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WJD mainly publishes articles reporting research results and findings obtained in the field of diabetes and covering a wide range of topics including risk factors for diabetes, diabetes complications, experimental diabetes mellitus, type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes, diabetic angiopathies, diabetic cardiomyopathies, diabetic coma, diabetic ketoacidosis, diabetic nephropathies, diabetic neuropathies, Donohue syndrome, fetal macrosomia, and prediabetic state.

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OPINION REVIEW

Diabetes and COVID-19: Diseases of racial, social and glucose intolerance

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Abstract

Diabetes and coronavirus disease 2019 (COVID-19) are worldwide pandemics that have had a major impact on public health throughout the globe. Risk factors for developing diabetes and having adverse outcomes of COVID-19 appear to be similar; metabolic factors (such as obesity), non-White ethnicity and poorer socioeconomic status appear to be risk factors for both. Diabetes and COVID-19 have a significant effect on populations adversely affected by health inequality. Whilst we hope that COVID-19 will be mitigated by widespread use of vaccines, no such prospect exists for mitigating the pandemic of diabetes. In this brief opinion review, I compare risk factors for diabetes and adverse outcomes of COVID-19 and argue that tackling health and social inequality is likely to play a major role in solving the global diabetes pandemic and improve outcomes of COVID-19.

Key Words: Diabetes; COVID-19; Ethnicity; Health inequality; Social inequality; Risk factors

Core Tip: Diabetes and coronavirus disease 2019 are both global pandemics that cause more severe disease in people of non-White ethnicity and lower socioeconomic status. Improving social justice and reducing health inequalities will reduce the risk of both conditions considerably.

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INTRODUCTION

Diabetes and coronavirus disease 2019 (COVID-19) are two global pandemics that have sharply contrasting features but also some significant similarities. COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), emerged in 2019 and rapidly became a global public health emergency, leading to implementation of extraordinary public health measures and huge economic and societal costs[1]. At the time of writing, the condition has caused over 2000000 deaths worldwide[2]. However, this is likely to be less than 50% of the deaths due to diabetes in 2020; the condition caused 4200000 deaths worldwide in 2019[3], illustrating the fact that the diabetes pandemic has been perhaps more slow burning but no less fatal. The global diabetes prevalence in 2019 was estimated to be 9.3% (463000000 people), rising to 10.2% (578000000) by 2030 and 10.9% (700000000) by 2045[4].

In this viewpoint, I compare and contrast the two pandemics and their intersection, with particular reference to data from the United Kingdom.

DIABETES AND COVID-19 ARE RACIALLY INTOLERANT

Diabetes and ethnicity

For many years it has been recognised that type 2 diabetes mellitus (T2D) affects certain ethnic groups more than others. In the United Kingdom, this was first described in the Southall study, focusing on ethnicity in West London[5]. Older studies suggested a five-fold increased risk for the development of T2D amongst South Asians compared to White Europeans, although more recent data suggests that this risk is more in the region of 2-2.5 times greater[6]. There is also data to suggest that South Asians develop diabetes around 5 years earlier than their White European counterparts[7-9], and as duration of diabetes is a significant risk factor for development of complications, this means that South Asians are more likely to be susceptible to complications of diabetes at an earlier age. Indeed, complications such as cardiovascular disease, renal disease and eye disease are up to 50% higher than that of White Europeans[9-13]. Amongst other ethnicities in the United Kingdom, Black African and Caribbean ethnicities also show an increased risk for the development of T2D of around 1.5-2 times that of White Europeans[14].

The reason for the increased risk of T2D amongst South Asians is far from clear. Bhopal[14] proposed a four stage model suggesting that South Asian babies are genetically programmed to be small but with a high fat mass and low muscle mass with fewer pancreatic β-cells. In childhood and early adulthood, excess energy intake and lower physical activity leads to intra-abdominal fat accumulation, exacerbating insulin resistance with high insulin, glucose and triglycerides, a fatty liver and subsequent diabetes as β-cell failure ensues. Suggested factors contributing to this predisposition include genetic and epigenetic factors, low birthweight with rapid "catch-up" growth, ectopic fat within the liver and pancreas, low levels of adiponectin and high levels of leptin[15].

Whilst inherited effects may predispose to disease, cultural and lifestyle factors are likely to have a major impact on development of the condition. Dietary surveys suggest that a high proportion of daily energy intake originates from saturated fats and carbohydrates amongst South Asians[6]. Smoking is also common amongst South Asian men, in particular of Bangladeshi and Pakistani origin. South Asian subjects also appear to have a more sedentary lifestyle compared to Europeans[16]. Diabetes is commoner amongst more socially deprived cohorts in the United Kingdom, and non-White ethnicities are over-represented amongst socially deprived groups in the United Kingdom[17].

COVID-19 and ethnicity

At the height of the COVID-19 pandemic, it became increasingly clear that certain ethnic groups were more severely affected by SARS-CoV-2 infection[18]. In the United Kingdom, data from over 6000000 adults from 1205 general practices suggested that compared to White Europeans, the hazard ratio (HR) for death in men from COVID-19 (adjusted for age, body mass index and deprivation) amongst British Indians was 1.59 [95% confidence interval (CI) 1.25-2.01], British Pakistanis 1.84 (1.39-2.44), British Bangladeshis 2.27 (1.65-3.12), British Caribbeans 2.06 (1.65-2.57) and British Black Africans 3.03 (2.42-3.80)[19]. Similar data was seen for admission to hospital with severe COVID-19.

The cause of this excess risk of death and adverse outcome from COVID-19 amongst

non-White ethnicities is unclear but likely to be multifactorial. Underlying genetic factors may be important but as yet not ascertained, but it is notable that disparate ethnic groups are more severely affected, so a common genetic factor seems less likely. Increased risk of metabolic conditions such as diabetes, obesity and hypertension are also seen in these groups, perhaps suggesting an underlying predisposition to metabolic conditions and COVID-19[6,14].

Furthermore, socioeconomic factors and overcrowded housing are also cited as possible contributing factors. In particular, multigenerational households, with the old and young living in close proximity, is likely to increase risk of exposure of the elderly to SARS-CoV-2 and make it more difficult for infected patients to self-isolate. In addition, non-White ethnic groups work in more exposure prone settings, such as cleaners, health care workers, carers and taxi drivers.

DIABETES AND COVID-19 ARE SOCIALLY INTOLERANT

Diabetes and socioeconomic deprivation

There is considerable data to suggest that the prevalence of T2D is increased in areas of lower socioeconomic status. The British 1958 birth cohort study measured glycated haemoglobin at age 45 years and showed a higher prevalence of values of 5.5% (37 mmol/mol) and above in people with occupational social class 3, 4 and 5 compared to higher social class groups[20]. The Whitehall II study undertook doctor diagnosis and oral glucose tolerance tests to identify T2D, and amongst men the incidence of T2D in the lowest employment grade was more than two times that of the highest employment grade, even when adjusted for obesity and sedentary lifestyle[21]. More recent data confirms that prevalence of T2D is strongly associated with socioeconomic deprivation, most pronounced in the 40-69 year age band[17]. Interestingly, a cross-sectional school-based study of 4804 United Kingdom children aged 9-10 years, suggested that socioeconomic status of the child impacted metabolic indices according to ethnicity; White European children of lower socioeconomic status had poorer metabolic indices, whereas amongst South Asian children, socioeconomic status did not appear to affect metabolic indices[22].

Socioeconomic deprivation may also impact treatment of diabetes. In the United Kingdom, it has been shown that more deprived areas have lower attainment for diabetes care processes or diabetes targets compared to less deprived areas[23].

COVID-19 and socioeconomic deprivation

The data on over 6000000 patients from 1205 United Kingdom general practices referred to above also showed a significant impact of deprivation on the development of COVID-19 adverse outcomes[19]. A five unit increase in the Townsend material deprivation score led to a HR for death of 1.50 (95%CI 1.40-1.61) and similar increased risk of hospital admission for men and women from COVID-19. Data from the Office of National Statistics confirm this. The death rate of the population in the most deprived areas was 128.3 deaths per 100000, which was more than double that of the least deprived areas where the death rate was 58.8 deaths per 100000[24].

COVID-19 (LIKE DIABETES) IS GLUCOSE INTOLERANT

As the COVID-19 pandemic progressed, emerging data showed that people with diabetes and hypertension were uniquely at risk for increased severity of SARS-CoV-2 infection[25]. Amongst intensive care patients with COVID-19 in China, 22% of 32 patients who died had diabetes[26], and risk of admission to intensive care was doubled in patients with diabetes[27]. Subsequent studies suggested between 12%-16% of patients with severe disease had diabetes[28,29], and mortality was up to three-fold higher[30,31]. This mirrors previous data on outbreaks of other coronavirus infections (SARS and Middle East Respiratory Syndrome) and severe influenza from H1N1 pandemics, which also showed that diabetes was an important risk marker for adverse outcomes[32-34].

In the United Kingdom, the largest dataset to have reported on this topic examined over 61000000 individuals on general practice registers. Of these, 263830 (0.4%) had type 1 diabetes (T1D), and 2864670 (4.7%) had T2D[35]. One third of all deaths from COVID-19 occurred in people with diabetes (31.4% in people with T2D and 1.5% in people with T1D). The HRs for in-hospital death from COVID-19 (adjusted for age,

sex, deprivation, ethnicity, geographical region) compared to people without diabetes were 3.51 (95%CI 3.16-3.90) in people with T1D and 2.03 (95%CI 1.97-2.09) in people with T2D. When adjusted for previous hospital admission with cardiovascular disease or heart failure, the HRs reduced to 2.86 (95%CI 2.58-3.18) for T1D and 1.80 (95%CI 1.75-1.86) for T2D.

A large United Kingdom study of a cohort of patients with diabetes and COVID-19 found that poor glycaemic control prior to hospital admission was associated with an increased risk of in-hospital death[36]. Compared with people with a haemoglobin A1c (HbA1c) of 48-53 mmol/mol (6.5%-7.0%), people with an HbA1c of 86 mmol/mol (10.0%) or higher had increased COVID-19-related mortality (HR 2.23, 95%CI 1.50-3.30, $P < 0.0001$ in T1D and HR 1.61, 1.47-1.77, $P < 0.0001$ in T2D). In people with T2D compared to those with HbA1c of 48-53 mmol/mol, mortality from COVID-19 was significantly higher in those with an HbA1c > 59 mmol/mol (7.5%) (HR 1.22, 95%CI 1.15-1.30, $P < 0.0001$). In a United States study of 451 patients with diabetes and/or uncontrolled hyperglycaemia, mortality rate was 28.8% in patients with uncontrolled hyperglycaemia compared with 6.2% in patients without hyperglycaemia ($P < 0.001$)[37]. In a retrospective analysis of 952 cases of COVID-19 in patients with T2D in China, well-controlled blood glucose in hospital (capillary blood glucoses 3.9 to 10.0 mmol/L) was associated with lower mortality compared to individuals with poorly controlled glycaemia (capillary blood glucoses frequently > 10.0 mmol/L) (HR 0.14, 95%CI 0.03-0.60)[38].

Why should diabetes increase the risk of adverse outcomes in patients with COVID-19? The presence of diabetes does appear to impair immune responsiveness, and poor glucose control appears to impair several aspects of the immune response to viral infection whilst also increasing the risk of secondary bacterial infection[39]. There appears to be a J-shaped curve between HbA1c and risk of hospital admission with infection[40]. Diabetes per se does not appear to increase the risk of infection with SARS-CoV-2, only its severity.

Many patients with T2D have central obesity, which also appears to be an independent risk factor for adverse outcomes, independent of diabetes status[41]. This may be due to the accompanying low grade inflammation and release of adipocytokines such as tumour-necrosis factor-alpha or transforming growth factor-beta from adipocytes, which may impair immune response[42]. Obstructive sleep apnoea or heart failure, common co-morbidities associated with obesity, may impair respiratory capacity thereby inhibiting adequate ventilation and exacerbating respiratory compromise[43].

People with diabetes frequently have co-morbid complications such as chronic kidney disease or cardiovascular disease. Acute kidney injury is known to be an adverse risk factor in COVID-19 infection[44], and people with diabetes have an increased risk of acute kidney injury[45].

Further interest has focused on the angiotensin-converting enzyme-2 receptor, which is known to facilitate SARS-CoV-2 spike protein binding and cellular infection[46]. Human pancreatic tissue widely expresses angiotensin-converting enzyme-2, and it has been suggested that viral infection may cause acute β-cell dysfunction, leading to hyperglycaemia[47,48]. Indeed, there is growing evidence that acute hyperglycaemia occurs in COVID-19 infection, and a number of reports from the United Kingdom suggest that hyperglycaemic emergencies are a common presenting finding in COVID-19 infection[49,50].

The common risk factors for diabetes and severe COVID-19 infection are shown in Table 1.

WHY DO PEOPLE WITH DIABETES, NON-WHITE ETHNICITY AND LOWER SOCIOECONOMIC GROUP GET POORER OUTCOMES WITH COVID-19?

The preceding discussion suggests that adverse outcomes associated with COVID-19 and T2D have similar risk factors; non-White ethnicity, poorer socioeconomic status and metabolic factors such as obesity and metabolic syndrome. Why should this be?

The common factor in all of these risk factors is health inequality. The World Health Organization states that factors contributing to health inequality include where we are born, how we live and how we work[49]. Public Health England described an "un-level playing field" whereby a social gradient means that people who have a good start in life, feel in control of their life, have good and fair employment, a healthy standard of living and a safe home and good community have much better health outcomes compared to those who do not have these[50]. In 2010 in the United Kingdom, the

Table 1 Common risk factors for diabetes and adverse outcomes of coronavirus disease 2019

Common risk factors
Hypertension
Obesity
Glucose intolerance
Non-White ethnicity
Lower socioeconomic status
Cancer
Chronic kidney disease

Marmot review on social inequality suggested that "inequalities that are preventable by reasonable means are unfair. Putting them right is a matter of social justice"[51].

Concerted action to reduce health and social inequalities is likely to reduce the huge health inequalities seen in both the diabetes and COVID-19 pandemics. Some potential solutions are outlined in Table 2.

CONCLUSION

The COVID-19 pandemic will hopefully be tackled by widespread vaccination over the coming year. However, it is unlikely that the pandemic of T2D will be tackled in 2021. A major way to deal with the diabetes pandemic is to tackle health and social inequalities that lead to great disparities in health between ethnic and socioeconomic groups. It is my earnest hope that once the COVID-19 pandemic is over, the world will turn to tackling the much more difficult issue of health and social inequality that blights the lives of millions throughout the world.

Table 2 Potential interventions to reduce health inequality and rate of diabetes increase

Potential interventions
National programmes to improve the nation's health focus on improved diet and physical activity
Green solutions to transport/energy
"Fat/Sugar tax" and use funds to subsidise healthy food
Reduce licensing of unhealthy eating places in poorer areas
Minimum alcohol unit pricing
Tackle advertising of calorie dense foods to children and prevent sponsorship of sports by unhealthy food companies
Education for children to increase physical activity in and improve knowledge of healthy living in schools
Improve culturally appropriate interventions to educate people living with long term conditions

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