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Brief Report

Diabetic retinopathy is independently associated with increased risk of intubation: A single centre cohort study of patients with diabetes hospitalised with COVID-19

Antonella Corcillo [a,b,*], *Siew Cohen* [b], *Adrian Li* [b], *James Crane* [b], *Dulmini Kariyawasam* [b], *Janaka Karalliedde* [a,b,*]

[a] *School of Cardiovascular Medicine & Sciences, King's College London, 3.11 Franklin-Wilkins Building, Waterloo Campus, Stamford Street, London SE1 9NH, UK*

[b] *Guy's and St Thomas NHS Foundation Trust, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK*

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ABSTRACT

In our study of 187 patients with diabetes hospitalised with COVID-19 we observed a more than 5 fold increased risk of intubation in patients with diabetic retinopathy. Further studies are required to understand the mechanisms that explain the associations between retinopathy and other indices of microangiopathy with severe COVID-19.

1. Introduction

Male gender, age, obesity and admission blood glucose levels are associated with poor outcomes in people with diabetes hospitalised with COVID-19 infection [1,2]. Diabetic retinopathy is a manifestation of microvascular disease and endothelial dysfunction and may be a surrogate index of generalized microangiopathic processes that affects the vasculature not only in the eye but in other organs [3,4]. A recent study demonstrated a composite index of microvascular disease, defined as advanced retinopathy and/or diabetic kidney disease and/or history of diabetic foot ulcer, was associated with

* Corresponding authors at: Diabetes and Endocrine Day Centre, 3rd Floor Southwark Wing, Guy's Hospital, Great Maze Pond, London SE1 9RT, UK (A. Corcillo).

E-mail addresses: Antonella.Corcillo@kcl.ac.uk (A. Corcillo), j.karalliedde@kcl.ac.uk (J. Karalliedde).

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early mortality in patients with COVID-19 infection [2]. However, this study did not report the independent effect if any of retinopathy on COVID-19 outcomes and there is no information in the current literature if the presence of diabetic retinopathy is associated with severe COVID-19 infection. We therefore evaluated in a single center study whether in patients with diabetes hospitalized with COVID-19 the presence of retinopathy was associated with a more severe manifestation of COVID-19 as defined by need for tracheal intubation.

2. Material and methods

We studied 187 consecutive patients with diabetes (179 type 2 diabetes and 8 type 1 diabetes) hospitalised at one hospital with COVID-19 between the 12th of March and the 7th of April 2020. All patients had positive polymerase chain reaction COVID-19 swab test. Diabetic retinopathy status and grade (by monoscopic fundus photos of dilated pupils with a non-mydriatic camera) was obtained via NHS Diabetic Eye Screening data [5] within 12 months of COVID-19 hospitalisation. Macrovascular complications was defined as cardiovascular and/or cerebrovascular disease. Chronic kidney disease (CKD) was defined as pre-admission (within 12 months) estimated glomerular filtration rate (eGFR) by MDRD equation of < 60 ml/min. Ethnicity was self-reported and recorded at time of eye screening.

Descriptive statistics were used for the analysis of demographic and clinical features. Patients who were intubated and those who were not were compared by an unpaired t test (for continuous normally distributed variables), Mann–Whitney test (for continuous variables not normally distributed) and ^{2} test (for categorical variables). Correlation analysis (Spearman correlation) of the variable was used to test for associations between need for intubation and a number of other variables. Variables that were significant at the p 0.10 in univariate analysis with intubation were introduced in a logistic multivariate analysis to retain factors that enabled meaningful clinical interpretation beyond statistical significance [6,7]. This approach prevents eliminating a potentially important confounder too early in the modeling process [6,7]. Further, such purposeful selection algorithms have been demonstrated to identify and retains confounders correctly at a larger rate than other more stringent selection procedures [6,7].

A two-tailed p value < 0.05 was considered significant. Statistical analyses were performed with SPSS version 25.0 (SPSS, Chicago, IL, USA).

3. Results and discussion

The mean age of the cohort was 68 (range 22–97) years and 60% were male with 44% of African-Caribbean ethnicity, 39% Caucasian and 17% other (included 8% of Asian origin).

Mean (±standard deviation) pre-admission HbA1c was 8.6% ±2.7% (70 ± 29 mmol/mol). Diabetic retinopathy was reported in 67 (36%) of patients, the majority with background retinopathy (n = 52, 80%) and 15 (20%) had more advanced retinopathy (pre-proliferative or proliferative retinopathy) documented on recent eye screening.

Of the 187 patients, 49 (26%) were intubated. The clinical features and variables associated in univariate analysis with intubation are shown in Table 1. Age, duration of diabetes, macrovascular complications and presence of CKD were negatively associated with intubation. In contrast, retinopathy and obesity were positively associated with intubation.

When comparing patients who were intubated to those who were not, we observed similar results with lower age, shorter duration of diabetes, lower prevalence of macrovascular disease and CKD, and more prevalent retinopathy and obesity (Supplementary Table 1). We did not observe any significant association between intubation and other variables including gender, ethnicity, use of renin-angiotensin-aldosterone system blockers, type of diabetes, hypertension, renal function (serum creatinine or eGFR) and glucose level at time of admission, or pre-admission HbA1c. There was no significant association observed between retinopathy and ethnicity or between retinopathy and renal function at admission. Of the cohort we studied, 60 (32%) died and we did not observe any association of retinopathy on mortality. Of the patients who were intubated, 17 died and in the group who were not intubated, 43 died. We did not have complete data for pre-admission HBA1c (data unavailable n = 83), duration of diabetes (data unavailable n = 23), plasma glucose levels at admission (data unavailable n = 19) and BMI (data unavailable n = 67). However, there were no significant differences in intubation risk or prevalence of retinopathy observed between patients with and without complete data.

In the multivariable logistic regression analyses, where all variables that were associated in univariate analyses with intubation at p 0.10 were included, lower age (OR 0.89, 95% CI 0.84–0.95) and retinopathy (OR 5.81, 95% CI 1.37–24.66) were

Table 1 – Univariate correlation between intubation and selected clinical characteristics in a cohort of 187 patients with diabetes hospitalized with COVID-19.

Variable	Coefficient of Correlation (r Value)	p-value
Gender	0.02	0.83
Age	0.39	<0.001
Duration of diabetes	0.17	0.03
HbA_1c	0.09	0.34
Macrovascular complications	0.25	0.001
Presence of chronic kidney disease	0.14	0.06
Plasma glucose level at admission	0.05	0.47
eGFR at admission	0.10	0.16
Retinopathy	0.13	0.09
Hypertension	0.02	0.79
BMI 30 kg/m^2	0.23	0.01

Abbreviations : BMI = body mass index. eGFR = estimated glomerular filtration rate

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independently and significantly associated with increased risk of intubation ($p < 0.001$ for all). The overall performance of the model was reasonable with a Nagelkerke pseudo R2 of 0.49 suggesting that 49% of the variance of intubation is explained by the variables in the model. Duration of diabetes, macrovascular complications, CKD and BMI 30 kg/m^2 were not significantly associated with increased risk of intubation in multivariable logistic regression analysis.

4. Discussion

In our single centre study of 187 people with diabetes hospitalised with COVID-19, we observed a novel association between diabetic retinopathy and need for intubation. Our results suggest that people with diabetic retinopathy have a more than fivefold increased risk of intubation. We also noted that younger age was associated with increased risk of intubation, and this may in part be explained by potential selection bias, as more elderly and frail patients with multimorbidity may have been less likely to be intubated due to their poorer prognosis.

We did not observe any association between retinopathy on mortality which is in contrast with the CORONADO study where an association between a composite microvascular complications endpoint of advanced retinopathy and/or diabetic kidney disease and/or history of diabetic foot ulcer and day 7 mortality was observed [2]. Renal function measured at time of admission to hospital or pre-admission CKD (eGFR < 60 ml/min) were not significantly associated with intubation in our cohort. However, we could not evaluate if pre-admission albuminuria or neuropathy status were associated with intubation as we did not have data for these variables before COVID-19 hospitalisation.

Due to the cross-sectional design of our study, we cannot prove causality. Further, our study was not designed to identify the mechanisms that may explain the association between retinopathy and risk of intubation. We hypothesise that retinopathy is an index of diabetic microangiopathy and that people with diabetes with endothelial dysfunction/-damage may be more vulnerable/or less likely to recover from severe COVID-19 that results in hypoxia and respiratory failure that requires invasive ventilator support. Pre-existing endothelial dysfunction and microangiopathy have been described by Whyte et al as possible major contributors to the severity of adult respiratory distress syndrome in COVID-19 patients [3]. Dysregulation of lung perfusion and hypoxemic vasoconstriction are hypothesized as possible explanations for this association between microvascular disease and poor COVID-19 outcomes [3]. Endothelial damage and pulmonary microvascular thrombosis found in severe COVID-19 patients may thus be enhanced in patients with diabetes who have surrogate evidence of microangiopathy such as retinopathy. Further detailed studies that have direct measures of microangiopathy and endothelial function and their relationship to adverse COVID-19 outcomes are needed to explain our observations.

Our study has several limitations. We evaluated patients at a single centre and the majority of patients had background retinopathy. Further studies where larger numbers of patients with more advanced retinopathy are needed to establish if there is a gradient of risk between stages of retinopathy and adverse COVID-19 outcomes. We were unable to collect complete data for pre-admission HBA1c, duration of diabetes and BMI in all patients. However, patients with these missing data did not differ in prevalence of retinopathy or risk of primary endpoint. Finally, our data from an ethnically diverse urban cohort may not be applicable to all populations.

The strengths of our study include the use of robust diabetic eye screening data from digital records, analysis of consecutive patients admitted during a fixed time period and the inclusion of patients treated at a single large centre with standardised clinical pathways and treatments.

5. Conclusion

In conclusion, our study reports the first description of diabetic retinopathy as a potential risk factor for poor COVID-19 outcomes. The more than 5 fold increased odds of intubation in patients with diabetic retinopathy was independent of conventional risk factors for poor COVID-19 outcomes. Our findings may help clinicians better risk stratify people with diabetes at high risk of adverse COVID-19 outcomes and establish a platform for further studies to understand the mechanisms between endothelial dysfunction/microangiopathy and susceptibility to severe COVID-19 infection.

Authors contributions, funding

All authors have read and approved the submission of the manuscript. No founding sources have been used to contribute to this manuscript.

Declaration of Competing Interest

No author has any conflict of interest with the content of this manuscript.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2020.108529.

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