabetes are evaluated in the same period. Fasting blood sugar, post prandial blood sugar, urine routine, glycated haemoglobin, urine culture and sensitivity by Kirby Bauer method of every subject enrolled in the study is done.

INCLUSION CRITERIA:

Female patients with diabetes mellitus aged 18 years and above.

EXCLUSION CRITERIA:

1. Patients with symptoms of urinary tract infection.

2. Bladder catheterization during the 2 months before enrolment in the study.
3. Instrumentation of urogenital tract 2 months before enrolment in the study.
4. Pregnancy.
5. Use of antibiotics during previous 14 days.
6. Recent hospitalization or surgery within the past 4 months.
7. Gynecological infections

INVESTIGATIONS DONE

1. Fasting blood sugar
2. Post prandial blood sugar
3. Glycated haemoglobin
4. Urine routine
5. Urine culture and sensitivity

DETAILS OF STUDY SUBJECTS

During initial visit, relevant history was elicited from patients regarding age, known duration of diabetes, medication, pregnancy, history for urinary tract infection, history of previous catheterization, instrumentation, history of white discharge and history of pruritis vulva. Fasting, post prandial plasma glucose and glycated haemoglobin tests were done on the patients and control group. Clean catch mid-stream urine specimen was collected and culture and microscopic tests were done. The urine samples were collected during the non-menstrual period.

DEFINITIONS

Diabetes mellitus: Diagnosis of diabetes mellitus was made in accordance with the criteria of the American Diabetes Association. A patient was diagnosed to be a diabetic if she had

a) Symptomatic of diabetes plus random plasma glucose >200mg/dl or
b) Fasting plasma glucose $\geq$ 126 mg/dl or
c) Two hour plasma glucose $\geq$200mg/dl or
d) Glycated haemoglobin $\geq$ 6.5

Asymptomatic bacteriuria: Asymptomatic bacteriuria is defined as presence of atleast **10^5 colony forming units per ml** of 1 or 2 bacterial species in a culture of clean voided midstream urine specimen from an individual without symptoms of urinary tract infection.[24]

Contaminated Urine: Contaminated urine is defined as the presence of at least 3 different microorganisms in 1 urine specimen.

Leucocyturia: It is defined as the presence of **more than 10 leukocytes per high power field** in the sediment of centrifuged urine

DETAILS OF MATERIALS

Urine specimen was collected by clean catch mid stream method. Patients were explained about the methods of collecting clean catch mid stream urine and elderly female patients were provided with a nursing assistant for cleaning the external genitalia. Urine was collected in a sterile wide mouthed screw cap bottle for culture purpose and another sample collected for microscopic examination of leucocyturia.

The number of white blood cells per cubic millimeter of urine was estimated using haemocytometer in microscope.

Urine samples were streaked on nutrient agar and Macconkey agar for confirmation of bacterial growth. Identification of urine isolates was performed using conventional methods and in-vitro susceptibility to antimicrobial drugs was tested by Kirby-Bauer disc diffusion method. Antibiotic sensitivity tests were done using the standard amounts of antibiotics (Amoxicillin, Gentamicin, Cotrimoxazole, Ciprofloxacin, Cefotaxime, Doxycycline, Norfloxacin, Cetriaxone, Amikacim, Nitrofurantoin, piperacillin-tazobactum, carbepenems) and report was obtained at the end of 48 hours. And then Fasting, 2 hour post prandial venous blood samples were drawn and plasma glucose values were estimated.

ETHICAL APPROVAL

Ethical approval was obtained from the ethical committee of SRI DEVARAJ URS MEDICAL COLLEGE, TAMAKA.

CONSENT

Informed consent was obtained from the patients and the control group.

STATISTICAL ANALYSIS

- Data collected are coded & entered in to MS Excel spread sheet.

- Analysis is performed with SPSS software.

METHODS OF URINE SAMPLE COLLECTION

Urine sample can be collected by:

1. Clean catch midstream specimen
2. Surapubic aspiration of urine
3. Bladder catheterization

Clean catch mid stream specimen is collected as follows:

Patient must have a full bladder. Patient removes underclothing and stands with legs on either side of toilet. Separate labia with left hand and clean the vulva front to back with a sterile swab. Without interrupting the stream catch urine in sterile bottle and complete voiding. This method is followed because the distal urethra normally contains bacteria and so the first voided urine is contaminated with the bacteria. So mid stream urine collection is done.

Suprapubic aspiration of urine is done when it is not possible to obtain uncontaminated samples or in symptomatic patients with low bacteria counts. This method is not routinely followed. Patient must have a full bladder which can be percussed and if still in doubt, localize bladder using ultrasound. With patient lying supine, choose site in midline 2.5cm above pubic symphysis and clean skin with spirit impregnated sterile gauze. Insert a 21 gauge needle attached to a 10ml syringe directly downwards and aspirate urine.

QUANTITATIVE URINE CULTURE

Bacteriological loop technique:

This is the most commonly employed method. In this standard platinum loops or disposable sterile loops designed to deliver either 0.01ml or 0.0001ml of urine are used. The urine should be mixed thoroughly before I- plating. Flame a inoculating loop and allow it to cool without touching any surface. Insert the loop vertically into the urine to allow urine to adhere to the loop. Spread the loopful of urine to the surface of blood agar. The loop is touched to the center of the plate from which the inoculum is spread in a line across the diameter of the plate. Without flaming insert the loop vertically into the urine again for transfer of a loopful to an indicator medium. Incubate plates for at least 24hours at 350 to 370C in air. The colonies are counted on each plate. The number of colonies are multiplied by 1000 (if a 0.01ml loop is used) or by 100 (if a 0.001ml loop is used) to determine he number of microorganisms per milliliter in the original specimen. The former medium gives quantitative measurement of bacteriuria and the latter a presumptive diagnosis of the bacterium. The isolates are identified by their properties. Reincubate plates with no growth or scanty growth for an additional 24hours before discarding the plates.

ANTIBIOTIC SENSITIVITY TESTS

Pathogenic bacteria exhibit very great variation in susceptibility to antibiotics and chemotherapeutic agents. Therefore, it is essential to determine the susceptibility of isolates of pathogenic bacteria to antibiotics that are most likely to be used in treatment. Antibiotic sensitivity is routinely done by Kirby-Bauer disc diffusion method.[25] The disc diffusion method uses filter paper discs 6.00mm in diameter, charged with appropriate concentration of the drugs. A suitable dilution of a broth culture or a broth suspension of the test bacterium is flooded on the surface of a solid medium (Mueller-Hinton agar). The plate is tilted to ensure

uniform spreading and the excess broth is pipetted off. After drying the plate, antibiotic discs are applied with sterile forceps. After overnight incubation, the degree of sensitivity is determined by measuring the zones of inhibition of growth around the discs.

Growth will be inhibited around discs containing antibiotics to which the bacterium is susceptible but not around those to which it is resistant. The results are reported as 'sensitive' or 'resistant' to the different drugs.

Picture 1: Bacteriological Loop

Picture 2: Antibiotic Culture sensitivity

RESULTS

In this study, 100 women with diabetes mellitus and 100 age matched non diabetic women who make up the control group were studied.

Statistical analysis:

Data was entered into Microsoft excel data sheet and was analyzed using SPSS 22 version software. Categorical data was represented in the form of Frequencies and proportions. **Chi-square test** was used as test of significance for qualitative data.

Continuous data was represented as mean and standard deviation. **Independent t test or Mann Whitney U test** was used as test of significance to identify the mean difference between two quantitative variables and qualitative variables respectively.

Graphical representation of data: MS Excel and MS word was used to obtain various types of graphs such as bar diagram and Pie diagram.

p value (Probability that the result is true) of <0.05 was considered as statistically significant after assuming all the rules of statistical tests.

Statistical software: MS Excel**,** SPSS version 22 **(**IBM SPSS Statistics, Somers NY, USA) was used to analyze data. EPI Info (CDC Atlanta), Open Epi, Med calc and Medley's desktop were used to estimate sample size, odds ratio and reference management in the study.

Table 1: Age distribution of subjects between cases and controls

		Group			
		Cases		Controls	
		Count	%	Count	%
Age	<40 years	18	18.0%	12	12.0%
	41 to 50 years	29	29.0%	33	33.0%
	51 to 60 years	26	26.0%	37	37.0%
	61 to 70 years	20	20.0%	14	14.0%
	>70 years	7	7.0%	4	4.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 5.256$, df = 4, p = 0.262

Among cases majority of subjects were in the age group 41 to 50 years and among controls majority of them were in the age group 51 to 60 years. There was no significant difference in age distribution of subjects between two groups.

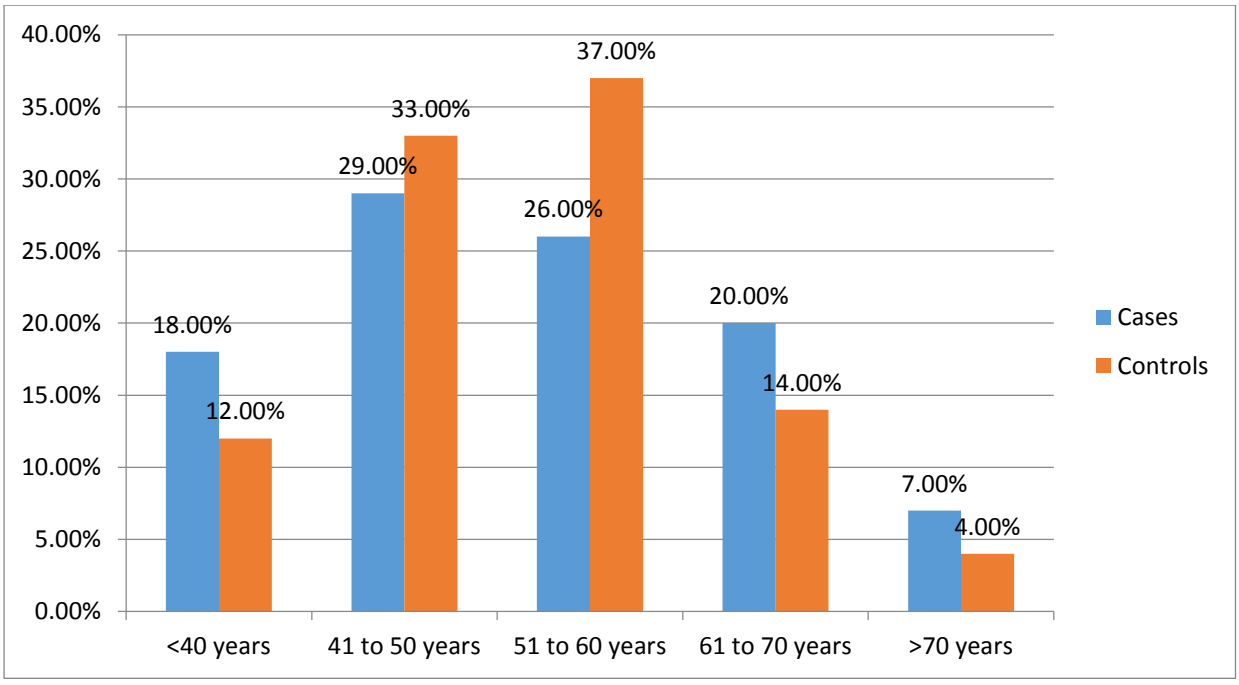

Figure 1: Bar diagram showing Age distribution of subjects between cases and controls

Table 2: Mean Age distribution of subjects between two groups

		Age		P value
		Mean	SD	
Group	Cases	54.3	12.4	0.087
	Controls	51.5	10.2	

Mean age of cases was 54.3 ± 12.4 years and 51.5 ± 10.2 years. There was no significant difference between two groups with respect to age distribution.

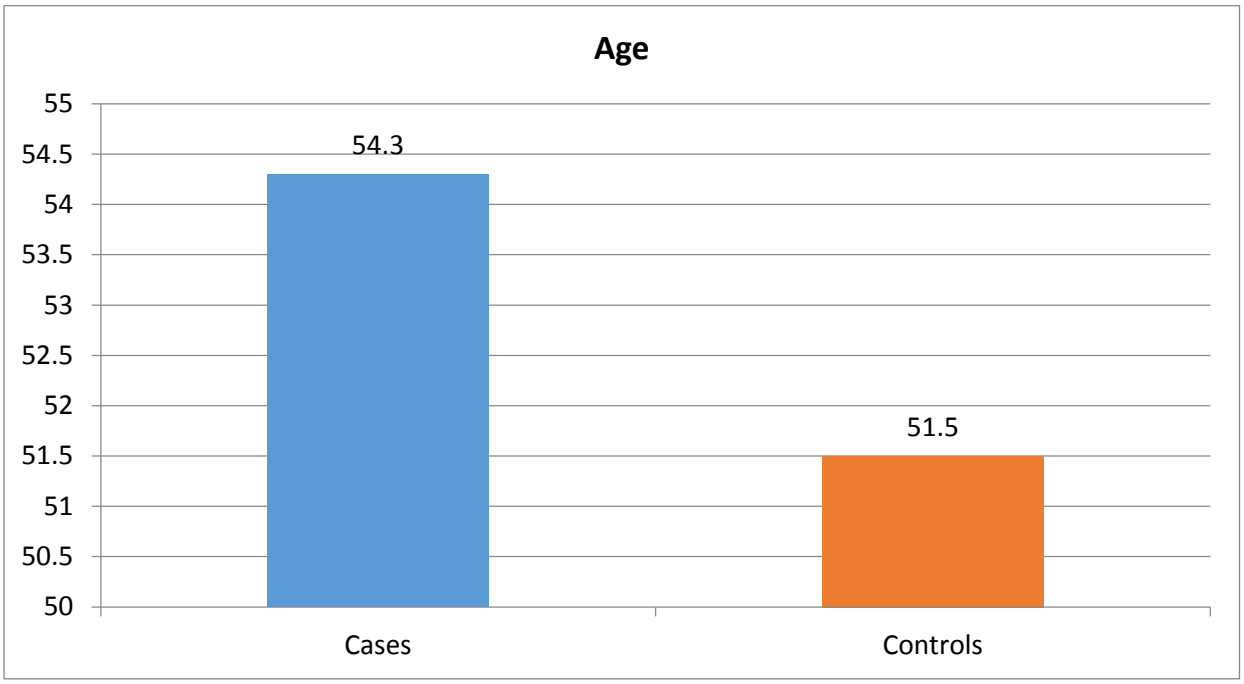

Figure 2: Bar diagram showing Mean Age distribution of subjects between two groups

Table 3: Mean FBS, PPBS and HbA1c between two groups

	Group				P value
	Cases		Controls		
	Mean	SD	Mean	SD	
FBS	134.0	44.7	85.3	7.7	<0.001*
PPBS	209.3	57.7	139.4	14.0	<0.001*
HbA1c	7.7	2.0	5.5	0.7	<0.001*

Among cases Mean FBS was 134 ± 44.7 mg/dl, mean PPBS was 209.3 ± 57.7 mg/dl and mean HbA1c was 7.7 ± 2 mg/dl. Among controls Mean FBS was 85.3 ± 7.7 mg/dl, mean PPBS was 139.4 ± 14 mg/dl and mean HbA1c was 5.5 ± 0.7 mg/dl. There was significant difference in FBS, PPBS and HbA1c between two groups. Cases had higher FBS, PPBS and HbA1c

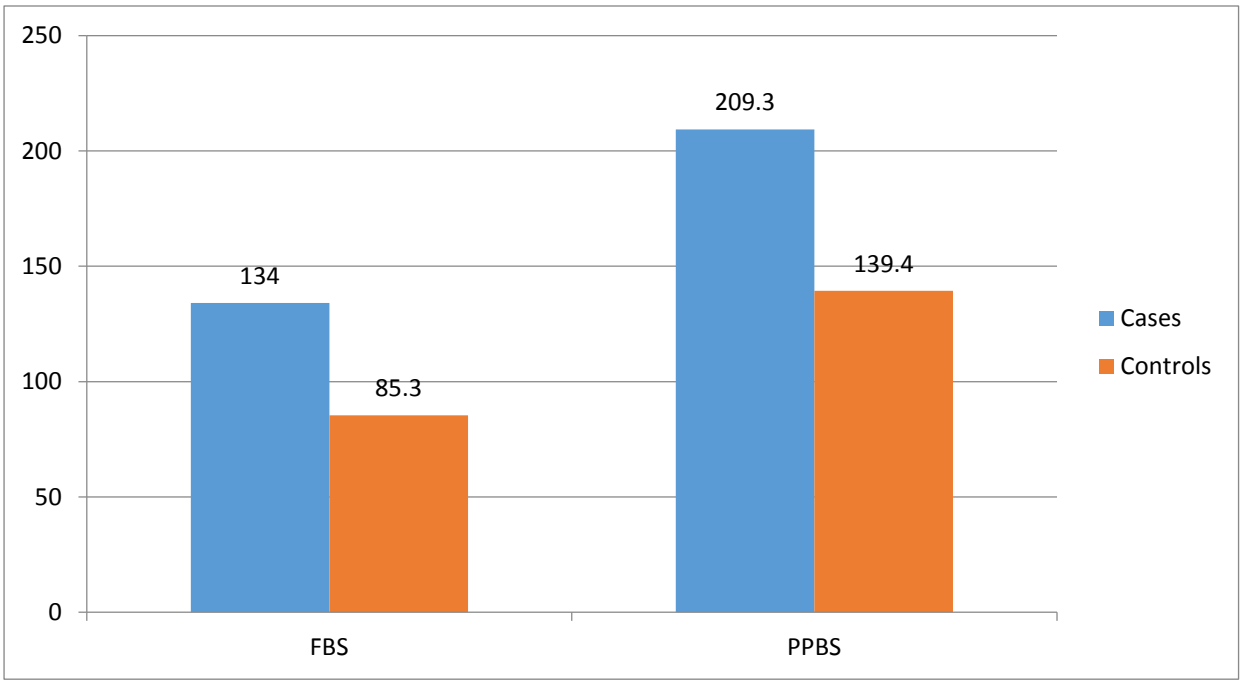

Figure 3: Bar diagram showing Mean FBS, PPBS and HbA1c between two groups

Table 4: FBS comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
FBS	<80 mg/dl	10	10.0%	28	28.0%
	81 to 110 mg/dl	29	29.0%	72	72.0%
	>110 mg/dl	61	61.0%	0	0.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 87.83$, df = 2, p <0.001*

Majority of subjects 61% among cases had FBS >110 mg/dl and none in controls had FBS >110 mg/dl. This difference in FBS distribution between two groups was statistically significant.

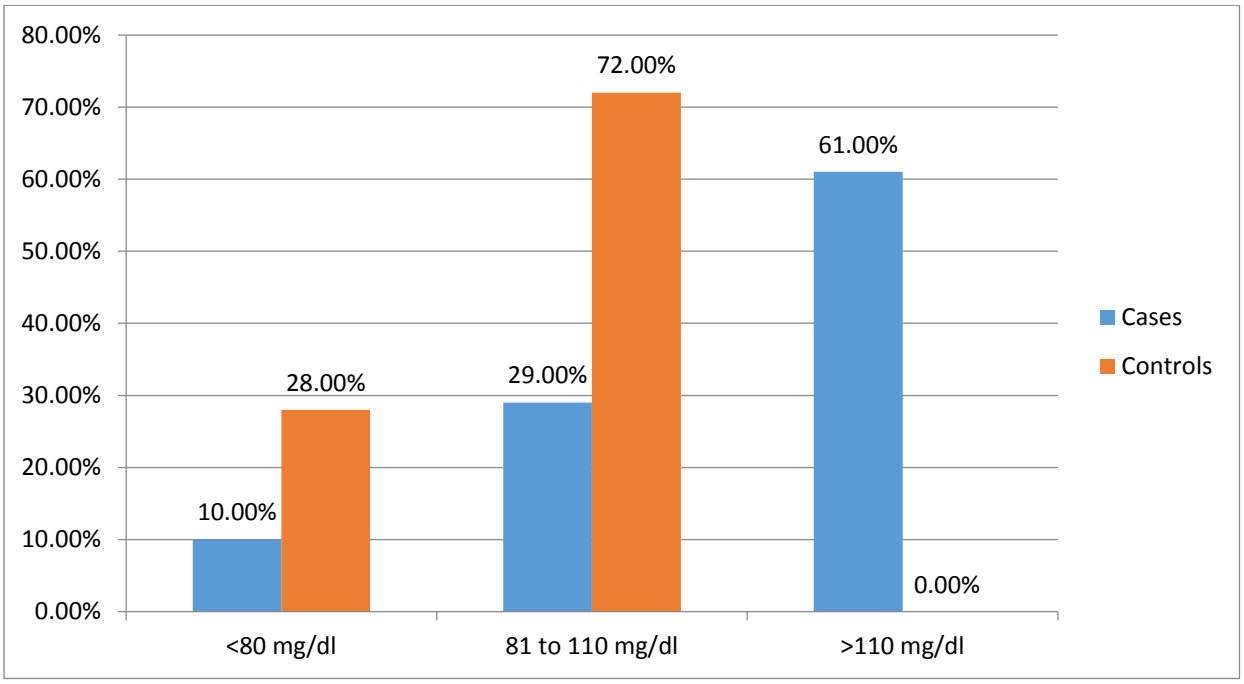

Figure 4: Bar diagram showing FBS comparison between two groups

Table 5: PPBS comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
PPBS	121 to 160 mg/dl	24	24.0%	93	93.0%
	161 to 200 mg/dl	28	28.0%	7	7.0%
	201 to 240 mg/dl	20	20.0%	0	0.0%
	241 to 280 mg/dl	15	15.0%	0	0.0%
	281 to 320 mg/dl	9	9.0%	0	0.0%
	>320 mg/dl	4	4.0%	0	0.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 101.29$, df = 5, p <0.001*

There was significant difference in PPBS distribution between two groups, cases had higher PPBS values than controls.

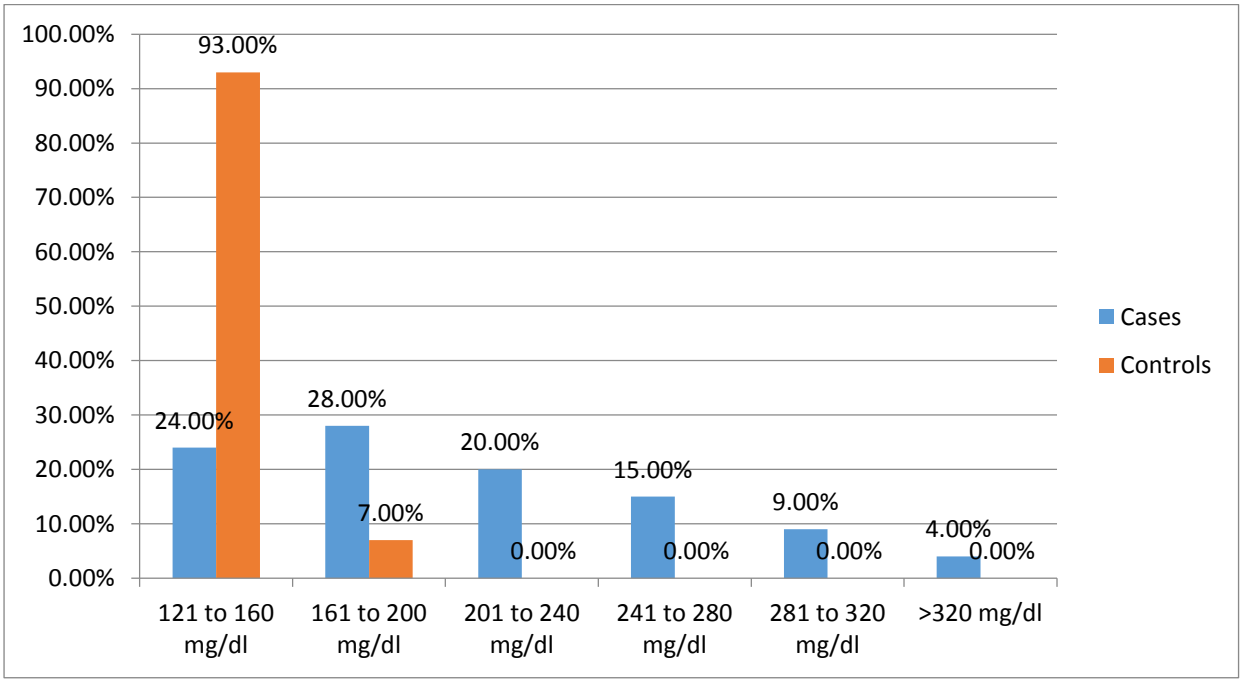

Figure 5: Bar diagram showing PPBS comparison between two groups

Table 6: HbA1c comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
HbA1c	<5.7	18	18.0%	74	74.0%
	5.8 to 6.4	12	12.0%	17	17.0%
	6.5 to 7.5	23	23.0%	9	9.0%
	7.6 to 8.5	17	17.0%	0	0.0%
	8.6 to 9.5	10	10.0%	0	0.0%
	9.6 to 10.5	11	11.0%	0	0.0%
	>10.5	9	9.0%	0	0.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 88.07$, df = 6, p <0.001*

Cases had higher HbA1c values than controls. This difference in distribution of HbA1c was statistically significant.

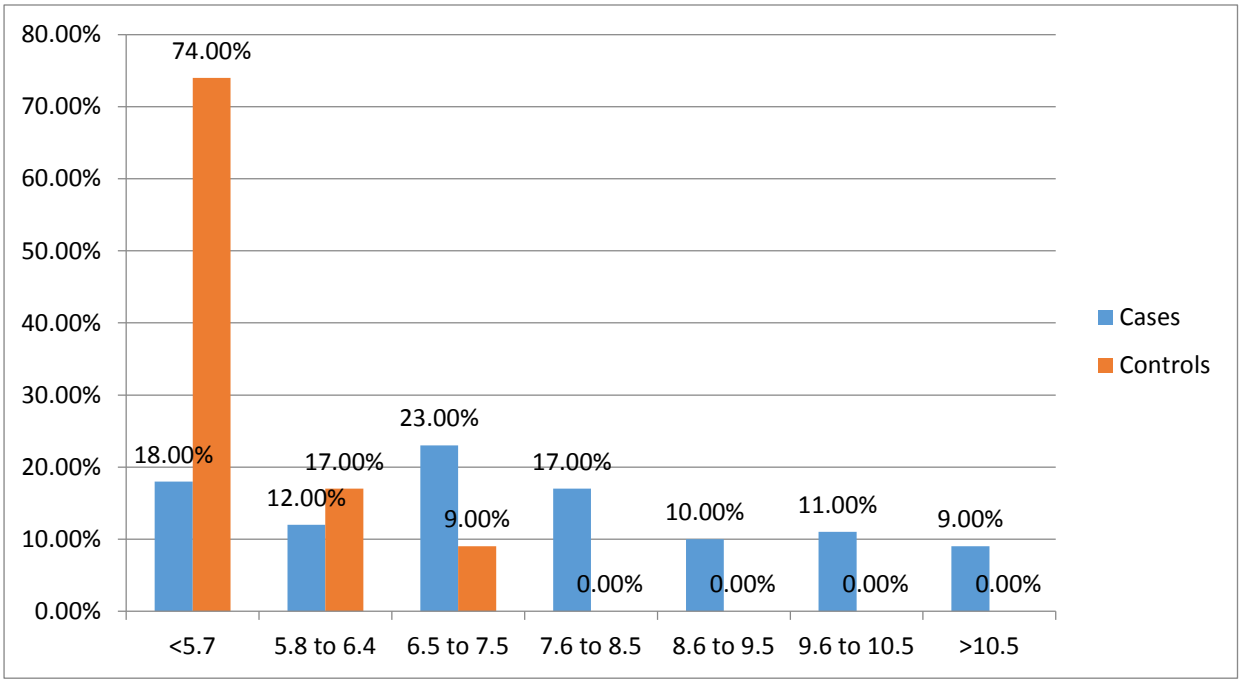

Figure 6: Bar diagram showing HbA1c comparison between two groups

Table 7: Macroalbuminuria comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
Macroalbuminuria	Present	16	16.0%	2	2.0%
	Absent	84	84.0%	98	98.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 11.96$, df = 1, p = 0.001*

Among cases 16% had Macroalbuminuria and among controls 2% had macro albuminuria. This difference in distribution of subjects with respect to Macroalbuminuria was statistically significant.

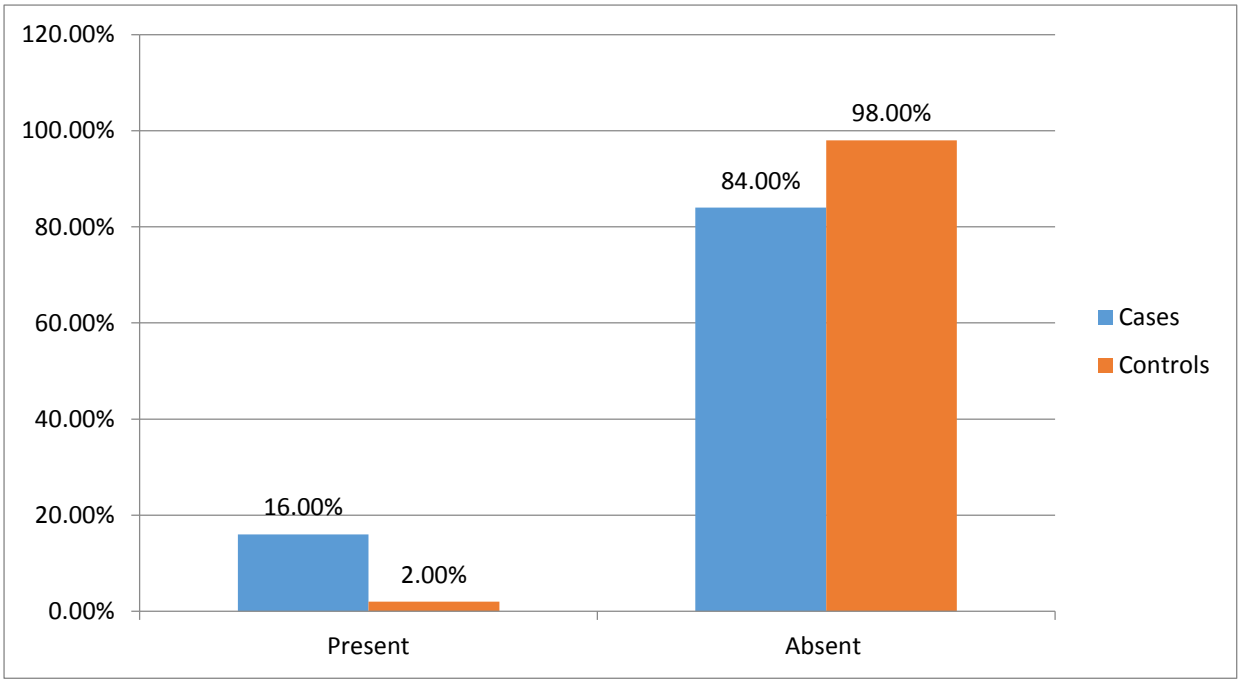

Figure 7: Bar diagram showing Macroalbuminuria comparison between two groups

Table 8: Leucocyturia between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
Leucocyturia	Absent	76	76.0%	94	94.0%
	Present	24	24.0%	6	6.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 12.71$, df = 1, $p < 0.001$*

Among cases 24% had Leucocyturia and among controls 6% had Leucocyturia. This difference between cases and controls was statistically significant.

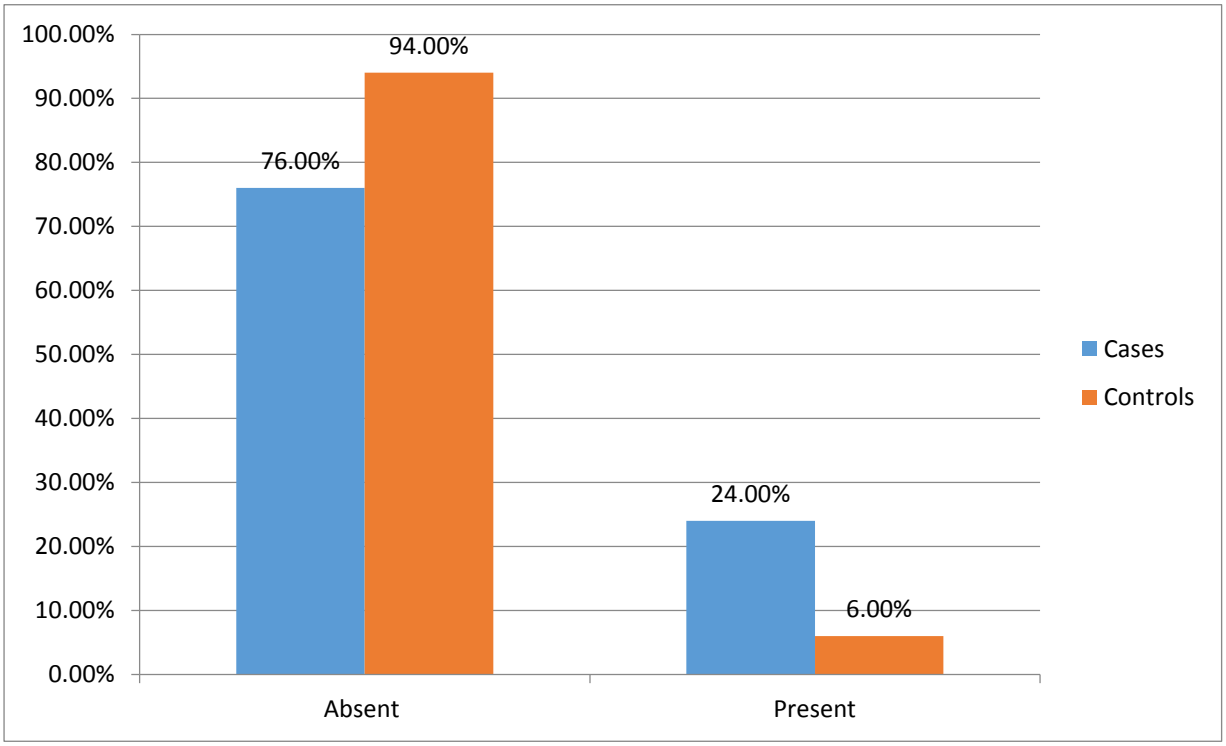

Figure 8: Bar diagram showing Leucocyturia between two groups

Table 9: ASB comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
ASB	Absent	71	71.0%	92	92.0%
	1+	29	29.0%	8	8.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 14.62$, df = 1, $p < 0.001$*

Among cases 29% had 1+ ASB and among controls 8% had ASB. There was significant difference in ASB between two groups. Cases had higher proportions of ASB than controls.

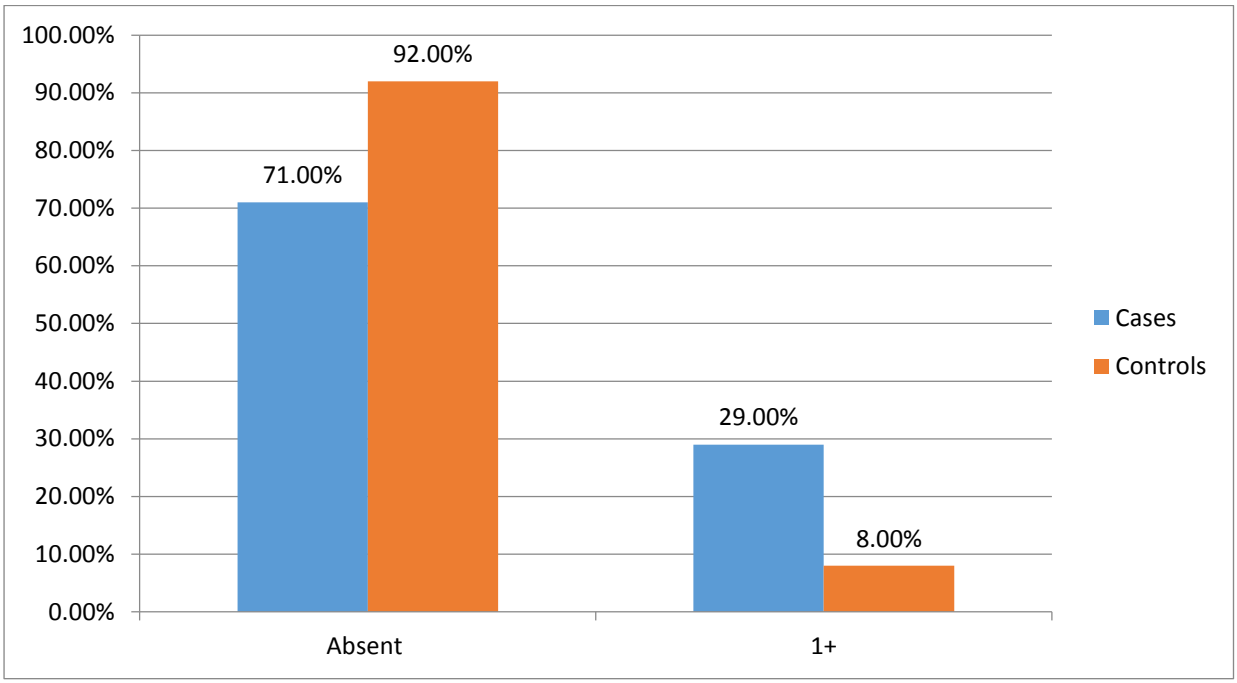

Figure 9: Bar diagram showing ASB comparison between two groups

Table 10: Bacterial Isolates comparison between two groups

		Group			
		Cases		Controls	
		Count	%	Count	%
Bacterial Isolate	Absent	71	71.0%	92	92.0%
	E.coli	23	23.0%	7	7.0%
	Proteus	3	3.0%	0	0.0%
	Co.Neg.Staph	2	2.0%	1	1.0%
	Klebsiella	1	1.0%	0	0.0%
	Total	100	100.0%	100	100.0%

$\chi 2 = 15.57$, df = 4, p = 0.004*

Most common organism isolated in cases and controls was E coli, 23% in cases and 7% in controls. There was significant difference in bacterial isolate between two groups.

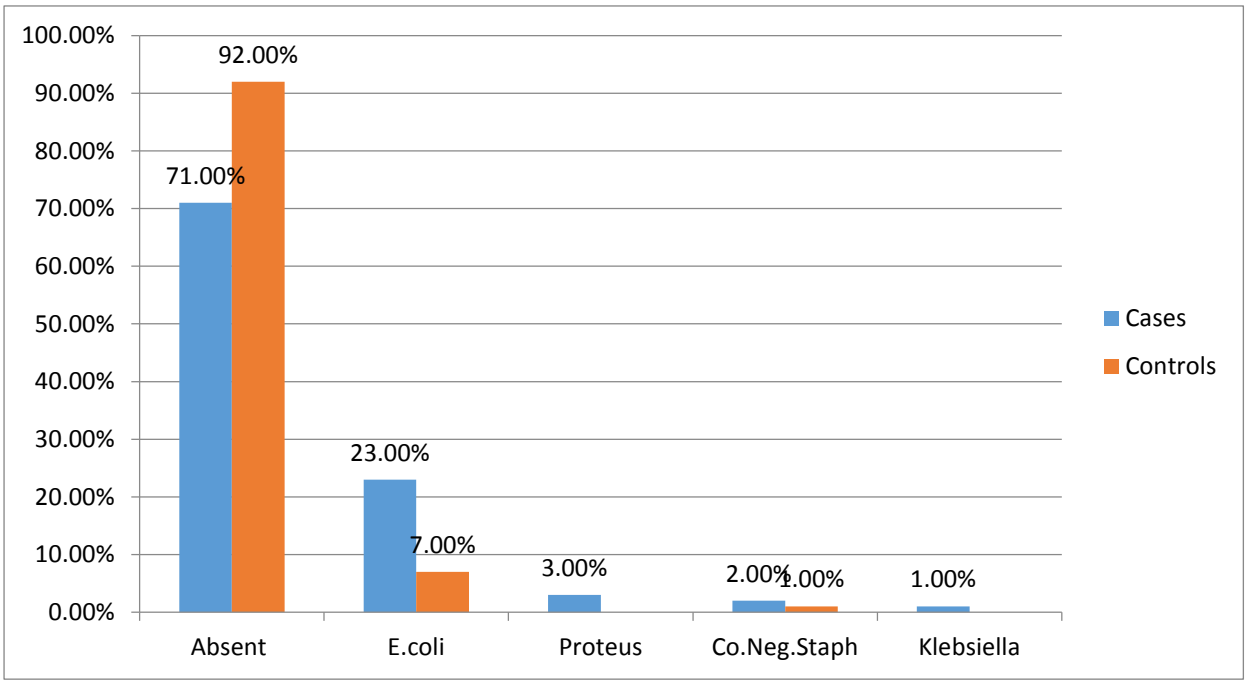

Figure 10: Bar diagram showing Bacterial Isolates comparison between two groups

Table 11: Duration of Diabetes among cases

		Group	
		Cases	
		Count	%
Duration of Diabetes	<5 years	34	34.0%
	6 to 10 years	36	36.0%
	11 to 15 years	18	18.0%
	16 to 20 years	10	10.0%
	>20 years	2	2.0%

Among cases majority of them 36% had diabetes for 6 t o10 years, 34% had diabetes for <5 years, 18% had diabetes for 11 to 15 years, 10% had diabetes for 16 to 20 years and 2% had diabetes for >20 years.

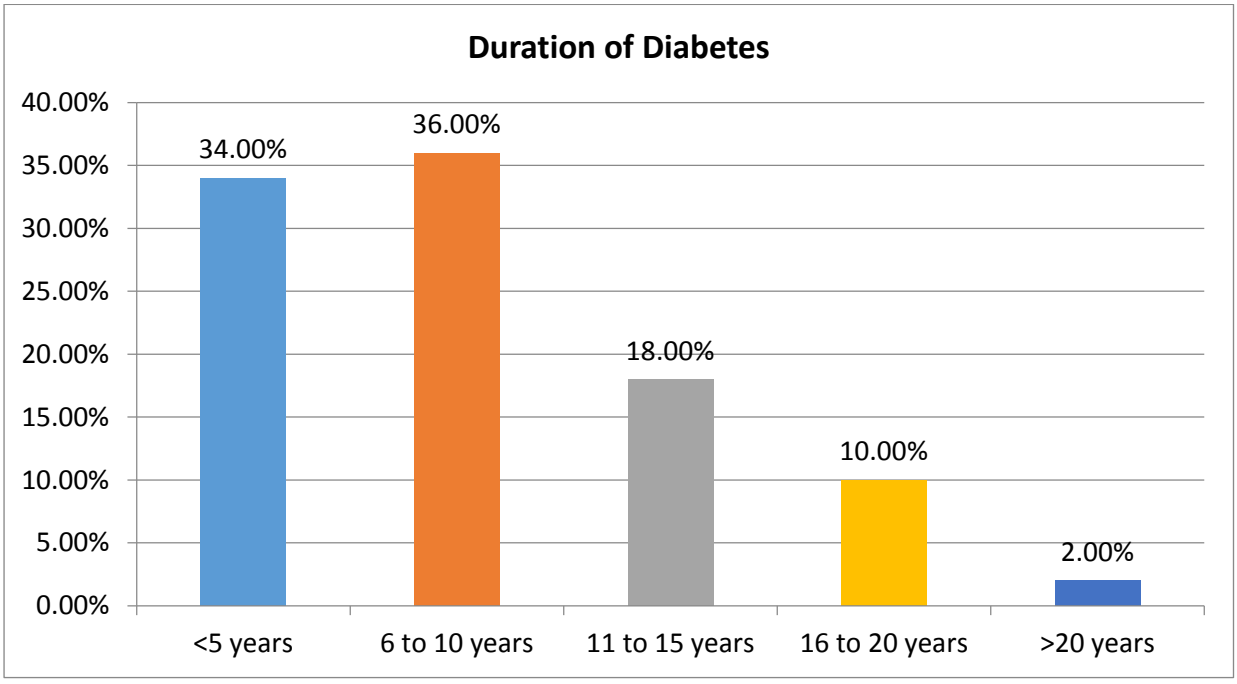

Figure 11: Bar diagram showing Duration of Diabetes among cases

Table 12: Glucosuria findings among cases

		Group	
		Count	%
Glucosuria	Absent	80	80.0%
	Traces	7	7.0%
	1+	3	3.0%
	2+	10	10.0%
	Total	100	100.0%

Among cases 7% had traces of Glucosuria, 3% had 1+ and 10% had 2+ Glucosuria.

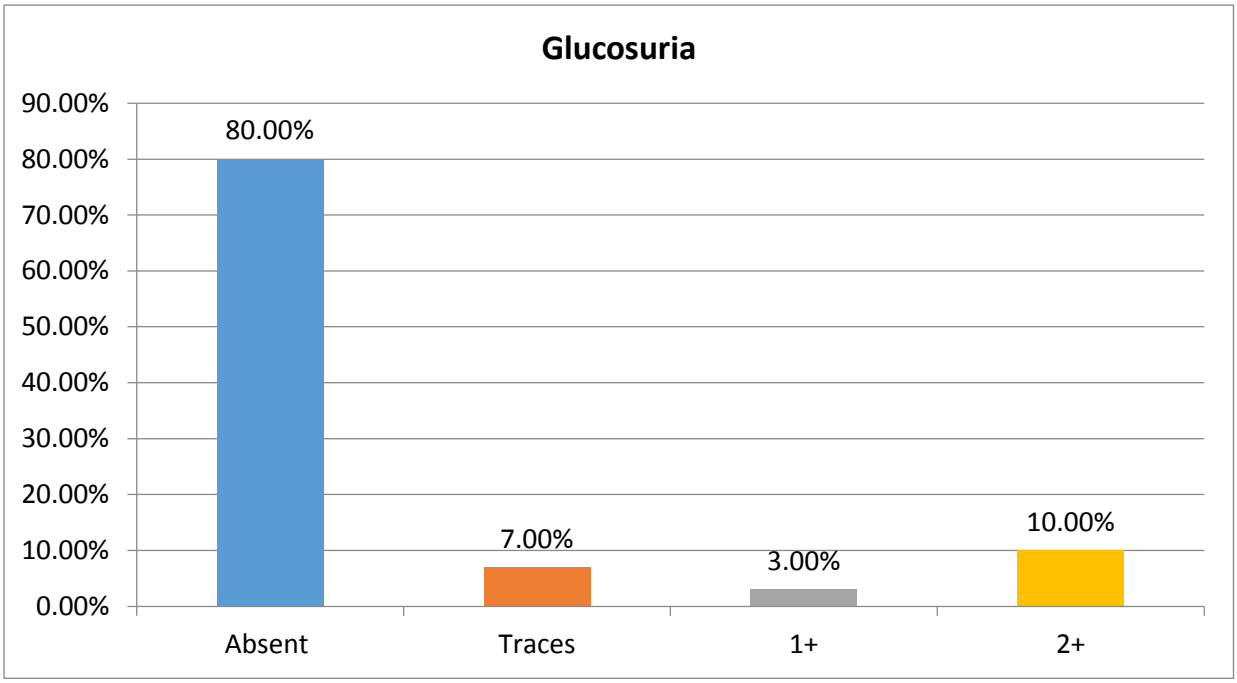

Figure 12: Bar diagram showing Glucosuria findings among cases

Table 13: Antibiotic Sensitivity pattern among subjects with ASB

		Group				P value
		Cases		Controls		
		Count	%	Count	%	
Amoxicillin	Resistant	9	31.0%	2	25.0%	0.741
	Sensitivity	20	69.0%	6	75.0%	
Gentamycin	Resistant	9	31.0%	3	37.5%	0.729
	Sensitivity	20	69.0%	5	62.5%	
Cotrimoxazole	Resistant	7	24.1%	3	37.5%	0.451
	Sensitivity	22	75.9%	5	62.5%	
Doxycycline	Resistant	10	34.5%	3	37.5%	0.874
	Sensitivity	19	65.5%	5	62.5%	
Ceftazidime	Resistant	2	6.9%	2	25.0%	0.144
	Sensitivity	27	93.1%	6	75.0%	
Ceftriaxone	Sensitivity	29	100.0%	8	100.0%	-
Ciprofloxacin	Resistant	11	37.9%	3	37.5%	0.982
	Sensitivity	18	62.1%	5	62.5%	
Norfloxacin	Resistant	7	24.1%	3	37.5%	0.451
	Sensitivity	22	75.9%	5	62.5%	
Nitrofurantoin	Resistant	11	37.9%	2	25.0%	0.498
	Sensitivity	18	62.1%	6	75.0%	
Amikacin	Resistant	11	37.9%	4	50.0%	0.538
	Sensitivity	18	62.1%	4	50.0%	
Piperacillin Tazobactum	Resistant	3	10.3%	1	12.5%	0.862
	Sensitivity	26	89.7%	7	87.5%	
Carbepenems	Sensitivity	29	100.0%	8	100.0%	-

There was no significant difference in Antibiotic sensitivity pattern between cases and controls among subjects with ASB. Majority of them in both groups were sensitive for all the antibiotics.

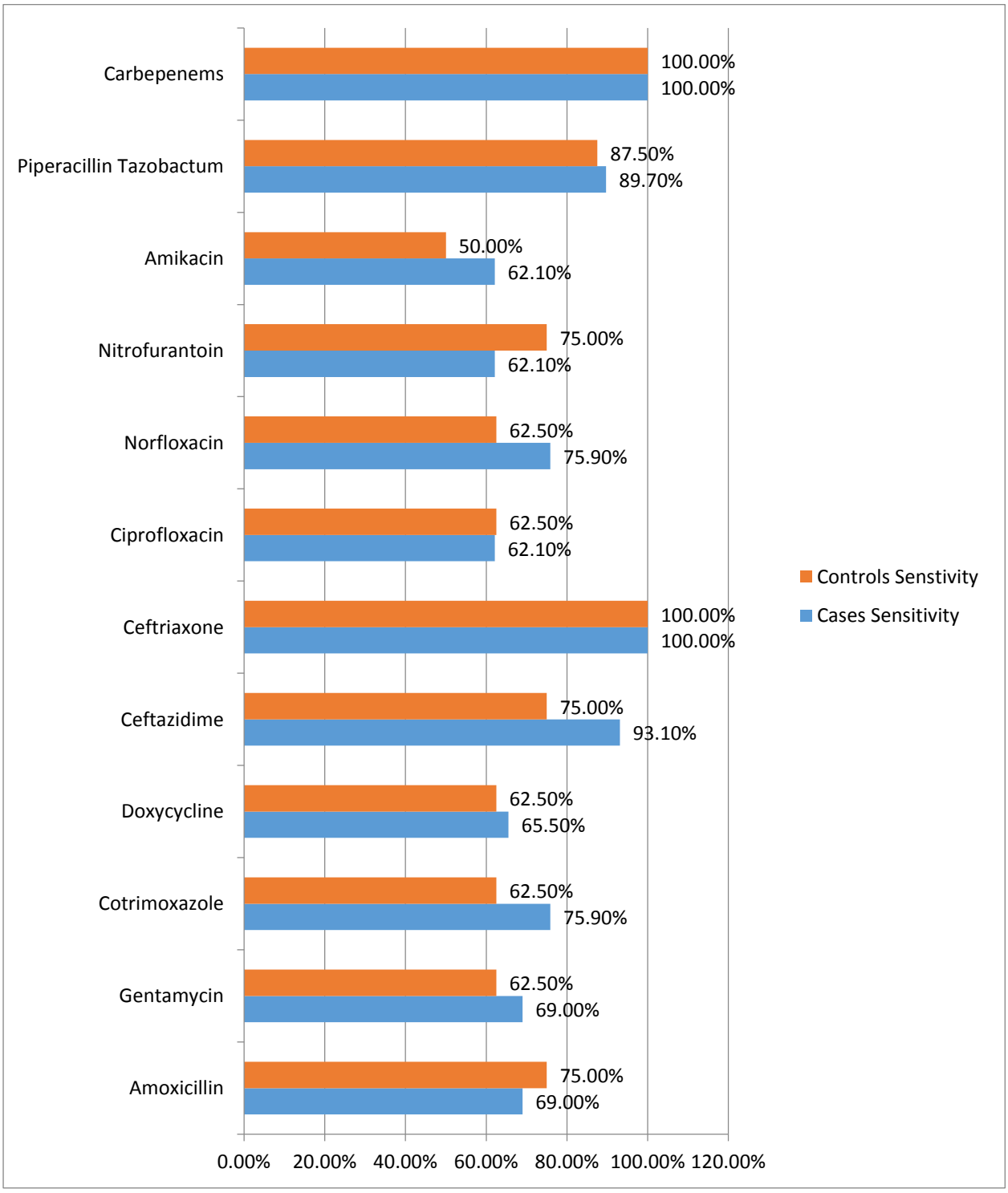

Figure 13: Bar diagram showing Antibiotic Sensitivity pattern among subjects with ASB

Table 14: Distribution of Age, Glycemic profile among cases with respect to ASB

	ASB				P value
	ASB +ve		ASB -ve		
	Mean	SD	Mean	SD	
Age	55.1	13.0	54.0	12.2	0.686
FBS	165.1	46.1	121.3	37.5	<0.001*
PPBS	251.7	55.0	192.0	49.6	<0.001*
HbA1c	8.4	2.3	7.5	1.8	0.038*
Duration of Diabetes	10.1	6.1	7.5	5.0	0.036*

There was significant difference in Mean FBS, PPBS, HbA1c and duration of diabetes among subjects with ASB + ve and ASB –ve in cases group. Subjects with ASB + ve had higher FBS, PPBS, HbA1c and duration of diabetes than ASB –Ve subjects.

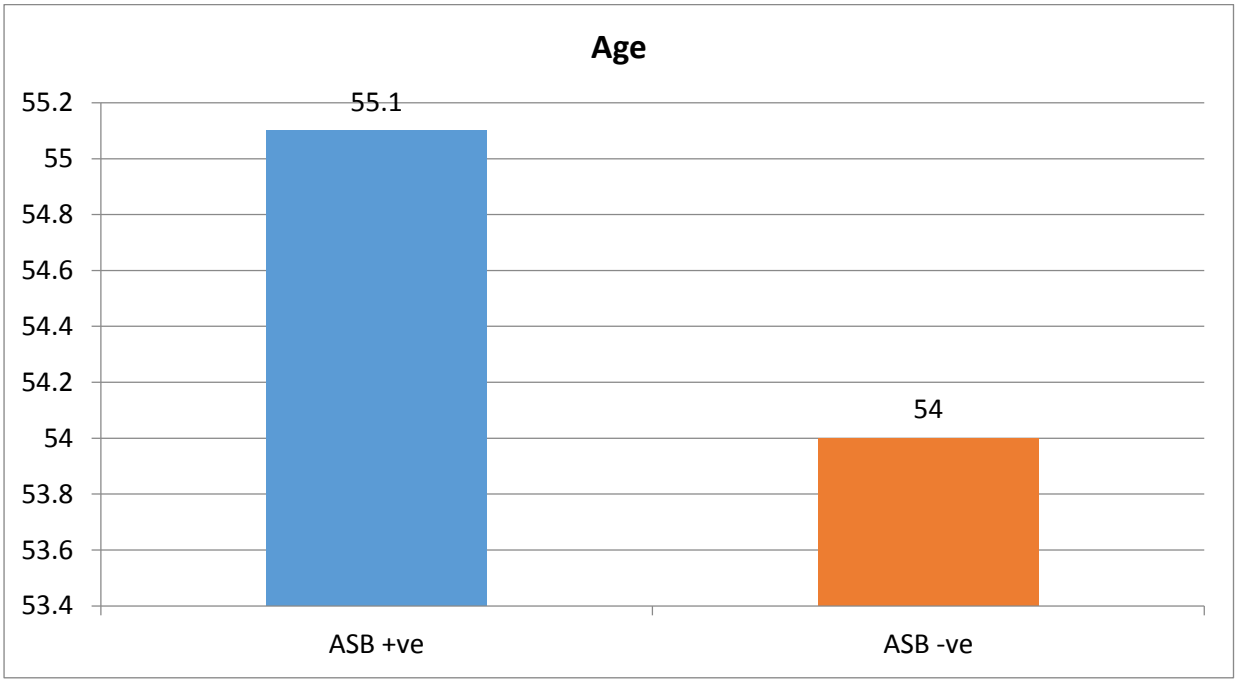

Figure 14: Bar diagram showing Age distribution between ASB +ve and ASB -ve subjects in cases group

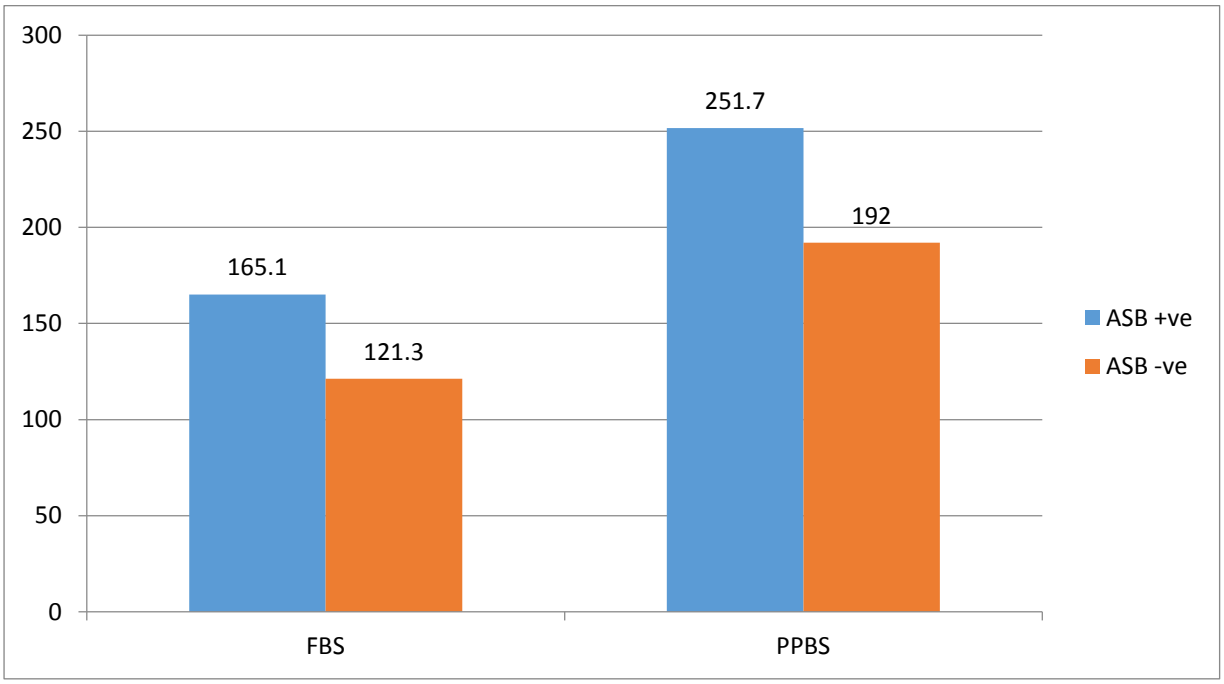

Figure 15: Bar diagram showing Distribution of Glycemic profile among cases with respect to ASB

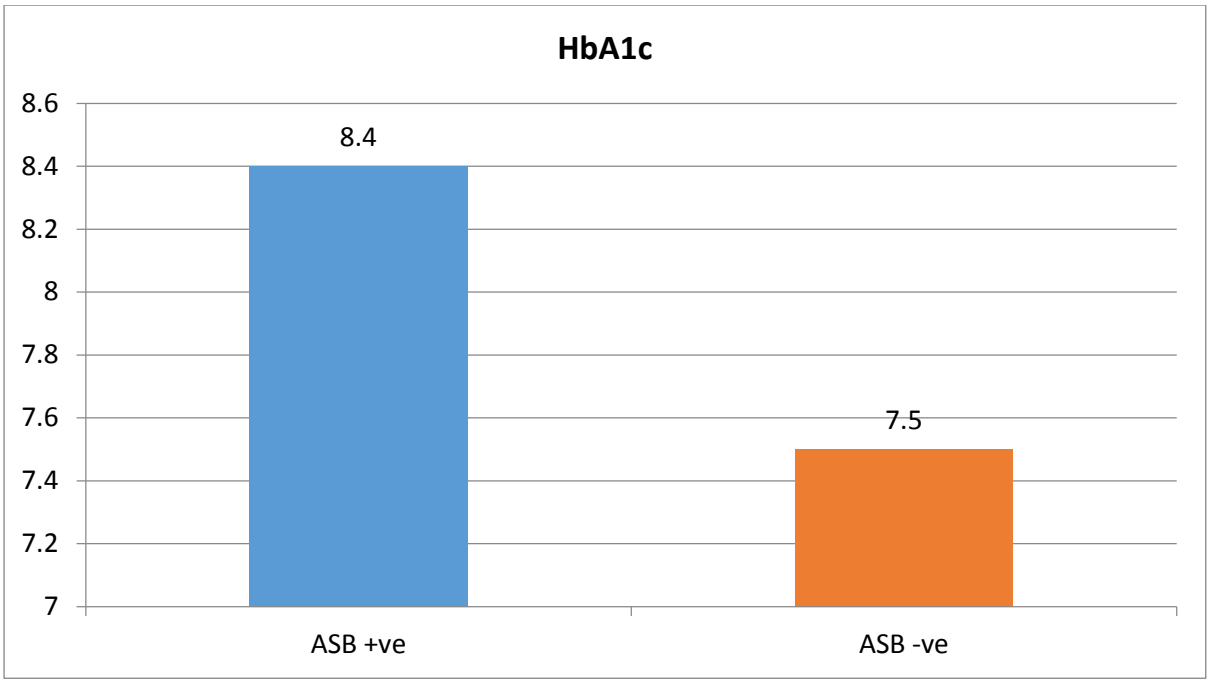

Figure 16: Bar diagram showing Distribution of HbA1c among cases with respect to ASB

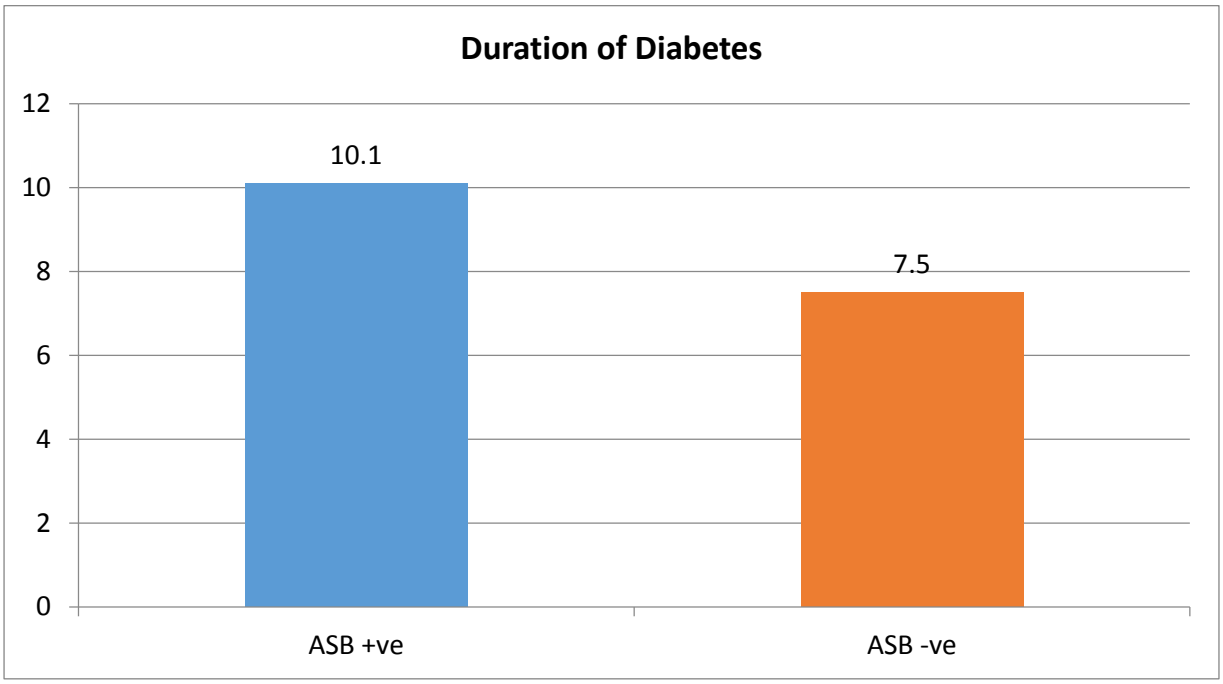

Figure 17: Bar diagram showing Distribution of duration of diabetes among cases with respect to ASB

Table 14: Association between Glucosuria and ASB in cases

		ASB			
		ASB +ve		ASB -ve	
		Count	%	Count	%
Glucosuria	Nil	19	65.5%	61	85.9%
	1+	2	6.9%	1	1.4%
	2+	6	20.7%	4	5.6%
	Traces	2	6.9%	5	7.0%
	Total	29	100.0%	71	100.0%

$\chi 2 = 7.806$, df = 3, p = 0.05

Among cases there was no significant association between Glucosuria and ASB findings. Among subject with ASB positive 6.9% had 1+, 20.7% had 2+ and 6.9% had traces of Glucosuria, were as among subjects with ASB –Ve, 1.4% had 1+, 5.6% had 2+ and 7% had traces of Glucosuria.

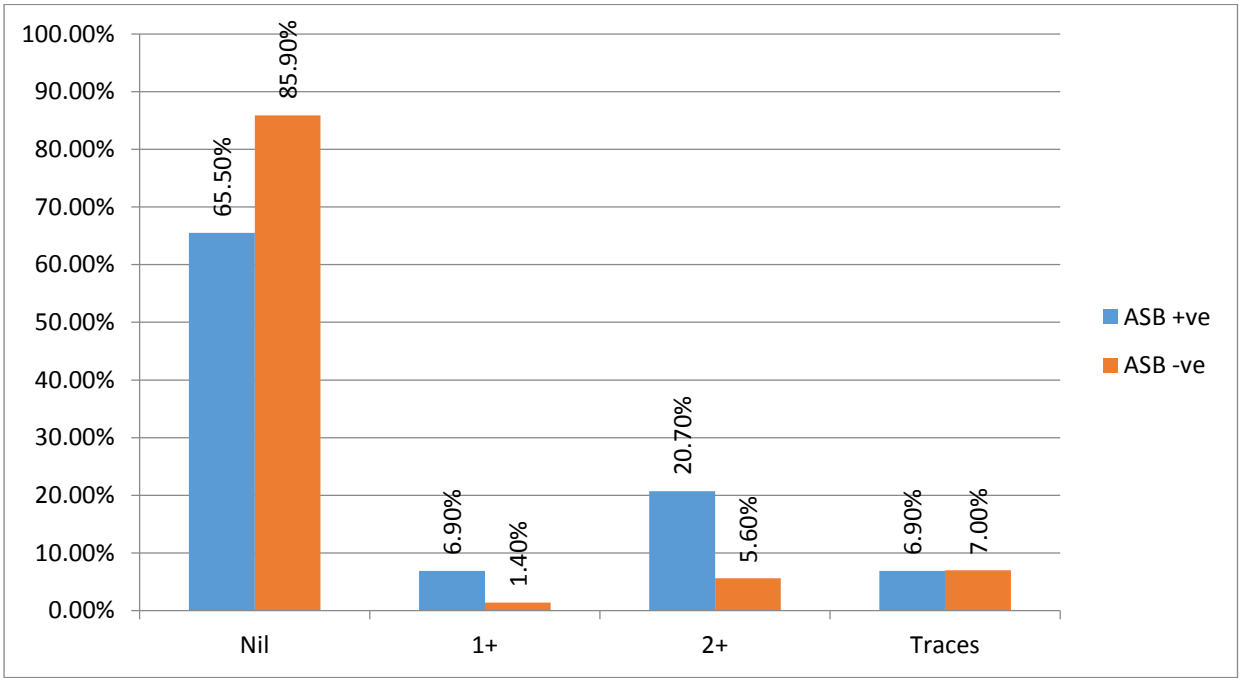

Figure 18: Bar diagram showing Association between Glucosuria and ASB in cases

DISCUSSION

In this study, it was found that the prevalence of asymptomatic bacteriuria is higher in women with diabetes (29%) than in women without diabetes (8%). This result was higher when compared to previous studies which showed 21% in Karachi[26], 26% in Nigeria[27] and 19% in Bahrain. The population studies in these reports are comparable to the number of patients in this study. Some studies have even reported much lower values of between 5.8 - 19%[28]. The variations in percentages of ASB have been attributed to factors such as geographical variations, ethnicity of the subjects and variation in the screening test[29]. The prevalence of ASB is about 3 times higher in diabetic women (ranging from 15% to 30%) than in non-diabetic women (less than 10%).[30,31] In the Netherlands, a prevalence of 26% among women with diabetes compared to 6% in non-diabetic women was reported.[32]

There was significatnt association between poor glycemic control and ASB. Among cases Mean FBS was 134 ± 44.7 mg/dl, mean PPBS was 209.3 ± 57.7 mg/dl and mean HbA1c was 7.7 ± 2 mg/dl. There was significant difference in Mean FBS, PPBS, HbA1c and duration of diabetes among subjects with ASB + ve and ASB –ve in cases group. Subjects with ASB + ve had higher FBS, PPBS, HbA1c and duration of diabetes than ASB –ve subjects. As per study conducted by singhal et al percentage prevalence of patients in group A ASB(+) with HbA1c levels >7 (poor glycemic control) is 92.3% is signi cantly higher than the percentage prevalence in ASB(-)HbA1C levels >7(poor glycemic control) is 54.5% (p=0.001).[33]

Many studies reveal that the type-2 diabetes leads to micro and macro vascular complications.[34] Among cases there was no significant association between Glucosuria and ASB findings. Among subject with ASB positive 6.9% had 1+, 20.7% had 2+ and 6.9% had

traces of Glucosuria, were as among subjects with ASB –Ve, 1.4% had 1+, 5.6% had 2+ and 7% had traces of Glucosuria.

In this study there was significant association between presence of leucocyturia, macroalbuminuria and ASB in diabetic women. Several studies described the incidence of proteinuria, glucosuria, leucocyturia and bacteriuria which are the major risk factors among the diabetic woman for ASB and UTI.[30,31,32] Early detection of leucocyturia is indication for the presence of bacterial infection. The findings of the urine analysis clearly indicate the incidence of leucocyturia which reveals the severity of the ASB and UTI.[35]

In this study most common organism isolated in cases and controls was E coli, 23% in cases and 7% in controls. There was significant difference in bacterial isolate between two groups. However, the result is consistent with the majority of reports where E. coli had been reported to be the major pathogen in ASB.[36,37,38,39] This is why in general practice most work on pathogenesis of UTI focuses on E. coli because of its high prevalence in UTI.[40] Another report from previous study noted a changing pattern of ASB with Klebsiella species accounting for the majority (42.4%) of asymptomatic bacteriuria among diabetics.[41] Another recent study in Nigeria reported Staphylococcus aureus to be the most common uropathogen isolated from both diabetics and non-diabetics with ASB.[42]

There was no significant difference in Antibiotic sensitivity pattern between cases and controls among subjects with ASB. Majority of them in both groups were sensitive for all the antibiotics. Bacterial isolates from urine samples of cases and controls were sensitive to most of the conventional antibiotics. The sensitivity of most common bacterial isolate, E.coli in this study is in agreement with previous reports.[43] However Multi drug resistance of E. coli is a common phenomenon as reported by other authors[44,45,46]

No consensus exists regarding the treatment of asymptomatic bacteriuria in diabetic patients. Many experts recommended treating ASB in diabetic patients because of the frequency and severity of upper urinary tract infections. On the other hand, few experts believe that the benefit of treatment of asymptomatic bacteriuria is doubtful. This contrast is the result of a lack of follow up studies of diabetic women with untreated asymptomatic bacteriuria. At this time, whether treatment of diabetic patients with asymptomatic bacteriuria prevents the development of symptomatic urinary tract infection or a decline in renal function is not clear. Long term follow up studies may show whether asymptomatic bacteriuria becomes symptomatic and affects renal function in diabetic patients and whether treatment of asymptomatic bacteriuria is warranted. There is also likely to be a benefit associated with the treatment of asymptomatic bacteriuria in the first six months after renal transplantation.[47] However in pregnant women the identification and treatment of asymptomatic bacteriuria do prevent pyelonephritis.[48]

SUMMARY

This study has shown the prevalence of ASB is higher in diabetic women than in women without diabetes. The prevalence ASB in diabetic women was 29% and among the non-diabetic was 8%.

The study has shown that age is not the risk factor for the diabetic women. Women with longer duration of diabetes had a grater risk of ASB. Poor metabolic control of diabetes was associated with significant risk of ASB in women with ASB. Statistically significant elevation of both FBS and PPBS was found in bacteriuric diabetic women. There is a significant association between macroalbuminuria and ASB in diabetic women (p= 0.001). Among cases 24% leuocytouria and among control 6% had leucocyturia. In this Study Escherichia coli was the commonest cause of ASB in diabetic women. Among the 29 were bacteriuric women, 23 isolates were E.coli, 1 was Klebsiella pneumoniae, 3 were Proteus mirabilis and 2 were Coagulase negative sthaphylococci. Majority of the isolates were susceptible to conventional antibiotics. Certain isolates exhibited some bacterial resistant to the antimicrobials.

CONCLUSION

- Urinary tract infection is major disease burden for many patients with diabetes
- asymptomatic bacteriuria in several fold more common among women with diabetes
- The longer the duration of diabetes greater is the risk of asymptomatic bacteriuria among diabetic women.
- A significant impairment of metabolic control of diabetes increases the risk of developing asymptomatic bacteriuria.
- The risk factors of asymptomatic bacteriuria in diabetic women include poor glycemic control, glucosuria and macro albuminuria
- Escherichia coli is the most common causative organism of asymptomatic bacteriuria in diabetic women.
- From this study, it can be safely assumed that antibiotics can be started on diabetic patients with leucocyturia early, pending culture and sensitive results. The antibiotic sensitivity depends on the prevalence of E.coli sensitivity.

BIBILIOGRAPHY

1. Gandhi J, Dagur G, Warren K, Smith N, Khan SA. Genitourinary Complications of Diabetes Mellitus: An Overview of Pathogenesis, Evaluation, and Management. Current diabetes reviews. 2016 Oct 19.

2. Hirsch IB. Glycemic variability and diabetes complications: does it matter? Of course it does!. Diabetes care. 2015 Aug 1;38(8):1610-4.

3. Deraje A, Shenoy S, Dhanshree B, Adhikari P. Asymptomatic Bacteriuria with Escherichia coli in Type 2 Diabetic Patients: An Unresolved Riddle. British Journal of Medicine and Medical Research. 2016 Jan 1; 11(3):1.

4. Renko M, Tapanainen P, Tossavainen P, Pokka T, Uhari M. Meta-analysis of the significance of asymptomatic bacteriuria in diabetes. *Diabetes Care*. 2011 Jan. 34(1):230-5.

5. Rubin RH, Shapiro ED, Andriole VT, Davis RJ, Stamm WE. Evalua- tion of new anti-infective drugs for the treatment of urinary tract infection. Clin Infect Dis 1992;15:Supl 1:S216-S227.

6. Suzanel E. Geerlings. Asymptomatic bateriuria may be considered a complication in women with diabetes- Diabetes Care – volume 23, No 6, June 2000.

7. 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):1.

8. Makuyana D, Mhlabi D, Chipfupa M, Munyombwe T, Gwanzura L. Asymptomatic bacteriuria among outpatients with diabetes mellitus in an urban black population. The Central African journal of medicine. 2001 Dec;48(7-8):78-82.

9. Deraje A, Shenoy S, Dhanshree B, Adhikari P. Asymptomatic Bacteriuria with Escherichia coli in Type 2 Diabetic Patients: An Unresolved Riddle. British Journal of Medicine and Medical Research. 2016 Jan 1;11(3):1.

10. J Janifer. Prevalence of lower urinary tract infection in South Indian type 2 diabetic subjects- Indian Journal of Nephrology.

11. Nongrum S, Thaledi S, Singh VA, Narang VK, Mehta S, Garg R, Shinu P, Sharma T. Association of Uropathogens with Asymptomatic Urinary Tract Infection in Diabetes Mellitus Patients. Int. J. Curr. Microbiol. App. Sci. 2016;5(10):355-61.

12. Lin E, Bhusal Y, Horwitz D, et al. Overtreatment of enterococcal bacteriuria. *Arch Intern Med*. 2012 Jan 9. 172(1):33-8.

13. Harding GK, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engl J Med*. 2002 Nov 14.

347(20):1576-83.

14. Barnabas R. Asymptomatic bateriuria and leucocyturia in Type 1 diabetic children and young adults. Diabetes Care 26:2209-2210,2003.

15. Cattell WR, Lefford MJ. Bacteriological Examination of Urine. *British Medical Journal*. 1963;1(5323):97-100.

16. Pozzilli P, Leslie RD. Infections and diabetes: mechanisms and prospects for prevention. *Diabet Med* 1994; 11: 935-41.

17. Joshi N, Caputo GM, Weitekamp MR. Infections in patients with diabetes mellitus. *N Eng J Med* 1999; 341: 1906-12.

18. Geerlings SE. Consequences of Asymptomatic bateriuria in women with diabetes mellitus. Arch Intern Med. 2001; 161:1421-1427.

19. Geerlings SE. Pathogenesis of bacteriuira in women with diabetes mellitus. Int J Antimicrob Agents.2002 Jun ;19(6): 539-45.

20. Keane EM. Prevalence of Asymptomatic bateriuria in subjects with NIDDM in San Luis Valley of Colorado. Diabetes Care, Vol 11, Issue 9 708-712

21. Patterson JE, Andriole VT. Bacterial urinary tract infections in diabetes. Infect Dis Clin North Am. 1995;9:25–51.

22. Hoepelman, IM. Urinary tract infection in patients with diabetes mellitus. Int. J. Antimicrob. Agents. 1994;4:113–116.

23. Kelestimur F. Asymptomatic bateriuria in patients with diabetes mellitus. Mikrobiyol Bull 1990;24:12632.

24. Platt R. Quantitative definition of bacteriuria. The American journal of medicine. 1983 Jul 28;75(1):44-52.

25. Clinical and Laboratory Standards, Wayne PA. Performance standards for antimicrobial disk susceptibility tests. Approved standard. Clinical and Laboratory Standards Institute 2006; ninth edition Document M2-A9.

26. Snydman DR. Posttransplant microbiological surveillance. Clin Infect Dis 2001;33:Suppl 1:S22-S25.

27. Alebiosu CO, Osinupebi OA, Olajubu FA. Significant asymptomatic bacteriuria among Nigeria type 2 diabetics. J. Nat. Med. Assoc. 2003;95(5): 344-348

28. Baqai R, Aziz M, Rasool G. Urinary tract infection in diabetics patients and biofilm formation of uropathogens. Infect. Dis. J. Pak. 2008;17(1): 21-24.

29. Assel MT, AI-Meer FM, AI-Kuwari MG, Ismail MF. Prevalence and predictor of asymptomatic bacteriuria among pregnant women attending Primary health care in Qatar Middle East. J. Fam. Med. 2009; 4:14-17.

30. Harding GK, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in diabetic women with asymptomatic bacteriuria. *N Engle J Med* 2003; 348 (10): 957-8.

31. Deraje A, Shenoy S, Dhanshree B, Adhikari P. Asymptomatic Bacteriuria with Escherichia coli in Type 2 Diabetic Patients: An Unresolved Riddle. British Journal of Medicine and Medical Research. 2016 Jan 1;11(3):1.

32. Geerlings SE, Stolk RP, M. Camps MJL, Netten PM, Hoekstra JB, Bouter PK, et al. Asymptomatic bacteriuria may be considered a complication in women with diabetes. Diabetes Care 2000b; 23: 744-749.

33. Singhal S, Himanshu D, Vaish AK, Singh M, Rana H. A Study of Asymptomatic Bacteriuria in North Indian Type 2 Diabetic Patients. J Diabetes Metab 2015;6: 620.

34. Ramchandran A, Snehalatha C, Shyamala P, VijayV, Viswanathan M. High prevalence of NIDDM and IGT in an elderly south Indian population with low rates of obesity. Diabetes Care 1994; 17: 1190-2.

35. Bonadio, M., Meini, M., Spetaleri, P. Gilgi, C. Current microbiological and clinical aspects of urinary tract infections. Eur. J. Urol, 2001; 40, 439- 45.

36. Assel MT, AI-Meer FM, AI-Kuwari MG, Ismail MF. Prevalence and predictor of asymptomatic bacteriuria among pregnant women attending Primary health care in Qatar Middle East. J. Fam. Med. 2009;4:14-17.

37. Olaitan JO. Asymptomatic bacteriuria in female students population of a Nigeria University. Int. J. Microbiol. 2006; 2(2): 4-9.

38. Baqai R, Aziz M, Rasool G. Urinary tract infection in diabetics patients and biofilm formation of uropathogens. Infect. Dis. J. Pak. 2008;17(1): 21-24.

39. Harding GK, Zhanel GG, Nicolle LE, Cheang M. Antimicrobial treatment in Diabetic women with asymptomatic bacteriuria N. Engl. J. Med. 2002;347:1576-1583.

40. Johnson JR. Microbial virulence determinants and the pathogenesis of Urinary tract infection. Infect. Dis. Clin. North. Am. 2003;17:261-265

41. Alebiosu CO, Osinupebi OA, Olajubu FA. Significant asymptomatic bacteriuria among Nigerian type 2 diabetics. J Natl Med Assoc 2003; 95: 344-351.

42. Omoregie R, Erebor JO, Ahonkhai I, Isibor JO, Ogofere H. Observed changes in the prevalence of uropathogens in Benin City, Nigeria. Nz J Med Lab Science 2008; 29-31

43. Olusanya N, Olutiola PO. Studies of bacteriuria in patients and students, in lle-lfe, Nigeria. West Afr. J. Med. 3(3): 177-183.

44. Bonadio M, Costrarelli 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 Infections Diseases 2006; 6 (54): 1 – 7

45. Ophori EA, Imade P, Johnny EJ. Asymptomatic bacteriuria in patients with diabetes. J Bacteriol Research 2010; 2 (2): 14-17.

46. Hamdan HZ, Ziad AHM, Ali SK, and Adam I. Epidemiology of urinary tract infections and antibiotics sensitivity among pregnant women at Khartoum North Hospital. Annals Clin Microbiol Antimicrob 2011; 10(2)

47. Snydman DR. Posttransplant microbiological surveillance. Clin Infect Dis 2001;33:Suppl 1:S22-S25.

48. Nicolle LE. Screening for asymptomatic bacteriuria in pregnancy. In: Canadian Task Force on the Periodic Health Examination. Canadian guide to clinical preventive health care. Ottawa, Ont.: Health Canada, 1994:100-5.

PROFORMA

1. **Name:**
2. **OP/IP no:**
3. **Age:**
4. **Chief Complaints**
5. **Past History:**
6. **General physical examination:**
7. **Systemic Examination: Cardiovascular System, Respiratory system, Abdomen, Nervous system**
8. **Investigations:**

   Fasting blood sugar

   Post Prandial Blood sugar

   Urine routine

   Glycated haemoglobin

   Urine culture and sensitivity