Impact of Infection on Glycemic Control in Diabetic Patients; a Hospital-based Cohort Study in Pakistan

Sher M. Sethi, MBBS[1], Iffat Khanum, FCPS[2], Umair Javed, MBBS[3], Sania Sabir, BS-MT[1]

[1]*Internal Medicine, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan.*

[2]*Infectious Diseases, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan .*

[3]*Cardiology, Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan.*

Corresponding Author
Sher M. Sethi, MBBS

Mobile:
0092-3132551542

E mail:
sher.sethi@gmail.com

Key words:
Bacterial infections; diabetes mellitus; glycemic control; Hb A1c; pneumonia; urinary tract infection.

Background and study aim: In developing countries with high diabetes rates, it is essential to recognize the effect of infection on the glycemic control. The purpose was to determine how infection affects glycemic control, specifically HbA1c. The secondary objective was to compare infection-related outcomes between good versus poorly controlled diabetes.

Methods: A cohort study conducted from July 2019 to June 2020 at the Aga Khan University Hospital, Karachi. A patient's HbA1c before infection is called pre-infection HbA1c; the HbA1c after 3 months is called post-infection HbA1c. Pre-infection HbA1c were subcategorized into two groups, i.e. poor and good glycemic control. Comparison of infection related outcomes between these two groups was done using the chi-square test.

Results: A total of 168 patients had infection and diabetes. The mean age was 67.6 years and 86 (51.2%) were males. Seventy patients (41.7%) had good-control, while 98 patients (58.3%) had poor-control. The mean pre-infection HbA1c in good-control diabetic patients was 6.2% while in poor-control was 8.5% (p: 0.000). While the mean post-infection HbA1c in the good-control was 6.9% and in the poor-control was 8.3% (p: 0.010). The poor-control group had a higher infection-related death rate (62.5% vs. 37.5%, p: 0.72), and multiple sites of infection (65.2% vs. 34.8%, p: 0.47). In the poor-control group, there was a higher rate of re-infection (52.8 vs. 47.2%, p: 0.45), whereas the rate of septic shock was similar (50%, p: 0.42).

Conclusion: Based on our study, we conclude that infection had variable effect on glycemic control . Moreover, diabetes per se had a major effect on infection risk, its severity, and mortality, regardless of glycemic control.

INTRODUCTION

Diabetes is described as a metabolic disorder that elevates blood glucose levels. In 2017, the prevalence of diabetes worldwide was estimated at around 8.4%, and it is expected to rise further in the coming decades **[1]**. Infections had a significant impact and are associated with increased morbidity and mortality in diabetes patients **[2]**. Not only this, it had also been identified that diabetic patients had an increased risk of acquiring infection **[3]**.

Uncontrolled diabetes had a catastrophic relationship with infections. Diabetic patients with higher glysated hemoglobin A1c (HbA1c) had an elevated long term risk of infection **[4]**. One study of the Danish population reveals that there is a hazard ratio of 1.64 of infections in individuals with an HbA1c of 10.5% **[5]**. On the other hand, there is insufficient evidence that controlling blood sugars has any positive impact on risk of infection and its prevention **[6]**.

For a developing country with high prevalence of diabetes, it is of the utmost importance to recognize the effect of infection on glycemic control. The rationale to conduct this

study was to identify the impact of infection on glycemic control i.e. HbA1c in diabetic patients. It will provide us useful information about the role of glycemic variation and its impact on infection. Secondary objectives were to compare the outcomes (infection related mortality, re-infection, multiple sites of infection, septic shock and length of hospital stay among patients with good and poor glycemic control.

METHODS

Study setting and duration

It is a cohort study conducted at the Aga Khan University Hospital (AKUH), Karachi, Pakistan. Aga Khan University Hospital is a tertiary care hospital with 650 beds. It is one of the few hospitals in the country which has Joint Commission International Accreditation (JCIA). The study duration was one year from July 2019 to June 2020.

Study design

This cohort study was conducted on patients admitted to the Department of Internal Medicine at the Aga Khan University Hospital. Patients with diabetes aged 18 or older were selected. The presence of diabetes in patients is identified by HbA1c > 6.5% and/or the use of oral hypoglycemic agents and/or insulin **[7]**. Their record was reviewed and infections were identified on the basis of the following three criteria: a) laboratory parameters that favors infection like cultures growing micro-organisms, high white cell counts and increase inflammatory markers **[8]** b) radiological imaging that suggests presence of infection that includes ultrasound or cross section images showing collection or inflammation **[9]** c) clinical presentation like fever, productive cough, dysuria, purulent discharge that indicate presence of infection **[10]**. All the patients who had newly diagnosed diabetes were excluded.

HbA1c and Glycemic groups

Patients whose HbA1c was checked within three months prior to the infection were termed as pre-infection HbA1c. The records of the patients were followed after three months. All those individuals whose HbA1c was evaluated after three months of infection were labelled as post-infection HbA1c.

All pre-infection HbA1c were subcategorized into two groups that include poor and good glycemic control. The study defined poor glycemic control as HbA1c ≥ 7% and good glycemic control as HbA1c ≤ 6.9% **[11]**. Comparative analysis was done between patients with infections and poor glycemic control and those with good glycemic control.

Definition of the outcomes

Primary outcome was to identify the level of pre and post infection HbA1c. Secondary outcomes were infection-related mortality, multiple sites of infection, re-infection, septic shock and length of the hospital stay. Infection related mortality was defined as mortality due to the severity of infection and septic shock. Multiple sites of infection means presence of infection in two or more areas of the body. Re-infection was characterized as patients who recovered from infection and became infected again within 6 months. Septic shock was defined as those individuals who had evidence of infection with hemodynamic compromise. Length of hospital stay was the duration of hospitalization of patients

Recruitment of data

Demographics including age, gender, type of diabetes and other co-morbidities were recorded. Glycemic groups were identified on the basis of HbA1c. Different types of infections that were diagnosed were documented. The outcomes of patients were also noted. Clinical presentations on the initial hospital encounter were documented. Radiological features, laboratory parameters and microbiological cultures were also recorded in the study.

Data Analysis

Data analysis was done using IBM Statistical Package for the Social Sciences (SPSS) Version 26. Categorical variables were reported as frequency and percentage while quantitative variables were reported with mean and standard deviation. The continuous and categorical variables were compared using independent sample t-test with level of significance of 0.05. The proportions were compared between groups with chi square with a level of significance of 95%.

RESULTS

Inclusion of the patients

A total of 428 patients were admitted with various infections from July 2019 to June 2020 at the Aga Khan University Hospital, Karachi. Out of these, 228 patients (53.2%) were found to have diabetes. Sixty patients (26.4%) were excluded because of the presence of newly diagnosed diabetes. A total of 168 patients (73.6%) met the inclusion criteria and were included in the study.

Demographics and outcomes of the patients

The mean age of the patients was 67.6 (± 12.0) years and 86 patients (51.2%) were males. Hypertension was the major co-morbid illness found in 147 patients (87.5%). Seventy patients (41.7%) had good glycemic control while 98 patients (58.3%) had poor glycemic control. The three main infections encountered in our study were pneumonia (n: 85, 50.6%), urinary tract infections (n: 62, 36.9%) and osteomyelitis (n: 31, 18.5%). The outcomes were as follows: re-infections (n: 36; 21.4%), multiple sites of infection (n: 23, 13.7%), septic shock (n: 20, 11.9%) and infection related mortality (n: 16, 9.5%). The mean length of hospital stay was 7.1 (± 5.6) days. Table 1 shows the detailed features of these patients.

Diagnostic evidence of infections

The presence of an infection was identified via three different processes. These include clinical presentation, radiological features and laboratory parameters. The most common clinical features at time of admission were fever (n: 92, 54.8%), dyspnea (n: 74, 44%), cough (n: 50, 29.8%) and altered mentation (n: 45, 26.8%). The radiological features suggesting infections were present in 94 patients (56%). These features were infiltrates or consolidation on a chest x-ray representing pneumonia, ultrasound showing thick trabeculated urinary bladder suggesting cystitis, and computed tomographic scan and magnetic resonance imaging showing purulent collection and bony enhancements suggesting abscess and/or osteomylitis. Laboratory parameters showed a high mean white cell count of 13.9 x 109/uL at initial presentation. They had elevated mean maximum levels of C-reactive protein (16.8 ± 36.6 mg/L) and procalcitonin (15.8 ± 26.6 ng/ml). Microbiological cultures revealed organisms in 98 patients (58.3%). Common micro-organisms identified were Streptococcus Pneumoniae, Klebsiella Pneumoniae, Pseudomonas Aeuroginosa, Escherichia coli, and Staphylococcus Aureus. Table 2 demonstrates the features for diagnosing infections.

Comparison of Pre- & Post-infection HbA1c

The mean pre-infection HbA1c in diabetic patients with good control was 6.2% while in poor control groups it was 8.5% (p = 0.000). After 3 months of recovery from the infection, the mean post-infection HbA1c in the good control group was 6.9% and in the poor control group was 8.3% respectively (p = 0.010).

Glycemic control and outcomes

While comparing the outcomes between good and poor glycemic control, we didn't find any statistically significant difference. The poor glycemic control group had a higher infection-related mortality (62.5%), and multiple sites of infection were more common in that group (65.2%). A higher risk of re-infection (52.8%) was observed in the poor glycemic control group, whereas the risk of septic shock was similar in both (50%) groups. Table 3 shows the comparative analysis between the two groups.

The mean length of hospital stay in patients with good glycemic control was 7.3 days. In contrast, the mean length of hospital stay in patients with poor glycemic control was 7.0 days. (Figure 1)

Table 1: Demographic Features and Characteristics of the diabetic patients.

	N (%)
Mean age ± S.D. (in years)	67.6 ± 12.0
Gender	
• Male	86 (51.2)
• Female	82 (48.8)
Diabetes	
• Type I	8 (4.8)
• Type II	160 (95.2)
Co-morbid (other than diabetes)	
• Hypertension	147 (87.5)
• Coronary artery disease	82 (48.8)
• Chronic kidney disease	49 (29.2)
• Stroke	28 (16.7)
• Airway disorders	23 (13.7)
• Atrial fibrillation	11 (6.5)
• Thyroid dysfunction	8 (4.8)
Glycemic Control	
• Good	70 (41.7)
• Poor	98 (58.3)
Diagnosis	
• Pneumonia	85 (50.6)
• Urinary tract infections	62 (36.9)
• Osteomyelitis	31 (18.5)
• Others [a]	16 (19.5)
Outcomes	
• Infection related mortality	16 (9.5)
• Re-infection	36 (21.4)
• Multiple sites of infection	23 (13.7)
• Septic Shock	20 (11.9)
• Mean length of hospital stay (in days)	7.1 ± 5.6

[a] Other diagnosis includes cellulitis, acute cholecystitis, fungal infections and abdominal sepsis.

Table 2: Clinical, Laboratory and Radiological Evidence of Infections.

	N (%)	
Clinical Features (on presentation)		
• Fever	92 (54..8)	
• Cough	50 (29.8)	
• Dyspnea	74 (44)	
• Urinary complaints	21 (12.5)	
• Purulent discharge	19 (11.3)	
• Altered mentation	45 (26.8)	
• GI disturbances	24 (14.3)	
• Others	11 (6.5)	
Radiological signs of infection	94 (56)	
Culture growing organism	98 (58.3)	
	Mean ± Standard deviation	Normal Reference range
Laboratory Parameters		
• Total leukocyte count (initial)	13.9 ± 6.7	4 – 10 x 10^9/uL
• Total leukocyte count (maximum)	17.4 ± 8.5	4 – 10 x 10^9/uL
• C-reactive protein (initial)	14.9 ± 24.3	0 – 5 mg/L
• C-reactive protein (maximum)	16.8 ± 36.6	0 – 5 mg/L
• Procalcitonin (initial)	8.4 ± 24.4	< 0.5 ng/ml
• Procalcitonin (maximum)	15.8 ± 26.6	< 0.5 ng/ml
• Erythrocyte sedimentation rate	83.4 ± 26.2	0 – 20 mm/1^{st} hr

Table 3: Comparison of glycemic control and outcomes.

	Good	Poor	
	N (%)	N (%)	p-value
Infection related Mortality	6 (37.5)	10 (62.5)	0.722
Re-infection	17 (47.2)	19 (52.8)	0.457
Multiple Sites of Infections	8 (34.8)	15 (65.2)	0.471
Septic Shock	10 (50)	10 (50)	0.421

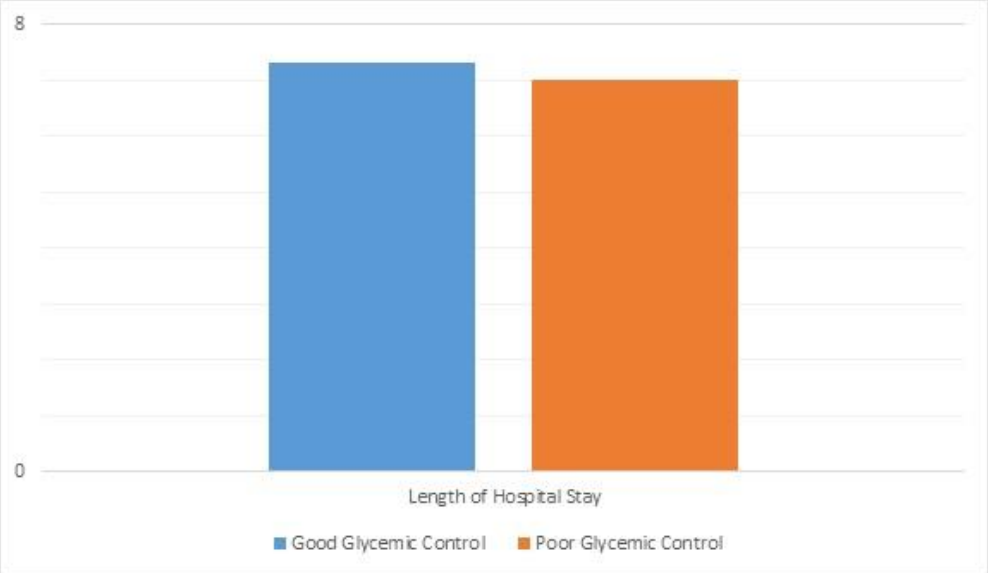

Figure 1: Length of hospital stay in good versus poor glycemic control patients.

DISCUSSION

Diabetes is highly prevalent in our sub-continent region as almost half of the patients admitted to our tertiary care hospital had diabetes. Majority of the patients had poor glycemic control. Pneumonia and urinary tract infections were the most common infections encountered in our diabetic population. Our cohort study indicates that infections can increase HbA1c levels in patients with well-controlled diabetes, but not significantly in patients with poorly controlled diabetes. We also didn't observe any significant association between glycemic control and infection-related mortality, septic shock, multiple sites of infections, re-infections and length of hospital stay.

There are various hypotheses that chronic hyperglycemia can suppress the immunity of patients and make them more vulnerable to infections. The most common sites of infection in diabetic patients are the urinary tract, skin and soft tissues and respiratory tract **[12]**. Similar to this, pneumonia, urinary tract infection and osteomyelitis were common in our study population. Pulmonary infections tend to have a higher prevalence in the diabetes population **[13]**. Respiratory tract infections are more severe in diabetics when compared with non-diabetics **[14**. We also observed that 50.6% of our diabetic patients admitted with pneumonia. The prevalence of urinary tract infection in diabetic patients is 10-12% in the African population **[15]**. Interestingly, the Pakistani population had a higher prevalence of 52.7% **[16]**. In our study, 36.9% of patients with diabetes had urinary tract infection.

Glycated hemoglobin (HbA1c) is an effective predictor of glycemic control in diabetic patients. Higher HbA1c levels are associated with major complications and unfavorable outcomes **[17]**. According to Ross et al., every 1% increase in HbA1c level leads to a 4.2% increase in the risk of postoperative infection **[18]**. In our study population, the proportion of infection was also higher in poorly controlled diabetes (n: 98, 58.3%).

Intensive glycemic control is well-known to prevent diabetic microvascular complications **[19]**. The impact of intensive glycemic control on risk and severity of infections is not evaluated **[20]**. Mor et al. states that strict glycemic control can prevent infection in type 2 diabetes mellitus

patients.5 Ikeda et al. report that hepatitis C patients had pre-treatment HbA1c of 5.85% and post-treatment HbA1c of 5.65% **[21]**. To evaluate this, we compare HbA1c levels before and after infections. We identified that patients with good glycemic control had a mean HbA1c level of 6.2% which increased to 6.9% post-infection (after 3 months). On the other hand, in poor glycemic control patients had a mean HbA1c level of 8.5% pre-infection and 8.3% post-infection. This could be due to the fact that our patients with poorly controlled diabetes were treated aggressively with higher doses of insulin.

A cohort study identified that poor glycemic control is associated with a 3 fold increase risk of infection-related mortality **[22]**. Zoppini et al. reports high incidence and underestimation of infection associated mortality in diabetic patients **[23]**. A recent study on the diabetic population reports a mortality of 10.6% with COVID-19 pneumonia **[24]**. Similarly, we report a mortality of 9.6% in our study population. Patients with uncontrolled diabetes were more affected (62.5%) but there was no significant difference between glycemic controls.

Uncontrolled diabetes is an independent risk factor for relapse of infection via various mechanisms **[25]**. Pal et al. reported higher risk of re-infection with COVID-19 in poorly controlled diabetic patients **[26]**. In our study, we identified a high prevalence (21.4%) of patients with relapse or re-infections. No major difference was observed in re-infection rates between the well-controlled and uncontrolled glycemic groups (47.2% versus 52.8%).

Diabetes can suppress the immune system of an individual and result in infections at various sites of the body. The major primary sites of infection in diabetic patients are urinary tract infection, respiratory tract infection, skin and soft tissue infections **[12]**. Uncontrolled diabetes poses a significant risk of acquiring bacterial, viral and fungal infections **[27]**. It was identified in our study that diabetes can promote infections in different areas of the body together as 23 patients (13.7%) had infections in more than one area of the body in our study. The most common co-infections were pneumonia and urinary tract infection occurring in our study population.

Sepsis in diabetes is a leading cause of mortality globally. It is said that diabetic patients have a 2 to 6 fold increase risk of sepsis as compared to non-diabetics **[28]**. Contrary to this, Chang et al. found no significant differences in mortality between diabetics and non-diabetics with severe sepsis **[29]**. We have also found that septic shock was present in 20 patients (11.9%). Septic shock was not affected by glycemic status, since both glycemic groups had 50% of the patients. The mean length of hospital stay in diabetic patients is approximately 8 days **[30]**. Surprisingly, a recent meta-analysis shows that patients with higher HbA1c had a shortened hospital stay **[31]**. In our study, the mean duration of hospital stay was 7.1 days. Additionally, we noted that patients with well-controlled diabetes stayed longer than those with poorly controlled diabetes but this difference did not reach statistical significance.

There are certain limitations in our study which we need to acknowledge. Firstly, it's a single centered study with a small sample size, so the data cannot be generalized to the whole population. Secondly, we had used HbA1c as a marker for glycemic control and hadn't compared fasting and post-prandial sugars in the diabetic individuals.

To our knowledge, it is the first study that has compared the variation in HbA1c after infections. Though this study had a small sample size, it has provided us with valuable and useful information. Acute infections had a potential to elevate HbA1c levels even after recovery from infection. It is widely known that uncontrolled diabetes can increase the risk and severity of infection. But the data on well-controlled diabetes is scarce.

In our study, we found that there was no difference in infection related outcomes between patients with good and poorly controlled diabetes but infections can disturb glycemic control and required rigorous monitoring of blood glucose for any alteration or adjustment of anti-diabetic medications.

CONCLUSION

We conclude from our study that infection had variable effect on glycemic control. Beside this, diabetes per se had a major influence on risk of infection, its severity and mortality irrespective of glycemic control. The diabetic patient is more vulnerable, so any infection they develop requires urgent medical attention.

Acknowledgment: None.

Funding

None. Author funded

Conflict of interest

None.

Ethical Exemption:

As it is an observational study with no direct interaction with the patients, the study proposal was reviewed by the Ethical Review Committee of the institute and ethical exemption was granted. (ERC No: 2019-1907-5019).

HIGHLIGHTS

1) It is essential to recognize the effect of infection on glycemic control in developing countries with high diabetes rates.
2) The results of our study indicate that different infections had different effect on on glycemic control, i.e. hemoglobin A1c.
3) Regardless of glycemic control, diabetes itself has a significant effect on infection risk, severity, and mortality.
4) The effects of infection did not differ significantly between those with well-controlled diabetes and those with poorly controlled diabetes.

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