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# Caring for patients with diabetes during COVID-19 pandemic: Important considerations for pharmacists



RSAP

Mohamed Hassan Elnaem<sup>a,b,\*</sup>, Ejaz Cheema<sup>c</sup>

<sup>a</sup> Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

<sup>b</sup> Quality Use of Medicines Research Group, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia

<sup>c</sup> School of Pharmacy, University of Birmingham, Edgbaston, Birmingham, UK

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Keywords:	The current pandemic of the COVID-19 infection, coupled with the increased global burden of diabetes, has
COVID-19	imposed significant challenges to the healthcare providers in providing effective and sustained care to patients
Diabetes	with diabetes during the ongoing pandemic. It is, therefore, important for healthcare providers to understand
Pharmacists	and follow the recommended changes in the delivery of care, lifestyle modifications, and pharmacotherapy to ensure optimal care to the patients during and post-pandemic era. This commentary aims to discuss the impact of
	COVID-19 on diabetes care and the important considerations for pharmacists during this pandemic.

## Suspected association of diabetes with COVID-19

Evidence suggests that patients with chronic diseases such as diabetes are at increased risk of acquiring COVID-19 and associated disease complications with higher mortality.<sup>1,2</sup> However, newly published data from Italy suggest that diabetes does not typically increase the individual's risk of developing COVID-19 infection, but it is more likely to worsen the clinical outcomes.<sup>3</sup> Possible explanations for worsening clinical outcomes in COVID-19 positive patients with diabetes include a relatively higher risk of organ dysfunction and immune-inflammatory response.<sup>3</sup> Based on these underlying pathophysiological changes, some potential adjustments for diabetes medications might be implemented to help mitigate the course of illness.

# Potential adjustments in the pharmacotherapy

At the time of intercurrent illness, patients with diabetes are at a higher risk of developing hyperglycemia and therefore, more prone to the development of dehydration, diabetic ketoacidosis (DKA) or Hyperosmolar hyperglycemic state (HHS).<sup>4</sup> Consequently, pharmacists need to educate patients to help them manage these symptoms. The pharmacists' support is crucial for the patients in reducing their risk of developing acute complications and associated hospital admissions.

# Insulin

The insulin requirements are estimated to increase during the acute illness due to the upregulation of counter-regulatory hormones such as cortisol.<sup>5</sup> Patients with type 1 diabetes should receive supplementary doses of short-acting insulin in case of elevated blood glucose levels.<sup>5</sup> Meanwhile, if blood glucose levels are lower than the target value, insulin doses may be reduced by 10-20% with the consideration of omitting mealtime insulin doses if little or no carbohydrate is consumed.<sup>4</sup> Overall, insulin dose adjustments should be made under direct medical supervision, with all attempts not to stop insulin completely among patients with type 1 diabetes. Meanwhile, patients with type 2 diabetes who had significantly higher blood glucose levels may need increments in their insulin requirements by 10-20%.<sup>6</sup> Besides, an increase in the frequency of blood glucose monitoring should be considered during the time of acute illness.<sup>5</sup> Consequently, the monitored blood glucose levels and dietary carbohydrate intake are bases for further adjustment in insulin requirements.

#### Metformin

The majority of clinical guidelines endorse metformin as a first choice antidiabetic due to its efficacy, lower hypoglycemia risk, and medication-induced weight loss.<sup>7</sup> Nevertheless, the medication-induced gastrointestinal symptoms could aggravate the risk of dehydration and potentially impose risk on the renal function; therefore, temporary

\* Corresponding author. Department of Pharmacy Practice, Faculty of Pharmacy, International Islamic University Malaysia, Kuantan, Pahang, Malaysia. *E-mail addresses:* drmelnaem@gmail.com, drmelnaem@iium.edu.my (M.H. Elnaem), e.cheema@bham.ac.uk (E. Cheema).

https://doi.org/10.1016/j.sapharm.2020.05.030 Received 28 May 2020; Accepted 28 May 2020 Available online 31 May 2020 1551-7411/ © 2020 Elsevier Inc. All rights reserved. discontinuation of the medication may be warranted.<sup>5</sup> Also, metformin should be temporarily discontinued in the presence of concurrent illnesses that can elevate the risk of renal disease such as severe infection and shock.<sup>4</sup> In the absence of acute illness, pharmacists should educate patients about the proper management of the gastrointestinal symptoms to avoid the risk of dehydration while maintaining good glycaemic control.

## Gliclazide

Gliclazide is known to be associated with the risk of hypoglycemia, particularly in case of poor appetite, so a dose reduction should be considered.<sup>6</sup> However, as hyperglycemia is more common during the intercurrent illness, a further increase in the doses could be made accordingly.<sup>4</sup> Furthermore, frequent blood glucose monitoring would help healthcare providers in adjusting the treatment that could be continued during the time of acute illness.<sup>5</sup>

#### Dipeptidyl Peptidase-4 inhibitors (DPP4i)

As highlighted earlier, the critical responses to COVID-19 infection are modulated through an inflammatory pathway, and anti-inflammatory medications are of utmost importance besides the targeted antivirals.<sup>8</sup> Moreover, diabetes medications that have been reported to exert anti-inflammatory actions such as Dipeptidyl Peptidase-4 inhibitors (DPP4i) are sought to reduce the severity of the inflammatory mediated acute complications of COVID-19 infection, although their exact clinical benefit remains uncertain.<sup>9</sup> On the other hand, considering that DPP4 is known to activate T-cells and promote inflammation, there are also concerns about the potential increase in the risk of infections associated with DPP4i.<sup>10</sup> Therefore, there is a need for rigorous large-scale data to confirm the assumptions of a prospective role of diabetic medications with anti-inflammatory actions on the exact outcomes or severity of the COVID-19 infection.

#### Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

Similar to DPP4i, SGLT2i exerts an anti-inflammatory effect that suggests an impact on the severity of COVID-infection.<sup>11</sup> SGLT2i has been reported to be associated with favorable cardiovascular and renal outcomes among patients with diabetes and, as such, could be a reasonable option where there is a risk on the integrity of heart and kidneys.<sup>11</sup> Furthermore, SGLT2i has been commended for its weight reduction properties.<sup>7</sup> However, in the presence of acute illness, loss of appetite, and gastrointestinal discomfort, it would be recommended to temporarily stop this medication to reduce the risk of developing further complications such as DKA.<sup>12</sup> Generally, patients on SGLT2i should be adequately educated by pharmacists on how to recognize the signs and symptoms of euglycemic DKA.<sup>13</sup> Furthermore, patients should be advised regarding the risk of developing urogenital infections that have been previously reported among SGLT2i users, particularly among female patients.<sup>14</sup>

## Pioglitazone

Despite having an anti-inflammatory action, pioglitazone could lead to fluid retention that could further complicate the management in diabetic patients with concurrent cardiovascular conditions such as heart failure.<sup>15</sup> Besides, it may cause weight gain, which is a concern, particularly in the time of pandemic where patients may already be at increased risk of weight gain due to their sedentary lifestyle.<sup>7</sup> Given these concerns, pioglitazone should be among the least recommended options for the management of diabetes during COVID-19.

#### GLP-1 receptor agonist

The use of GLP-1 receptor agonists has been markedly rising, considering its reported cardiovascular outcomes, lower hypoglycemia risk, and minimal impact on weight.<sup>7</sup> However, like metformin, gastrointestinal symptoms such as nausea and vomiting are common. Furthermore, there are several case reports of DKA incidence in patients prescribed with exenatide and liraglutide.<sup>4</sup> In addition, there have been instances of acute pancreatitis with the use of GLP-1 receptor agonists. However, recent evidence from a meta-analysis did not support any increased risk among patients with type 2 diabetes.<sup>16</sup> Nevertheless, patients should be adequately educated to recognize the associated symptoms that are also overlapping with DKA clinical presentation.<sup>4</sup> As such, if DKA or pancreatitis is suspected, this medication should be discontinued, and patients should be referred to seek medical consultation.

## Statin therapy

Statin therapy has been an integral component of CVD prevention among patients with type 2 diabetes.<sup>17</sup> Statins by virtue of their antiinflammatory effect could be helpful in the management of viral illnesses such as COVID-19<sup>18</sup> and have also been listed for off-label use in some of the current COVID-19 treatment protocols due to their immunomodulatory effects.<sup>19</sup> However, statins may exhibit drug-drug interactions with antiviral agents used in the COVID-19 treatment protocols. The current evidence, however, does not indicate the need to discontinue statin therapy for diabetic patients infected with COVID-19 infection.<sup>20</sup>

## Issues with diabetes care in the post-pandemic era

In the ongoing discussions to adopt "new normal" to the general lifestyle and businesses, it is expected that health care services will undergo significant changes to accommodate for the delivery of patient care in the post-COVID-19 era.<sup>21</sup> It is likely to witness a widescale application of telehealth and the use of wearable technologies for effective self-management and proper patient monitoring.<sup>2</sup> Furthermore, what has been previously regarded as add-on solutions for certain patients' groups will be a routine of care for the majority of the patients.

# The impact of social distancing on the self-management of diabetes

Diabetes is likely to be associated with an increased risk of disordered eating behaviors attributed to mental health issues, including depression, anxiety, and other psychosocial problems that require dedicated care.<sup>22</sup> These issues are expected to be further amplified due to a significant reduction in the direct social interactions coupled with a sedentary lifestyle following restrictions on outdoor exercises.<sup>12</sup> Given the expected negative impact of social distancing on the self-management of diabetes, pharmacists would need to educate patients to help them manage their disease in these challenging times.

#### The challenge of attaining optimal glycemic control

Evidence suggests that patients with suboptimal diabetes control tend to be at a significantly higher risk of acquiring infections, which indicates the need for attaining optimal glycemic control.<sup>23</sup> Recent reports highlighted the potential impact of glycemic control on the specific risk profile of COVID-19 infected patients<sup>12</sup>; however, the epidemiological data is not comprehensive and rigorous enough to support this finding. Given the incidence and severity of complications associated with diabetes, such as cardiovascular and renal complications, achieving adequate glycemic control is challenging but equally an important step in the management of diabetes.

#### The need for frequent blood glucose monitoring

Diabetic patients with suspected fever are required to follow the sick day rules of diabetes with more frequent blood glucose monitoring to assess the need to discontinue or adjust the prescribed diabetes therapies.<sup>12</sup> Considering the changes in the diet and exercise habits, more fluctuations in the blood glucose levels are expected to be encountered. Pharmacists should, therefore, recommend frequent blood glucose monitoring to such patients.

# Pharmacists-led support for patients with diabetes in the postpandemic era

Pharmacy professionals are critical in the preparation of an optimal response to the COVID-19 pandemic.<sup>24</sup> The following recommendation can help pharmacists deliver effective care to patients with diabetes during and post-COVID-19 era.

#### Adequate medication supply

Pharmacists need to act proactively to ensure the delivery of adequate and safe supply of medications to their patients.<sup>25</sup> Pharmacy departments are therefore expected to extend the scope of remote mobile services, drive-through, and home delivery services to limit the need for frequent visits to the pharmacies by patients.<sup>26</sup> In addition, it is essential for pharmacists to optimize the medication supply to lessen the extent of unused medications that could unnecessarily compromise the medication storage and potentially affect the quality of medication use.<sup>27</sup>

# Telepharmacy counseling and monitoring

In the era of general restrictions on face-to-face communication, it would be exemplary for pharmacists to show their empathy, care, and skills to support patients with their medication-related queries remotely. As defined by the American Society of Hospital Pharmacists (ASHP), telepharmacy is the remote provision of pharmacy services by qualified pharmacy personnel.<sup>28</sup> As one of the most accessible health care team members, it is expected that the remote counseling services in the pharmacy settings will be expanded significantly. As there is evidence to support the use of technology-based solutions to promote the self-management of diabetes, there will be an increasing need to develop new models of remote value-added services in diabetes care.<sup>29</sup> As such, the expanded application of technology solutions would be expected to provide a solution for ensuring effective patient monitoring programs.

#### Integration of the emerging evidence into clinical practice

The current pandemic has led to the introduction of emerging and rapidly changing evidence related to the COVID-19 and its management. Many potential therapies are currently being tested for their potential efficacy against the virus, with many more expected to be introduced. Furthermore, a number of drugs that were initially considered to be effective with promising results had been declared ineffective following the conclusion of new trials.<sup>30</sup> Healthcare professionals, including pharmacists, are therefore required to assess, follow, and promptly integrate the updated information into their patient-related care.

#### Clinical pharmacy support services

Evidence suggests that the involvement of pharmacists in diabetes care has been associated with a positive impact on the clinical and humanistic outcomes for patients.<sup>31</sup> Pharmacists are, however, required to provide continued and extended support to their patients during the

COVID-19 pandemic to ensure better adherence to the diabetes pharmacotherapy with the aim of achieving better glycemic control for their patients.  $^{32}$ 

#### Conclusion

There are several considerations for pharmacists when providing care to patients with diabetes during the current COVID-19 pandemic. Pharmacists can effectively contribute to the overall optimization of diabetes care through safe and optimized medication supply, telepharmacy counseling, remote monitoring, and provision of clinical pharmacotherapy services.

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#### Declaration of competing interest

The authors have no competing interests to be declared.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.sapharm.2020.05.030.

#### References

- Klonoff DC, Umpierrez GE. COVID-19 in patients with diabetes: risk factors that increase morbidity. *Metabolism*. 2020;154224. https://doi.org/10.1016/j.metabol. 2020.154224.
- Muniyappa R, Gubbi S. COVID-19 pandemic, Corona Viruses, and diabetes mellitus. *Am J Physiol Endocrinol Metab.* 2020:736–741. https://doi.org/10.1152/ajpendo. 00124.2020.
- Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest. 2020 https://link. springer.com/content/pdf/10.1007/s40618-020-01236-2.pdf, Accessed date: 11 May 2020 Accessed.
- 4. TREND UK. Managing Diabetes during Intercurrent Illness in the Community. 2018; 2018.
- Lea-Henry TN, Baird-Gunning J, Petzel E, Roberts DM. Medication management on sick days. Aust Prescr. 2017;40(5):168–173. https://doi.org/10.18773/austprescr. 2017.057.
- Australian Diabetes Educators Association. Clinical Guiding Principles for Sick Day Management of Adults with Type 1 and Type 2 Diabetes. 2016; 2016.
- Endocrine Malaysian, Metabolic Society (MEMS) Department of Medicine NU of MMC. Quick Reference Guide for Recommendations in the Clinical Practice Guidelines (CPG) for the Management of Type 2 Diabetes Mellitus. fifth ed. 2016; 2016.
- Cao X. COVID-19: immunopathology and its implications for therapy. Nat Rev Immunol. 2020;20(5):269–270. https://doi.org/10.1038/s41577-020-0308-3.
- Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? *Diabetes Res Clin Pract*. 2020;162:108125. https://doi.org/10.1016/j.diabres.2020.108125.
- Pal R, Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? *Diabetes Res Clin Pract.* 2020;163:108146. https://doi.org/10.1016/j. diabres.2020.108146.
- Ceriello A, Stoian AP, Rizzo M. COVID-19 and diabetes management: what should be considered? *Diabetes Res Clin Pract.* 2020;163:108151. https://doi.org/10.1016/j. diabres.2020.108151.
- Gupta R, Ghosh A, Singh AK, Misra A. Clinical considerations for patients with diabetes in times of COVID-19 epidemic. *Diabetes Metab Syndr Clin Res Rev.* 2020;14(3):211–212. https://doi.org/10.1016/j.dsx.2020.03.002.
- Menghoum N, Oriot P, Hermans MP, Mariage JL. Diabetic euglycemic ketosis or ketoacidosis in individuals with type 2 diabetes treated by SGLT2 inhibitors: a series of Belgian clinical cases. *Rev Med Interne*. 2020;41(4):226–231. https://doi.org/10. 1016/j.revmed.2019.12.006.
- 14. Garnock-Jones KP. Saxagliptin/dapagliflozin: a review in type 2 diabetes mellitus. Drugs. 2017;77(3):319–330. https://doi.org/10.1007/s40265-017-0697-1.
- Jearath V, Vashisht R, Rustagi V, Raina S, Sharma R. Pioglitazone-induced congestive heart failure and pulmonary edema in a patient with preserved ejection fraction. J Pharmacol Pharmacother. 2016;7(1):41–43. https://doi.org/10.4103/0976-500X. 179363.
- Cao C, Yang S, Zhou Z. GLP-1 receptor agonists and pancreatic safety concerns in type 2 diabetic patients: data from cardiovascular outcome trials. *Endocrine*. February 2020:1–8. https://doi.org/10.1007/s12020-022-0223-6.
- Elnaem M, Nik Mohamed M, Huri HZ, et al. Statin therapy prescribing for patients with type 2 diabetes mellitus: a review of current evidence and challenges. J Pharm BioAllied Sci. 2017;9(2):80. https://doi.org/10.4103/JPBS\_J0\_17.
- 18. Schönbeck U, Libby P. Inflammation, immunity, and HMG-CoA reductase inhibitors:

statins as antiinflammatory agents? *Circulation*. 2004;109(21 suppl L) https://doi. org/10.1161/01.cir.0000129505.34151.23.

 Hospital MG. Massachusetts General Hospital COVID-19 Treatment Guidance. 2020; 2020.

- Dashti-Khavidaki S, Khalili H. Considerations for statin therapy in patients with COVID-19. *Pharmacotherapy*. 2020:19–21. https://doi.org/10.1002/phar.2397.
- Dawoud D. Emerging from the other end: key measures for a successful COVID-19 lockdown exit strategy and the potential contribution of pharmacists. *Res Soc Adm Pharm.* 2020. https://doi.org/10.1016/j.sapharm.2020.05.011.
- Gonzalvo JD, Hamm J, Eaves S, et al. A practical approach to mental health for the diabetes educator. AADE Pract. 2019;7(2):29–44. https://doi.org/10.1177/ 2325160319826929.
- Rhee JJ, Zheng Y, Liu S, et al. Glycemic control and infections among US hemodialysis patients with diabetes mellitus. *Kidney Int Rep.* April 2020. https://doi.org/ 10.1016/j.ekir.2020.04.020.
- Arain S, Thalapparambath R, Al Ghamdi FH. COVID-19 pandemic: response plan by the Johns Hopkins Aramco Healthcare inpatient pharmacy department. *Res Soc Adm Pharm.* May 2020. https://doi.org/10.1016/j.sapharm.2020.05.016.
- Zheng SQ, Yang L, Zhou PX, Li HB, Liu F, Zhao RS. Recommendations and guidance for providing pharmaceutical care services during COVID-19 pandemic: a China perspective. Res Soc Adm Pharm. 2020(49):1. https://doi.org/10.1016/j.sapharm. 2020.03.012 0.
- 26. Pharmaceutical Services Programme M of HM. COVID-19 infographic |

pharmaceutical services programme. https://www.pharmacy.gov.my/v2/en/covid-19, Accessed date: 21 May 2020 Accessed.

- 27. Maharana S, Paul B, et al. Storage, reuse, and disposal of unused medications: a cross-sectional study among rural households of Singur, West Bengal. Int J Med Sci Publ Health. 2017;6(7) https://go.gale.com/ps/i.do?id=GALE%7CA501599147& sid=googleScholar&v=2.1&it=r&linkaccess=abs&issn=23204664&p=AONE& sw=w, Accessed date: 21 May 2020 Accessed.
- Alexander E, Butler CD, Darr A, et al. ASHP statement on telepharmacy. Am J Heal Pharm. 2017;74(9):e236–e241. https://doi.org/10.2146/ajhp170039.
- Greenwood DA, Gee PM, Fatkin KJ, Peeples M. A systematic review of reviews evaluating technology-enabled diabetes self-management education and support. J Diabetes Sci Technol. 2017;11(5):1015–1027. https://doi.org/10.1177/ 1932296817713506.
- Tang Wei, et al. Hydroxychloroquine in Patients Mainly with Mild to Moderate COVID-19: An Open-Label. Randomized: Controlled Trial.; 2020.
- Siaw MYL, Ko Y, Malone DC, et al. Impact of pharmacist-involved collaborative care on the clinical, humanistic and cost outcomes of high-risk patients with type 2 diabetes (IMPACT): a randomized controlled trial. *J Clin Pharm Ther*. 2017;42(4):475–482. https://doi.org/10.1111/jcpt.12536.
- Kharjul M, Braund R, Green J. The influence of pharmacist-led adherence support on glycaemic control in people with type 2 diabetes. *Int J Clin Pharm.* 2018;40(2):354–359. https://doi.org/10.1007/s11096-018-0606-z.