Consequences of the COVID-19 pandemic for patients with metabolic diseases

The COVID-19 pandemic has stretched healthcare resources and caused severe knock-on effects on patients with metabolic diseases worldwide. We encourage clinicians and patient-interest groups in the field of diabetes and metabolism to raise their voices to ensure adequate care and admission of patients.

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Patients with metabolic diseases are facing increased challenges in the COVID-19 pandemic, as a consequence of the prolonged lockdown, the exhaustion of healthcare systems, the viral disease itself and the effects of medications introduced for the treatment of SARS-CoV-2 infection. COVID-19 and metabolic disease currently cause substantial collateral damage for patients and pose new challenges to the entire metabolic health community that must be addressed. We, as a global team of experts representing six continents, are united in our views that we must raise our voices, given the current catastrophic situation that we are currently facing in caring for our patients. Decreased access to primary-care providers and a high demand for the care of critically ill patients with COVID-19 divert hospital staff and resources, which consequently are lacking in other areas of care. This situation poses a substantial risk for all patients with chronic diseases, particularly those with chronic metabolic disease. Below, we outline the main areas that, in our view, demand more attention or further consideration.

Treatment of patients with COVID-19 and metabolic disease

Dexamethasone therapy, as a new standard for patients with symptomatic COVID-19, and the need for supplemental oxygen treatment add new challenges in the management of hospitalized patients with metabolic disease and COVID-19 (ref. [1]). Currently, dexamethasone remains one of the few drugs, if not the only drug, that clearly decreases mortality among patients with COVID-19 in critical condition. However, high-dose glucocorticoid therapy, particularly in states of sepsis and inflammation, induces and aggravates hyperglycaemia and metabolic acidosis[2]. Glucocorticoids are the most common reason why people with COVID-19 and diabetes develop life-threatening hyperglycaemic hyperosmolar states. Physicians treating patients with COVID-19 must be trained in how to control these metabolic disorders, typically through a process involving early intravenous insulin therapy. However, increased mortality has recently been reported in patients with COVID-19 who received insulin treatment[3]. This finding highlights the need for frequent blood glucose testing, ideally with continuous glucose monitors, to detect and avoid life-threatening hypoglycaemic or hyperglycaemic episodes.

In addition, we have witnessed increases in blood pressure and oedema in patients with diabetes who received dexamethasone. Although dexamethasone is a potent synthetic glucocorticoid with very little mineralocorticoid effect, it nevertheless induces hypertension. Because dexamethasone actively promotes aquaporin-2 expression, the vasopressin-regulated water channel that controls renal fluid reabsorption, it causes water retention and hypertension. This mechanism might explain the occurrence of hypertension and oedema in patients with COVID-19-induced renal damage or existing diabetic nephropathy, and it further complicates patients' respiratory status. Indeed, hepatic ACE2 expression is elevated in people with non-alcoholic fatty liver disease and diabetes[4]. Therefore, both the acute and chronic effects of this treatment on metabolic complications must be considered.

Furthermore, dexamethasone might induce apoptosis in pancreatic beta cells. Because pancreatic islets might be affected by SARS-CoV-2, a combined effect of the infection plus systemic inflammation and dexamethasone may trigger beta-cell failure and insulin-dependent diabetes, although dexamethasone could potentially prevent virus-induced autoimmune diabetes[5].

Finally, sepsis and viral infections can impair adrenal function[6]. Thus, dexamethasone withdrawal even after 10 days, when adrenal glands may have been damaged by septic inflammation, could lead to adrenal suppression, particularly if dexamethasone was administered in combination with antiviral drugs that are metabolized via cytochrome CYP3A, such as remdesivir[7]. We therefore recommend long-term metabolic monitoring of all patients with COVID-19 who are treated with dexamethasone.

Ensuring access to medical care

In the first wave of the pandemic, the *New England Journal of Medicine* published a prophetic editorial describing the "untold toll of the pandemic on patients without COVID-19"[8]. This scenario has become the bitter truth. According to the World Health Organization, 155 countries partially or completely ceased their clinical programmes for the treatment of patients with metabolic diseases and related complications. A global survey of 47 countries has reported that diabetes is one of the conditions experiencing a significant decrease in access to care during the COVID-19 pandemic[9].

The prolonged lockdown, with cessation or drastic decreases in the care provided for non-coronavirus-related medical problems, has caused substantial collateral damage in

patients with metabolic disease. A recent study has reported that deaths in England in the first 19 weeks of 2020 exceeded those in the corresponding previous 3-year weekly averages by 50.5% for people with type 1 diabetes and 64.3% for people with type 2 diabetes[1]. Evidence from other nationwide disasters indicates that such disruptions can worsen diabetes outcomes during and after these events[10]. Thus, we must prepare for the long-term consequences of suboptimal diabetes control, such as cardiovascular and microvascular complications, if we cannot provide adequate patient care.

People with diabetes or obesity are at high risk of developing severe or even lethal COVID-19 (refs. [10,11]). A clear correlation exists between hyperglycaemia and uncontrolled diabetes with cardiovascular complications and serious illness in people with SARS-CoV-2 infection. Furthermore, viral infection and inflammation exacerbate hyperglycaemia and complicate diabetes management[8,9,12–14]. Because of delayed or otherwise limited access to hospital care, patients, as well as the healthcare professionals or relatives caring for them, must be aware of the elevated risk of diabetic ketoacidosis or hyperosmolar coma, which can occur at home. This critical situation is relevant not only for people with diabetes but also for all individuals contracting a chronic disease who are affected by the pandemic, such as those with cancer or with psychiatric diseases and depression, who carry an additional burden in the pandemic.

Two additional ways in which the pandemic negatively affects people with diabetes are decreased access to primary-care providers and the presence and spread of false or misleading information. First, some people will not visit physicians for fear of contracting COVID-19. If they do seek help, the availability of both primary-care providers and specialist hospital physicians may be greatly curtailed because of increased COVID-19 related workloads and infection-control procedures, which have decreased the level of personal contact in healthcare settings. Second, dubious, incomplete or false information spreads easily during the current pandemic. We have witnessed patients arbitrarily change their drug treatments because of unfounded concerns about interactions with COVID-19. The medical community must tackle such misinformation and reassure patients, but providing patients with thorough evidence-based information is time consuming and typically lags behind the spread of misinformation.

Lessons can be learned from a comparison of how various healthcare systems worldwide have responded to the pandemic. The most striking difference in the international response was in speed and decisiveness, ranging from fast and well controlled (as in Singapore, Switzerland, the Netherlands and the first wave in Germany) to slow and protracted (as in the United States and Brazil). Citizens in Hong Kong or Singapore benefited from governments proactively confronting the pandemic by applying a 'prioritization matrix' for directing care for patients with diabetes, according to which patients in high-risk groups were closely monitored through telemedicine approaches[14]. Similarly, whereas some countries have pushed the implementation of innovative digital-care support (such as Singapore, France, the United Arab Emirates, South Korea, India, Germany and Switzerland), including 24-hour telephone support, digital consultations and patient education programs—others (such as the United Kingdom and United States) have hesitated in applying telemedicine approaches for patients with diabetes.

How people cope with the pandemic depends on the amount of incomplete or false information that is spread or insufficiently scrutinized. People in countries with comprehensive control over the flow of information (such as China) or with a high sense of community (such as Singapore, Hong Kong, South Korea and Japan) have been less vulnerable to misleading information and more inclined to follow guidelines on the use of face masks and social distancing than countries where the uncontrolled spread of false information has resulted in wider societal reluctance to participate in basic public-health measures for pandemic control (such as the United States or Germany during its second wave).

In many African countries and low-income countries, the lockdown has increased health inequalities. Lockdowns have caused economic hardships in regions where most of the population depends on day-to-day work for survival, thus leaving people unable to pay for their medications[15]. As a result, people with diabetes have needed to ration insulin, decrease self-monitoring of blood glucose levels or delay taking oral antidiabetes medications. The consequence of these tragic circumstances will be an increase in severe cases of diabetic foot ulcers, diabetic ketoacidosis and hyperosmolar, nonketotic coma.

Acute care of patients with diabetes-related foot disease

Acute diabetic foot syndrome is an acute medical emergency requiring a timely multimodal treatment regimen including antibiotics, immobilization, interventional radiology, reconstructive orthopaedic surgery and rehabilitation in a qualified wound-healing and foot centre to prevent amputation, sepsis or even death. If not recognized properly, diabetic foot ulcers are associated with higher premature mortality rates than coronary artery disease, peripheral artery disease or even stroke. The COVID-19 pandemic has had drastic effects on patients with diabetic foot syndrome. Diabetes-related major amputations have increased by 300% over prepandemic levels in the United States and other Western countries[16]. Major limb loss substantially affects quality of life, results in excessive costs to the health system and is associated with a 70% 5-year relative mortality rate. Given the extent of these effects and the incidence of severe diabetic foot events, this problem has been described as "a pandemic within the pandemic"[17].

Many hospital triage systems favour the admission of patients with SARS-CoV-2 infection over severely ill patients with diabetes-related foot disease. Although patients with mild or absent symptoms of SARS-CoV-2 infection are kept in hospital care because of dementia or other reasons that prevent them from being discharged to quarantine at home or in nursing homes, we have observed delayed admission and management of patients with foot disease who need immediate and complex care in most diabetes centres worldwide.

We believe that the wider medical community is not sufficiently aware of the potentially life-threatening and debilitating course of disease in people with diabetic foot disease, who are often socially disadvantaged and have a higher likelihood of unemployment, alcohol misuse and poor living conditions. In this pandemic, the lack of adequate medical insurance coverage[18] and of patient-advocacy groups for this vulnerable demographic has been disastrous. We must confront governments and health authorities to ensure appropriate care for these patients.

Care of patients with obesity

Lockdowns, either partial or total, and extensive working from home have isolated many people with severe obesity, a condition often accompanied by depression. Depression and a lack of physical exercise lead to further weight gain and worsening of associated cardiovascular and metabolic comorbidities[18].

For patients with diabetes, obesity and associated cardiovascular risk factors, the closure and slow reuptake of bariatric (metabolic) surgery poses an inappropriate and unacceptable risk that must be resolved.

In most countries, nonurgent elective surgery procedures have been suspended to preserve hospital resources for COVID-19 treatment. As a result, the waiting lists for bariatric surgery are rapidly increasing. Although guidelines for bariatric/metabolic surgery during and beyond the COVID-19 pandemic have been issued that recommend surgery within 90 days for the most urgent cases, hospital resources are so stretched that delays of more than 90 days have become the norm in most healthcare settings. Waiting times for bariatric surgery, on the basis of existing waiting lists, are predicted to increase four to six times in many bariatric centres worldwide.

Awareness of this problem is urgently needed among the entire medical community and all stakeholders involved in resolving the ongoing crisis. We must ensure that providing adequate care for patients with severe COVID-19 does not compromise the provision of hospital care for patients with metabolic emergencies. This predicament can be overcome only if we continue to involve all partners in our healthcare systems, nursing homes, care services and social organizations, as well as families and the rest of society. Commitment and solidarity are needed from all of us[19].

Enabling early vaccination

Now that the first COVID-19 vaccines are being rolled out globally, we must advocate for the inclusion of patients with metabolic disease in early phases of vaccination programs. Even if patients with diabetes are given priority for vaccination, owing to their elevated mortality risk, logistic challenges may occur[20]. In previous years, the uptake of recommended vaccinations against influenza, pneumococcal and hepatitis B virus by people with diabetes has been comparatively low. People with diabetes with high rates of chronic disease complications, who are also at the highest risk of infections including tuberculosis and influenza, have shown the lowest uptake with consultation, as well as the poorest vaccination performance. Therefore, we must immediately consider pre-emptive, comprehensive community interventions to raise awareness of and adherence to COVID-19 vaccination programmes[20], with information campaigns specifically tailored to the needs of patient subgroups.

The current global immunization plans are hampered by the overall scarcity of vaccination doses, which has become the largest obstacle to success, instead of the selection of wrong priorities. Primarily high-income countries have saved large numbers of vaccination doses for their own citizens and will experience no delays or only slight delays in their vaccination plans. As a consequence, many low-income countries will unfortunately have a prolonged shortage of vaccine doses.

How to avoid collateral damage after the pandemic

In the coming months, we will experience further increases in the incidence of diabetes mellitus and in late or urgent complications of diabetes, owing to the disruptive changes in the delivery of care. Reductions in nursing and physician staff in diabetes and endocrinology wards in recent years, as a result of the reimbursement structure in Western health care systems, have been an additional predicament in the pandemic crisis. Because diabetologists are fully trained internists in most countries, they have been drafted to treat patients with COVID-19, thus diverting even more resources away from patients with metabolic disease. Countries with developed healthcare systems, high intensive-care capacities and effective digital patient management have performed better than those without these resources. Thus, we must avoid cutting healthcare resources after the end of this pandemic, because doing so would hinder the ability to address future emergencies, such as the next pandemic. We must reallocate hospital resources to the points of need. Financially restrained hospitals may otherwise be tempted to take advantage of the temporary closure of wards to further cut services in metabolic medicine, because they generate less revenue than those offering highly interventional procedures.

On a more positive note, the differences in the global response to the COVID-19 pandemic have taught us to revisit more effective ways of healthcare delivery by focusing on empowerment and regular monitoring to protect vulnerable individuals during emergencies. Unfortunately, this lesson has been learned from many unnecessary deaths of people with diabetes and without COVID-19.

Coping with the pandemic crisis poses a unique challenge for society and our health systems, which transcends the current acute emergency situation and will have consequences for future care management, particularly regarding care for patients with diabetes. Given the expectation that the current situation may last for months, or even several years, we must take action so that we remain able to provide evidence-based care for patients with chronic metabolic diseases. ❐

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