Optimizing diabetes mellitus care to improve COVID-19 outcomes in resource-limited settings in Africa

Andrew Peter Kyazze, Felix Bongomin, Sandra Ninsiima, Gloria Nattabi, Winnie Nabakka, Rebecca Kukunda, Henry Odanga, Phillip Ssekamatte, Joseph Baruch Baluku, Davis Kibirige and Irene Andia-Biraro

***Abstract*:** Diabetes mellitus (DM) is an important risk factor for both severe disease and death due to coronavirus-2019 (COVID-19). About 19 million of the 463 million persons living with DM (PLWD) globally are found in sub-Saharan Africa (SSA). The dual burden of DM and poverty in SSA, coupled with the rising number of cases of COVID-19 in this region, predisposes PLWD to inadequate care and poor glycemic controls due to the disruption to the economy and the healthcare system. The risk of acquisition of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) among PLWD is the same as those in the general population. Therefore, the standard preventive measures outlined by the World Health Organization must be strictly adhered to. In addition, maintaining adequate glycemic control is associated with better outcomes in DM patients with COVID-19. In SSA, adequate supply of DM medication while patients stay at home is crucial to minimize routine hospital visits since DM clinics are usually overcrowded and have longer waiting times, which may maximize risk of SARS-CoV-2 transmission to PLWD across the region. Psychosocial support to improve adherence to anti-hyperglycemic medications may improve COVID-19 outcomes. Trained healthcare professionals should diagnose and evaluate severity comprehensively as well as evaluate the need for in-patient care for PLWD with COVID-19 irrespective of disease severity. Due to the increased risk of severe disease, a multi-disciplinary approach to the management of COVID-19 in PLWD should preferably be in a setting where close monitoring is available, typically a health facility, even for mild disease that may require home management according to local guidelines. In conclusion, DM complicates COVID-19 outcomes and the on-going COVID-19 pandemic adversely affects DM care at individual and global public health levels. PLWD should be prioritized as COVID-19 vaccines are being rolled out.

Keywords: Africa, coronavirus disease-2019, COVID-19, diabetes mellitus

Received: 29 December 2020; revised manuscript accepted: 23 March 2021.

Ther Adv Infectious Dis

2021, Vol. 8: 1–11

DOI: 10.1177/20499361211009380

Correspondence to:
Andrew Peter Kyazze
Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda
kyazzeandrew@gmail.com

Felix Bongomin
Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

Department of Medical Microbiology & Immunology, Faculty of Medicine, Gulu University, Gulu, Uganda

Sandra Ninsiima
Gloria Nattabi
Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

Winnie Nabakka
Rebecca Kukunda
Henry Odanga
Department of Medicine, Uganda Martyrs Hospital Lubaga, Kampala, Uganda

Phillip Ssekamatte
Department of Immunology and Molecular Biology, School of Biomedical Sciences, Makerere University College of Health Sciences, Kampala, Uganda

Joseph Baruch Baluku
Division of pulmonology, Mulago National Referral Hospital, Kampala, Uganda

Directorate of Programs, Mildmay Uganda

Davis Kibirige
Department of Medicine, Uganda Martyrs Hospital Lubaga, Kampala, Uganda

Medical Research Council/Uganda Virus Research Institute and the London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda

Introduction

On 17 November 2019, the Chinese city of Wuhan reported the first case of a pneumonia-like illness that was later named coronavirus disease 2019 (COVID-19).[1,2] Since the announcement of the index case, the virus has spread rapidly, initially in the Hubei province of China and then to other countries all over the world. On 11 March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic.[3] By 12 March 2021, over 128,000,000 people have suffered from COVID-19, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) and 2,615,000 people have unfortunately succumbed to it.[4]

SARS-CoV-2, the etiologic agent of COVID-19, is highly transmissible through person-to-person

Irene Andia-Biraro
Department of Medicine, School of Medicine, Makerere University College of Health Sciences, Kampala, Uganda

Medical Research Council/Uganda Virus Research Institute and the London School of Hygiene and Tropical Medicine Uganda Research Unit, Entebbe, Uganda

Department of Clinical Research, Faculty of Infectious and Tropical Disease (ITD), London School of Hygiene and Tropical Medicine, London, UK

spread *via* respiratory droplets and aerosols.[5,6] The spectrum of clinical presentation of COVID-19 varies widely, from asymptomatic or mild upper respiratory tract infection in the majority of the cases to moderate and severe viral pneumonia resulting in severe respiratory distress syndrome (SARS) and death in about 5%–10% of all the patients with COVID-19.[1] Severe COVID-19 has been associated with older age, especially those 60 years or older, living in a long-term care facility, and presence of comorbidities, especially hypertension, diabetes mellitus (DM), cardiac disease, chronic obstructive pulmonary disease (COPD), and obesity.[1,3,7–9] Consequently, higher mortality has been recorded amongst individuals with the above risk factors,[1,7–9] despite the inherently low mortality rate of COVID-19.[2] In resource-limited settings that are already overburdened with other chronic communicable diseases, human immunodeficiency virus (HIV) infection and tuberculosis (TB) were found to be risk factors for poor outcomes, especially death.[10] In this article, we review the current state of the COVID-19 pandemic in Africa and its impact on DM care, and we suggest strategies to minimize potential COVID-19-related complications to the growing number of persons living with DM (PLWD) in Africa.

Methods

An iterative search for articles was made on Medline through PubMed and Google scholar databases using the key words "Diabetes Mellitus" OR "DM" OR "Hyperglycemia: AND "COVID-19", OR "SARS-Cov-2" OR "Coronavirus disease-2019" AND "Africa". Articles that detailed strategies for prevention of COVID-19 or treatment of COVID-19 in PLWD, with a particular focus in resource limited settings or Africa were reviewed. References of the selected articles were also reviewed. Data on COVID-19 and DM were retrieved from Woldometer and the WHO website.[4,11]

The COVID-19 pandemic in Africa

A high number of COVID-19 cases and mortality has been reported in high income countries such as the United States (US), United Kingdom (UK), Italy, and other European countries.[12] Contrary to an earlier prediction by the WHO and health observers that the pandemic would adversely affect resource-limited settings, for reasons that remain unclear to date, there have been lower numbers of reported cases and deaths resulting from COVID-19 in these settings, despite the limited healthcare resources.[13] Possible postulations to explain this paradox are a comparatively younger population, previous exposure to coronaviruses, and previous infections that could prime the immune system to fight SARS-CoV-2.[14] However, in the past few months, there has been an exponential increase in the number of COVID-19 cases across African countries, in part attributed to increased testing capacity and easing of initial stringent preventative measures like lockdowns.[4]

Africa's first COVID-19 case was reported in Egypt on Valentine's Day of 2020. Since then, as of 9 March 2021, Africa has recorded a total of over 4 million cases and 106,000 deaths.[4] Compare this to the US, which has recorded 29,746,271 cases with 538,708 deaths.[4] In a further comparison, the UK has 4.2 million cases and 125,000 deaths while similar figures are seen in Italy.[4]

DM and DM care in Africa

There are about 463 million PLWD globally.[15] Of these, 19 million are found in sub-Saharan Africa (SSA).[15] It is predicted that SSA will see a 143% increase in number of PLWD by the year 2045 – the highest projected rise in the world.[15] More than half of adults living with DM are undiagnosed in Africa and the majority of deaths due to DM occur in those aged less than 60 years.[15] The quality of DM care in SSA has been described as poor, and this has been attributed to the weak framework for management of chronic illnesses and segmented health systems.[16,17] Few PLWD in Africa have access to diagnostic and blood glucose monitoring equipment.[18] Essential DM medicines like insulin and oral anti-hyperglycemic agents are in limited supply.[18] Moreover, the majority of healthcare workers providing DM care on the continent do not have specialized training to offer comprehensive DM care.[18]

In studies performed across Africa, it has been shown that routine DM care is expensive. For example, routine DM care in Mali costs about 21.2 US dollars[19] while in Nigeria, 73 US dollars is the direct monthly cost of DM care for children

and adolescents with DM.[20] A monthly dose of metformin costs a wage equivalent of about 3 day's work in Kenya while in Ghana, it costs 6 day's wages.[16] This economic burden among largely disadvantaged communities in Africa impairs optimal glycemic control, resulting into short- and long-term complications, including severe COVID-19.

DM and other previous viral outbreaks

DM has been widely documented as a leading risk factor for various past viral diseases outbreaks – a risk that is attributed to the reduced immunity amongst DM patients.[21–23] DM was an associated risk factor in the 2012 Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) outbreak, with an estimated mortality rate of about 35%.[24] During the 2009 H1N1 influenza virus outbreak, DM increased the risk of intensive care unit (ICU) admission by fourfold.[25] DM was also an independent risk factor for severe complications and mortality from the SARS-CoV-1 outbreak in 2002.[26]

DM and COVID-19

DM is an important co-morbidity and a risk factor for severe disease and poor outcomes among patients with COVID-19 across all income settings.[27]

In studies performed in China, the prevalence of DM amongst COVID-19 patients presenting with severe disease (dyspnea, respiratory rate ≥ 30 breaths per minute, blood oxygen saturation $\leq 93\%$, PaO2:FiO2 < 300, and/or pulmonary infiltrates on $> 50\%$ of lung fields on radiological imaging) ranged from 7% to 22%.[2,28] In the same setting, the odds ratio for death from COVID-19 was nearly three times higher among PLWD than in the general population,[1] with a threefold increase in mortality.[26] In Italy – a country that had a higher fatality rate compared with China – approximately 35.5% of patients who died from COVID-19 had DM.[29] A nationwide study in China revealed that DM was an independent risk factor for ICU admission and invasive mechanical ventilation after adjusting for other important confounding risk factors like age, smoking, and other comorbidities.[30] Nearly 32% of COVID-19 associated deaths in a UK survey had type 2 DM and had an odds ratio for dying from the disease of about two times higher than people without DM.[31]

The strong association between DM and COVID-19 has been observed even in resource-limited settings. In September 2020, the Ugandan Ministry of Health announced that 80% of the country's then 75 deaths had underlying DM.[32] This statistic can, however, be attributed to the relatively low number of cumulative COVID-19 cases and deaths by September 2020 in Uganda. About 18% (1 in 5) of COVID-19 deaths on the African continent has been linked to DM according to the WHO, and the risk of death increases for those above 60 years of age.[18]

The mechanisms underlying the increased risk of COVID-19 severity among patients with pre-existing DM remains unknown. However, it is postulated to be due to a higher affinity of cellular binding; efficient viral entry; reduced viral clearance; increased susceptibility to hyperinflammation; cytokine storm; and defective T-cell function characterized by defective phagocytosis by neutrophils, macrophages, and monocytes; decreased neutrophil chemotaxis as well as dampened innate cell-mediated and adaptive immune responses.[23,33,34] These changes are attributable to chronic hyperglycemia due to poorly managed DM. The unanswered question is, what strategies do/should we have in place to minimize SARS-CoV-2 infection and complications of COVID-19 disease among PLWD in resource-limited settings in Africa?

Strategies to optimize DM care and improve COVID-19 outcomes in resource-limited settings

Optimizing glycemic control and use of measures to prevent the spread of the SARS-Cov-2 virus is critical for DM patients in resource-limited settings. The following plausible measures could be applied to PLWD in resource-limited settings, especially Africa based on widely agreed to solutions from high income settings.

Prevention of spread of the SARS-CoV-2 virus

Recent evidence suggests that PLWD are not at increased risk of acquisition of the virus even though they stand a higher risk of progressing to severe disease and death once infected.[35] There is minimal evidence that recommends any special measures to protect PLWD from getting infected with SARS-CoV-2.[36] Methods for the prevention

Table 1. Key recommendations for prevention of the spread of SARS-Cov-2 amongst PLWD.

Physical distancing
Wearing of a face mask
Regular hand washing with soap or alcohol-based sanitizer
Regulated education about COVID-19 prevention
Prioritizing vaccination of PLWD when vaccines become available
Use of home visits, home drug delivery and telemedicine to follow up PLWD

COVID-19, coronavirus-2019; PLWD, persons living with diabetes mellitus; SARS-Cov-2, severe acute respiratory syndrome coronavirus-2.

of SARS-CoV-2 spread in the general population are thus equally effective in the DM population. A summary of key recommendations for prevention of the spread of SARS-Cov-2 amongst PLWD is listed in Table 1. These preventive measures, however, need to be instituted at both individual and healthcare system level.[28]

The WHO recommends methods for prevention of SARS-CoV-2 virus spread like physical distancing, staying at home or avoiding crowded places, wearing of a face mask, and regular hand washing with soap or alcohol-based sanitizers, and the same should be practiced by PLWD.[11] However for PLWD, social distancing measures limit access to health services, insulin, and blood pressure monitoring equipment, as well as affecting the psychosocial well-being of the patients.[28] Many people in resource-limited settings earn by the day through daily casual work in crowded places and, as such, cannot afford to stay at home or even practice physical distancing. One simulation estimates that lockdowns have caused an additional 9% of the population in SSA to fall into extreme poverty and 30% have lost their savings.[37] Therefore, social protection measures are needed for PLWD, considering that they already face catastrophic costs related to the management of DM and its complications.[38] The wearing of masks is stifled by the prices of masks and limited knowledge of use of the same. Modelling studies show that, in resource-limited settings, targeted distribution of masks to high risk groups such as the elderly is the optimal way to reduce infections and mortality.[39] It follows that PLWD, a high-risk group for severe disease, need to be prioritized in mass mask distribution campaigns.

Hand hygiene by the more mobile hand sanitizer is expensive to sustain and, unfortunately, in resource-limited settings, there is also limited availability of water and soap for hand washing.[40] The use of the latter is a cheaper option, however, and prioritization of improving access to water and soap should be integrated into COVID-19 programs in resource-limited settings.[40] The sensitization of the above WHO recommended measures should continue, especially amongst PLWD in resource-limited settings despite the above-mentioned challenges.

DM management requires lifestyle modifications like exercising regularly and maintaining a healthy diet. In addition, patients need to have good adherence to medication, which usually requires hospital visits to refill medication and monitor for complications. These are all difficult to achieve with encouragement of measures like isolation, physical distancing, and even nationwide lockdowns.[41] A US survey amongst PLWD found that about a third of participants reported a less healthy diet and up to half were not exercising as before the COVID-19 pandemic.[42]

Healthy diets are hard to maintain since access to healthy foods is restricted.[28] Other safe measures, such as deliveries, for accessing this food leads to extra charges being incurred that may end up being unaffordable and not feasible for an ordinary DM patient in a resource-limited setting. Access to healthy foods for PLWD should be prioritized through the help of community-based healthcare teams and patient clubs, which can be empowered to provide food deliveries at a cheaper or no cost.

PLWD should also be taught adaptive measures such as calorie calculation and, where possible, have addition of insulin to their regimens with education on dose adjustment based on calorie intake even for patients with type 2 DM.[28] If getting out of one's homestead is prohibited, home-based exercises such as sit ups, push-ups, elastic bands, walking around one's homestead, jumping, and hopping can be done for cardiovascular and muscle fitness.[43] These will minimize virus spread without compromising glycemic control.[28]

Adequate supply of medication while patients stay at home is crucial to minimize routine hospital visits since DM clinics are often crowded and pose a risk of being COVID-19 hotspots. The supply of medicine during the pandemic is best effected through telemedicine but, given the low usage of this in resource-limited settings, another option is to have caregivers or members of patient support groups who are at a lower risk picking up medicines for the PLWD.[28] This, however, poses a risk of secondary virus transmission through the caregivers. Periods for drug refills should, as a matter of policy, be extended to have drugs refilled for longer periods of time, for example, 3 months or more to further minimize routine hospital visits for those unable to avoid hospital visits for drug refills and ensure an adequate supply of drugs to PLWD. This of course poses a risk of strain on healthcare systems in resource-limited settings since these are already faced with issues of unavailability of anti-hyperglycemic medicines that were present prior to the COVID-19 pandemic. Life-threatening complications of DM should be attended to with immediate attention and PLWD should be educated about the importance of not delaying hospital visits due to vigilance in observing the WHO COVID-19 prevention guidelines.

During this pandemic, follow up of PLWD should not be neglected by health workers, and these should undertake proactive reviews of patients with DM.[36] DM care can also be de-escalated to allied health workers like nurses to add to the human resource for reviewing patients without necessitating hospital visits.[36] Also, resource allocation to DM and other non-communicable disease care should be increased at national levels in this period to overcome the challenges of drug stock outs.[36]

However, the above-mentioned WHO guidelines, in addition to the infodemic spread of information regarding COVID-19, are bound to cause feelings of fear, anxiety, and helplessness amongst PLWD. Stress has a well-known negative physiological effect on the glycemic control of PLWD but feelings of stress and anxiety can also lead to poor adherence to anti-hyperglycemic medication, which can further expose them to poor COVID-19 outcomes once infected.[44,45] These effects can be prevented and overcome through regulating COVID-19-related news on a personal and community level, especially if not from trusted sources like national health ministries or the WHO. Regular contact with family, friends, and patient support group members *via* modern communication technology like telephones and video chatting platforms can be used to overcome the effects of social isolation,[46] although the latter may not be widely applicable in resource-limited settings due to low numbers of smart phone users and internet subscribers. Other social effects like fear of loss of jobs may prevent PLWD from adhering to recommended WHO guidelines such as physical distancing. Employers should arrange "work from home" strategies for their employees with DM to prevent them from undergoing the conundrum of fear of losing their jobs and fear of contracting the virus at the work place at the same time. In a UK survey, two-thirds of employees with diabetes approached revealed not feeling safe while at work during the pandemic, while about 50% reported no efforts by the employer to ensure physical distance in workplaces.[47]

Distribution of culturally adapted educational material about the pandemic to PLWD may be beneficial, especially if done in the patient's most understood languages.[36] The role of educational materials given to people with chronic conditions during periods of national emergencies has been demonstrated to be effective before and could help ease fears and anxiety among PLWD.[36]

There is no definitive treatment for COVID-19. However, with more than 10 promising vaccine candidates, PLWD should be a priority population for vaccination once vaccines are more widely rolled out. In early December 2020, the UK and Canada championed the use of COVID-19 vaccine in the general population outside of clinical trial settings. However, vaccine hesitancy among African population, and the cold chain required for most of the candidate vaccines, may affect uptake and effectiveness in many countries.[48]

The most important measure, however, should be to maintain glycemic control since a good pre-infection glycemic control has been associated with better outcomes.[49] For this reason, regular glucose lowering therapy should continue and should not be compromised on the premise of some anti-hyperglycemic agents such as metformin and sodium glucose co-transporter-2 inhibitors (SGLT-2) being linked to worse outcomes of

Table 2. Key recommendations for prevention of severe COVID-19 disease in PLWD.

Prompt symptom notification to local health workers
Prompt diagnosis and evaluation of severity and need for hospitalization
Close monitoring of PLWD diagnosed with COVID-19
Blood glucose control with anti-hyperglycemic agents
Regulated education about COVID-19 prevention

COVID-19, coronavirus-2019; PLWD, persons living with diabetes mellitus.

COVID-19 as no conclusive research has been done to this effect.[26]

Prevention of severe disease in PLWD infected with SARS-CoV-2

Although studies show that PLWD are at higher risk of severe disease, the majority of these patients develop mild disease that is manageable at home with supportive care.[50] Katulanda and colleagues advise that PLWD should promptly notify their local healthcare providers when they develop symptoms suggestive of SARS-CoV-2 infection.[28] Prompt diagnosis and evaluation of severity as well as need for in-patient services should be done by a trained healthcare worker.[28] Due to the risk of severe disease, management of COVID-19 in PLWD should preferably be in a setting, e.g., a health facility, where close monitoring is available even for mild disease that may require home management according to local guidelines. To ensure the feasibility of the above measures, health ministries need to build a strong, community-based partnership.[36] An example is through the deployment of community-based village-level health workers who are trained to identify and link suspected patients to proper diagnostic and treatment centers. Points of contact in case of worsening of symptoms or development of emergencies should be clearly defined and communicated to PLWD to reduce lost time when seeking healthcare.[36]

As a general rule, good blood glucose control should be ensured while managing DM patients with COVID-19.[51] For those preferentially managed at home, regular monitoring through telephone calls and home visits with appropriate personal protective equipment (PPE) are central to be able to detect any complications early on, especially deranged glycemic levels, deterioration of clinical status, and development of acute complications like diabetic ketoacidosis (DKA). Since blood glucose control is vital, anti-hyperglycemic therapy should be instituted or continued for all cases in addition to regular monitoring of glucose and healthy diets.[28] Supportive measures like anti-pyretics, adequate hydration and steam inhalation as a form of treatment should be initiated as early as possible in the course of the illness.[28,52] Table 2 shows a summary of key recommendations for prevention of severe COVID-19 disease in PLWD.

Therapeutic management of PLWD with SARS-CoV-2

All oral anti-hyperglycemic drugs should be continued in mild and moderate COVID-19 if the patient is drinking and eating appropriately, but should be discontinued in severe disease or ICU admission due to the increased risk of other complications like lactic acidosis and worsening renal dysfunction by metformin and risk of hypoglycemia in sulfonylureas use.[26,51,53] SGLT-2 inhibitors, although rarely prescribed in resource-limited settings, pose a high risk of euglycemic DKA and hypovolemia in moderate, severe, and critical cases and, as such, should be avoided.[26,51] Other oral anti-hyperglycemics, such as dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists, that are rarely prescribed in resource-limited settings can all be used with similar restraints in those with severe/critical disease.[26] Insulin is safe to use at all stages of the disease and has additional anti-inflammatory benefits.[54] Better glycemic control among patients that need insulin is, however, best achieved with infusion in DM patients with COVID-19.[55]

Subcutaneous insulin is also the preferred glycemic control therapy, even for non-critical patients.[56] For inpatients, sliding scale, a method still widely practiced in resource-limited settings, should be avoided due to wider fluctuations of blood glucose resulting in overall poor glycemic control.[57] This is quite a challenge in resource-limited settings since insulin infusion pumps are a rare mode of insulin delivery and, in these settings, rapid-acting boluses of insulin should be used.[58] In resource-limited settings, where there may not be regular glucose monitoring, less strict

glucose targets >10 mmol/l (>180 mg/dl) should be acceptable to prevent the risk of hypoglycemia,[28] but stringent control (140–180 mg/dl) should be maintained for critically ill patients.[59] Above all, doses for insulin should depend on the severity of the COVID-19 disease, risk of hypoglycemia, renal function, nutritional status, concomitant medications, and blood glucose trends.[51,60]

The use of aspirin and angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers in DM patients with COVID-19 should be continued as the benefits of use clearly outweigh any speculative risks of doing so.[61,62] Statin therapy use is still encouraged due to its beneficial immunomodulatory effects and evidence of reduction of disease severity during the 2009 H1N1 virus outbreak and among patients with influenza.[63]

Paracetamol should be used as the preferred analgesic and anti-pyretic therapy as non-steroidal anti-inflammatory drugs are thought to further suppress immunity and hence delay recovery.[50,64]

The use of glucocorticoid steroids such as dexamethasone and prednisone as adjunct treatment for COVID-19 in PLWD should be done cautiously and, where possible, input from a diabetologist/endocrinologist should be sought.[65] Where available and affordable, other safer drugs like tocilizumab with similar anti-inflammatory effects should be used instead of steroids.[65] However, since these drugs are expensive and inaccessible to majority of PLWD in limited-resource settings, medical practitioners are left with glucocorticoid steroids as the only option for countering the inflammatory response of COVID-19.

Glucocorticoid steroids when used in PLWD, whether on inpatient and outpatient basis, increase glucose levels,[66] yet glucose control is a vital aspect of COVID-19 treatment in PLWD.[51] However, the magnitude and duration of the hyperglycaemic response is dependent on the dose and type of glucocorticoid steroid (long acting *versus* short acting/ medium acting).[66,67]

Oral anti-hyperglycaemic drugs have a limited role in the treatment of hyperglycaemia induced by glucocorticoid steroids, especially for PLWD due to reduced safety and efficacy as well as slow onset and, as such, are not advised for treatment of glucocorticoid-induced hyperglycaemia in PLWD.[68] The use of insulin therapy in addition to oral anti-hyperglycaemic drugs (if not contraindicated) remains the recommended mainstay of treatment for PLWD on treatment with glucocorticoid therapy in both inpatient and outpatient settings due to the ease of titrating doses, efficacy, and relative safety in most conditions where glucocorticoid therapy is necessitated.[68] Patient weight and glucocorticoid dose determine the insulin dose to be administered.

For patients on long-acting glucocorticoids such as dexamethasone, a long-acting insulin like glargine should be added to their hypoglycaemic regimen, if not already prescribed, at an initial dose of 0.1 IU/kg/day and then titrated according to the glucocorticoid dose as shown in Table 3 below.[66,68,69] Long-acting insulins are, however, not accessible or affordable in most resource-limited settings[70]; thus, pre-mixed insulin regimens such as mixtard insulin given twice daily can be used as a suitable alternative.[71]

Patients treated with an intermediate acting glucocorticoid such as prednisone should have intermediate insulin (NPH/NPL) added to their regimen if not already on it, with an initial dose of 0.1 IU/kg/day and the doses titrated as shown in Table 3 below.[68] Individual long-acting/intermediate-acting total insulin doses can be increased/decreased by 20% every 48–72 h if blood glucose is more than 140 mg/dl or less than 72 mg/dl before the next insulin dose, respectively, while maintaining the desired aforementioned glucose targets of 140–180 mg/dl.[68]

Table 3. Dose titration of insulin in PLWD on glucocorticoid therapy.[69,72].

Dexamethasone dose (mg/day)	Insulin glargine/ detemir dose (IU/ kg/day)	Prednisone dose (mg/day)	Insulin NPH/NPL dose (IU/kg/day)
⩾8	0.4	⩾40	0.4
6	0.3	30	0.3
4	0.2	20	0.2
2	0.1	10	0.1

IU, international units; NPH, neutral protamine Hagedorn; NPL, neutral protamine lispro; PLWD, persons living with diabetes mellitus.

Table 4. Sick day rules for PLWD diagnosed with COVID-19.

Continue oral anti-hyperglycemic drugs if mild–moderate disease but stop in severe and critical COVID-19 disease
Continue insulin therapy for patients already on it irrespective of disease severity
Use insulin for all patients with severe to critical COVID-19 disease
Continue statins, aspirin and ACEIs/ARBs
Use paracetamol as anti-pyretic and stop NSAIDs
Use insulin in addition to oral anti-hyperglycemic drugs (if not contraindicated) for countering glucocorticoid induced hyperglycemia.

ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin 2 receptor blockers; COVID-19, coronavirus-2019; NSAIDS, nonsteroidal anti-inflammatory drugs; PLWD, persons living with diabetes mellitus.

Patients in outpatient departments must be taught these insulin adjustments to ensure glucose control and avoid hypoglycemia at home. Table 4 summarizes the sick day rules for PLWD with COVID-19 disease.

Conclusions

In conclusion, there is a strong association between DM and COVID-19, with DM increasing risk of severe COVID-19 and death. There are no published special or evidence-based preventative measures for COVID-19 infection amongst PLWD; however, WHO recommendations should work effectively as well in this population. Regular standard of care for PLWD should continue while minimizing person-to-person contact. Oral anti-hyperglycemic agents should be avoided in all severe cases of COVID-19. There is need for more research on chemoprophylactic drugs for COVID-19 in PLWD. Also, PLWD should be prioritized as COVID-19 vaccines are being rolled out.

Authors contributions

Conceptualization: Andrew Peter Kyazze, Irene Andia-Biraro, Felix Bongomin, Sandra Ninsiima.

Retrieval of articles for review: Felix Bongomin, Joseph Baluku Baruch, Andrew Peter Kyazze.

Original draft: Andrew Peter Kyazze, Felix Bongomin, Joseph Baluku Baruch.

Critical revision of original draft and approval of final manuscript: Irene Andia-Biraro, Davis Kibirige, Phillip Ssekamatte, Sandra Ninsiima, Winnie Nabakka, Rebecca Kukunda, Gloria Nattabi, Henry Odanga.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Ethical approvals

No ethical board approval was needed for this work because it did not involve any human or animal trials.

ORCID iD

Felix Bongomin https://orcid.org/0000-0003-4515-8517

References

1. Zhou F, Yu T, Du R, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020; 395: 1054–1062.
2. Azar WS, Njeim R, Fares AH, *et al*. COVID-19 and diabetes mellitus: how one pandemic worsens the other. *Rev Endocr Metab Disord* 2020; 21: 451–463.
3. Velavan TP and Meyer CG. The COVID-19 epidemic. *Trop Med Int Health* 2020; 25: 278–280.
4. Reported Cases and Deaths by Country, Territory or Conveyance, https://www.worldometers.info/coronavirus/?utm_campaign=homeAdvegas1? (2021, accessed 9 March 2021).

5. Klompas M, Baker MA and Rhee CJJ. Airborne transmission of SARS-CoV-2: theoretical considerations and available evidence. *JAMA* 2020; 324: 441.
6. Tang S, Mao Y, Jones RM, *et al*. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. *Environ Int* 2020; 144: 106039.
7. Williamson EJ, Walker AJ, Bhaskaran K, *et al*. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020; 584: 430–436.
8. Fisman DN, Bogoch I, Lapointe-Shaw L, *et al*. Risk factors associated with mortality among residents with coronavirus disease 2019 (COVID-19) in long-term care facilities in Ontario, Canada. *JAMA Netw Open* 2020; 3: e2015957.
9. Wang B, Li R, Lu Z, *et al*. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging* 2020; 12: 6049–6057.
10. Boulle A, Davies M-A, Hussey H, *et al*. Risk factors for COVID-19 death in a population cohort study from the Western Cape Province, South Africa. *Clin Infect Dis*. Epub ahead of print August 2020. DOI: 10.1093/cid/ciaa1198.
11. World Health Organisation. Coronavirus disease (COVID-19) advice for the public, https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public (2020, accessed 7 December 2020).
12. BBC News. Covid-19 pandemic: tracking the global coronavirus outbreak, https://www.bbc.com/news/world-51235105 (2020, accessed 7 December 2020).
13. Mbow M, Lell B, Jochems SP, *et al*. COVID-19 in Africa: dampening the storm? *Science* 2020; 369: 624–626.
14. Nordling L. Africa's pandemic puzzle: why so few cases and deaths? *Science* 2020; 369: 756–757.
15. International Diabetes Federation. *IDF diabetes atlas 9th edition*. Brussels, Belgium: International Diabetes Federation, 2019. https://www.diabetesatlas.org/en/(2020, accessed 7 December 2020).
16. Mercer T, Chang AC, Fischer L, *et al*. Mitigating the burden of diabetes in sub-Saharan Africa through an integrated diagonal health systems approach. *Diabetes Metab Syndr Obes* 2019; 12: 2261–2272.
17. Assah F and Mbanya JC. Diabetes in Sub-Saharan Africa. In: *Diabetes mellitus in developing countries and underserved communities*. Cham: Springer, 2017, pp.33–48.
18. World Health Organisation. Nearly 1 in 5 COVID-19 deaths in the African region linked to diabetes, https://www.afro.who.int/news/nearly-1-5-covid-19-deaths-african-region-linked-diabetes (2020, accessed 7 December 2020).
19. Beran D, McCabe A and Yudkin JS. Access to medicines versus access to treatment: the case of type 1 diabetes. *Bull World Health Organ* 2008; 86: 648–649.
20. Onyiriuka N, Ezomo O and Onyiriuka RC. Cost of treating Insulin-requiring diabetes in children and adolescents. *J Inst Med* 2012; 34: 2–8.
21. Shah BR and Hux JE. Quantifying the risk of infectious diseases for people with diabetes. *Diabetes Care* 2003; 26: 510–513.
22. Muller LM, Gorter KJ, Hak E, *et al*. Increased risk of common infections in patient with type 1 and type 2 diabetes mellitus. *Clin Infect Dis* 2005; 41: 281–288.
23. Hodgson K, Morris J, Bridson T, *et al*. Immunological mechanisms contributing to the double burden of diabetes and intracellular bacterial infections. *Immunology* 2015; 144: 171–185.
24. Badawi A and Ryoo SG. Prevalence of comorbidities in the Middle East respiratory syndrome coronavirus (MERS-CoV): a systematic review and meta-analysis. *Int J Infect Dis* 2016; 49: 129–133.
25. Allard R, Leclerc P, Tremblay C, *et al*. Diabetes and the severity of pandemic influenza A (H1N1) infection. *Diabetes Care* 2010; 33: 1491–1493.
26. Singh AK and Khunti K. Assessment of risk, severity, mortality, glycemic control and antidiabetic agents in patients with diabetes and COVID-19: a narrative review. *Diabetes Res Clin Pract* 2020; 165: 108266.
27. Mantovani A, Byrne CD, Zheng M-H, *et al*. Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: a meta-analysis of observational studies. *Nutr Metab Cardiovasc Dis* 2020; 30: 1236–1248.
28. Katulanda P, Dissanayake HA, Ranathunga I, *et al*. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. *Diabetologia* 2020: 63: 1440–1452.
29. Onder G, Rezza G and Brusaferro S. Case-fatality rate and characteristics of patients dying

in relation to COVID-19 in Italy. *JAMA* 2020; 323: 1775–1776.

30. Guan W, Liang W, Zhao Y, *et al.* Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J* 2020; 55(5): 2000547.

31. Barron E, Bakhai C, Kar P, *et al.* Associations of type 1 and type 2 diabetes with COVID-19-related mortality in England: a whole-population study. *Lancet Diabetes Endocrinol* 2020; 8: 813–822.

32. 80% of COVID-19 deaths had diabetes, https://www.independent.co.ug/80-of-covid-19-deaths-had-diabetes-moh/ (2020, accessed 7 December 2020).

33. Muniyappa R and Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab* 2020; 318: E736–E741.

34. Shima T, Fukushima K, Setoyama H, *et al.* Differential effects of two probiotic strains with different bacteriological properties on intestinal gene expression, with special reference to indigenous bacteria. *FEMS Immunol Med Microbiol* 2008; 52: 69–77.

35. Fadini G, Morieri M, Longato E, *et al.* Prevalence and impact of diabetes among people infected with SARS-CoV-2. *J Endocrinol Invest* 2020; 43: 867–869.

36. Hartmann-Boyce J, Morris E, Goyder C, *et al.* Diabetes and COVID-19: risks, management, and learnings from other national disasters. *Diabetes Care* 2020; 43: 1695–1703.

37. Teachout M and Zipfel C. *The economic impact of COVID-19 lockdowns in Sub-Saharan Africa*. International Growth Centre, London, United Kingdom, 2020. https://www.theigc.org/wp-content/uploads/2020/05/Teachout-and-Zipfel-2020-policy-brief-.pdf

38. Moucheraud C, Lenz C, Latkovic M, *et al.* The costs of diabetes treatment in low-and middle-income countries: a systematic review. *BMJ Glob Health* 2019; 4: 3–7.

39. Worby CJ and Chang H-H. Face mask use in the general population and optimal resource allocation during the COVID-19 pandemic. *Nat Commun* 2020; 11: 4049.

40. Brauer M, Zhao JT, Bennitt FB, *et al.* Global access to handwashing: implications for COVID-19 control in low-income countries. *Environ Health Perspect* 2020; 128: 057005.

41. Sciberras J, Camilleri LM and Cuschieri S. The burden of type 2 diabetes pre-and during the COVID-19 pandemic–a review. *J Diabetes Metab Disord* 2020; 19: 1–9.

42. Impact of COVID-19 on the diabetes community in the United States, https://d-qa.com/impact-of-covid-19-on-the-usa-diabetes-community/?utm_source=Closer+Look+Subscribers+2018&utm_campaign=4285f7ac19-2020-04-19_WIR_4%2F13-4%2F1704_18_2020&utm_medium=email&utm_term=0_c55d924bf1-4285f7ac19-409220105 (2020, accessed 3 December 2020).

43. Füzéki E, Groneberg DA and Banzer W. Physical activity during COVID-19 induced lockdown: recommendations. *J Occup Med Toxicol* 2020; 15: 25.

44. Grenard JL, Munjas BA, Adams JL, *et al.* Depression and medication adherence in the treatment of chronic diseases in the United States: a meta-analysis. *J Gen Intern Med* 2011; 26: 1175–1182.

45. Qiu J, Shen B, Zhao M, *et al.* A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *Gen Psychiatr* 2020; 33: e100213.

46. World Health Organization. *Mental health and psychosocial considerations during the COVID-19 outbreak*, 18 March 2020. 2020. World Health Organization; Geneva, Switzerland. https://www.who.int/docs/default-source/coronaviruse/mental-health-considerations.pdf (2020, accessed 7 December 2020).

47. Coronavirus - Safety at work, https://www.diabetes.org.uk/get_involved/campaigning/coronavirus/safety-at-work (2020, accessed 24 December 2020).

48. Cobos Muñoz D, Monzón Llamas L and Bosch-Capblanch X. Exposing concerns about vaccination in low-and middle-income countries: a systematic review. *Int J Public Health* 2015; 60: 767–780.

49. Zhu L, She Z-G, Cheng X, *et al.* Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. *Cell Metab* 2020; 31: 1068–1077.e3.

50. Gupta R, Ghosh A, Singh AK, *et al.* Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr* 2020; 14: 211–212.

51. Apicella M, Campopiano MC, Mantuano M, *et al.* COVID-19 in people with diabetes:

understanding the reasons for worse outcomes. *Lancet Diabetes Endocrinol* 2020; 8: 782–792.

52. Abdi A, Jalilian M, Sarbarzeh PA, *et al*. Diabetes and COVID-19: a systematic review on the current evidences. *Diabetes Res Clin Pract* 2020; 166: 108347.
53. Bornstein SR, Rubino F, Khunti K, *et al*. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020; 8: 546–550.
54. Longo M, Caruso P, Maiorino MI, *et al*. Treating type 2 diabetes in COVID-19 patients: the potential benefits of injective therapies. *Cardiovasc Diabetol* 2020; 19: 1–5.
55. Sardu C, D'Onofrio N, Balestrieri ML, *et al*. Outcomes in patients with hyperglycemia affected by Covid-19: can we do more on glycemic control? *Diabetes Care* 2020; 43: 1408–1415.
56. Mendez CE and Umpierrez GE. Pharmacotherapy for hyperglycemia in noncritically ill hospitalized patients. *Diabetes Spectr* 2014; 27: 180–188.
57. American Diabetes Association. 15. Diabetes care in the hospital: standards of medical care in diabetes—2020. *Diabetes Care* 2020; 43(Suppl. 1): S193–S202.
58. Peric S and Stulnig TM. Diabetes and COVID-19: disease—management—people. *Wien Klin Wochenschr* 2020; 132: 356–361.
59. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, *et al*. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med* 2009; 360: 1283–1297.
60. Moghissi ES, Korytkowski MT, DiNardo M, *et al*. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. *Diabetes Care* 2009; 32: 1119–1131.
61. Vaduganathan M, Vardeny O, Michel T, *et al*. Renin–angiotensin–aldosterone system inhibitors in patients with Covid-19. *N Engl J Med* 2020; 382: 1653–1659.
62. Chow JH, Khanna AK, Kethireddy S, *et al*. Aspirin use is associated with decreased mechanical ventilation, ICU admission, and in-hospital mortality in hospitalized patients with COVID-19. *Anesth Analg* 2021; 132: 930–941.
63. Castiglione V, Chiriacò M, Emdin M, *et al*. Statin therapy in COVID-19 infection. *Eur Heart J Cardiovasc Pharmacother* 2020; 6:258–259.
64. Day M. Covid-19: ibuprofen should not be used for managing symptoms, say doctors and scientists. BMJ. 2020 Mar 17;368:m1086. doi: 10.1136/bmj.m1086. PMID: 32184201.
65. Deng F, Gao D, Ma X, *et al*. Corticosteroids in diabetes patients infected with COVID-19. *Ir J Med Sci* 2021; 190: 29–31.
66. Wexler DJ. Coronavirus disease 2019 (COVID-19): issues related to diabetes mellitus in adults. https://www.uptodate.com/contents/covid-19-issues-related-to-diabetes-mellitus-in-adults (2020, accessed 7 December 2020).
67. Bellido V and Pérez A. Inpatient hyperglycemia management and COVID-19. *Diabetes Ther* 2021; 12: 121–132.
68. Perez A, Jansen-Chaparro S, Saigi I, *et al*. Glucocorticoid-induced hyperglycemia (糖皮质激素诱导的高血糖). *J Diabetes* 2014; 6: 9–20.
69. Clore JN and Thurby-Hay L. Glucocorticoid-induced hyperglycemia. *Endocr Pract* 2009; 15: 469–474.
70. Mendis S, Al Bashir I, Dissanayake L, *et al*. Gaps in capacity in primary care in low-resource settings for implementation of essential noncommunicable disease interventions. *Int J Hypertens* 2012; 2012: 584041.
71. Garber AJ. Premixed insulin analogues for the treatment of diabetes mellitus. *Drugs* 2006; 66: 31–49.
72. Saigí I and Pérez A. Management of glucocorticoid induced hyperglycemia. *Rev Clin Esp* 2010; 210: 397–403.