

The Increasing Prevalence of Diabetes Mellitus in COVID-19 Patients in North Sudan: Is it a Matter of Diabetogenicity?

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Abstract

Background: COVID-19 had made more than 197 million infections and 4 million deaths. So we need to assess the prevalence of diabetes mellitus among COVID-19 patients and its effect on the final outcome.

Objectives: We aim to assess the prevalence, risk factors and outcome of diabetes among COVID-19 patients.

Methods: This was a prospective, cross-sectional, hospital-based study enrolled 400 COVID-19 patients and was conducted in COVID-19 isolation centers in North Sudan.

Results: Males constituted 275 (68.9%) of the study participants, and the majority of participants were aged between 40 and 60 years 150(37.4%). The prevalence of DM was found to be 49.25% in the study participants. Diabetics were significantly more likely to have a respiratory rate higher than 30 ($P=0.012$), and oxygen saturation less than 93% ($P<0.001$), to develop shock ($P=0.004$), to require oxygen therapy ($P<0.001$), to get intubated ($P<0.001$), to develop respiratory failure and organ failure ($P<0.001$), and to have a poorer outcome ($P<0.001$). New-onset diabetes occurred in 20 (5%) participants and their mortality was higher compared to non-diabetic patients ($P=0.04$). The

total mortality of participants was 15.8%. Factors associated with poorer outcome were: older age ($P<0.001$), and having type I diabetes ($P=0.025$).

Conclusion: The prevalence of diabetes is very high among COVID-19 patients, and is associated with a more severe disease and a poorer outcome. New onset diabetes was associated with poorer outcome compared to non-diabetics.

Keywords: COVID-19; Diabetes Mellitus; Diabetogenicity

List of abbreviations: ACE2: Angiotensin Converting Enzyme 2; COVID-19: Coronavirus Infection Disease 2019; CVD: Cardiovascular Disease; DM: Diabetes Mellitus; FBS: Fasting Blood Sugar; H1N1: Influenza A; HbA1c: Glycated Hemoglobin; HTN: Hypertension; MERS-COV: Middle East Respiratory Syndrome Coronavirus; PCR: Polymerase Chain Reaction; RBS: Random Blood Sugar; SARS: CoV-2; 2HPP: 2 Hours Post-Prandia Sugar

Introduction

Coronavirus infection disease 2019 (COVID-19) which is due to SARS COV-2 has been increasing continuously, currently (August 2021) COVID-19 infection exceed 197 million persons and has caused over 4 million deaths [1]. Diabetes Mellitus has high prevalence among general population, so it is crucial to understand COVID -19 trends in diabetic patients.

Diabetes mellitus in acute infections can increase risk of morbidity and mortality due to compromised immunity. Bad glycemic control (HbA1C >9%) is linked to 60% of hospitalization and severity of pneumonia [2]. Diabetes Mellitus increased mortality and morbidity in past viral pandemics and diabetes was considered as an independent risk factor for mortality and morbidity of the SARS-COV-1 outbreak in 2002-2003 [3].

In Influenza A (H1N1) in 2009, DM increased the risk of hospitalization by 3 times and risk of intensive care unit admission by 4 folds [4].

Half of the affected population were found to have DM in MERS-COV 2012 outbreak and the odds ratio for MERS-COV severity range was about (7.2 - 15.7) in diabetic patients compared to general population. Mortality rate of diabetic patients exceeded a third in MERS outbreak [5,6].

Recently, DM, hypertension, and cardiovascular disease were considered as high risk for COVID-19 infection, despite variability of prevalence in many studies from different countries. Many Chinese studies about COVID-19 found high prevalence of hypertension, diabetes, and CVD patients. Diabetic patients are more vulnerable to severe critical disease varying between 14-32% in many studies [7].

Finally, apart from the usual mechanisms (impaired neutrophil chemotaxis and phagocytosis) by which diabetes predisposes to infections in general, there are several specific factors responsible for increasing the risk and severity of SARS-COV-2 among diabetics: ACE-2 receptors may play a major role in SARS COV-2 effect on blood glucose, ACE2 receptors are synthesized in the pancreas, and hyperglycemia even without being diabetic up to 3 years was noticed with SARS COV infection indicating transient damage to beta cells. So, it is critical to monitor blood glucose especially in acute presentations [8]. Increased Furin: diabetes associated with increase in Furin, which is type -1 membrane-bound protease, belonging to the prp-protien convertase subtilisin | kexin family (PCSK). Its involved in the entry of SARS COV-2 into the cell and an increased furin has been

reported in diabetics which might facilitate viral replication [9]. Impaired T-cell function: alteration in CD4 lymphocyte have been reported in animal models with MERS [10]. Lymphocytopenia has been observed in pts with COVID-19 and correlate with prognosis [11]. Increased interleukin-6(IL-6): several cytokines are increased in COVID-19 infection [12]. Monoclonal antibody against IL-6 receptor (tocilizumab) is being tested in a trial in COVID-19 [13].

Methods

Study Design

This was a prospective, cross-sectional, hospital-based study.

Study Area

This study was conducted in the COVID-19 Isolation Centers of North Sudan, including isolation centers in: Dongola, Karema, Atbara, and Shandi cities.

Study Duration

The study was conducted during the period of September 2020 to November 2020.

Study Population

The study population was all adult COVID-19 patients who were diagnosed by Polymerase Chain Reaction (PCR) in isolation centers.

Inclusion Criteria

- Patient who accepted to participate in the study.
- Being an adult (18 years and above).
- Diagnosed as COVID-19 by PCR.
- Admitted to one of the COVID-19 isolation centers involved in the study.

Exclusion Criteria

- Refusal of patient to participate in the study.
- Age less than 18 year old.

Sampling

Total coverage sampling method was used in this study and the total number was 400 patients.

Data collection method & tool

Data were collected using a structured interview questionnaire; the questionnaire was filled directly from the patients and from their medical files.

For all the patients involved in the study a Random Blood Sugar (RBS), Fasting Blood Sugar (FBS), and 2 Hours Post-Prandial (2HPP) glucose measurements were done, if one of the previous tests showed abnormally elevated glucose level then HbA1c level test would be performed.

The questionnaire involved data regarding: Socio-demographic characteristics (gender, age, residence, marital status), co-morbid conditions. Diabetes related data (random blood glucose at presentation, and discharge, symptoms, duration of symptoms, type of diabetes, and type of medication), COVID-19 related data (presenting symptom, place of receiving care, type of medication received, need for intubation, complications, and the final outcome), Family history (diabetes, hypertension, and asthma), long term drugs, and social habits.

Data Analysis

Data was reviewed, ordered, and coded, and then Statistical Package for Social Sciences (SPSS) version 20 was used for data analysis. Descriptive statistics (mean, median and standard deviation) were used to analyze the participant data like age, blood pressure measurement, RBS and FBS. Mann-Whitney U test was used to test for significant difference in the mean arterial pressure of diabetic and non-diabetic COVID-19 patients. Chi-Square test and Fisher Exact test were used to test

for a significant difference in the presentation of diabetic and non-diabetic COVID-19 patients, additionally; Chi-Square test was used to test for a significant difference between diabetic and non-diabetic COVID-19 patients in terms of: type of management needed, complications, and outcome. Finally, Chi-Square test was used to test a significant association between socio-demographic characteristics, social habits, and the type of diabetes to the outcome of the study participants.

Ethical Consideration

Ethical approval for the conducting of this study was obtained from the Research Ethics Committee of Sudan Medical Specialization Board (SMSB) and the Ministries of Health in North Sudan.

Informed consent was obtained from all individuals prior to their participation in the study; participants were informed that their participation in the study is voluntary and that they have the right to withdraw at any time. The dignity and confidentiality of the participants were preserved throughout the study.

Results

A total of 400 COVID-19 patients were included in the study with 177 diabetic patients and 223 non diabetic (this later including 20 newly discovered), Prevalence of DM was 49.25% (197; 177 previously known diabetic, 20 newly discovered DM). 68.9% of the participants were males, and 37.4% were in the age group of 40 to 60 years. 63.3% of them were from urban areas and the majority of them (75.6%) were married, as shown in Table 1.

Factor	N	%
Gender		
Male	275	68.9
Female	125	31.1
Age		
18 – < 40	110	27.6
40 – < 60	150	37.4
60 – < 80	130	32.5
>80	10	2.6
Marrital Status		
Married	302	75.6
Single	98	24.4
Residency		
Urban	251	63.3
Rural	149	36.7

Table 1: Demographic factor of the participants

The most frequent comorbidity was cardiovascular disease (12.5%) and the least was malignancy (0.2%), a considerable portion of the participants had a family history of DM (37%), HTN (27.2%), and COVID-19 (29.2%). The most frequent social

habits of participants in the study were smoking (19.2%), 16.3% of the study participants were taking long-term medications (Table 2).

Factor	N	%
• Chronic Illness		
DM	177	44.2
Heart disease	50	12.5
Stroke	6	1.5
Liver disease	4	1.0
Renal problem	19	4.8
Asthma	12	3.0
Malignancy	1	0.2
• Family History		
DM	148	37.0
HTN	109	27.2
COVID-19	116	29.2
• Social habits		
Smoking	77	19.2
Snuffing	34	8.5
Alcohol	11	2.8
• Medications		
Yes	335	83.7
No	65	16.3

Table 2: Comorbidities, Social habits and Medications of study participants

The majority of the diabetic patients (69%) had type 2 diabetes (Table 3). Duration of diabetes extended from 3 months to 30 years with a mean duration of 8.8 years (± 6.4). 36.9% and 35% of the diabetic patients in our study had diabetes for 1 -5 years and 5 -10 years, respectively. Among the diabetics involved in the study, 65.7% were on insulin and 34.3% were on oral anti-diabetic medications.

Most of the patients in our study had fever (85.8%) and cough (80%). On the other hand, the least frequent presentations were

PaO₂ less than 300 mmHg (1%), shock (2.8%), and vomiting (7.8%). Most of the participants received: antibiotics (96.2%), dexamethazone steroids (75.5%), Oxygen (59%), and (31.5%) of them were intubated. The most frequent complication among the study participants was respiratory failure (19.8%), followed by organ failure in (11%) of the study participants, and shock in (6.5%). The Majority (84.3%) of the study candidates made a full recovery (Table 4).

Factor	N (177)	% (100)
• Type of DM		
Type 1 (IDDM)*	55	31.0
Type 2 (NIDDM)#	122	69.0
• Duration		
< 5 years	66	37.3
5 – 10 years	62	35.0
> 10 years	39	22.0
• Medications		
OHA\$	61	34.4
Insulin	116	65.5

*IDDM insulin dependent diabetes mellitus

NIDDM non-insulin dependent diabetes mellitus

\$ OHA oral hypoglycemic agents

Table 3: Types, duration and medications of DM among study participants

Factor	N	%
• Symptoms		
Fever	343	85.8
Cough	320	80.0
Diarrhea	110	27.5
Headache	84	21.0
Vomiting	31	7.8
RR > 30	101	25.2
SpO ₂ < 93%	96	24.0
Shock	11	2.8
• Treatment		
Antibiotics	385	96.2
Steroids	302	75.5
Oxygen	236	59.0
Intubation	126	31.5
• Complications		
Respiratory Failure	79	19.8
Shock	26	6.5
Organ Failure	44	11.0
• Outcome		
Recovery	337	84.3
Death	63	15.8

Table 4: Presentations, Complications and Outcome of COVID-19 among study participants

Chi-square test and Fisher exact test revealed no significant difference in the clinical presentation of diabetic patients and non-diabetic patients (Table 5) in most of the tested variables except in: having a respiratory rate more than 30 ($P=0.012$), Oxygen saturation less than 93% ($P<0.001$) and shock ($P=0.004$), a statistically significant difference was found and frequency of these signs were more in diabetic than in non-diabetic patients. Chi-square test revealed a statistically significant difference between diabetic patients and non-diabetic patients in receiving steroids which was received more by non-diabetic patients ($P=0.021$), oxygen, which was received more by diabetic patients ($P<0.001$) and intubation, being more frequently done for diabetic patients ($P<0.001$). Chi-square showed a statistically significant difference in complications between diabetic patients and non-diabetic patients. All COVID-19 complications were present more frequently among diabetics ($P<0.001$). Respiratory failure was present in 33.9% of diabetic patients compared to 8.5% only among non-diabetics. Shock was present in 12.4% of diabetics and 1.8% of non-diabetics. Finally, Organ failure was present in 20.9% of diabetic patients

compared to 3.1% among non-diabetics. Significant differences in the outcome was found between Diabetic patients and non-diabetic patients ($P<0.001$), with a higher death rate among diabetic (24.3%) compared to non-diabetic patients.

A statistical difference in the outcome was found between married and single patients, with higher mortality among married patients ($P<0.001$). Additionally, a significant difference was revealed between different age groups with mortality increasing with increase in age ($P<0.001$), being 0.9% among participants aged between 18-40 yrs, 15.2% among participants aged between 40-60 yrs, and 26.2% among participants aged between 60-80 yrs. No difference was found in the outcome between those who smoke, take snuff, or drink alcohol and those who don't. Chi-square test revealed a significant difference when comparing the outcome and the type of DM with higher mortality rates in patients with type 1 DM (35.8%) compared to those who have type 2 diabetes (18.6%) ($P=0.025$), as shown in Table 6.

Factor	Diabetic (%)	Non diabetic (%)	P. value
• Symptoms			
Fever	88.1	84.2	0.332
Cough	82.4	78.5	0.397
Diarrhea	24.9	29.6	0.347
Headache	19.8	22.0	0.680
Vomiting	7.9	7.6	0.915
RR > 30	31.6	20.0	0.012
SpO ₂ < 93%	33.9	16.1	< 0.001
PaO ₂ < 300	1.7	0.4	0.326
Shock	5.6	0.4	0.004
• Treatment			
Antibiotics	94.4	97.8	0.129
Steroids	81.4	70.9	0.021
Oxygen	72.9	48.0	< 0.001
Intubation	46.3	19.7	< 0.001
• Complications			
Respiratory Failure	33.9	8.5	< 0.001
Shock	12.4	1.8	< 0.001
Organ Failure	20.9	3.1	< 0.001
• Outcome			
Recovery	75.7	91.0	< 0.001
Death	24.3	9.0	< 0.001

Table 5: Comparison of severity of COVID-19 between Diabetic patients and Non-diabetic patients

Factor	Recovery	Death	P. value
● Age			
18-40 yrs	99.1	0.9	< 0.001
40-60 yrs	84.8	15.2	
60-80 yrs	73.8	26.2	
>80 yrs	40.0	60.0	
● Gender			
Male	82.9	17.1	0.361
Female	87.1	12.9	
● Residency			
Urban	84.5	15.5	0.973
Rural	83.8	16.2	
● Marrital status			
Married	80.5	19.5	< 0.001
Single	96.7	3.3	
● Type of DM			
Type 1	64.2	35.8	0.025
Type 2	81.4	18.6	
● Smoking	77.9	22.1	0.128
● Snuffing	85.3	14.7	0.861
● Alcohol	72.7	27.3	0.390

Table 6: Risk factors for the outcome of COVID-19 in study population

Discussion

To the best of our knowledge this is the first study about the prevalence of diabetes among patients of COVID 19 in Sudan. A total of 400 COVID-19 patients were recruited from COVID-19 centers in the Northern States of Sudan. The prevalence of diabetes was found to be 49.3% of the participants, most of them had type II diabetes (69%). This result is comparable to that of a study conducted in Saudi Arabia where they found 45.3% of COVID-19 patients had diabetes mellitus [14] and higher than studies conducted in Italy and China where they found the prevalence of diabetes was 35.5% and 20% respectively [15,16].

Results from systemic reviews also showed lower frequencies of diabetes among COVID-19 patients where it was 14.5%, 9.8%, and 9.7% [17-19]. According to the World Health Organization (WHO), the prevalence of diabetes is increasing in low and middle income countries, and this explains why a higher percentage of COVID-19 patients in our study and the Saudi Arabia study in comparison to international studies [14,20].

Diabetic patients in this study had a more severe COVID-19 infection. Diabetics were significantly more likely to have a respiratory rate higher than 30, oxygen saturation less than 93%, and were more likely to develop shock. There was also a significant association between having diabetes and requiring oxygen and intubation, suggesting a more severe form of COVID-19 is present among diabetic patients. Furthermore, the complications of COVID-19 (respiratory failure and organ failure) were significantly more common among diabetic than in non-diabetic patients. On the other hand, the diabetic COVID-19 patients had a significantly higher mortality (24.3%) compared to non-diabetic patients (9%). This finding is consistent with the findings of the previously conducted studies, where they showed that diabetes is a risk factor for developing severe COVID-19 infection, a higher risk for complications and a higher risk of death [15,17,19,21]. Additionally, there was a statistically significant association between the type of diabetes and the outcome, type I diabetic COVID-19 patients had higher mortality (35.8%) compared to type 2 diabetic patients (18.6%). This finding contradicts the finding of a previous study, where type 2 diabetes was associated with a poorer COVID-19 outcome [22].

COVID-19 seems to have a diabetogenic effect, in this study out of the 223 non-diabetic patients, 20 (5%) developed diabetes and this is double of what was revealed in study conducted in North Sudan where the prevalence of undiagnosed diabetes was found to be 2.6% [23], and this may indicate that COVID 19

has an effect on the prevalence of diabetes. On the other hand the prevalence of diabetes was found to be 18.7% and 19.1% in two separate studies conducted in north Sudan [24,25]. The prevalence of DM was far high than the study conducted in ATH "the same hospital" about the pattern of disease in which they found that the prevalence of DM among admitted patients was 6% which may also reflect the diabetogenicity of COVID-19 [26]. Interestingly our study revealed a very high prevalence of diabetes among COVID 19 patients in North Sudan, so from the previous studies and our study the prevalence of diabetes mellitus is increasing rapidly and this may indicate the diabetogenicity of COVID 19. Furthermore, those with newly diagnosed diabetes had a significantly higher mortality (25%) compared to non-diabetic patients (8.9%). This finding is similar to the finding of a previous study, where new onset diabetes was found to be associated with a poorer COVID-19 prognosis, this latter study also suggested that when compared to patients with pre-existing diabetes, patients with newly onset diabetes also have a worse outcome [27]. In this study 337 (84.3%) achieved full recovery and 63 (15.8%) died. The mortality rate is higher than that reported in other countries, as the case-fatality rate in the United States is 1.8% and 2.9% in the United Kingdom. However, it's comparable to that of neighboring countries, as in Yemen the rate is 19.8% and 7.2% in Syria [28]. The discrepancy in the mortality rate could be explained by the difference in the medical facilities available in a developed country (United States or the United Kingdom) and a developing country such as Sudan.

This poor outcome among patients with diabetes who acquire COVID-19 or those who develop diabetes during the COVID-19 infection could be explained by the abnormal immunity of diabetic patients, as studies showed that diabetics have an abnormal phagocyte function, an impaired T-cell mediated immunity, in-effective microbial clearance, and abnormal cytokines production, all of which could aid in the formation of the "cytokines storm" responsible for COVID-19 related complications and subsequently death [15,29,30].

An additional finding of this study is that age was found to be significantly associated with poor outcome and the mortality increased with increasing age confirming the fact that COVID-19 is more lethal among the elderly population [18,21,22].

Limitations

This study has limitations, being hospital based with a relatively small sample size when compared to prevalence of the

disease and the cross sectional design does not allow for the determination of the temporal relationship between risk factors and outcome. This study may not be truly representative of all patients of COVID-19 and involvements of patient was from isolation centers and not from homes isolation, glycemic control were not followed during admission and therefor were not tested for association with outcome, despite this limitation this study is novel and reflects the prevalence and risk factors associated with diabetes among COVID-19 patients.

Conclusion

In conclusion, the prevalence of diabetes among Sudanese COVID-19 patients is very high, COVID-19 seems to have a diabetogenic effect, as 5% of non-diabetic patients in this study developed diabetes after being infected with COVID-19, and the mortality is 15.8% and the risk factors for poor outcome were age and type 1 DM.

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