Original Article:

Incidence of infections in hospitalized subjects with diabetes mellitus

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ABSTRACT

Background: The risk of infection is higher in patients with diabetes mellitus (DM) compared to those without DM and significantly affects morbidity and mortality when these patients are admitted to a hospital. Hence, this study was undertaken to determine the type of infections, presentation of illness and to correlate with the severity of diabetes.

Method: We studied 115 patients with DM (60 males) admitted in acute medical ward of our Institute with subacute, acute and chronic illnesses in all of them. Blood glucose and glycosylated haemoglobin were (HbA_{1c}) determined by the standard methods. The type of organisms isolated from blood/urine/ pus /sputum and drug sensitivity pattern was determined.

Results: Coronary artery disease (CAD) was seen in 22.6%, retinopathy in 2.6% and nephropathy in 9.6% of cases. Eighty six of the 115 patients (75%) had infections. Of these, acute, subacute and chronic presentation were seen in 67, 12 and 7 patients respectively; 76 had community acquired infections and nosocomial infection were seen in 10 cases. Pulmonary infections were most common (29.1%) followed by urinary tract infection (26.7%). Of the 86 patients with infection 9 had HbA_{1c} < 7% , 56 had HbA_{1c} of 7%-10%, and 21 patients had HbA_{1c} of >10%. The mean HbA_{1c} in patients with sepsis/multiorgan dysfunction syndrome (MoDS) was 11.3 ±2.8% as against 8.4% ± in the non sepsis group.

Conclusion: We observed that infections were a common cause of hospital admissions in patients with uncontrolled DM.

Key words: *Diabetes, Infection, HbA1c, Sepsis, Hospitalization*

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INTRODUCTION

Diabetes mellitus is a global disease with a huge adverse impact on health and mortality, particularly from cardiovascular disorders. In 2010, it was estimated that around 285 million people had the condition and it has been calculated that this may increase to as many as 438 million by the year 2030.[1] Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes worldwide, accounting for 90% of cases globally[2,3] An epidemic of T2DM is under way in both developed and developing countries. Sex, age, and ethnic background are important factors in determining the risk of developing T2DM.[4] Diabetes mellitus is considered as a secondary immune deficiency disorder by World Health Organization[5] as the disease is characterised by frequent, severe, prolonged and recurrent infections due to alteration of the immune response mechanisms. Despite recent advances in the management of both diabetes and infectious diseases, diabetic patients remain at increased risk of infection. Factors such as frequent hospitalizations, diabetic ketoacidosis, peripheral vascular

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disease, neuropathy, gastro paresis, chronic renal failure requiring dialysis and blood transfusion also predispose to infection.

It is widely known that urinary tract infection (UTI) is more common in subjects with diabetes mellitus.[6] Certain renal tract infections, including emphysematous pyelonephritis and cystitis, perinephric abscess, and candidiasis, show close association with diabetes mellitus. These, together with renal papillary necrosis, form the basis of UTI.[6-8] Diabetic patients have been found to have 5-fold frequency of acute pyelonephritis at autopsy than non diabetics.[9] The incidence of bacteraemia in diabetic men with good control of blood sugar is reported to be similar as in non diabetic men; however, in pregnant diabetic women it is 2-4 times as common as in control groups. Most urinary tract infections in patients with diabetes mellitus are relatively asymptomatic. Diabetes mellitus predisposes to much more severe infections, especially in patients with poor diabetic control, acute ketoacidosis, or diabetic complications such as nephropathy, vasculopathy and neuropathy. This asymptomatic infection can lead to severe kidney damage and cause renal failure.[9] Bacteraemia is very common among diabetic patients because if unrecognizable and inadequately treated, it can lead to low grade foci of inflammation that can ultimately result in serious renal damage.[10]

Gram-positive cocci such as *S. pneumoniae* are responsible for the majority of infections in diabetic patients, followed by agents such as *H. influenza*.[11,12] Diabetes patients may develop a more severe disease due to the organisms such as *S. pneumoniae*, and have higher rates of hospitalization and development of complications such as bacteremia. Diabetes has been associated with an increased risk of recurrent bacterial pneumonia.[13] *H. influenzae* is not more common in diabetics, although it may be more common in the elderly, in whom type 2 diabetes is also prevalent.[14] Aerobic Gram-negative organisms and staphylococcal infections typically are the most important causes of nosocomial pneumonia in diabetic patients.

Furthermore, approximately 25% of nosocomial infections are polymicrobial.[15] Bacterial pneumonia in diabetic individuals, especially when caused by Klebsiella and Staphylococcus, is associated with the more severe course of the disease and more frequent need of mechanical ventilatory support.[16] The mortality rates for all hospitalized patients with nosocomial pneumonia was range from 30%-50% and are even higher in diabetic patients.[17]

The onset of lung tuberculosis (TB) is not more common in diabetics than in the general population.[18,19] Lung tuberculosis is a common accompaniment of diabetes and the cause of insulin resistance and “brittleness”. The incidence of lung tuberculosis is increased in uncontrolled diabetics and in patients with severe diabetes requiring large doses of insulin. The problems in diabetics with lung tuberculosis include a severe form and more aggressive course of the disease, a higher tendency to destruction and cavitation, and more common resistance to anti tuberculotics (especially in patients with poor glycaemic control).[19]

Primary pneumonia might be caused by mucormycosis, *Aspergillus* spp, Coccidioides immitis, and *Cryptococcus neoformans*.[18] Attention must be paid to patients on antibiotics. Although mucoromycosis typically causes a fulminant rhino cerebral infection, mucormycosis rarely presents as a primary pulmonary infection with hemoptysis.[20] Poorly controlled diabetics are more prone to Mucor infections. Although rare, both cocidioidomycosis and cryptococcal pneumonia may be more common in diabetics than in nondiabetics.[20] Although diabetic patients may have a high carrier rate of *Candida albicans* and a higher

risk of infectious complications of Candida spp., including oral candidiasis, vulvovaginal candidiasis, and fungal urinary tract infections, pneumonia is not a usual complication.[21] The aim of this observational, retrospective study was to analyze the particularities of infections which appeared in patients with diabetes admitted in the acute medical ward.

MATERIAL AND METHODS

Patients with diabetes mellitus (n=115) who were hospitalized for various reasons were selected for the study. Patients were categorised into two groups as patients with and without infection. Diagnosis of diabetes was made based on American Diabetes Association (ADA) 2010 guidelines[1] i.e., glycosylated haemoglobin (HbA_{1c}) ≥ 6.5% or fasting blood glucose ≥ 126 mg /dL were included in the study. All patients underwent detailed clinical evaluation at admission. Height, weight, body mass index (BMI) was calculated. Detailed history of present illness with duration was noted. The duration of diabetes mellitus and type are documented. History of diabetes associated complications comprising retinopathy, nephropathy, neuropathy, coronary artery disease, cerebrovascular disease, peripheral arterial disease was noted. Infections proved by or culture positivity of body fluids [sputum, blood, urine, wound swabs, vaginal swabs, cerebrospinal fluid (CSF), and any other secretions] proved by clinical, serological, radiological, histo-pathological, examination were included in the study. Patients with positive for viral infections, chemotherapy or immunosuppressant drugs, uremia, haemolytic anaemia, major blood loss or chronic malaria were excluded from the study. This study was approved by the Institutional Ethics Committee of Nizam's Institute of Medical Sciences, Hyderabad, India. Written informed consent from the patients and approval from ethics committee were obtained prior to the study.

Laboratory investigations

Fasting blood glucose, postprandial blood glucose were estimated by commercially available kit by fully automated analyzer whereas HbA_{1C} was determined by high performance liquid chromatography (HPLC) method. Culture sensitivity of the body fluids (sputum, blood, urine, wound swabs, vaginal swabs, CSF, and any other secretions) according to the infection suspected were done and treatment given appropriately. Necessary radiological investigations [chest radiograph, ultra sonogram of abdomen, computed tomography (CT) abdomen, CT chest, magnetic resonance imaging (MRI) brain, CT para nasal sinuses were done.

Statistical analysis

Results of continuous measurements are presented as mean ± standard deviation and results of categorical measurements are presented in number (%). Statistical analysis was done by using SPSS version 14 software. Association between categorical variables was studied using Chi square test. A P-value <0.05 was considered significant.

RESULTS

The demographic characteristics of the patients are shown in Table 1. The mean age of patients was 54.0 (range 13 to 93) years. Mean BMI was 26.4 ± 5.6 (range 12.9 to 51.7) kg/m^2. Maximum number of subjects had BMI of 26-30 kg/m^2 (over weight) (Table 1).

Of the 115 subjects, 86 patients had infections whereas 29 subjects did not have infection. Out of the 86 infection cases, 67 presented as acute, 12 as subacute, whereas 7 presented as chronic cases. Among 86 infected patients, the community acquired infection was observed in 76 cases and nosocomial were seen in 10 cases (Table 1).

Fever (65.2%), shortness of breath (47.8%) and cough (33.9%), were among the most common

Table 1: Demographic details of study subjects

Characteristics	Cases (n=115)
Age (years)*	54.9 ± 12.9
Males:Females	60:55
BMI (kg/m^2)	26.4 ± 5.6
Co-morbidities	
CAD (%)	22.6
CVD (%)	9.0
Nephropathy(%)	9.5
Retinopathy (%)	2.6
Type of presentation	
Subacute (%)	14.0
Acute (%)	77.9
Chronic (%)	8.1
Aetiology	
Infective (%)	74.78
Non-infective (%)	25.22
Type of infection	
Community acquired (%)	84.4
Nosocomial (%)	11.6

* data are expressed as mean ± standard deviation
BMI + body mess index; CAD = Coronary arteny disease; CVD =

symptoms observed at the time of admission. Of 115 subjects, 49 individuals had co-morbidities, majority of them (22.6%) had coronary artery disease, retinopathy (2.6%), nephropathy (9.56%) respectively (Table 1). Of 86 subjects with infection, 67 had acute onset of illness, 12 patients had sub acute onset, and 7 patients had chronic illness.

Of the 29 non-infective patients, underlying aetiologies included diabetic ketoacidosis (DKA), Hyper osmolar non-ketotic coma (HONK), coronary artery disease (CAD), cerebrovascular accident (CVA), seizures, peripheral neuropathy. Eighty six (74.8%) patients were admitted with infection as the underlying diagnosis.

Among the patients with no infection (n=29), 10 patients were diabetes mellitus related. In the subgroup without infection, there were 15 males. Mean age was 54.8 ±26.7 (range 13-88) years. Mean BMI was 26.9 ± 7.4 (range 14.0-51.7) kg/m^2. Mean fasting blood glucose was 230.9 ±75.3 (range 136-442) mg/dL. The mean postprandial blood glucose was 349.8±109.5 mg/dL range (236-500). The mean ± SD HbA_{1c} was of 9.3% ± 2.5% (range 6.2%-15.5%) in patient without infection.

In patients without infection, the aetiology included diabetes related (DKA, HONK) and non-diabetes causes including CVA, CHF, AKI, seizures, neuropathy etc. Mean ± SD HbA1c values in diabetes related subgroup was 10.8% ± 3.4%. In patients with non diabetes aetiology, the mean ± SD HbA_{1c} value was 8.6% ±2.8%.

Patients with infection were divided based on whether the admission was related to various infections. The severity of admissions was decided based on whether there was sepsis or multi-organ involvement versus localised organ involvement. In the present study, 74.8% patients had infections. The most common infections was found to be pulmonary 25 (29.1%), urinary tract infections 23 (26.7%) respectively (Table 2).

The organisms were isolated in 54 patients from blood/urine/pus/sputum. This constituted 62.8% of patients with infective aetiology. *E. coli* was the most common infectious organism isolated in 26 patients. *Klebsiella* were isolated in 6, *Acinetobacter* in 3 and *Pseudomonas* in 2 patients. Methicillin sensitive *S.aureus* (MSSA, n=1) and methicillin resistant *S.aureus* (MRSN, n=2) were isolated in 3 patients. (Table 3). Three patients had smear microscopy

Table 2: Infections in patients with diabetes millitus at the time admission

Diagnosis	No.	%
GI	6	7.0
Others	6	7.0
Pulmonary	25	29.1
Renal	5	5.8
Sepsis/MODS	8	9.3
ST Abscess/Cellulitis	9	10.5
Tuberculosis	4	4.7
UTI	23	26.7
Total	86	100.0%

GI = gastrointestinal; MODS = multiple organ dysfunction syndrome; ST = soft tissue; UTI = urinary tract infection

Table 3: Type of organisms isolated from blood/ urine/ pus / sputum in 54 patients

Organism	No. of cases
Eschaerichia coli	26
Klebsiella pneumoniae	6
Mycobacterium tuberculosis	3
Acenetobacter sp	3
Pseudomonas aeruginosa	2
Staphylococcus	3
Candida	3
Mucor mycosis	3
Enterococcus	3
Elizabethkingia meningoseptica	1
Burkholderia	1

(n=54)

positive for acid-fast bacilli. The other organisms such as Enterobacter, Burkholderia, *E. kingae*, Enterococcus were also isolated. Six patients had fungal infections with 3 patients having Candida infection and 2 patients found to have rhino cerebral mucor mycosis and one patient found to have pulmonary zygomycosis on mucosal biopsy. Four patients had mixed infections with more than one organism.

Blood glucose and HbA_{1c} in fasting and postprandial glucose were measured in both groups. In patients with infection, the mean ± SD fasting blood glucose was 207.4 ± 62.1 (range 124-424) mg/dL. The mean ± SD postprandial blood glucose was 296.8 ± 69.5 (range 208-508) mg/dL. Mean ± SD HbA_{1c} was 9.1 ± 2.2 (range 6.1-17.3)%.

In patients without infection, fasting blood glucose ranged from 136 to 442mg/dl with a mean of 230.9 ±75.3 mg/dL. Postprandial blood glucose ranged from 236 to 599 mg/dl with a mean of 349.8±109.5 mg/dL. HbA_{1c} ranged from 6.2 to 15.5% with a mean of 9.3 ± 2.5%.

As shown in Table 4, most of the cases with acute illness had presented with HbA1c 7%-10% and >10%, , whereas in cases with chronic illness the HbA1c was in the range of 7%–10%. Among 86 cases with infection 9 individuals had HbA1c < 7% , 56 patients had HbA_{1c} of 7%-10%, and 21 patients had Hb A1c of >10% (Table 5). The mean HbA1c in the patients with sepsis/multiorgan dysfunction was 11.3% as against 8.4% in the non-sepsis group. Thus, a high HbA_{1c} values was noted in the with diabetes patients hospitalised with sepsis as against those admitted with localised infections. None of the patients who presented with TB, Soft tissue abscess/cellulitis or other manifestations such as infective endocarditis, epididymoorchitis, mucormycosis had HbA^{1c} levels > 10%. Majority (95.5%) of patients with sepsis had HbA_{1c} >7% against 87% of patients without sepsis (p= 0.0001).

Table 4: HbA_{1c} status in sub-acute, acute and chronic presentation

HBA_{1c} (%)	Type of presentation*			
	Sub-acute	Acute	Chronic	Total
<7	0	7	2	9
7 to 10	10	41	5	56
>10	2	19	0	21
Total	12	67	7	86

* data presented as No.of cases.

DISCUSSION

In the present study, the majority of the patients with infection presented with systemic infections like pulmonary, UTI, skin and soft

Table 5: HbA1c status in patients with diabetes mellitus at the time of admission

Infection	HbA_{1c}			Total
	< 7%	7-10%	>10%	
GIT	2	3	1	6
Pulmonary	2	17	6	25
Renal	0	3	2	5
Sepsis/MODS	0	1	7	8
SSTI	1	8	0	9
UTI	1	17	5	23
Tuberculosis	1	3	0	4
Others	2	4	0	6

GIT = gastrointestinal tract; SSTI = skin and soft tissue infections; UTI = urinary tract infection

tissue, sepsis, MODS, GI infections and pulmonary tuberculosis. Among the pathogens, *E.coli* was the most common organism followed by Klebsiella, Mycobacterium, Acenitobacter, Staphylococcus, Enterococcus etc. Among the culture positive microorganisms *E. coli* 17 (31.5%), Klebsiella 4 (7.4%), Enterobacter 1 (1.9%), showed extended spectrum beta lactamase (ESBL) activity and one *Staphylococcus aureus* showed methicillin resistance. ESBL microbes showed resistance to ampicillin+sulbactum, amoxycillin, ceftriaxone, cefaperazone+sulbactum, gentamicin, tobramycin, ciprofloxacin, and levofloxacin. Most of the microorganisms producing ESBLs were sensitive to carbapenems like imepenem, meropenem, ertapenem, and dorepenem. Since the present study was conducted in a tertiary care center, rare infections like *Elizabethkingia meningoseptica*, *Burkholderia pseudomallei*, Madura foot, mucor mycosis were also seen. In a study[22] five most common infections encountered were UTI (28.6%), tuberculosis (20.1%), skin and soft tissue infections (14.3%), bacterial pneumonia (10.4%), and foot infections (10.4%).

Pneumonia is an important infection in patients with diabetes and is frequently caused by staphylococci or Gram-negative bacilli. Wheat et al[23] observed pneumonia was a contributing factor in 25% of the fatal cases of diabetic ketoacidosis in one series. In Patients with diabetes mellitus with pneumonia, *Klebsiella pneumonia, E.coli and Staphylococcus* aureus were the most frequent causes.[24] Staphylococcus is one of the major pathogen in the aetiology of both nosocomial pneumonia and community-acquired and in diabetic patients.[25] Studies have shown that in patients with diabetes had higher incidence of nosocomial pneumonia due to staphylococci because of high nasal carriage rate.[25-27] About 30% of patients with diabetes are nasal carriers of *Staphylococcus aureus* as compared to 11% of healthy individuals.[25] It was shown to be more influenced by the degree of glycaemic control. The rate of nasal carriage of *Staphylococcus aureus* was shown to be directly related to the HbA_{1c} level.[28] In the present study 29.7% patients were affected by respiratory infections, most common presentation being fever, cough and shortness of breath. Sputum culture showed presence of *Klebsiella pneumoniae*, MRSA, *Acinetobacter, Enterococcus* pathogens. The HbA^{1c} was < 7% in 2 cases, >7%-10% in 17 cases and >10% in 6 cases. The incidence of pulmonary infections was high in HbA1c >7%-10% group confirming that poor glycaemic control may prone for pulmonary infections.

In a study[29] the prevalence of lower UTI was significantly higher in female than in male type 2 diabetes patients. In this study,[29] *E. coli* was isolated from 71% of the subjects, Klebsiella spp. from 13.5%, Pseudomonas spp. from 9%, Enterobacter spp. and Citrobacter spp. in 2%, and non-fermenting gram negative bacilli and the Proteus spp in 1%.[29] The authors[29] found that sulbactum/cefoperazone and pipercillin/ tazobactum were highly sensitive to both Gram-positive cocci and Gram-negative bacilli. Gram-negative bacilli were found to be more sensitive than gram positive cocci to aminoglycosides such as netilmicin, amikacin, and tobramycin. Netilmycin is a derivative of gentamicin that is less nephrotoxic and ototoxic. It is less active against Pseudomonas but it inhibits a number of strains of *E. coli* as well as Klebsiella resistant to tobramycin.

In a study[30] authors found no relationship between HbA_{1c} and bacteriuria in 752 type 2 diabetes patients. In this study,[30] the mean HbA1c was 11.5% in bacteriuric and 11.4% in non-bacteriuric women with diabetes; *E. coli* was the most common organism isolated.[30] Patients with emphysematous pyelonephritis usually present with a fever of rapid onset, chills, flank pain, nausea, and vomiting, occasionally accompanied by an abdominal mass. Failure of fever to resolve after three or

four days of treatment of a urinary tract infection in a diabetic patient should arouse concern about the possibility of this uncommon complication. In our study 5 of 86 with infection patients had upper UTI. Among them 2 patients presented as right emphysematous pyelonephritis,1 patient presented as left emphysematous pyelonephritis, 1 patient presented as right renal abcess, 1 patient presented as left renal abcess.

In systemic review[23] on infections and diabetes, 72% patients with emphysematous pyelonephritis, 80% emphysematous cystitis, 57% patients with papillary necrosis, 36% of patients with perinephric abscess, and 10% patients with metastatic infection had diabetes mellitus.[23] According to Evanoff et al,[31] over 90% of cases occur in patients with diabetes. Papillary necrosis complicates 21% of cases.[31] Studies suggests that *E. coli* was responsible for lower UTI in 50% and 75% of cases are caused by *E. coli*, and most of the rest are caused by other Gram-negative bacilli.[8]

In a study[32] majority of patients (n = 251; 87.8%) were initially admitted to medical wards. Overall hospital mortality was 21.6%, median length of stay for surviving patients was 9 days. The most common source of infection was the urinary tract (27.3%), followed by respiratory tract (25.2%), biliary tract (16.8%) and skin and soft tissue (13.6%). All other sources of infection combined were rare (8.4%) and for 25 patients (8.7%), the source of infection remained unknown.[32] In the present study, incidence of sepsis was seen in 25.6% of the cases. The most common source of infection is UTI, followed by respiratory tract infections. Incidence of MODS was 9.3%. Two patients died of sepsis due to multiorgan failure. Blood culture showed the presence of *E.coli*, ESBL activity, others included MRSA, *Acenetobacter loweffi*, Enterococcus, *Elizabethkingia meningoseptica, Burkholderia pseudomallie, Pseudomonas aueriginosa*. All the patients showed poor glycemic control (HbA_{1c}) >10%).

A study[23] observed that investigated patients hospitalized with tuberculosis over a 6-year period found that 13.2% had diabetes, a percentage that increased steadily with time.[33] In a smaller but similar Pakistani study,[34] nearly half of the sample had abnormal glucose tolerance.[34] A study of bacterial infections in hospitalized diabetic patients in Papua New Guinea showed that the annual incidence of tuberculosis was 11 times higher than in the general population.[35] In addition to an increased risk of tuberculosis, diabetic patients are prone to unusual forms, including predominant lower lobe involvement, multilobar disease and a higher incidence of pleural effusion.[36] In our study we found four cases with tuberculosis. All four cases presented with fever, cough and shortness of breath. Two patients had haemoptysis. In these cases, their HbA_{1c} levels were > 9% indicating poor glycaemic control. In a recent study, diabetic patients admitted with sepsis was associated with increased 30-day mortality.[37]

In conclusion, in the present study, we found that infective aetiologies accounted for majority of hospital admissions in uncontrolled diabetes. In the infective group, there was a good correlation between infections and higher HbA_{1c} levels especially with serious multiorgan involvement and sepsis. Patients with sepsis were more likely to present with very high HbA_{1c} levels (>10%) whereas patients with longstanding infections were unlikely to be associated with elevated HbA^{1c}.

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