National Journal of Physiology, Pharmacy and Pharmacology

RESEARCH ARTICLE

Impact of HbA1c levels on asymptomatic bacteriuria in type 2 diabetes mellitus

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Received: June 23, 2019; **Accepted:** July 17, 2019

ABSTRACT

Background: Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Infections occur more commonly in patients with DM due to the hyperglycemic medium that increases the virulence of pathogen. **Aims and Objectives:** The present study was aimed to determine the impact of poor glycemic control as a risk factor for symptomatic urinary tract infection (UTI) in diabetic patients with asymptomatic bacteriuria (ASB) during follow-up. **Materials and Methods:** This was a cross-sectional observational study conducted at Vinayaka Missions Medical College on diabetic patients. Hemoglobin Alc (HbA1c) was quantified spectrophotometrically using HbA1c test kits. All participants were instructed strictly to collect midstream urine sample. Urine samples collected from participants were inoculated on blood agar and MacConkey agar and incubated for overnight at 370°C. If growth occurs, organism was identified by standard microbiological procedures. Symptomatic UTI surveillance was done by instructing participants to contact research personnel if any new symptom/symptoms occurred (follow-up period 3 months) that suggested UTI. **Results:** A total of 225 participants were included in the study and categorized as diabetic (n = 175) and non-diabetic as control group (n = 50). A total of 107 diabetic patients had <7 HbA1c levels, 12 (11.21%) urine specimens collected from these patients yielded bacterial growth. Sixty-eight patients had ≥7 HbA1c levels, 19 (27.94%) urine specimens collected from these patients yielded bacterial growth. Among the patients with <7 HbA1c levels, 16.6% of patients developed symptomatic UTI and among the patients with ≥7 HbA1c, 5 (26.3%) patients developed symptomatic UTI. **Conclusion:** Poor glycemic control can show the impact on ASB to develop symptomatic UTI.

KEY WORDS: Poor Glycemic Control; Asymptomatic Bacteriuria; Urinary Tract Infection

INTRODUCTION

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. It is associated with decrease in production and utilization of insulin, resulting in body's inability to utilize nutrients properly.[1] Diabetes influences in excess of 194 million individuals around the world with high rates of mortality and horribleness. Its predominance is more in India, China, and the USA and is relied onto reach 333 million by 2025.[2] The rising frequency of DM and the sheer number of individuals with DM living in India have given this nation the questionable refinement of being the "diabetes capital" of the world.[3]

Access this article online	
Website: www.njppp.com	Quick Response code
DOI: 10.5455/njppp.2019.9.0725717072019	

Infections are common in patients with DM due to the hyperglycemic medium that enhances the pathogenic virulence, reduced production of interleukin, causing chemotaxis and phagocytic activity dysfunction, damaged neutrophil function, glycosuria and gastrointestinal, and urinary tract dysmotility. These can also be accompanied by other complications that are related to neuropathy causing

malfunctions of the bladder that can cause a higher risk of infection, especially urinary tract infections (UTIs).[4]

Glycemic control is based on glycated hemoglobin Alc (HbA1c) examinations. HbA1c is the gold standard to control a patient's blood glucose concentration. DM is stated as under good control if the levels of HbA1c <7% and DM are unregulated the HbA1c >7%. HbA1c is now used as an indicator and marker that are significant for glucose control describing the mean plasma glucose from 6 to 8 weeks before. Poor glycemic control in diabetic patients leads to various complications including infections.

UTI is an important clinical problem for people with diabetes. This observation is most apparent in the increased severity of this infection that may occur in diabetic patients. Serious complications of urinary infection, such as emphysematous cystitis, pyelonephritis, or renal and perinephric abscess, occur virtually only in diabetic patients.[5]

Asymptomatic bacteriuria (ASB) is one of the common problems seen in diabetic patients preceding symptomatic UTI.[6]

The significance of ASB is vague. The prevalence of ASB in diabetic patients varies from 9 to 27% in different studies which are certainly higher as compared to healthy individuals; the various risk factors which lead to increased prevalence of ASB in diabetic patients are immune system dysregulation, development of bladder dysfunction, and prostatism. Many studies have reported that ASB has a higher prevalence in diabetic individuals as compared to non-diabetics.[7]

The previous studies reported that the association between poor glycemic control (HbA1c levels >7.0%) and incidence of ASB was investigated among diabetic patients. Various researchers in the U.S. recommend treating ASB in diabetic patients due to the frequency and severity of upper UTIs.[8] In contrast, European researchers believe that the advantage of the treatment is doubtful.[9]

This difference is due to a lack of follow-up studies among diabetic patients with untreated ASB. It is not clear whether treatment if ASB in diabetic patients will prevent development of symptomatic UTI.

Hence, the present study was aimed to determine the impact of poor glycemic control as a risk factor for symptomatic UTI in diabetic patients with ASB during follow-up.

MATERIALS AND METHODS

This was a cross-sectional observational study conducted at Vinayaka Missions Medical College on diabetic patients after obtaining written informed consent. The institutional ethical committee clearance obtained. One hundred and seventy-five diabetic patients and 50 non-diabetic individuals as controls were included in the study. While screening for ASB, patients with symptomatic UTIs, renal failure, obstructive uropathy, indwelling catheters, pregnant females, and patients who had undergone antimicrobial therapy in the past 15 days were excluded from the study.

Glycated HbA1c Quantification

HbA1c was quantified spectrophotometrically using HbA1c test kits. Briefly, hemolysate was made from heparin anticoagulant whole blood samples. The HbA1c fraction was then specifically eluted after washing away the HbA1a+b fraction and quantified by direct photometric reading at 415 nM. Poor glycemic control was defined as HbA1c >7.0% as recommended by the American Diabetes Association.[10]

Microbiological Investigation

All participants were instructed strictly to collect midstream urine sample. Urine samples collected from participants were inoculated on blood agar and MacConkey agar and incubated for overnight at 37°C. If growth occurs, organism was identified by standard microbiological procedures.

The Diagnosis of Asymptomatic Bacteriuria[11]

For asymptomatic women, bacteriuria is defined as two consecutive voided urine specimens with isolation of the same bacterial strain in quantitative counts of greater than or equal to 10^5 cfu/mL.

For asymptomatic men, a single, clean-catch, voided urine specimen with one bacterial species isolated in a quantitative count of greater than or equal to 10^5 cfu/mL.

Symptomatic UTI Surveillance

Participants were instructed to contact research personnel if any new symptom occurred (follow-up period 3 months) that suggested UTI. A standardized interview was then conducted, and, if infection was thought to be likely (presence of dysuria, urgency, or frequency).

Statistical analysis was performed by simple percentage method.

RESULTS

A total of 225 participants were included in the study and categorized as diabetic (n = 175) and non-diabetic as control group (n = 50). Of 225 diabetic patients, 111 were female and 114 were male. Thirty-one (17.71%) urine specimens yielded growth. Majority of specimens yielded growth were from female patients 22 (70.97%). Only five urine samples yielded growth from non-diabetic participants and accounted for 8%.

A total of 107 diabetic patients had <7 HbA1c levels, 12 (11.21%) urine specimens collected from these patients yielded bacterial growth. Sixty-eight patients had ≥7 HbA1c levels, 19 (27.94%) urine specimens collected from these patients yielded bacterial growth. The prevalence of ASB was found to be high in patients with poor glycemic control (HbA1c ≥ 7%) [Table 1].

Among the patients with <7 HbA1c levels, 12 patients had ASB. During the follow-up period, of 12 patients with ASB, 2 (16.6%) patients developed symptomatic UTI and among the patients with ≥7 HbA1c, of 19 patients with ASB, 5 (26.3%) patients developed symptomatic UTI [Table 2]. No symptomatic UTI noticed in control group during follow-up.

Escherichia coli was the predominant isolate which accounted for 35.48% followed by *Klebsiella* species (29.03%) and *Staphylococcus* species (12.90%) [Table 3]. In control group (non-diabetic participants), five urine samples yielded the growth and all were identified as of *E. coli* and no other bacteria were observed.

Nitrofurantoin was found to be the most susceptible antibiotic against all isolates except *Proteus mirabilis*. Cotrimoxazole was also found to be the most effective antibiotic against all bacterial isolates [Table 4]. All isolates from control subjects were found to be susceptible to nitrofurantoin.

DISCUSSION

The aim of this study was to assess the impact of poor glycemic control as a risk factor for symptomatic UTI in diabetic patients with ASB during follow-up. It was observed that the presence of bacteria (ASB) in urine samples among diabetic with poor glycemic control was high and accounted for 27.92%, which is high compared to patients with good glycemic control (11.21%). Patients with ASB and poor glycemic control are more prone to develop symptomatic UTI than non-diabetics and also ASB is prevalent among this population.

Table 1: Association of HbA1c levels with ASB

HbA1c	Number of diabetic patients	ASB (%)	No ASB (%)
≤7	107	12 (11.21)	95 (88.78)
>7	68	19 (27.94)	49 (72.6)
Total	175	31	144

HbA1c: Hemoglobin Alc, ASB: Asymptomatic bacteriuria

Table 2: Association of HbA1c levels with ASB and risk of UTI

HbA1c	ASB (%)	UTI during follow-up (%)
≤7	12	2 (16.6)
>7	19	5 (26.3)
Total	31	7 (22.5)

HbA1c: Hemoglobin Alc, UTI: Urinary tract infections, ASB: Asymptomatic bacteriuria

DM has been commonly associated with UTI. The mechanism of pathogenesis for this association has not been fully elucidated. However, it is suggested that high glucose concentration in urine may favor the growth of pathogenic microorganisms, either in the form of symptomatic UTI or ASB. The difference between symptomatic UTI and ASB has major clinical implications. Both UTI and ASB denote the presence of bacteria in the urinary tract, usually accompanied by white blood cells and inflammatory cytokines in the urine. However, ASB occurs in the absence of symptoms attributable to bacteria in the urinary tract. The diagnosis of ASB requires the presence of $\geq 10^5$ bacterial CFUs/mL, except in catheter-associated disease, in which $\geq 10^2$ CFUs/mL is the cutoff.[12]

In our study, ASB was accounted for 17% in diabetic patients which is in consistent with other studies.[13] Majority of specimens yielded growth were from female patients 22 (70.97%). Only five urine samples yielded growth from non-diabetic participants and accounted for 8%. As per the study conducted by Singhal *et al*., the prevalence of ASB in diabetics was 28.2% as compared to 7.5% in non-diabetic patients. The prevalence of ASB was higher among female diabetic patients (39.1%) as compared to females in non-diabetic participants (10.8%). The prevalence of ASB in male diabetic patients was higher (17.3%) as compared to females in non-diabetic participants (4.2%)[5].

The prevalence of ASB was less compared to the study conducted by Venkatesan *et al*., in which they found the prevalence of ASB to be 32% in 100 diabetic patients (Ses

Table 3: Bacteriological profile of ASB in diabetic patients

Bacteria	*n* (%)
Escherichia coli	11 (35.48)
Klebsiella sp.	9 (29.03)
Staphylococcus sp.	4 (12.90)
Citrobacter sp.	4 (12.90)
Proteus mirabilis	2 (6.45)
Pseudomonas aeruginosa	1 (3.23)
Total	31 (100)

Table 4: Antibiotic susceptibility pattern of bacterial isolates

Bacteria	NIT	AMP	COT	OF	NF	CTR
Escherichia coli (11)	10	0	9	7	5	6
Klebsiella sp. (9)	5	0	7	3	3	1
Staphylococcus sp. (4)	4	2	4	2	3	1
Citrobacter sp. (4)	4	3	3	2	1	1
Proteus mirabilis (2)	0	1	2	2	2	2
Pseudomonas aeruginosa (1)	1	0	0	0	1	1

NIT: Nitrofurantoin, AMP: Ampicillin, COT: Cotrimoxazole, OF: Ofloxacin, NF: Norfloxacin, CTR: Ceftriaxone

and 50 females), of which 20 (62.5%) were female and 12 (37.5%) were male.[14] However, the study conducted by Vishwanath *et al*. showed that ASB was present in 4 (4%) of 100 patients with Type 2 DM.[15]

In our study, diabetic patients with <7 HbA1c levels, 12 patients had ASB. During the follow-up period, of 12 patients with ASB, 2 (16.6%) patients developed symptomatic UTI and among the patients with ≥7 HbA1c, of 19 patients with ASB, 5 (26.3%) patients developed symptomatic UTI. Incidence of symptomatic UTI was found to be high in patients with poor glycemic controls. Our results are in comparison with the study conducted by Singhal *et al*.[5]

In our study, *E. coli* (35%) was the predominant isolate followed by *Klebsiella* species (29%). These results are comparable with the study conducted by Venkatesan *et al*.[14] As per Venkatesan *et al*., *E. coli* (37.5%) was the most prevalent organism isolated from urine cultures in their study followed by *Klebsiella pneumoniae* (18.7%). However, in the present study, no *Candida* species was isolated. Our results are not comparison with the observations of Bissong *et al*.[16] In their study, coagulase-negative staphylococci was the predominant isolate (36.3%) isolated, followed by *Klebsiella* (15.9%), *Candida* (13.7%), *E. coli* (10.8%), and *Serratia* (10.8%).

In the present study, antibiotic susceptibility testing was performed. Nitrofurantoin was found to be the effective antibiotic against majority of bacterial isolates except *P. mirabilis*. As per Boyko *et al*., among the antibiotics, aminoglycosides (34%), nitrofurantoin (21%), and gatifloxacin (14%) had excellent activity against the isolates and could be used for empirical treatment.[17] Venkatesan *et al*. observed that *E. coli*, the most prevalent organism in their study, was most sensitive to nitrofurantoin, amikacin, and gentamicin.[14]

Limitations of the present study are less sample size, follow-up of patients was done only for short duration (3 months) and we believe that few of our female patients did not reveal information regarding recent sexual activity which could be the risk factor for the development of symptomatic UTI.

CONCLUSION

Poor glycemic control can show the influence on ASB to develop symptomatic UTI.

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How to cite this article: Danasegaran M, Balaji PV, Moinuddin SK, Nazeer HA. Impact of HbA1c levels on asymptomatic bacteriuria in type 2 diabetes mellitus. Natl J Physiol Pharm Pharmacol 2019;9(10):987-990.

Source of Support: Nil, **Conflict of Interest:** None declared.