

# Asymptomatic urinary tract infections and associated risk factors in diabetes mellitus patients attending a diabetes center of Peshawar, Pakistan

Mohammad Jawad, Shaheen Ali Khan, Seema Ashraf, Abdul Jalil Khan, Kashif Ali Sameen, Saman Khan

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**Author Information**

*Dr. Mohammad Jawad* Lecturer, Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar. (Corresponding Author)  
Email: mdrjawad@yahoo.com

*Dr. Shaheen Ali Khan* Trainee Medical Officer, Medicine and Allied, Rehman Medical Institute, Peshawar.

*Dr. Seema Ashraf* Assistant Professor, Department of Community Medicine, Rehman Medical Institute, Peshawar.

*Dr. Abdul Jalil Khan* Assistant professor Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar.

*Dr. Kashif Ali Sameen* Assistant Professor, Institute of Public Health and Social Sciences, Khyber Medical University, Peshawar.

*Dr. Saman Khan* Medical Officer, Sugar Hospital and Research Center, Peshawar.

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**ABSTRACT**

**Introduction:** Type 2 Diabetes patients are at increased risk of urinary tract infections that, if neglected, can result in chronic renal disease and end stage renal failure. Asymptomatic bacteriuria (ASB) is a feature of type 2 diabetics and can be a silent forerunner of future symptomatic urinary tract infections.

**Objective:** To determine the magnitude of asymptomatic urinary tract infections in type 2 diabetics and investigate possible associated factors.

**Materials & Methods:** A cross sectional study was conducted at Sugar Hospital and Research Center, Peshawar over 04 months (March to May 2018) on all type 2 diabetic patients presenting during the study period through convenience sampling. A mid-stream urine sample was collected and microscopically examined for leucocytes; a dipstick was used to detect nitrates. All relevant patient information was noted, and a comparison was made between ASB and non ASB groups. Data were analyzed by SPSS 22 for descriptive and comparative statistics, keeping  $p \leq 0.05$  as significant.

**Results:** A total of 363 diabetic patients were included, of which 28.6% (n=104) had ASB. Mean age was  $50.39 \pm 11.74$  years, and 63.4% (n=230) were females, of whom 61.7% (n=223) were stay at home mothers; 54.3% (n=197) had been diabetic for 5-10yrs. The mean HbA1c value was  $9.98 \pm 2.68$ , and 27.5% (n=100) were on insulin; 7.7% (n=28) had BMI > 30. Complications such as retinopathy and nephropathy were 26.4% (n=96) and 33.9% (n=123) respectively; 26.7% (n=97) of the subjects were hypertensive. A positive association was found between gender, occupation, nephropathy and ASB ( $p < 0.05$ ).

**Conclusion:** Asymptomatic urinary tract infections were present in a significant number of subjects and showed a positive association with gender, occupation and nephropathy.

**Keywords:** Diabetes mellitus; Urinary tract infection; Asymptomatic Bacteriuria.

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**INTRODUCTION**

Diabetes has reached pandemic levels and is threatening to get worse over the coming years, with 177 million people being affected globally; WHO expects this number to double by the year 2030 and become the 7<sup>th</sup> leading cause of mortality in the world.<sup>1,2</sup>

Pakistan is also in the path of this progressive tidal wave with the number of diabetics progressively increasing over the years. According to WHO (2011) prevalence of diabetes is 12.9 million. Of this number, 9.4 million are diagnosed cases, 38 million are pre-diabetic. This number is expected to increase to 14 million by 2030.<sup>3,4</sup>

The genitourinary system faces several long term repercussions of Diabetes mellitus in the long run, with the most important one being infections, such as bacterial Urinary Tract Infections (UTI).<sup>5,6</sup> Diabetics also tend to present with Asymptomatic Bacteriuria (ASB) which can be the forebearer of symptomatic and complicated UTI. If ASB is left untreated, it tends to predispose patients to recurrent and complicated UTIs that can lead to further complications such as acute Pyelonephritis and Gram-Negative septicemia, eventually leading to long-term ramifications such as renal scarring. The end point of all this is chronic kidney disease. Diabetes is thought to increase the risk of UTIs by 60% and lead to 2-4 fold increase in genital tract infections.<sup>7</sup>

An overall increased incidence of UTIs has been reported in diabetes in several different studies and all types of UTIs are thought to occur more frequently within this population. A study based in the United Kingdom showed that 4.69% diabetics suffer from UTIs annually and this number is almost double when compared with non-diabetic persons.<sup>8</sup>

Global literature documented variable prevalence of asymptomatic UTIs within diabetics with estimates ranging from 8%–38.3%.<sup>7,9-14</sup>

A meta-analysis based on 22 studies in 2011 reported ASB in 12.2% diabetics versus 4.5% healthy controls.<sup>15</sup> The risk of ASB is not gender specific and found equally in both males and females with long standing DM.

Glycemic control was not a risk for development of ASB.<sup>15</sup> It is more common in the elderly, and also shows an association with abnormalities of the urinary tract and urethral instrumentation or manipulation (Urethral catheters, stents, etc.).<sup>16,17</sup> A recent study from India found that 30% of their hospitalized diabetic population had ASB.<sup>18</sup>

The present study was conducted to document the magnitude of asymptomatic urinary tract infections in type 2 diabetic patients attending a diabetic center, and to describe factors associated with it.

### MATERIALS & METHODS

A cross sectional study was carried out at Sugar Hospital and Research Center, Peshawar during the timeline of 1<sup>st</sup> Feb. 2018 to 31<sup>st</sup> May 2018.

All type 2 diabetic patients presenting during the study period were included through Non-Probability Convenience sampling. The sample size was calculated through Open EPI with 5% precision, 95% Confidence Interval by taking prevalence of asymptomatic Urinary Tract Infection 38.3% as measured in a study conducted in Kohat.<sup>9</sup>

Exclusion criteria included patients with symptoms of UTI (dysuria, urgency, frequency, supra-pubic pain or tenderness, fever) or those who had taken antibiotics within the preceding 2 weeks, and those with a history of anatomical and neurologic urinary tract abnormalities.

#### Data collection procedure

Ethical approval was first taken from the Hospital Ethical Committee. All diabetic patients of both genders, aged over 12 years, visiting the diabetic clinic were included in the study. Written informed consent was taken from all the patients. Glycosylated Hemoglobin (HbA1c) was measured for all patients included in the study.

Mid-stream urine (MSU) sample was taken in a sterile container. All samples were sent to the laboratory, where slides were made for microscope examination for the presence of leukocytes. Urine combo strip was used to detect the presence of nitrates and albumin. Samples which had >5 leukocytes/HPF and were nitrate positive were considered a UTI.<sup>1,19</sup>

Study participants were divided into 2 groups i.e. Group 1, designated patients with UTI (ASB group) and Group 2 designated no UTI (Non-ASB group).

#### Data collection and analysis

Data were collected on predesigned questionnaires and analyzed on SPSS version 22. Appropriate descriptive statistics values were calculated for both Qualitative (Gender, occupation, residence, socioeconomic status, treatment modality, retinopathy, nephropathy and HTN) and Quantitative variables (Duration of Diabetes Mellitus, Age, BMI, and Glycosylated

Hemoglobin HbA1c).

For qualitative variables percentage and frequency were calculated. For quantitative variables mean ± standard deviation were calculated. Student's T-test and Chi Square test were applied to look for statistical difference in both groups with regard to all variables; p≤0.05 was taken as statistically significant. Association of ASB with different factors was noted and plotted in graphs, bar charts and tables.

### RESULTS

A total of 363 patients were enrolled in the study, out of which 36.6% (n=133) were males while 63.4% (n= 230) were females. Mean age of patients was 50.39±11.74 years. Mean HbA1c of subjects was 9.98±2.68.

Asymptomatic UTI was present in 28.6% (n=104). Figure 1 shows the graphical presentation of it.

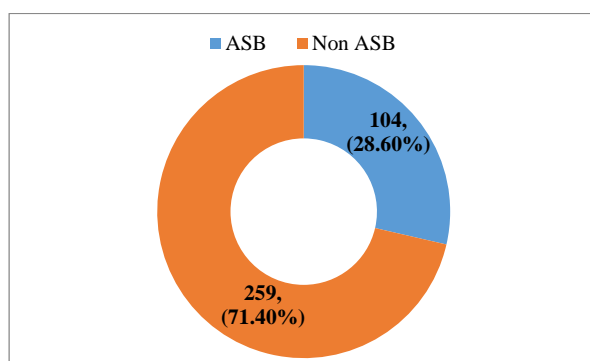


Figure 1: Distribution of ASB in type 2 diabetics (n=363).

The demographic characteristics of subjects are described in Table 1.

Table1: Demographic characteristics of Subjects (n=363).

Characteristics		n (%)
Gender	Females	230 (63.4)
	Males	133 (36.6)
Occupation	Housewife	124 (61.7)
	Office Job	62 (17.1)
	Field Job	45 (12.4)
	Unemployed	22 (6.1)
	Others	10 (2.8)
Address	Rural	145 (39.9)
	Urban	218 (60.1)
Income	<20000/month	159 (43.8)
	>20000/month	204 (56.2)

Analysis was also done for disease related factors and complications. Duration of diabetes was ≤5yrs in 22.6% (n=82), while 54.3% (n=197) had diabetes for >5yrs but <10yrs while 23.1% (n=48) patients had it for more than 10 yrs. Mean HbA1c level was 9.98±2.68.

Only 27.5% (n=100) of subjects were using insulin, while the rest i.e. 72.5% (n=263) were taking oral hypoglycemic agents for control of their diabetes; 46.6% (n=169) had BMI <25, and 45.7% (n=166) had >25 but <30 BMI while only 7.7% (n=28) had BMI >30.

Studying the complications of diabetes mellitus, it was found that 26.4% (n=96) had retinopathy; nephropathy, as determined by urine dipstick test for albumin, was present in 33.9% (n=123); additional comorbidities, primarily hypertension, were found in 26.7% (n=97) patients.

For the purpose of accuracy and precision patients were further divided into well-controlled diabetics and uncontrolled diabetics, with the cutoff value being set at an HbA1c of 7.0 to see the exact correlation of diabetic control with ASB. It was found that 21% patients with well-controlled diabetes had ASB while 30% patients with uncontrolled diabetes had it (p=0.16.)

The data set was divided into 2 groups on the basis of UTI. Further analysis was based on these two groups. The general characteristics of patients in both groups are summarized in Table 2.

Mean age of patients in Group I was 51.05±12.58 years and Group II was 50.13±11.40 years (p=0.153). The ages of subjects were further subdivided into 4 groups; 4.4% (n=16) were aged 10-30 years, 47.9% (n=174) patients were 31-50 years, 43.8% were 51-70 years old and 3.8% (n=14) were >70 years.

Female gender predominated in both groups but significantly more in Group I; 81.73 % (n=85) of the patients in Group 1 and 55.98% (n=145) in Group 2 were females (p<0.001).

**Table 2: Demographic characteristics of subjects based on ASB and non-ASB groups (n=363).**

Characteristics		Group I (104) n (%)	Group II (259) n (%)	p value
Gender	Females	85 (81.73)	145 (55.98)	<0.001
	Males	19 (18.26)	114 (44.01)	
Occupation	Housewife	83 (79.80)	141 (54.44)	<0.001
	Office Job	10 (9.61)	52 (20.07)	
	Field Job	05 (4.80)	40 (15.44)	
	Unemployed	04 (3.84)	18 (6.94)	
	Others	02 (1.92)	08 (3.08)	
Address	Rural	42 (40.38)	103 (39.76)	0.914
	Urban	62 (59.61)	156 (60.23)	
Income	< 20000/month	39 (37.5)	120 (46.33)	0.125
	> 20000/month	65 (62.5)	139 (53.66)	

The 2 groups were analyzed for disease duration, glycemc control, use of insulin, BMI, retinopathy, nephropathy and HTN. Summary of results is described in Table 3. A significant difference among the ASB and Non-ASB groups was found for

the presence of nephropathy (p<0.001), while differences for all other factors were non-significant. Mean HbA1c levels were 10.50 ± 2.78 in Group I and 9.77 ± 2.62 in Group II (p=0.413).

**Table 3: Comparison of disease related factors of ASB and non-ASB groups (n=363).**

Factors related to disease and its complications		Group I (104) n (%)	Group II (259) n (%)	p value
Duration of DM	≤5yrs	23 (22.11)	59 (22.77)	0.868
	>5yrs <10yrs	55 (52.88)	142 (54.82)	
	≥10yrs	26 (25)	58 (22.39)	
Mean HbA1c level		10.50±2.78	9.77±2.62	0.413
Use of Insulin	Yes	29 (27.88)	71 (27.41)	0.928
	No	75 (72.11)	188 (72.58)	
BMI	≤25	46 (44.23)	123 (47.49)	0.820
	>25 <30	49 (47.11)	117 (45.17)	
	≥30	09 (8.65)	19 (7.33)	
Retinopathy	Yes	33 (31.73)	63 (24.32)	0.148
	No	71 (68.26)	196 (75.67)	
Nephropathy	Yes	56 (53.84)	67 (25.86)	<0.001
	No	48 (46.15)	192 (74.13)	
H/o HTN	Yes	26 (25)	71 (27.41)	0.639
	No	78 (75)	188 (72.58)	

Age, gender and glycemc control were analyzed on the basis of controlled and uncontrolled diabetes mellitus groups keeping HbA1c of 7.0 as the cutoff value. The number of males & females were determined in each group. The group with controlled HbA1c <7.0 had 52.7% (n= 30) females and 47.3% (n= 27) males. In the other group with an HbA1c >7.0, 34.6% (n=106)

were males and 65.3% (n=200) were females.

Regarding complications, 31.73% (n=33) in group I and 24.32% (n=63) in group II had retinopathy (p=0.150); 53.84% (n=56) in group 1 and 25.86% (n=67) in group 2 had nephropathy (p=0.05).

## DISCUSSION

UTI is very common amongst diabetics and asymptomatic UTI carries an added risk of complications, with its timely diagnosis being a real challenge for physicians. The present study found it to be quite frequent amongst our data set of diabetic patients i.e. 28.6% patients suffered from it, a result very similar to a study conducted in India in 2015 where 28.2% of the study population was afflicted.<sup>20</sup> However, other studies conducted in other regions around the globe show relatively less prevalence of ASB i.e. 20.9%, 16.9% and 12.2%.<sup>21-23</sup> This variance can be due to regional, local hygienic and ethnic practices.

Mean age of our study population was  $50.39 \pm 11.74$  years, with most of the subjects being middle aged (31-50yrs). This is in accordance with the fact that the mean age of diabetics, in Asia, is less as compared to other ethnicities.<sup>24</sup> The mean age of our subjects with ASB was found to be slightly higher and comparable to other foreign studies.<sup>25,26</sup> In a research paper, Hamdan HZ, et al, from Sudan, described no significant age difference in both study groups, with the average ages being 58.6 years and 57.9 years in the ASB and non ASB group respectively.<sup>21</sup>

Female gender prevalence is found in diabetics within Asia in contrast to Europe, where males dominate.<sup>24</sup> The present study also demonstrated a female predominance not only in the ASB but also the non-ASB. Moreover female gender showed a statistically significant association with ASB. These results are in concordance with many other studies.<sup>23,25,27,28</sup>

In this study, housewives were the most common stereotypical patient. This was true for both groups but more so for the ASB group. The study supports a strong positive association between ASB and occupation. This particular aspect has been infrequently studied. However a study from Ethiopia found that government employee's made up the bulk of ASB population followed by merchants and then housewives. However they did not find a significant association of occupation with UTI vs Non UTI groups.<sup>29</sup> One reason for our result being different is that females predominated our data set. Pakistan, being a low to middle income country, is still years behind in the level of female education with majority having limited to no education. The dominant occupation is stay at home mothers and the limited awareness and exposure can lead to poor hygienic practices, paired with poor glycemic controls leading to frequent UTIs.

Residence as in rural vs urban showed no statistical significance, though overall our population was urban. This finding was supported by a study done by Yismaw G, et al, in Ethiopia and Yu S, et al, in the U.S.<sup>29-30</sup>

In regard to the duration a patient had diabetes and the development of ASB, no significant association was found. Many other studies have reported similar findings.<sup>11,21,23</sup> However a meta-analysis found that patients with ASB had a slightly increased duration of diabetes by 0.17 year, but it was not statistically significant.<sup>23</sup> Another study conducted in KSA reported no positive association between the duration of diabetes and UTI.<sup>11</sup>

Various studies have reported a strong link between poor

glycemic control and development of UTIs.<sup>20,31</sup> However our result was contrary to this. HbA1c level was elevated in ASB group only by 0.7%. This result is supported by a meta-analysis based on 13 studies that reported no relationship between HbA1c levels and UTI. They found a 0.2% difference of HbA1c in both groups.<sup>23</sup> In other studies conducted in KSA, Sudan and Iran, no relationship of poor diabetic control and development of ASB could be established.<sup>11,21,32</sup>

Most of our patients were on oral hypoglycemic agents for diabetic control with only 27.5% being Insulin dependent. A comparison of the two groups found an almost equal percentage of patients in either group on Insulin, thus no relation between UTI and insulin dependency could be established. This was supported by an Indian study.<sup>19</sup> However, a general review of literature in this regard revealed conflicting results. In two studies, one from Iran<sup>32</sup> and the other from KSA,<sup>11</sup> a positive relationship between insulin and ASB was described. On the other hand Gutema T, et al,<sup>33</sup> found an inverse relationship between insulin and UTI. These differences are multifactorial and can be explained firstly by the fact that in our part of the globe, Insulin bears a stigma and is always a last resort for patients. They prefer to be on oral hypoglycemic agents for as long as possible even though they are actual candidates for Insulin therapy. Secondly, many patients are using sub-optimal doses of insulin or it is improperly stored or they are non-compliant. It is for these reasons that very few manage good glycemic control with Insulin. These theories are well supported by the high mean HbA1c levels of our data set and the minimal use of Insulin.

BMI of our study population was  $<30$  and we could not establish any relationship with ASB. Raofi A et al, found similar results in their study.<sup>32</sup> Another study out of Sudan observed similar findings.<sup>21</sup>

Our patient groups were then evaluated for diabetes related complications and a significantly positive association was found between ASB and nephropathy but none with retinopathy. Similarly in other studies investigators found a positive association between ASB and nephropathy.<sup>11,25</sup> In an Indian study<sup>34</sup> where they used serum creatinine to assess kidney function, no association could be found between nephropathy and UTI. The difference can be explained by a difference in nephropathy assessment tools.

Hypertension also showed no significant association with ASB. Our finding was concordant with a study by Gutema,<sup>33</sup> but in conflict with another study that found positive association between the two i.e. hypertension and ASB.<sup>11</sup> A six-years cohort study<sup>35</sup> found a significant difference between the incidence of hypertension in diabetic women with ASB compared to those without ASB (54% vs 37%;  $p=0.045$ ), but on multivariate analysis, a risk factor could not be established (odds ratio, 1.5; 95% confidence interval, 0.7-3.6). This difference may be explained by the fact that much of our population have inadequate healthcare, maintain poor and insufficient medical records and many have masked Hypertension.

## CONCLUSION

Asymptomatic urinary tract infection can occur in a substantial proportion of type 2 diabetics, being more common in females with inadequately controlled diabetes of a few years standing. Nephropathy appears to a complication associated with the asymptomatic UTI, while retinopathy and hypertension bear no association.

## Strengths and limitations

This study is unique in the sheer number of factors that have been included in regard to both the patient and disease. No other

Pakistani study has been known to have scrutinized so many associations. Secondly the number of our dataset is larger than any other studied in this regard in Pakistan.

Some limitations of our study are that firstly urinary culture & sensitivity was not done as confirmative for diagnosis. Secondly diagnosis of nephropathy was via dipstick albumin, that can also be positive in UTI. It would have been ideal to confirm its presence once the UTI had settled. Lastly, the patients' drug history was not examined in detail to look for any association of a specific anti-diabetic medication with UTI.

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