

The Increasing Prevalence of DM in COVID-19 Patients: 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. Therefore, we need to assess the prevalence of DM among COVID-19 patients and its effect on the 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 be 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-patients with diabetes ($P=0.04$). 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.

Key words: COVID-19, DM, Diabetogenicity, Isolation centres

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INTRODUCTION

Corona virus infection disease 2019 (COVID-19) is caused by SARS COV-2 and it has been increasing continuously in number of cases and mortalities. Currently, (August 2021), the COVID-19 infection affecting more than 197 million

persons and has been responsible of deaths of more than 4 million [1]. Diabetes mellitus (DM) has a high prevalence among general population; therefore, it is crucial to understand COVID -19 trends in patients with diabetes. DM in acute infections could increase the risk of morbidity and mortality due to patients' compromised immunity. Uncontrolled glucose level, which can be manifested by glycosylated haemoglobin (HbA1C) more than 9% is linked to 60% of hospitalization and severity of pneumonia [2]. DM had increased the mortality and morbidity in the past

viral pandemics, and it was considered as an independent risk factor for mortality and morbidity of the SARS-COV-1 outbreak in 2002-2003 [3]. In Influenza (H1N1) in 2009, DM increased the risk of hospitalization by three times and risk of intensive care unit admission by four folds [4]. Half of the affected population were found to have DM in Middle East Respiratory Syndrome Coronavirus (MERS-COV) 2012 outbreak and the odds ratio for MERS-COV severity ranged between (7.2 - 15.7) in patients with diabetes compared to general population. Mortality rate of patients with diabetes in COVID-19 was exceeded a third in MERS outbreak [5,6].

In recent studies DM, hypertension, and cardiovascular disease were considered as high risks for developing COVID-19 infection, despite variability of prevalence in many studies from different countries. Many Chinese studies dealing with COVID-19 found a high prevalence of hypertension, diabetes, and cardiovascular disease (CVD) in such patients. Patients with diabetes are more vulnerable to severe critical forms of disease varying between 14-32% in several studies [7]. Angiotensin Converting Enzyme 2 (ACE-2) receptors may play a major role in the effect of SARS COV-2 on blood glucose level. Evidence of presence of Hyperglycemia even without being diabetic up to 3 years was noticed with SARS COV infection indicating transient damage to beta cells. Therefore, it is critical to monitor blood glucose especially in acute presentations of the disease [8].

METHODS

This was a prospective, cross-sectional, hospital-based study conducted in the COVID-19 Isolation Centres of North Sudan, namely: Dongola, Karema, Atbara, and Shandi cities. The study was conducted during the period of September 2020 upto November 2020. We included all adult patients having COVID-19 who were diagnosed by Polymerase Chain Reaction (PCR) in the isolation centres. The inclusion criteria of the patients comprised of all adult (18 years and above) patient who accepted to participate in the study, with positive result of COVID-19 by PCR, and admitted to one of the COVID-19 isolation centres involved in the study. We excluded patients who refused to participate in the study, or their age was less than 18 years old. We used the total coverage technique as the sampling method to collect data from the total number of included participants. Thus, the total number of included participants 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, and 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

We reviewed data, ordered, and coded, and then we used Statistical Package for Social Sciences (SPSS) version 20 for data analysis. Descriptive statistics were used to analyze the participants' data. Mann-Whitney 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 patients with diabetes 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). More than two-third of the participants was males and more than one-third of them were in the age group of 40 to 60 years. Nearly two-third of them were from urban areas and the majority of them (75.6%) were married (Table 1).

Table 1: Demographic factor of the participants (N=400).

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
Marital Status		
Married	302	75.6
Single	98	24.4
Residency		
Urban	251	63.3
Rural	149	36.7

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).

Table 2: Comorbidities, social habits and medications of study participants (N=400).

Factor	N	%
Chronic Illness		
DM	177	44.2
Heart disease	50	12.5
Stroke	6	1.5
Liver disease	4	1
Renal problem	19	4.8
Asthma	12	3
Malignancy	1	0.2
Family History		
DM	148	37
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

The majority of the patients with diabetes (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 (\pm 6.4). 36.9% and 35% of the patients with

diabetes 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.

Table 3: Types, duration and medications of DM among study participants (N=400).

Factor	N (177)	100%
Type of DM		
Type 1 (IDDM)	55	31
Type 2 (NIDDM)	122	69
Duration		
< 5 years	66	37.3
5 - 10 years	62	35
> 10 years	39	22
Medications		
OHA	61	34.4
Insulin	116	65.5

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%), dexamethasone 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).

Table 4: Presentations, complications and outcome of COVID-19 among study participants (N=400).

Factor	N	%
Symptoms		
Fever	343	85.8
Cough	320	80
Diarrhea	110	27.5
Headache	84	21
Vomiting	31	7.8
RR > 30	101	25.2
SpO ₂ < 93%	96	24
PaO ₂ < 300	4	1
Shock	11	2.8
Treatment		
Antibiotics	385	96.2
Steroids	302	75.5
Oxygen	236	59
Intubation	126	31.5
Complications		
Respiratory Failure	79	19.8
Shock	26	6.5
Organ Failure	44	11
Outcome		

Recovery	337	84.3
Death	63	15.8

Chi-square test and Fisher exact test revealed no significant difference in the clinical presentation of patients with diabetes and non-patients with diabetes (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-patients with diabetes. Chi-square test revealed a statistically significant difference between patients with diabetes and non-patients with diabetes in receiving steroids which was received more by non-patients with diabetes ($P=0.021$), oxygen, which was received more by patients with diabetes ($P<0.001$) and intubation, being more frequently done for patients with diabetes ($P<0.001$). Chi-square showed a statistically significant difference in complications between patients with diabetes and non-patients with diabetes. All COVID-19 complications were present more frequently among diabetics ($P<0.001$). Respiratory failure was present in 33.9% of patients with diabetes 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 patients with diabetes compared to 3.1% among non-diabetics. Significant differences in the outcome were found between patients with diabetes and non-patients with diabetes ($P<0.001$), with a higher death rate among diabetic (24.3%) compared to non-patients with diabetes.

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 years, 15.2% among participants aged between 40-60 years, 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 do not. 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.

Table 5: Comparison of severity of COVID-19 between patients with diabetes and non-patients with diabetes (N=400).

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	0.68
Vomiting	7.9	7.6	0.915
RR >30	31.6	20	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	<0.001
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	<0.001
Death	24.3	9	<0.001

Table 6: Risk factors for the outcome of COVID-19 in study population (N=400).

Factor	Recovery	Death	P. value
Age			
18-40 years	99.1	0.9	
40-60 years	84.8	15.2	<0.001
60-80 years	73.8	26.2	
>80 years	40	60	
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	
Marital 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	0.39

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 centres 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 DM [9] and higher than studies conducted in Italy and China where they found the prevalence of diabetes was 35.5% and 20% respectively [10,11]. Results from systemic reviews also showed lower frequencies of diabetes among COVID-19 patients where it was 14.5%, 9.8%, and 9.7% [12-14]. 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 [15,9]. Patients with diabetes 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 patients with diabetes. Furthermore, the complications of COVID-19 (respiratory failure and organ failure) were significantly more common among diabetic than in non-patients with diabetes. On the other hand, the diabetic COVID-19 patients had a significantly higher mortality (24.3%) compared to non-patients with diabetes (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 [10,12,14,16]. 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 patients with diabetes (18.6%). This finding contradicts the finding of a previous study, where type 2 diabetes was associated with a poorer COVID-19 outcome [17].

COVID-19 seems to have a diabetogenic effect, in this study out of the 223 non-patients with diabetes, 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% [18], 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 [19,20]. 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 reflects the Diabetogenicity of COVID-19 [21]. 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 DM 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-patients with diabetes (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 is latter study also suggested that when compared to patients with pre-existing diabetes, patients with newly onset diabetes also have a worse outcome [22]. 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, its comparable to that of neighboring countries, as in Yemen the rate is 19.8%, and 7.2% in Syria [23]. 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 patients with diabetes, as studies showed that diabetics have an abnormal phagocyte function, an impaired T-cell mediated immunity, ineffective 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 [10,24,25].

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 [13,16,17].

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 centres and not from homes isolation, 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 seem to have a diabetogenic effect, as 5% of non-diabetic patients in this study develop 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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