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COVID-19 in Metabolism

Diabetes, glycaemic control, and risk of COVID-19 hospitalisation: Population-based, prospective cohort study

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ABSTRACT

Objective: We aimed to examine the prospective association of diabetes and glycaemic control with COVID-19 hospitalisation in a large community-based cohort study.**Methods and study design:** Participants ($N = 337,802$, aged 56.4 ± 8.1 yr; 55.1% women) underwent biomedical assessments at baseline as part of the UK Biobank prospective cohort study. The outcome was cases of COVID-19 serious enough to warrant a hospital admission from 16-March-2020 to 26-April-2020.**Results:** At follow up, 649 cases COVID-19 were recorded. In multivariable adjusted analyses, risk of COVID-19 was elevated in people with undiagnosed diabetes at baseline (A1C $\geq 6.5\%$) (risk ratio = 2.68; 95% confidence interval: 1.66, 4.33) and poorly controlled (A1C $\geq 8.6\%$) diagnosed diabetes (1.91; 1.04, 3.52). There was a dose-dependent increase in risk of COVID-19 with increasing A1C, that persisted in multivariable adjusted models (per SD [0.9%]: 1.07; 1.03, 1.11; $p[\text{trend}] < 0.001$).**Conclusion:** In this large community-based sample, higher levels of A1C within the normal range were a risk factor for COVID-19. Glucose regulation may play a key role in immune responses to this infection. Undiagnosed cases of diabetes in the general community may present a particularly high risk.

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1. Introduction

There is emerging evidence that diabetes increases the likelihood of a poor prognosis in COVID-19 patients [1]. Clinical studies in China, UK and Italy have suggested that diabetes may increase the risk of cohorts of patients hospitalised with COVID-19 progressing to intensive care and death [2,3]. Crucially, however, whether diabetes has a role as a risk factor in the occurrence of COVID-19- is unknown; accordingly, we examined the aetiological relation of both diabetes and A1C with new cases of COVID-19-hospitalisations in a large general population-based prospective cohort study.

2. Research design and methods

2.1. Study population

We used data from UK Biobank, a prospective cohort study, previously described [4]. Baseline data collection took place between 2006 and 2010 across twenty-two research assessment centres in the UK

giving rise to a sample of 502,655 people aged 40 to 69 years (response rate 5.5%) [4]. Ethical approval was received from the North-West Multi-centre Research Ethics Committee, and the research was carried out in accordance with the Declaration of Helsinki of the World Medical Association. Participants gave informed consent.

2.2. Biomedical assessments

Physician diagnosed diabetes and vascular/heart disease was self-reported. Further clinical data included resting seated blood pressure and a fasting blood sample from which various analytes were assessed, including total cholesterol, HDL cholesterol, A1C, C-reactive protein (CRP) [5]. Hypertension was defined as elevated blood pressure ($\geq 140/90$ mmHg) and/or use of anti-hypertensive medication. Waist-to-hip circumference was measured with a Seca 200 measuring tape using standard procedures. A ratio of ≥ 0.9 in men and ≥ 0.8 in women was used to denote central obesity.

2.3. Covariates

During the clinic visit, data were collected via self-report for age, sex, ethnicity (White, South Asian, Black, Chinese, other), educational attainment (college/degree or lower), smoking history (never, previous,

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current), units of alcohol intake, types of physical activity in the last four weeks (none, walking, exercise and sport, household maintenance work and gardening).

2.4. Ascertainment of hospitalisation for COVID-19

Linkages with COVID-19 test data were provided by Public Health England <http://biobank.ndph.ox.ac.uk/showcase/field.cgi?id=40100>. For the present analyses COVID-19 testing results from 16 March up to 26-April-2020 were included, covering the period in which testing was restricted to those with symptoms in hospital. These data can therefore be regarded as a proxy for hospitalisations for severe cases of the disease for England only. Participants from Scotland and Wales were therefore omitted from our analytical sample. COVID-19 disease tests were performed on samples from combined nose/throat swabs, using real time polymerase chain reaction (RT-PCR) in accredited laboratories [6].

2.5. Statistical analyses

In the first set of analyses we used established diabetes guidelines (i.e. NICE guidelines: <https://www.nice.org.uk/guidance/ng28/chapter/1-Recommendations>) to derive A1C cut-points. The cut points for the second set of analyses were data driven and involved splitting the sample into 5 evenly distributed groups. We fitted regression models to estimate risk ratios (RR) and 95% confidence intervals for associations between diabetes, A1C and COVID-19. Odds ratios were first adjusted for age and sex, followed by smoking, physical activity, alcohol, education, ethnicity, and finally adding hypertension, cardiovascular disease, central obesity, total and HDL cholesterol, CRP. Analyses were performed using SPSS Version 26.

3. Results

The sample comprised 337,802 participants (56.4 ± 8.1 years; 55.1% women) who were alive up to 5th March 2020, and had available data on diabetes diagnosis, A1C and covariates. Participants were largely white British (94.5%). Overall, 4.8% of study members reported a diabetes diagnosis. At follow up, 649 cases of COVID-19 were recorded. Compared to participants without a diagnosis and A1C below 6%, risk of COVID-19 was elevated in people with undiagnosed diabetes at baseline (A1C ≥ 6.5) (RR = 2.68; 95% confidence interval: 1.66, 4.33) and poorly controlled (A1C ≥ 8.6 %) diagnosed diabetes (1.91; 1.04, 3.52) (Table 1).

In analyses in which A1C was the exposure of interest there was a marked increased risk of COVID-19 with increasing levels of this characteristic. Thus, in age- and sex-adjusted analyses, people in the highest A1C group had twice the risk of being hospitalised for COVID-19 (2.13; 1.65, 2.74). Importantly, these raised RRs were apparent across the full A1C range and not just in people at the higher end of the continuum (p[trend] <0.001). There was some attenuation of this gradient after adjustment for covariates which included socio-economic status and health behaviours, but the relationship persisted. In fully adjusted models, we observed independent associations between several covariates and COVID-19, including age, male sex, smoking, physical inactivity, non-white ethnicity, alcohol, and central obesity (Table S1).

4. Discussion

We found evidence of a graded association between A1C and risk of COVID-19 in a large community-dwelling cohort. The accumulation of differentiated cytotoxic T cells have been linked to impaired glucose homeostasis in pre-clinical work [7], and associations between A1C and other types of infections have also been observed [8,9]. In several large primary care cohorts a range of infections were more frequent in people with diabetes with worse glycaemic control [10,11], which is consistent with our data. Thus, impaired glucose regulation may be an important mechanism partially explaining progression of COVID-19 infection.

In a previous meta-analysis containing 6 clinical studies from China, a higher proportion of patients with adverse COVID-19 disease progression were diabetic compared to those with a more favourable outcome [2]. From our data, we were not able to distinguish if infected patients survived thus could not fully disentangle associations between A1C and the course of COVID-19 infection. Nevertheless, our COVID-19 outcome was people with infection of sufficient severity to warrant inpatient care and excluded milder cases of infection.

Measures of A1C were collected at least ten years before infection thus ruling out possible reverse causation; that is, infection driving changes to glucose metabolism rather than the converse [12]. Although changes in glycaemic control might have occurred during follow-up causing misclassification, A1C remained relatively stable (baseline, 5.4 ± 0.8 vs. follow up, 5.5 ± 0.8 ; Pearson $r = 0.76$) in a sub-sample ($n = 12,863$) with repeat assessment after a median of 4.4 years. Thus, we speculate that chronically impaired glycaemic control may have an adverse impact on immune function thereby exacerbating responses to novel infections such as COVID-19. In particular, diabetes may inhibit neutrophil chemotaxis, phagocytosis, and intracellular destruction of microbes, thus

Table 1
Association between diabetes, A1C, and COVID-19 hospitalisation ($n = 337,802$).

	Cases/N	Relative risk (95% CI)		
		Model 1	Model 2	Model 3
Diabetes status				
None diagnosed/A1C < 6.0	535/308,180	1.0 (ref)	1.0 (ref)	1.0 (ref)
None diagnosed/A1C 6.0–6.5	39/11,018	1.93 (1.39, 2.68)	1.50 (1.08, 2.08)	1.34 (0.96, 1.88)
None diagnosed/A1C ≥ 6.5	18/2306	4.15 (2.69, 6.65)	3.04 (1.89, 4.90)	2.68 (1.66, 4.33)
Diagnosed/A1C < 7.0	27/9412	1.48 (1.01, 2.19)	1.17 (0.79, 1.73)	0.94 (0.64, 1.31)
Diagnosed/A1C 7.0–8.6	19/5176	1.90 (1.20, 3.01)	1.35 (0.91, 2.31)	1.15 (0.71, 1.84)
Diagnosed/A1C ≥ 8.6	11/1710	3.42 (1.88, 6.22)	2.39 (1.31, 4.38)	1.91 (1.04, 3.52)
A1C (%)				
≤ 5.10	94/71,289	1.0 (ref)	1.0 (ref)	1.0 (ref)
5.11–5.30	111/67,953	1.22 (0.93, 1.61)	1.20 (0.91, 1.58)	1.24 (0.94, 1.64)
5.31–5.50	122/67,966	1.33 (1.01, 1.74)	1.26 (0.96, 1.65)	1.30 (0.99, 1.71)
5.51–5.70	129/66,016	1.44 (1.10, 1.88)	1.29 (0.98, 1.69)	1.29 (0.98, 1.69)
>5.70	193/64,578	2.13 (1.65, 2.74)	1.64 (1.26, 2.13)	1.48 (1.19, 1.63)
p-Trend		<0.001	<0.001	<0.001

Model 1: adjusted age and sex.

Model 2: adjusted for age, sex, education, ethnicity, smoking, physical activity, alcohol.

Model 3: adjusted for age, sex, education, ethnicity, smoking, physical activity, alcohol, hypertension, CVD (heart attack, angina, or stroke), central obesity, total and HDL-cholesterol, C-reactive protein.

offering higher affinity cellular binding and efficient virus entry and decreased viral clearance [13]. There are also limitations of our work. Some cases of COVID-19 could have been captured in patients originally hospitalised for reasons other than the infection. By virtue of the fact people with diabetes are likely to present with more risk factors, these patients may have been prioritized for testing and some detection bias may have occurred. The UK Biobank data are predominantly white British, which may limit generalizability.

In conclusion, we observed an association between the full range of A1C values and risk of COVID-19 hospitalisation in a large community based cohort. This novel observation warrants replication in other cohort studies. On-going drug trials for the lowering of A1C levels could also be utilised to explore effects on COVID-19 prevention as a secondary outcome. Undiagnosed cases of diabetes in the general community may present a particularly high risk.

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CRedit authorship contribution statement

MH and GDB generated the idea for the present paper, and formulated an analytical plan; CRG prepared the data set; MH carried out all the data analyses and wrote the manuscript; All authors commented on an earlier version of the manuscript. MH will act as guarantors for this work. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of competing interest

None.

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