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Covid19 and Diabetes: Management and Risks

Dr.Ismail Nasir Alsmadi
Family Medicine. PHCC Qatar
ismadi65@hotmail.com
Dr.Gaber Ahmad Ekhtiar
Family Medicine. PHCC Qatar
jikhtiar@yahoo.com

Abstract:

Evidence relating to the impact of COVID-19 in people with diabetes (PWD) is limited but continuing to emerge. People with diabetes (PWD) have been identified as being at increased risk of serious illness from COVID-19. COVID-19 also presents substantial indirect risks to PWD through disruptions in health care and lifestyle factors. Understanding these risks and best ways to mitigate them in the short and longer term is key to facilitating informed decision-making during and after the COVID-19 pandemic. Evidence on the management of long-term conditions during national emergencies suggests various ways to mitigate the risks presented by these events.

Key words: People with Diabetes (PWD), COVID-19, $HbA_{1c,}$ BMI, hyperglycemia, metformin, chloroquine /hydroxychloroquine.

الملخص:

الأدلة المتعلقة بتأثير COVID-19 على الأشخاص المصابين بداء السكري (PWD) محدودة ولكنها مستمرة في الظهور. تم تحديد الأشخاص المصابين بداء السكري (PWD) على أنهم معرضون بشكل متزايد لخطر الإصابة بأمراض خطيرة من COVID-19. يمثل COVID-19 أيضًا مخاطر كبيرة غير مباشرة على الأشخاص المصابين بداء السكري من خلال الاضطرابات في الرعاية الصحية وعوامل نمط الحياة. يعد فهم هذه المخاطر وأفضل الطرق للتخفيف منها على المدى القصير والطويل أمرًا أساسيًا لتسهيل اتخاذ القرارات المستنيرة أثناء وبعد جائحة COVID-19. تشير الأدلة على إدارة الظروف طويلة الأجل أثناء حالات الطوارئ الوطنية إلى طرق مختلفة للتخفيف من المخاطر التي تقدمها هذه الأحداث.

الكلمات المفتاحية: الأشخاص المصابون بمرض السكريPWD , COVID-19، HbA1c ، مؤشر كتلة الجسم ، ارتفاع السكر في الدم ، الميتفورمين ، الكلوروكين / هيدروكسي كلوروكين.

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Introduction

People with Diabetes (PWD) appear to be at increased risk of more severe COVID-19 infection, though evidence quantifying the risk is highly uncertain. The extent to which clinical and demographic factors moderate this relationship is unclear, though signals are emerging that link higher BMI and higher HbA_{1c} to worse outcomes in PWD with COVID-19. As well as posing direct immediate risks to PWD, COVID-19 also risks contributing to worse diabetes outcomes due to disruptions caused by the pandemic, including stress and changes to routine care, diet, and physical activity. There is a high potential for COVID-19 to exacerbate existing health disparities, and research and practice guidelines need to take this into account.

DIABETES AND RISKS FROM COVID-19

COVID-19 Infection: Contracting the Disease

It is unclear if PWD are more likely to contract COVID-19. PWD are considered at increased risk of infection generally, which has been extended to COVID-19 (Gupta R, Ghosh A, Singh AK, Misra A. 2020). Community testing for COVID-19 remains limited; hence data predominantly come from hospitalized cohorts. Systematic reviews primarily consisting of data from China have estimated rates of 8% (95% CI6-11%) (Yang J, Zheng Y, Gou X, et al. 2020), 7.87% (95% CI 6.57-9.28^) (Emami A, Javanmardi F, Pirbonyeh N, Akbari A. 2020), and 9.7% (95% CI 6.9-12.5%) (Li B, Yang J, Zhao F, et al. 2020) of diabetes in people hospitalized with COVID-19.

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The percentage hospitalization appears higher in the U.S., where from February 12 to 28 March 2020, PWD accounted for 10.9% of all COVID-19 patients (similar to the proportion of the U.S. population with diabetes), 24% of hospitalized cases (non-intensive care unit [ICU]), and 32% of ICU admissions (CDC COVID-19 Response Team 2019-United States, February 12-March 28, 2020). A recent (preprint) U.K. study found uncomplicated diabetes to be the second most common comorbidity (19%) in patients hospitalized with COVID-19; complicated diabetes is reported in a figure only but prevalence looks to be approximately 6.5% (Docherty AB, Harrison EM, Green CA, et al. 28 April 2020).

COVID-19 Infection: Disease Severity

There is a notable paucity of data on what moderates the relationship between diabetes and COVID-19 severity. Increased age, being male, hypertension, and cardiovascular comorbidities are associated with increased risks for COVID-19 severity (Jordan RE, Adab P, Cheng KK. 2020) and are likely to be closely related to diabetes status. It is plausible that MBI (Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. 2020), ethnicity (Khunti K, singh AK, pareek M, Hanif W. 2020), type of diabetes, diabetes control, and certain medications (Aronson JK, Eerner RE. 22 March 2020) all may also play a role. In two cohort studies (France and the U.K., U.K. study preprint) in PWD hospitalized with COVID-19, higher BMI was positively associated with worse COVID-19 outcomes when compared with people with BMI 25-29.9 kg/m2 (Cariou B, Samy H, Wargny M, et al. 29 May 2020, NHS England 20 May 2020). Data on diabetes type and COVID-19 outcomes are only beginning to emerge, but preliminary (not yet peer reviewed) data from England suggests risks may be higher in people with type 1 diabetes

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compared with type 2 (though risk was increased in all PWD regardless of type) (NHS England 20 May 2020).

Association between Blood Glucose Control and COVID-19 Outcomes

There are limited data to date on the association between blood glucose control and COVID-19 outcomes. A retrospective study of 451 people with COVID-19 with diabetes and/ or hyperglycemia from the U.S. reported that people with uncontrolled hyperglycemia had longer length of stay and higher mortality compared with people without diabetes or uncontrolled hyperglycemia (Bode B, Garrett V, Messler J, et al. 9 May 2020). Another retrospective study of people with type2 diabetes from China reported that well controlled blood glucose correlated with improved outcomes in infected patients (Zhu L, She Z-G, Cheng X, et al. 2020). Two recent U.K. studies reported that diabetes was independently associated with a higher risk of death which increased with higher HbA1c (NHS England 20 May 2020, Williamson E, Walker AJ, Bhaskaran KJ, et al. 7 May 2020). Compared with people without diabetes, one study reported that PWD with HbA1c > 7.5% (58 mmol/mol) had a higher chance of in-hospital death than those with HbA1c < 7.5% (7.5% HR 1.50 (95% CI 1.40-1.60], ≥ 7.5% HR 2.36 [2.18-2.54]) (Williamson E, Walker AJ, Bhaskaran KJ, et al. 7 May 2020). In a separate analysis, PWD with HbA1c > 10% (86 mmol/mol) had a higher risk in-hospital death related to COVID-19 than those with an HbA1c of 6.5-7% (48-53 mmol/mol) (HbA1c > 10% compared with HbA1c 6.5-7% adjusted HR 2.19 (95% CI 1.46-3.29] for type 1 diabetes, 1.62 [95% CI 1.48-1.79] for type 2; in type 2 diabetes patients a significant difference was also detected when comparing HbA1c values > 7.5% [59 mmol/mol] to the reference category) (NHS England 20 May 2020).

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These data suggest that diabetes control pre-infection has a role to play in COVID-19 outcomes. In contrast, a French observational study in PWD hospitalized with COVID-19 did not find an association between long-term glucose control and COVID-19 outcomes but had a smaller sample (Cariou B, Samy H, Wargny M, et al. 29 May 2020).

Indirect Risks to PWD Posed by COVID-19

Health care services, and in some cases access to medication and supplies, have been disrupted by COVID-19. Evidence from other national emergencies shows that such disruptions can lead to worse diabetes outcomes during and after these events (Saulnier DD, Brolin Ribacke K, von Schreeb J. 2017- Ng J, Atkin SL, Rigby AS, Walton C, Kilpatrick ES. 2011). Diet and physical activity are mainstays of diabetes self-management and can reduce risk of worse outcomes in PWD and those with cardiometabolic multi-morbidities (Chudasama YV, Zaccardi F, Gillies CL, et al. 2020). Though yet to be addressed by the COVID-19 literature, the pandemic presents significant disruption to both: a U.S. survey of PWD found more than a third of respondents reported their diet is now less healthy, and half report exercising less (dQ&A, 2020). The current pandemic and social isolation are likely to increase rates of anxiety and depression, which may also lead to poor adherence of medications and worsening of risk factor control (Generad JL, Munjas BA, Adams JL, et al. 2011,Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. 2020).

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MANAGING DIABETES DURING THE COVID-19 PANDEMIC

Reducing Risk from COVID-19

There is little evidence on how PWD can reduce their risk during the COVID-19 frequent blood glucose monitoring (in people who self-monitor) has been pandemic beyond following general infection control guidance within each country. More suggested, though is unclear what evidence was used to make these recommendations (Gupta R, Ghosh A, Singh AK, Misra A. 2020).

Self-management

The wider literature on care of long-term conditions during national emergencies suggests a role for educational materials (Hartmann-Boyce J, Mahtani KR.2020). Evidence for interventions aiming to optimize self-management in PWD that are potentially feasible in disaster contexts include mobile phone apps (Aminuddin HB, Jiao N, Jiang Y, Hong J, Wang W. 8 February 2019), web-or computer-based interventions (Pal K, Eastwood SV, Michie S, et al. 2013), text messaging (Huang L, Yan Z, Huang H. 2019, Sahin C, Courtney KL, Naylor PJE, E Rhodes R. 2019), and self-monitoring of blood glucose (XU Y, Tan DHY, Lee JY-C. 2019,Malanda UL, Welschen LMC, Riphagen II, Dekker JM, Nijpels G, Bot SDM. 2012). However, the interventions tests may not be widely available or may require health care resources to be set up. In addition, choice of format should be tailored to patient preferences, which will vary by age and sociodemographic group (Woolley AK, Chudasama Y, Seidu SI, et al. 2020).

Diabetes Services

Guidelines for routine diabetes care during the COVID-19 pandemic vary by country.

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Themes are summarized in Table 2. Studies of remote consultations have generally found positive results, though their generalizability to the current pandemic may be limited (The Health Foundation. Interview with Professor Trish Greenhalgh. 30 March 2020). Within diabetes, there is little evidence to support or oppose remote support (Farrell K, Holmes-Walker DJ. 2011,Vina LV, Gomes MB, Zajdenverg L, Pavin EJ, Azevedo MJ; Brazilian type 1 Diabetes study Group, 2016).

Mental Health and Diabetes-Related Distress

There are overarching concerns about the impact of the COVID-19 pandemic on mental health and wellbeing (World Health Organization. 2020,Shelvin M, McBride O, Murphy J, et al. 18 April 2020). PWD are more prone to mental health issues than the general population (The All-Party Parliamentary Group for Diabetes (APPG Diabetes). 2020). Adherence to treatment can worsen when people are distressed or have depression (Generad JL, Munjas BA, Adams JL, et al. 2011), as seen both during and after disasters (Krousel-Wood MA, Islam T, Muntner P, et al. 2008, Khan Y, Albache N, Almasri I, Gabbay RA. 2019). We found no evidence directly pertaining to management of diabetes-related anxiety or distress during this pandemic. In the general literature, there is mixed evidence on interventions to reduce diabetes-related distress, and the vast majority of interventions tested involve face-to-face contact; an unsuitable format in the current context (Chew BH, Vos RC, Metzendorf MI, Scholten RJ, Rutten GE. 2017).

Managing COVID-19 in PWD

Management of PWD with COVID-19 generally follows standard sick-day rules.

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Medication

Most COVID-19-related consensus statements recommend stopping metformin and sodium-glucose transporter 2 inhibitors (SGLT2i) during acute illness and following the sick-day rules. Dipeptidyl peptidase 4 inhibitors (DPP-4i), glucagon-like peptide 1 receptor agonists (GLP-1RA), and insulin are the preferred options in particular for hospitalized patients (Ceriello A, Standl E, Catrinoiu D, et al; Diabetes and Cardiovascular Disease (D&CVD) EASD Study Group. 2020,Bornstein SR, Rubino F, Khunti K, et al. 2020). There has been some discussion regarding use of ACE inhibitors and angiotensin receptor blockers (ARBs) being associated with worse outcomes in COVID-19, particularly in PWD.

A number of studies are currently testing chloroquine/hydroxychloroquine for prevention or management of COVID-19. Careful glucose monitoring will be required in PWD due to these drugs' antidiabetic properties, with the potential risk of hypoglycemia that is associated with increased risk of cardiac arrhythmia, cardio-vascular events, and mortality (Wondafrash DZ, Desalegn TZ, Yimer EM, Tsige AG, Adamu BA, Zewdie KA. 2020).

Management in hospital

Guidance emphasizes the importance of referring to local specialist diabetes teams and of managing hyperglycemia (NHS London Clinical Networks. 2020). A narrative review suggests insulin is the preferred agent for control of hyperglycemia in this context (Gupta R, Ghosh A, Singh AK, Misra A. 2020). In the U.S., a major early focus for hospital management was to move inpatient care for PWD to "virtual" formats where possible, to reduce the need for personal protective equipment. This included use of electronic health records to interrogate data, telephone communication between diabetes care providers and inpatients and hospital staff,

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Expanded "diabetes self-management protocols" allowing selected inpatients to monitor their own glucose and self-administer insulin with oversight and advice from the virtual care team, and, in some institutions, initiating inpatient continuous glucose monitoring and/or flash systems. To minimize the need for ICU beds, several institutions launched subcutaneous insulin protocols for the treatment of diabetic ketoacidosis on floors with adequate nursing staffing. Virtual diabetes care teams focused on supporting transitions to lower levels of care or outpatient settings.

EXPERIENCES FROM COUNTRIES WITH HIGH RATES OF COVID-19

We summarize here experiences from four countries that have had significant COVID-19 outbreaks.

China

The guidance developed by the Chinese Geriatric Endocrine Society mainly focused on prevention and early discovery of hyperglycemic crises and management of medications and provided detailed instructions on how to get access to certified internet-based medical services through smartphones (Weiqing W, Zhongyan S, Guang W, et al. 2020,Linong J, Guangwei L, Oiuhong G, et al. 2020). And expert recommendation on insulin treatment of hyperglycemia in patients affected with COVID-19 was developed (Linong J, Jiajun Z, Zhiguang Z, et al. 2020).

Italy

Tragically, Italy has suffered among the highest numbers of deaths in the world (Remuzzi A, Remuzzi G. 2020). At the time of this writing, the death rate in Italy was estimated at 122.52 per 1,000 infections, i.e., a 10-fold

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higher rate than in Germany (14.14 per 1,000 infections) (Euronews. 2020). This could be due to demographic features of the Italian population, which include a large proportion (23%) of people aged ≥ 65 (Onder G, Rezza G, Brusaferro S. 2020). Access to diabetes clinics has been limited to urgent cases, and remote contacts via telephone or video telecom-sultation have been officially approved and reimbursed by the National Health System. Prescriptions of glucose-lowering agents requiring specialist approval (DPP-4i, SGLT2i, GLP-1RA, and new basal insulin analogs) were automatically renewed until the end of May. Special joint recommendations have been promptly issued by the Italian Society of Diabetes (SID), the Association of Italian Diabetologists (AMD), the Italian Society of Endocrinology (SIE), and the Italian Society of Pediatric Endocrinology (SIEDP) (SIE – 2020). The same organizations have opened a Facebook page entitled "One hour with AMD, SID, and SIEDP" allowing PWD and their relatives to contact specialists (SID- 2020).

Table 2- Selection of guidance and recommendations relating to routine care in PWD during COVID-19 pandemic

Service	**Recommendations**
Inpatient diabetes services	- Inpatient diabetes services will need to continue and potentially increase capacity, with need for team approach re: glycemic control and nutritional status, and consideration of "virtual visits" for reviews (see MANAGEMENT IN HOSPITAL) (68).
Urgent/ acute diabetes care (outpatient)	- face-to-face consultations should continue in the

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	following circumstances: a new diagnosis of T1D; urgent insulin start where symptomatic, HbA1c>10% (86mmol/mol), or ketones detected; teaching blood glucose monitoring for urgent reasons; or in cases where physical examination is essential (e.g., foot ulcer, infection, some points in pregnancy) (69) - Virtual (telephone, video, or e-mail) consultations should be used in the following circumstances: follow-up of new T1D diagnoses; vulnerable patients (recent hospital admission, recurrent severe hypoglycemia, HbA1c>11% (99 mmol/mol); intensive follow-up in high-risk situations; or where risk of attending an appointment face-to-face is greater than the benefits (69).
Routine diabetes care	- Consider routine diabetes care delivered virtually in the context of broader long-term condition management and prioritization, taking into account individual risk factors and clinical needs (68). - The following should be deferred: routine appointments where diabetes is stable and well-managed; face-to-face structured group education courses; flash glucose monitoring start sessions; where the risk of attending an appointment is

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	greater than the benefits; and where deferring appointments will not compromise clinical care (69).
Foot services for PWD	- May need to continue at full capacity with consideration of moving support to remote forms where possible (68); many of these services are essential (70). - Access to in-person support should continue for those with acute or limb-threatening problems (70) or where physical examination is essential (69). - All new referrals should ideally be reviewed within 24 h (70).
Pregnancy services for PWD	- May need to continue at full capacity with consideration of moving support to remote forms where possible (68). - In-person support will be essential for physical examinations and/ or teaching blood glucose monitoring at some points in pregnancy (69).
Blood tests for PWD	- Urgent blood test monitoring should continue (e.g., declining renal function, raised potassium, low sodium) (69).
Eye screening for PWD	- this was not mentioned in the guidance reviewed but we understand in most affected countries eye screening has been halted in view of high risk of transfer. Of note, evidence indicates that risk

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	stratifying is possible (71).

* PWD may be concerned about the need to visit hospital; they should be encouraged to contact their physician in case of any signs or symptoms related to acute diabetes complications.

A government web page providing simple and pragmatic recommendations has been created focusing on disruptions to physical activity and diet as a result of social confinement (Ministero della Salute. 2020).

U.K.

Over 90% of PWD in the U.K. are managed in primary care, by enhanced diabetes-skilled primary care physicians, nurses, and health care assistants. These models have shown to be effective in reducing hospitalizations, outpatient attendance, and admissions for diabetes-related complications (Seidu S, Davies MJ, Faroqi A, Khunti K. 2017). In March, the government issued guidance on social distancing and self-isolation (Public Health England. 2020). In England, people considered especially clinically vulnerable (including some but not all PWD) were contacted by the government with advice on shielding. All people at high risk, including PWD, were advised to only leave the house for limited periods for essential shopping and one form of exercise (NHS. 2020). The primary Care Diabetes Society and the Association of British Clinical Diabetologists have issued guidance on managing PWD in primary care (Association of British Clinical Diabetologists. 2020). The national charity Diabetes UK has been active in giving advice to PWD through their web-site and social media.

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Both primary and secondary cares are providing emergency and routine follow-up using telephone or video consultations including support for mental well-being, though there are some regional variations.

There has been an almost wholesale switch on virtual care for outpatient appointments but many failings in this approach. Phone visits provide a much lower rate of reimbursement than video visits, but many of the most vulnerable patients have inadequate equipment or connectivity to support video visits. Contacts with certified diabetes educators by phone or video are not reimbursed.

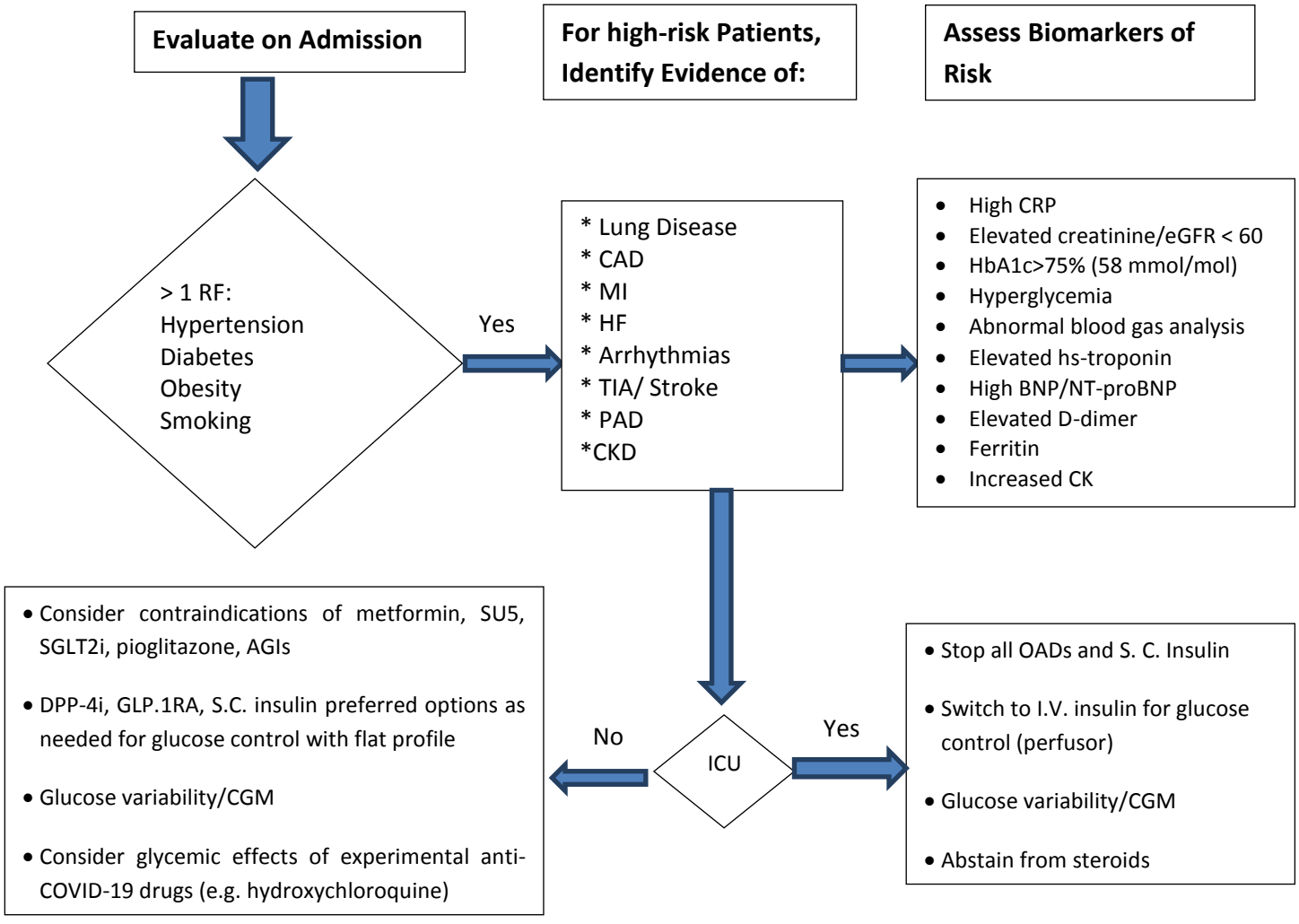

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Figure 2- Possible flowchart for management of people hospitalized with diabetes and COVID-19, reproduced with permission from Ceriello et al. (Onder G, Rezza G, Brusaferro S. 2020). ACEi, ACE inhibitors; AGIs, a-glucosidase inhibitors; BNP, brain natriuretic peptide; CAD, coronary artery disease; CGM, continuous glucose monitoring; CK, creatine kinase; CDK, chronic kidney disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate (mL/min/1.73m^2); MI, myocardial infarction; NT-proBNP, N-terminal prophormone of brain natriuretic peptide; OADs; and antidiabetes drugs; PAD, peripheral arterial disease; RF, risk factor; SUs, sulfonylureas; TIA, transient ischemic attack.

In date available through the end of March, relatively early in the U.S. COVID-19 course, approximately 80% of clinicians reported serious strain and nearly two-thirds were uncertain whether they would be able to keep their practices open due to insufficient financial resources and low volume of reimbursable work. Overall visits (Virtual and face-to-face) for chronic asymptomatic care were down ~ 50% (IQVIA. 2020).

AFTER COVID-19

There is much uncertainty as to how the COVID-19 pandemic will end and what will be left in its wake. Disruptions that arise due to national emergencies can lead to increased HbA1c in those affected up to 16 months later, with some evidence that this is particularly the case for people of lower socioeconomic status and those treated with insulin (Ng J, Atkin SL, Rigby AS, Walton C, Kilpatrick ES. 2011,Hartmann-Boyce J, Mahtani KR. 2020). A lack of access to routine health care is a leading cause of morbidity and mortality after disasters; stroke, acute myocardial infarctions, and diabetes complications are all shown to increase after the immediate threat has dissipated (Huang L, Yan Z, Huang H. 2019,Moddad AH, Mensah GA, Posner SF,

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Reed E, Simoes EJ, Engelgau MM; Chronic Diseases and Vulnerable Populations in Natural Disasters Working Group. 2005). Services such as diabetes clinics may also rethink their organization to minimize risk of ongoing transmission.

CONCLUIONS

The need for decisive action creates an important tension when evidence is limited. An example here is the classification of PWD as being at increased risk from COVID-19 and therefore subject to increased preventive measures. Though risk is clearly increased, quantification is scant. There is little to no evidence on potentially moderating factors, despite the fact that these data are routinely collected in data sets used for existing analyses; the results presented are often unadjusted and use single disease categories, ignoring potential differences between type 1 and type 2 diabetes and multimorbidities, which are associated with worse outcomes (Zemedikun DT, Gray LI, Khunti K, Davies MJ, Dhalwani NN. 2018).

In the face of a limited evidence base relating directly to COVID-19, decisions can be informed by international experiences to date and, to some extent, from the literature as it relates to other national emergencies. This latter source of evidence shows the toll of disruptions to diabetes care is often most pronounced after the acute phase of the emergency or disaster has passed. In some cases, the excess morbidity and mortality in the aftermath of national emergencies is higher than the toll during the emergency itself. History issue a stark warning here when considering the balance between diverting resources toward the acute COVID-19 crisis and maintaining routine care for people living with long-term conditions.

Finally, in reviewing what has been written on the topic of diabetes and COVID-19, we have been struck by two noticeable absences.

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The first is the absence of literature on wider contextual factors. PWD are likely to be impacted by COVID-19 just as much outside the health care seeting as within it, with particular concerns relating to disruptions to diet and physical activity, increased stress, and burdens on mental health and well-being, yet the literature to date focuses almost exclusively on clinical management. The other unspoken issue in the literature we reviewed is that of inequality. COVID-19 is not an equal-opportunity disease. The burden will disproportionally be borne by people from less-advantaged groups (Royal College of Physicians. 2020). Emerging data also suggests that COVID-19 may pose more of a risk to nonwhite ethnic group (Khunti K, singh AK, pareek M, Hanif W. 2020). Diabetes discriminates in similar ways, and the intersection of diabetes and COVID-19 creates a maelstrom in which existing health disparities risk exacerbation with profound and long-lasting consequences. COVID-19 holds a mirror to our health care systems and care of PWD; may we do all we can now to make that reflection favorable in hindsight.

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