HbA1C- Biomarker of COVID-19 Severity in Patients with Diabetes Mellitus

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ABSTRACT

Background: Coronavirus Disease 2019 (COVID-19) has affected millions of people worldwide. Diabetes is associated with an enormous health and financial burden. Comorbidity of diabetes and COVID-19 can lead to poor outcome. **Objective:** To determine the role of HbA1C as biomarker of COVID-19 severity in patients with diabetes mellitus. **Study Design:** Cross sectional study. **Settings:** Chemical Pathology section and COVID ward of Sheikh Zayed Hospital, Rahim Yar Khan Pakistan. **Duration:** 1st July 2021 to 31st December 2021. **Methods:** 110 diabetic patients diagnosed with COVID-19 of both genders aged 20-90 years were included in study using consecutive sampling technique. Non diabetics with COVID-19 and patients not willing to be included in the study were excluded. Blood samples were collected for inflammatory markers (C-reactive protein (CRP), Serum ferritin and lactate dehydrogenase (LDH)) and HbA1C. HbA1c was stratified as: <7%, 7%–9% and >9%. Severity of the disease was assessed by requirement of patient for oxygen mask, ventilator or death of the patient. Data was entered and analyzed using SPSS 20. After applying t-test p value <0.05 was taken as significant. **Results:** 110 diabetic patients hospitalized with COVID-19 were included in the study among which 68 (61.8%) were females and 42 (38.2%) were males. Mean age of the patients was 53.85±14.34 years and majority belonged to middle class. Inflammatory biomarkers serum ferritin, CRP and LDH showed a rising trend with increase in HbA1C. HbA1C was stratified in 3 categories; 21 (19.1%) patients had HbA1C <7%, 53 (48.2%) had HbA1C 7-9% and 36 (32.7%) had >9%. COVID-19 disease outcome was correlated with HbA1C categories and more severe disease was observed in patients with HbA1C >9% (p=0.000). **Conclusion:** Performing HbA1c test at admission is helpful in diabetics for assessing severity of COVID-19 disease. Special attention should be given to patients with uncontrolled diabetes with vigorous treatment modalities.

Keywords: COVID-19, Diabetes mellitus, Biomarker, HbA1C.

INTRODUCTION

A large number of people have been affected by Coronavirus disease (COVID-19) pandemic worldwide. The virus was identified as highly infectious and communicable, novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which affects the humans by attaching to angiotensin-converting enzyme 2 (ACE-2), a receptor for this virus.[1] Diabetes patients constitute a remarkable proportion of COVID-19 hospitalized patients. Diabetes prevalence of 7.4% to 20% was reported in COVID-19 hospitalized patients across Chinese provinces.[2]

COVID-19 poor prognosis is associated with many risk factors and diabetes mellitus (DM) has emerged as a major risk factor for poor prognosis of the disease.[3] In previous outbreaks of respiratory viral epidemics diabetes was associated with a higher death rate in affected patients.[4,5] Same was observed in SARS-CoV-2 pandemic where diabetic patients had a terrible increase in mortality as compared to the normal population.[6]

In T2DM there is pro-inflammatory remodeling at systemic and tissue level.[7] Diabetes affects both respiratory and immune systems as it causes damage to alveolar epithelium, pulmonary cilia dysfunction, alveolar collapse and increased vascular permeability and also causes impaired function of immune system.[8]

Likewise spleen, lymph node and lung architecture is damaged in severely ill COVID-19 patients and lymphopenia is also observed.[9] COVID-19 and diabetes both can damage the respiratory and immune systems synergistically.[8] Good glycemic control can improve the immune system as reported in previous studies therefore it should be of primary importance in diabetics with COVID-19 infection.[10] Glycosylated hemoglobin (HbA1c) provides glycemic control of past 3 months hence it is a good indicator of long-term glucose control.[11] It can help identifying the individuals with high-risk of COVID-19 disease severity having low awareness of good glycemic control.[12]

This study aims to assess role of HbA1C as biomarker of COVID-19 severity in patients with diabetes mellitus so as to direct more medical efforts toward patients with poorly controlled diabetes mellitus in order to minimize the social and financial burden associated with an imperceptive approach towards uncontrolled and well controlled diabetics.

The objective of the study was to determine the role of HbA1C as biomarker of COVID-19 severity in patients with Diabetes Mellitus.

METHODS

This cross-sectional study was conducted in chemical pathology section and COVID ward of Sheikh Zayed Hospital, Rahim Yar Khan from 1st July 2021 to 31st December 2021.

110 diabetic patients diagnosed with COVID-19 of both genders aged 20-90 years were included in study using consecutive sampling technique. Non diabetics with COVID-19 and patients not willing to be included in the study were excluded. Patients with comorbidities like cardiac diseases, cerebrovascular accident and other respiratory diseases were also excluded.

Blood samples were collected for inflammatory markers (C-reactive protein (CRP), Serum ferritin and lactate dehydrogenase (LDH)) and HbA1C. For patients with HbA1C done in past 6 months, this pre-infection result was included in study. CRP, LDH and HbA1C were performed on BC AU680 fully automated chemistry analyzer based on spectrophotometry. Serum ferritin was performed on Cobas e-411 electrochemiluminescence based immunoassay analyzer.

Demographic characteristics and all test results were recorded on a predesigned performa. HbA1c was stratified as: <7%, 7%–9% and >9%. Severity of the disease was assessed by requirement of patient for oxygen mask, ventilator or death of the patient. Data was entered and analyzed using SPSS 20. Qualitative data was presented as frequency and percentage while quantitative data was

given as mean and SD. Post stratification t-test was applied and p value <0.05 was taken as significant.

RESULTS

110 diabetics with COVID-19 were included in this study among which 68 (61.8%) were females and 42 (38.2%) were males. Mean age of the patients was 53.85$\pm$14.34 years and majority belonged to middle class. Demographic characteristics of patients are given in table 1. More diabetic patients with COVID-19 had HbA1c between 7% and 9%. Inflammatory biomarkers showed a rising trend with increase in HbA1C (Table 2). 21 (19.1%) patients had HbA1C <7%, 53 (48.2%) had HbA1C 7-9% and 36 (32.7%) had >9%. COVID-19 disease outcome was correlated with HbA1C categories and higher mortality was observed in patients with HbA1C >9% (Table 3).

Table 1: Demographic characteristics of patients

Demographic characteristics		Frequency	Percentage
Age (years)	**20-40**	20	18.2%
	41-60	60	54.5%
	61-80	24	21.8%
	>80	6	5.5%
	Total	110	100%
Gender	**Female**	68	61.8%
	Male	42	38.2%
	Total	110	100%
Socio-economic status	**Poor**	25	22.7%
	Middle class	47	42.7%
	High class	38	34.6%
	Total	110	100%

Table 2: Inflammatory biomarkers and HbA1C

Inflammatory Biomarkers	HbA1C			p value
	<7%	**7-9%**	**>9%**	
Ferritin (ng/ml)	655.3 + 168.22	1557.0 + 316.94	1700 + 1131	0.005
CRP (mg/L)	10.9 + 4.0	16.0 + 6.9	36.3 + 11.5	0.032
LDH (U/L)	307 + 34.2	534 + 104.6	668 + 65.2	0.000

Table 3: HbA1C and outcome in diabetic COVID-19 patients

HbA1C	N	Outcome			p value
		Oxygen	Ventilator	Mortality	
<7%	21 (19.1%)	15 (71.4%)	5 (23.8%)	1 (4.8%)	
7-9%	53 (48.2%)	15 (28.3%)	23 (43.4%)	15 (28.3%)	0.000
>9%	36 (32.7%)	3 (8.3%)	7 (19.5%)	26 (72.2%)	

DISCUSSION

In our study HbA1c was identified as a biomarker of COVID-19 severity. Female gender and middle-class socioeconomic status were significantly linked to hospitalization. While obesity and male gender were suggested as risk factors in previous research papers.[13-15] it was reported in previous publications that patients having poor glycemic control were more vulnerable to microbial infections, such as *Group B streptococci*, *Chlamydia pneumoniae*, *Mycobacterium tuberculosis*, *Klebsiella pneumoniae* infections with poor prognosis as compared to the patients having good glycemic control.[16-19] Besides, hyperglycemia also causes cell damage in SARS-CoV-2 infection by upregulating ACE-2 expression.[20] COVID-19 itself causes damage to pancreatic β cells thereby leading to impaired insulin production and altered glucose homeostasis as some studies have shown that few viruses can damage β-cells of pancreas directly,[21,22] and angiotensin converting enzyme 2 (ACE2) has higher expression in endocrine pancreas thereby acting as SARS-CoV-2 receptor.[23]

Prattichizzo *et al*. reported that HbA1C measured before or after hospitalization was directly associated with mortality or morbidity of COVID-19.[3] Additionally they also compared glycemic control of patients and poor glycaemic control was found to be associated with a higher risk of COVID-19 mortality.[3] Few researches concluded that absolute hyperglycemia in COVID-19 patients at hospitalization increases the severity of COVID-19 and it was independent of previous glycemic status but good glycemic control significantly improved the outcome in these patients.[24-25] As HbA1c is not affected by the stress hyperglycemia associated with acute illness[26] it may help in identification of new onset diabetes in COVID-19 patients. This New onset diabetes has been commonly identified in COVID-19 patients.[27]

Moreover, COVID-19 patients with this newly identified diabetes are at a greater risk of poor outcome.[28] Our study showed that among COVID-19 patients with diabetes, poor glycemic control and HbA1C>9% are associated with more severe disease thereby indicating the need and importance of good glycemic control.

CONCLUSION

It is concluded that HbA1c is helpful in diabetics for assessing severity of COVID-19 disease. As more severe disease was observed in patients with higher HbA1C level special care should be given to patients with poor glycemic control and uncontrolled diabetes to minimize economic and social burden.

LIMITATIONS

COVID-19 patients with diabetes mellitus admitted in hospital were included only. This is a single center study with limited sample size. Studies with large sample size including all COVID-19 patients with diabetes mellitus are required.

SUGGESTIONS / RECOMMENDATIONS

Diabetic patients should have a record of HbA1C to assess their glycemic control and in COVID-19 patients with diabetes mellitus more vigorous treatment should be offered to patients with poor glycemic control.

CONFLICT OF INTEREST / DISCLOSURE

None.

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