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COVID-19 IN DIABETIC PATIENTS: A REVIEW OF COMORBIDITES AND WORSE OUTCOMES

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ABSTRACT

Introduction: Coronavirus disease-19 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) with the first case being reported in Wuhan, China. The World Health Organization has declared this outbreak a global pandemic and social containment measures have been adopted worldwide. There is a high prevalence of concomitant conditions, including diabetes, cardiovascular disease, hypertension, obesity, and chronic obstructive pulmonary disease. Poor glyecemic control worsens outcomes for patients with COVID-19. **Methodology:** We systematically reviewed the literature on COVID-19 and its relevance to diabetes. A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words), including "COVID-19/SARS-CoV-2" and "diabetes/hyperglycemia." Pubmed, EMBASE, and Cochrane Library were searched up to October 10, 2020. After carefully reviewing the full length articles, 7 studies were included which showed the outcomes and prognostic factors of COVID-19 illness in diabetic patients. **Results:** Older age and male sex are epidemiological features related to a higher prevalence of COVID-19 and a more severe clinical course. Case fatality rate in diabetic patients was significantly higher than the non diabetic patients. Also poor prognosis was seen in Black, Asian, and mixed ethnicities compared with white people. Insulin infusion allowed achievement of glycemic targets and improved outcomes in patients with hyperglycemia with COVID-19. Metformin also showed promising outcomes in patients with diabetes. **Conclusion:** Diabetes was itself an independent risk factor for poor prognosis and worse outcomes in COVID-19 patients. A higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity in ethnic minorities than the white population might partly account for the increased risk of poor outcomes in these minority populations. Age is also one of the risk factor associated with worse outcomes. Antiviral therapy should be carefully tailored due to its interaction with the anti-diabetic agents.

KEYWORDS: We systematically reviewed the literature on COVID-19 and its relevance to diabetes.

INTRODUCTION

In December 2019, a cluster of atypical interstitial pneumonia cases caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in Wuhan, China. Following the rapid spread of COVID-19, WHO, on March 11, 2020, declared COVID-19 a global pandemic. As a result, social containment measures have been adopted worldwide, and health-care

systems are reorganized to cope with a growing number of acutely ill patients. Among those with severe COVID-19 and those who died, there is a high prevalence of concomitant conditions, including diabetes, cardiovascular disease, hypertension, obesity, and chronic obstructive pulmonary disease.[1] Data from two hospitals in Wuhan, including 1561 patients with COVID-19, showed that those with diabetes (9.8%) were more likely to require admission to an intensive care unit (ICU) or to die.[2] Diabetes is known to confer increased risk for infections. Previous studies have shown a J-curve relationship between HbA_{1c} and the risk of being admitted to hospital for infections in general and infections of the respiratory tract. An increased risk of infection was reported during previous outbreaks of severe acute respiratory syndrome[3] Middle East respiratory syndrome,[4] and H1N1 influenza virus.[5]

Patients with COVID-19 have a high prevalence of the cardiovascular disease.[6] Poor glycaemic control at hospital admission and during the hospital stay worsens outcomes for patients with COVID-19. Moreover, consideration should be given for a direct effect of SARS-CoV-2 on β-cell function and survival, causing worsening rapid and severe deterioration of metabolic control in people with pre-existing diabetes or leading to the development of new-onset diabetes.[7] This review summarized the data from published literature to describe the spectrum of outocomes in patients with diabetes and their associated comorbidities.

MATERIALS AND METHODOLOGY

We systematically reviewed the literature on COVID-19 and its relevance to diabetes. A comprehensive literature search was performed using a combination of keywords (MeSH terms and free text words), including "COVID-19/SARS-CoV-2" and "diabetes/hyperglycemia." Pubmed, EMBASE, and Cochrane Library were searched up to October 10, 2020. A limit of after 2019 was imposed since COVID-19 was first reported in late 2019. Additional articles were sought from the reference lists of the included studies. Two independent reviewers screened all articles identified from the literature search. We included studies on COVID-19 in adult patients. Case reports, case series, observational studies, non-randomized studies, and randomized trials published in English were included in this review. Conferences abstracts, letters to editors, commentaries, and editorials were also excluded. For eligible studies, study information including first authors, site of study, inclusion and exclusion criteria, sample size, age, and sex were recorded.

REVIEW

Potential prognostic factors

Age, sex, and ethnicity

Older age and male sex are epidemiological features related to a higher prevalence of COVID-19 and a more severe clinical course. In the early phase of the outbreak, the highest prevalence of COVID-19 occurred in older people in most regions of the world. The prevalence of diabetes increases with age in both the general population and in patients with COVID-19. Despite overall similar sex distribution of people infected with SARS-CoV-2 (male 51%, female 49%), the case-fatality rate has been higher in males (2.8%) than in females (1.7%).[8] Non-white ethnic groups seem to be at greater risk as indicated by HRs adjusted for age and sex, ranging between 1.83 and 2.17 for black, Asian or Asian British, and mixed ethnicities compared with white people.[19] The higher incidence and worse outcomes of COVID-19 reported in ethnic minority groups are unlikely to reflect biological factors and are predominantly due to lifestyle and socioeconomic factors.

Table 1: Study Characteristics.

Sr. No.	Study	Type	Total Patients (N)	Prevalence of diabetes (n)	Outcome	Total deaths	Deaths in the diabetic group	Odds Ratio
1.	Barron et al.[10]	Retrospective	61,414,470	3,193,552 (5.2%)	Mortality	23,698	7,867 (33.2%)	2.86 (2.58–3.18) for type 1 diabetes and 1·80 (1.75–1.86) for type 2 diabetes
2.	Holman et al.[11]	Cohort	NA	3,138,410	Mortality	NA	10,989 (0.35%)	3.51 (95% CI 3.16–3.90) in people with type 1 diabetes and 2.03 (1.97–2.09) in people with type 2 diabetes.
3.	Sardu et al.[11]	Retrospective	59	25 (44%)	Survival	NA		0.172 (0.051–0.576)
4.	Chen et al.[12]	Retrospective	904	135 (15%)	Mortality	92 (10.18%)		1.08 (1.01–1.16)
5.	Zhu et al.[13]	Retrospective	7337	952 (13%)	Mortality	198 (2.7%)	74 (7.8%)	1.49 (1.13–1.96)
6.	Yan et al.[14]	Retrospective	193	48 (25%)	Mortality	108 (55.95%)	39 (81.25%)	1.53 (1.02–2.3)
7.	Shi et al.[2]	Retrospective	1561	153 (9.8%)	Mortality	NA	31 (20.3%)	1.58 (0.84–2.99)

Comorbidities

Shi et al.[2] reported a retrospective analysis of patients with COVID-19, diabetic patients had a greater prevalence of hypertension (56.9%), cardiovascular disease (20.9%), and cerebrovascular disease (7.8%) than those without diabetes (28.8%, 11.1%, and 1.3%, respectively). Moreover, in the patients with diabetes, non-survivors had a greater prevalence of comorbidities than survivors (hypertension 83.9% vs. 50.0%; cardiovascular disease 45.2% vs. 14.8%; cerebrovascular disease 16.1% vs. 5.7%; chronic pulmonary disease 12.9% vs. 3.3%; and chronic kidney disease 6.5% vs. 3.3%).

Sardu et al.[15] reported a retrospective analysis of patients with COVID-19, diabetic patients had a prevalence of hypertension (72%) and cardiovascular disease (20.9%) than those without diabetes (28·8%, 11·1%, and 1·3%, respectively).

Holman et al.[11] reported a retrospective analysis of patients with COVID-19, diabetic patients had a prevalence of hypertension (4.6%%), cardiovascular disease (20%), and cerebrovascular disease (1.9%) than those without diabetes (28%, and 80% respectively).

Baron et al.[10] reported a retrospective analysis of patients with COVID-19, diabetic patients had a prevalence of hypertension (6.3%), cardiovascular disease (22.4%), and cerebrovascular disease (6.8%) than those without diabetes (93.7%, 77.57%, and 93.2%, respectively).

In a Cox multi-regression analysis reported by Chen et al.,[12] patients with diabetes had hypertension (HR 3.10, 95% CI 1.14–8.44), cardiovascular disease (1.87, 0.88–4.00), and chronic pulmonary disease (2.77, 0.90–8.54) were independent risk factors for in-hospital death.

Zhu et al.[13] reported a retrospective analysis of patients with COVID-19, diabetic patients had a prevalence of hypertension (54%), cardiovascular disease (13.5%), and cerebrovascular disease (5.6%) than those without diabetes (46%, 86.5%, and 95.4%, respectively).

Yan et al.[14] reported a retrospective analysis of patients with COVID-19, diabetic patients had a prevalence of hypertension (50%), cardiovascular disease (27.1%), and cerebrovascular disease (10.4%) than those without diabetes (50%, 72.9%, and 89.6%, respectively).

Table 2: Patients Comorbidities.

Sr. No.	Study	Prior Coronary heart disease		Prior Cerebrovascular disease		Prior Heart failure/ hypertension	
		Yes	No	Yes	No	Yes	No
1.	Barron et al.[10]	580,915 (22.43%)	2,589,335 (77.57%)	202,100 (6.8%)	2,968,150 (93.2%)	188,560 (6.3%)	2,981,690 (93.7%)
2.	Holman et al.[11]	51,435 (1.63%)	3,086,975 (98.27%)	60,255 (1.9%)	3,078,155 (98.1%)	144,870 (4.6%)	2,993,540 (95.4%)
3.	Sardu et al.[15]	5 (20%)	20 (80%)	NA		18 (72%)	7 (28%)
4.	Chen et al.[12]	91 (10.07%)	813 (89.93%)	52 (5.75%)	852 (94.25%)	273 (30.2%)	631 (69.8%)
5.	Zhu et al.[13]	110 (13.5%)	700 (86.5%)	45 (5.6%)	765 (94.4%)	438 (54%)	372 (46%)
6.	Yan et al.[14]	13 (27.1%)	35 (72.9%)	5 (10.4%)	43 (89.6%)	24 (50%)	24 (50%)
7.	Shi et al.[2]	32 (20.9%)	121 (79.1%)	12 (7.8%)	141 (92.2%)	87 (56.8%)	66 (43.2%)

Study	Covid related deaths		Coronary Heart disease		Cerebrovascular disease		Heart Failure	
	Male	Female	Admission	No admission	Admission	No admission	Admission	No admission
Barron et al.	5079 (64.5%)	2788 (35.5%)	3086 (39.2%)	4781 (60.7%)	1760 (22.3%)	6107 (77.6%)	1821 (23.14%)	6046 (76.86%)
Holman et al.	6740 (61.3%)	4249 (38.6%)	NA					

Glucose lowering medications

In the presence of mild COVID-19 in an out-patient setting, usual glucose-lowering therapies for patients with diabetes could be continued if the patient eats and drinks adequately and a more frequent blood glucose-monitoring regimen is implemented. Sardu et al. reported that insulin infusion allowed achievement of glycemic targets and improved outcomes in patients with hyperglycemia with COVID-19. Chen et al. reported better outcomes in patients treated with metformin but the drug should be stopped in patients with respiratory distress, renal impairment and heart failure.[16]

Therapies for COVID-19 in people with diabetes

Treatment with chloroquine or hydroxychloroquine can cause hypoglycaemia, particularly in patients on insulin or sulfonylureas, because of their effects on insulin secretion, degradation, and action.[17] Conversely, antiviral drugs such as lopinavir and ritonavir could lead to hyperglycaemia and worsen glycaemic control.[18]

DISCUSSION

Although data fully adjusted for comorbidities are not yet available, a higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity in

ethnic minorities than the white population might partly account for the increased risk of poor outcomes in these minority populations. In summary, available data suggest that age is associated with worse outcomes in COVID-19, and it can be hypothesized that this relationship is more potent in people with diabetes for at least three reasons. First, the prevalence of diabetes increases with age to reach a peak in people older than 65 years. Second, people older than 65 years are more likely to have a longer duration of diabetes and a greater prevalence of diabetic complications. Third, diabetes and older age often correlate with comorbidities such as cardiovascular disease, hypertension, and obesity. Arterial hypertension is by far the most frequent comorbidity seen in patients with COVID-19.[8] Obesity is also linked to more sever COVID-19 illness and death. Obesity and diabetes are prothrombotic conditions that might contribute to worse prognosis in patients with COVID-19.[19] Obesity and diabetes are characterised by chronic lowgrade inflammation with increased concentrations of pro-inflammatory leptin and reduced anti-inflammatory adiponectin. Additionally, people with obesity are often physically inactive, more insulin resistant, and with gut dysbiosis, which might increase the inflammatory response to infection with SARS-CoV-2. Moreover, individuals with obesity have lower vitamin D concentrations, which could also reduce the immune response.[20]

CONCLUSION

Diabetes was itself an independent risk factor for poor prognosis and worse outcomes in COVID-19 patients. A higher prevalence of cardiovascular risk factors such as hypertension, diabetes, and obesity in ethnic minorities than the white population might partly account for the increased risk of poor outcomes in these minority populations. Age is also one of the risk factor associated with worse outcomes. Antiviral therapy should be carefully tailored due to its interaction with the anti-diabetic agents.

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