**Consequences of the COVID-19 pandemic on patients with metabolic diseases**

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**Stretching health care resources, the COVID-19 pandemic has serious 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 voice to ensure adequate care and admission of our patients.**

Patients with metabolic diseases are facing increased challenges in the COVID-19 pandemic. These challenges are a consequence of the prolonged lockdown, exhaustion of our health care systems, the viral disease itself and the impact of medications introduced for the treatment of COVID-19 infection. COVID-19 and metabolic disease currently cause substantial collateral damage for our patients and new challenges for the entire metabolic health community that need to be addressed. We, as a global team of experts representing six continents, are united in our views that we need to raise our voice given the catastrophic situation we are currently facing when caring for our patients. Reduced access to primary care providers and a high demand for care of critically ill COVID-19 patients absorb hospital staff and resources, which, in turn, are lacking in other areas of care. This situation presents a substantial risk for all patients with chronic diseases, and especially for 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

The implementation of dexamethasone therapy as a new standard for patients with symptomatic COVID-19 disease and the need for supplemental oxygen treatment adds new challenges to the management of hospitalized patients with metabolic disease and COVID-19 1. Currently dexamethasone remains one of the few drugs, if not the only, clearly decreasing mortality of the COVID-10 patients in critical condition. However high-dose glucocorticoid therapy, especially in a state of sepsis and inflammation, will induce and aggravate hyperglycemia and metabolic acidosis 2. Glucocorticoids are the most common reason why individuals with COVID-19 and diabetes develop life-threatening hyperglycaemic hyperosmolar states. Physicians treating patients with COVID-19 need to be trained how to control these metabolic derangements, which typically involves early intravenous insulin therapy. However, increased mortality of patients with COVID-19 who received insulin treatment has recently been reported 3. This finding highlights the need for frequent blood glucose testing, ideally with continuous glucose monitors, to detect and avoid life-threatening hypoglycaemic or hyperglycemic 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 effects, it nevertheless induces hypertension. Since dexamethasone promotes actively aquaporin-2 the vasopressin regulated water channel that controls renal fluid reabsorption it will cause 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 further complicates the respiratory status of the patients. Indeed, hepatic ACE2 expression is increased in patients with NAFLD and diabetes 4. Therefore, both acute and chronic effects of this treatment on metabolic complications will have to be considered.

Furthermore, dexamethasone might induce apoptosis in pancreatic beta cells. As pancreatic islets might be affected by SARS-CoV-2, a combined effect of the infection as well as 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, especially 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 COVID-19 patients 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 about the “untold toll of the pandemic on patients without COVID-19” 8. This scenario has become the bitter truth. According to the WHO, 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 was one of the conditions experiencing a significant reduction in the access to care during the COVID-19 pandemic 9.

The prolonged lockdown with cessation or drastic reduction of care provided for non-coronavirus related medical problems cause significant collateral damage on patients with metabolic disease. A recent reported that deaths in England in the first 19 weeks of 2020 exceeded the corresponding previous 3-year weekly averages by 50.5% in individuals with type 1 diabetes and 64.3% in those with type 2 diabetes 1. Evidence from other nation-wide disasters shows that such disruptions can worsen diabetes outcomes during and after these events 10. Thus, we will need to prepare for the long-term consequences of suboptimal diabetes control, such as cardiovascular and microvascular complications, if we cannot provide adequate care for our patients.

Patients with diabetes or obesity are at high risk for developing severe or even lethal COVID-19 disease 10,11. A clear correlation exists between hyperglycaemia and uncontrolled diabetes with cardiovascular complications and serious illness in patients with SARS-CoV2 infection. Furthermore, viral infection and inflammation will exacerbate hyperglycaemia and complicate diabetes management 8,9,12,13. Patients, as well as health care professionals or relatives caring for them, need to be aware of the elevated risk of diabetic ketoacidosis or hyperosmolar coma, which can occur at home due to delayed or otherwise limited access to hospital care. This critical situation is not only relevant for diabetes patients – it matters for all individuals contracting a chronic disease, who are affected by the pandemic, such as oncological patients but also patients with psychiatric diseases and depression carrying an additional burden affected by the pandemic.

Two additional ways in which the pandemic negatively affects patients with diabetes are the reduced access to primary care providers and the presence and spread of false or misleading information. Firstly, some patients will not to visit a physician due to fear of contracting COVID-19. If they do seek help, the availability of both primary care providers and specialist hospital physicians may be significantly curtailed as a result of increased COVID-19 related workload and infection control procedures, which have reduced personal contact in healthcare settings. Secondly, dubious, incomplete or false information spreads easily during the current pandemic. We have witnessed patients that arbitrarily changed their drug treatment due to unfounded concerns about interactions with COVID-19. The medical community needs to tackle such misinformation and reassure our patients, but providing thorough evidence-based information is time consuming and typically lags behind misinformation.

Lessons can be learned from a comparison of how various health care system around the world responded to the pandemic. The most striking difference in the international response was in its speed and decisiveness, ranging from fast and well controlled (as in Singapore, Switzerland, the Netherlands and during the first wave in Germany,) to slow and protracted (eg, USA or Brazil). Citizens in Hong Kong or Singapore benefited from governments confronting this pandemic pro-actively by applying a “Prioritization Matrix” for directing care for patients with diabetes, according to which patients in high risk groups were closely monitored using telemedicine approaches. Similarly, whereas some countries have pushed the implementation of innovative digital care support (Singapore, France, United Arab Emirates, South Korea, India, Germany, Switzerland) - including 24 h telephone support, digital consultations and patient education programs – others (such as the UK or USA) have hesitated applying telemedicine approaches to patients with diabetes.

How people coped with the pandemic depended on the amount of incomplete or false information that was spread or not sufficiently scrutinized. People in countries with comprehensive control over the flow of information (such as China), or with a high sense of community (Singapore, Hong Kong, South Korea, Japan) were less vulnerable to misleading information and more inclined to follow guidelines on the wearing of face masks and social distancing than countries, were the uncontrolled spread of false information resulted in a wider reluctance within society to participate in basic public health measures for pandemic control (USA or Germany during its second wave).

In many African and low income countries, the lockdown has increased health inequalities. Lockdown have caused economic hardship in regions where most of the population depend on day-to-day work for survival, leaving patients unable to pay for their medication 15. As a result, diabetes patients have had to ration insulin, reduced self-monitoring of blood glucose levels or delayed oral anti-diabetes medication. The consequence of these tragic circumstances will be an increase of severe cases of diabetic foot ulcers, diabetic ketoacidosis and hyperosmolar, non-ketotic 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 orthopedic 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 carry a higher premature mortality than coronary artery disease, peripheral artery disease or even stroke. The COVID-19 pandemic has had a drastic impact on patients with diabetic foot syndrome. Diabetes related major amputations have increased dramatically by 300 % as compared to the pre-pandemic period in the US and other Western Countries 16. It is known that 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. The extent of this impact and the extent to which severe diabetic foot events are occurring has led to this problem being described as ´a pandemic within the pandemic´ 17.

Many hospital triage systems favor the admission of patients with COVID-19 infection over severely ill patients with diabetes-related foot disease. While patients with mild or without 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 care homes, we have observed delayed admission and management of patients with foot disease who need immediate and complex care in most diabetes centres around the world.

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

Care of patients with obesity

Lockdowns, either partial or total, and the extensive use of working from home have isolated many individuals with severe obesity, a condition often accompanied by depression. Depression, and the lack of physical exercise, will 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 re-uptake of bariatric (metabolic) surgery poses an inappropriate and unacceptable risk that needs to be resolved. In most countries, non-urgent elective surgery procedures have been suspended in order to preserve hospital resources for COVID-19. As a result, the waiting lists for bariatric surgery are increasing exponentially. Although guidelines for bariatric/metabolic surgery during and beyond COVID-19 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 health care settings. Waiting times for bariatric surgery are predicted based on existing waiting lists to increase 4 to 6 times in many of the bariatric centers around the world.

It is a matter of urgency that we raise awareness of this problem to the entire medical community and all the other stakeholders who are involved in resolving the ongoing crisis. We have to ensure that our providing adequate care for patients with severe COVID-19 does not compromise provision of hospital care for patients with metabolic emergencies. This predicament can only be overcome if we continue to involve all partners in our health care systems, retirement homes, care services and social organizations as well as families and the rest of society. It requires commitment and solidarity from all of us 19.

Enabling early vaccination

Now that the first vaccines against SARS-CoV-2 are being rolled out globally, we need to advocate for the inclusion of patients with metabolic disease in early phases of vaccination programs. But even if patients with diabetes are given priority for COVID-19 vaccines due to their elevated mortality risk, there may be logistic challenges 20. In previous years, uptake of recommended vaccinations against influenza, pneumococcal and hepatitis B virus by patients with diabetes has been comparatively low . Patients with diabetes with a high rate of chronic disease complications, who are also at highest risk for infections including tuberculosis, influenza and other infections, have shown the lowest uptake with consultation and poorest vaccination performance. Therefore, we need to consider now pre-emptive, comprehensive community interventions to raise awareness and adherence to COVID-19 vaccination programmes, 20 with information campaigns being specifically tailored to the needs of patient subgroups.

The current global immunization plans are hampered by the overall scarcity of vaccination dosages, which has become the biggest obstacle for success, instead of selecting wrong priorities. Primarily high-income countries have saved large numbers of vaccination doses for their own citizens and will not experience any or only a slight delay in their vaccination plans. As a consequence, mainy low-income countries will unfortunately suffer from a prolonged shortage of vaccine doses.

How to avoid collateral damage after the pandemic

In the coming months, we will experience a further increase in incidence of diabetes mellitus and a gain in late or urgent complications of diabetes due to the disruptive change in the delivery of care. Reductions in nursing and physician staff in diabetes and endocrinology wards in recent years due to the reimbursement structure in western health care systems were an additional predicament in the pandemic crisis. As diabetologists are fully trained internists in most countries they have been drafted to work with COVID-19 patients, deviating even more resources away from our patients with metabolic disease. Countries with developed health care systems, high intensive care capacities and effective digital patient management performed better than those who did not. Thus, we must avoid that health care resources will be cut down after the end of this pandemic as this would hamper our ability to deal with future emergencies, such as the next pandemic. We have to reallocate hospital resources to the point of need. Financial restraint hospitals may otherwise be tempted to take advantage of the temporary closure of our wards to cut down services in metabolic medicine further 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 the way how care can be delivered more effectively by focusing on empowerment and regular monitoring in order to protect vulnerable individuals during time of emergencies. Unfortunately, this lesson is learned by counting many unnecessary deaths of patients with diabetes but without COVID-19.

Coping with the pandemic crisis represents a unique challenge for societyand our health systems, which go beyond the current acute emergency situation but will have consequences for future care management, especially in regards to caring for our diabetes patients. Expecting that the current situation may last for months, or even several years, there is a strong need to take action so we remain able to provide evidence based care for patients with chronic metabolic diseases.

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**Conflict of Interest:**

Authors do not have any conflict of interest regarding the content of this comment.

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