

Review

Emerging evidence on the association between COVID-19 and Type 2 Diabetes

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Abstract

Objective: Published studies demonstrate that diagnosis with Type 2 diabetes (T2DM) places patients at risk of severe symptoms and increased mortality from COVID-19. The literature was reviewed to understand emerging evidence. **Method:** A review of published studies on COVID-19 in patients with diabetes was conducted to identify the needs and optimal practice for the local population diagnosed with diabetes at risk of COVID-19. **Key Findings:** The combined sample was n=18746 where all patients were diagnosed with T2DM and COVID-19. The severity of symptoms was reported in n=7646. Most reported were fever, (32%) cough (26%), and chest tightness (8%). The causes of death were reported in n=3260. The main causes of death were: COVID-19 (76%), acute respiratory distress (5%). Other comorbidities were reported in n= 6968. The most reported comorbidities were hypertension (38%), cardiovascular (10%), and pulmonary disease (3%). Other risk factors were reported in n= 6968. Those most reported were diabetes, (80%) cardiovascular abnormalities (10%), hyperglycemia not previously diagnosed as diabetes (9%). The reported effects of antidiabetic medications on COVID-19 disease were reviewed for emerging evidence. **Conclusions:** Published studies underline the importance of maintaining weight, glycemic control, good hydration, and exercising as much as possible. Patients need to be informed to present to hospital promptly if developing COVID-19 symptoms. Normal T2DM therapy can be maintained in patients with no, or mild, symptoms. On presentation to hospital with severe COVID-19 disease, diabetes control maybe maintained with insulin, concurrent with hydration and metabolic parameters maintenance until the patient is recovered.

Keywords: Coronavirus, COVID-19, Diabetes Medications, Type 2 Diabetes.

Introduction

The disease caused by the novel coronavirus SARS-Cov-2 (COVID-19) is one of the fastest spreading respiratory system transmitted conditions, and is currently responsible for 13,141,232 cases with 7,660,786 recovered and 573,344 deaths globally [1]. The disease was declared a pandemic, triggering widespread simultaneous lockdowns around the world, with a fluctuating mortality rate around the globe [2]. Currently there is no cure for COVID-19, with a number of pharmacological treatments currently undergoing clinical trials. The virus enters the body via the respiratory system causing a range of symptoms including

a high-grade fever, a new or continuous cough, myalgia, gastrointestinal symptoms, and a loss or change in taste or smell [3]. They range from mild, to severe potentially life-threatening, causing hospitalization with pneumonia, acute respiratory distress syndrome (ARDS), multi-organ failure, and death [4].

Studies have described those with obesity, diabetes, and pre-existing cardiovascular conditions as 'at risk groups' and they were the basis of the recommendations on shielding from the World Health Organisation (WHO) [5]. Type 2 diabetes (T2DM) was one of the conditions classed as a risk factor to experience severe COVID-19 symptoms with a higher death rate especially in patients with poor glycemic control [6].



Method

A literature search was conducted using ScienceDirect®, Google® scholar and PubMed®. The search terms used were <coronavirus>, <diabetes> and <type 2 diabetes>. The search was limited to 2019 and 2020 (Fig 1). A total of 10 studies were analyzed.

All articles were screened and reviewed to fit the criteria to assess the association between T2DM and COVID-19 (Appendix 1).

Owing to the lack of randomized controlled trials, it was not possible to combine data from all studies for meta-analysis, so only a narrative review was possible on the information available (Table 1).

Results

All patients reported in the studies selected had been diagnosed with T2DM and COVID-19; there were four domains selected to measure the studies risk of bias score:

1. The study reported on symptoms severity.
2. The study reported on causes of death.
3. The study reported on one or more other risk factors e.g., hypertension, age, obesity, etc.
4. Diabetes medication continued.

The combined sample was n=18746 where all patients were diagnosed with T2DM and

COVID-19. Severity of symptoms was reported in n=7646, and the most reported symptoms were fever, (32%) cough (26%), and chest tightness (8%). Causes of death were reported in n=3260 by Huang et al, [4], Zhu et al [6], and Roncon et al [8]. The main causes of death were: COVID-19 (76%) and acute respiratory distress (ARD) (5%). Other comorbidities were reported in n= 6968 by Huang et al [4], Desai et al [11], and Zhou and Tan [12]. The most reported comorbidities were hypertension (38%), cardiovascular (10%), and pulmonary disease (3%). Other risk factors were reported in n= 6968 by Huang et al [4], Desai et al [11], and Zhou and Tan [12]. The most reported risk factors were diabetes, (80%) cardiovascular abnormalities (10%), hyperglycemia not previously diagnosed as diabetes (9%).

Diabetes medications were continued in n= 3185 and stopped in n= 15561 patients. Some medications used to treat diabetes were reported to contribute to poorer outcomes, if risk mitigation was not considered [15]. The authors concluded that metformin was found to contribute to dehydration leading to lactic acidosis and acute kidney injury. They also concluded that the sodium-glucose-co- transporter 2 inhibitors (e.g., canagliflozin, dapagliflozin, and empagliflozin) should not be initiated or continued during the COVID-19 infections as, in addition to increasing the risk of dehydration and acute kidney injury, they can cause ketoacidosis. Bornstein et al [15] stated that glucagon-like peptide-1 receptor

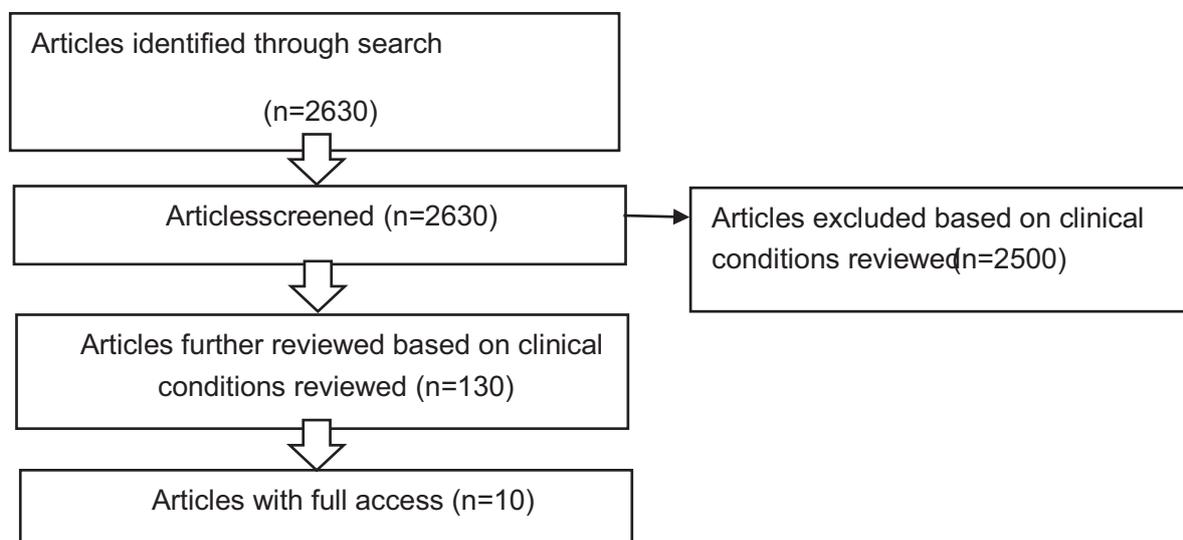


Figure 1: Inclusion and exclusion criteria of literature used.

Appendix 1: Final selected papers list (Columns contains a quotation from papers)

Reference	Design	Population	Intervention	Measured outcomes	Results	Conclusion
Zhu et al., 2020 ⁶	Cohort	7336	Assessing blood glucose levels of T2DM with COVID-19 and	Mortality	Patients had higher mortality (7.8% versus 2.7%: adjusted hazard ratio, 1.49) with multiple organ injury in comparison to those patients that were nondiabetic	Showed patient with improved glycemic control had better outcome with COVID-19 in T2DM patients
Huang et al., 2020 ⁴	Systematic review	6452	The need for ICU, poor outcome, severe mortality and disease progression	Mortality, severe COVID-19, acute respiratory distress syndrome, ICU and disease progression	T2DM was associated with composite poor outcome (RR2.38 [1.88, 3.03], p<0.001; I ² : 62%) and its subgroup which comprised of mortality (RR 2.12[1.44, 3.11], p<0.001; I ² :72%), severe COVID-19 (RR 2.45 [1.79, 3.35], p<0.001; I ² :45%), ARDS (RR 4.64 [1.86, 11.58], p=0.001; I ² :9%), and disease progression (RR 3.31 [1.08, 10.14], p=0.04; I ² : 0%)	Sever mortality rates were observed in patient with diabetes that were diagnosed with COVID-19
Kumar et al., 2020 ⁷	Systematic review	114	Assessing studies with patient with COVID-19 in patient hospitalized in ICU	Requiring invasive ventilation, requiring ICU care or progressive disease or refractory disease	Diabetes was found to be significantly associated with mortality of COVID-19 with a pooled odds ratio of 1.90 (95% CI: 1.37e2.64; p <0.01). Diabetes was associated with severe COVID-19 with a pooled odds ratio of 2.75 (95% CI: 2.09e3.62; p<0.01).	Diabetic patient showed to have a 'two-fold increase in mortality as well as severity of COVID-19' compared to those that had no diagnosis of diabetes. Kumar et al., 2020
Roncon et al., 2020 ⁸	Systematic review	1382	IC admission in T2DM patients- using Newcastle Ottawa quality assessment scale.	To assess the risk of ICU admission and mortality risk in diabetic COVID-19 patients.	DM results showed to be the second more frequent comorbidities. DM patients had a significant increased risk of ICU admission (OR: 2.79, 95% CI 1.85–4.22, p<0.0001, I2=46%). In 471 patients (mean age 56.6 years, 294 males) analyzed for the secondary outcome diabetic subjects resulted to be at higher mortality risk (OR 3.21, 95% CI 1.82–5.64, p < 0.0001, I2=16%).	Diabetic patients with COVID-19 had an increased risk of ICU admission with a higher rate of mortality
Zhang et al., 2020 ⁹	Cohort	74	To assess HbA _{1c} in T2DM patients with COVID-19	To describe characteristics of COVID-19 patients with type 2 diabetes and to analyze risk factors for severity	Twenty-seven patients (36.5%) were severe and 10 patients (13.5%) died.	T2DM patient showed to be more susceptible to COVID-19 in comparison to the overall population Zhang et al., 2020

Reference	Design	Population	Intervention	Measured outcomes	Results	Conclusion
Raoufi et al., 2020 ¹⁰	Cohort	117	CT results, and HbA _{1c} values were measured to assess severity	Chest CT scores were defined by summation of individual scores from 5 lung lobes	Chest CT severity scores were not significantly different to patient that were T2DM with COVID-19 in comparison to non-diabetic COVID-19 patients. Also, the mortality and recovery rates were similar between the two groups (p = 0.54 and p = 0.85, respectively)	Chest CT severity scores were not significantly different to patient that were T2DM with Corvid-19 in comparison to non-diabetic COVID-19 patients
Desai et al., 2020 ¹¹	Systematic review	2084	Assess COVID-19 symptoms in elderly patients	Mortality rate	T2DM and covid 19 patient with a mean age >50 years was 13.2% whereas other studies with relatively younger patients mean age <50 years had a pooled prevalence of 9.0%	The overall prevalence of COVID-19 was shown to be higher in elderly patient with T2DM in comparison to the younger population
Zhou and Tan 2020 ²²	Cohort	881	Patient capillary blood glucose were taken to assess severity	Mortality	56.6% (499/881) of the tests showed abnormal BG levels, including 29.4% (58/197) of the pre-prandial BG tests and 64.5% (441/ 684) of the postprandial tests. 69.0% (20/29) patients were considered with non-ideal BG levels. And 10.3% (3/29) of the patients suffered at least one episode of hypoglycemia (b3.9 mmol/L).	T2DM is seen to be a comorbidity causing severe symptoms in COVID-19
Guo et al. 2020 ¹³	Cohort	174	To assess if T2DM is a risk factor of COVID-19	C- reactive protein test and D-dimer test were used to assess severity in patients	COVID-19 patient without comorbidities but T2DM were at higher risk of severe pneumonia, release of tissue injury related enzymes due to dysregulation of glucose metabolism	T2DM should be considered as a risk factor for a rapid progression and deterioration in symptoms in patients with COVID-19
Wang et al 2020 ¹⁴	Cohort	132	Bloods were monitored to assess severity of covid 19	HbA _{1c} was monitored in patient alongside SaO ₂ Mortality rate was also assessed	Correlation analysis showed that there was a linear negative correlation between SaO ₂ and HbA _{1c} (r = -0.22, P = 0.01), while there was a linear positive correlation between serum ferritin, CRP, Fbg, and ESR levels and HbA _{1c} (p<0.05).	High level of HbA _{1c} is said to cause inflammation and hyper coagulation and low saturation O ₂ in COVID-19 patients and the mortality rate 27.7% higher in patient with diabetes

Table 1: Risk of bias score

Reference	The study reported on symptoms severity	The study reported on causes of death	The study reported on one or more other risk factors	Diabetes medication continued or stopped	Total score	Inclusion	Exclusion
Zhu et al. 2020 ⁶	Yes	No	Yes	Continued	3	T2DM and COVID-19, between 18 and 75 years of age	No electronic record, pregnant, has organ injury or cancers, laboratory results not available
Huang., et al. 2020 ⁴	Yes	No	Yes	Not clear	2	T2DM and COVID-19 and need for ICU	Other co-morbidities
Kumar et al. 2020 ⁷	Yes	Yes	No	Not clear	2	T2DM and COVID-19	Not reported
Roncon et al. 2020 ⁸	Yes	Yes	Yes	Not clear	3	T2DM and COVID-19 and need for ICU	Not reported
Guo et al. 2020 ¹³	Yes	Yes	Yes	Continued	4	T2DM and COVID-19	Not reported
Raoufi et al. 2020 ¹⁰	No	No	Yes	Continued	2	T2DM and COVID-19	Not reported
Wang et al. 2020 ¹⁴	Yes	No	Yes	Not clear	2	T2DM and COVID-19	Not reported
Desai et al. 2020 ¹¹	No	No	Yes	Continued	2	T2DM and COVID-19	Not reported
Zhang et al. 2020 ⁹	Yes	Yes	Yes	Not clear	3	T2DM and COVID-19	Not reported
Zhou and Tan 2020 ¹²	No	No	No	Continued	1	T2DM and COVID-19	Not reported

agonists (e.g., insulin glargine with lixisenatide, dulaglutide, exenatide-extended release, liraglutide, lixisenatide, and semaglutide) can be continued subject to monitoring and correcting dehydration. Dipeptidyl peptidase-4 inhibitors (e.g., alogliptin, linagliptin, saxagliptin, and sitagliptin) were generally well tolerated and could be continued [15]. Lastly, they reported that insulin was found to be the most beneficial and best tolerated, and should always be continued.

Narrative analysis

Zhu et al [6] examined the association between glycemic control and outcome in

patients with COVID-19 and pre-existing T2DM. In their retrospective multi-center study, they concluded that T2DM is a major co-morbidity of COVID-19. Zhu et al [6] explained that glycemic control in T2DM is an important factor in how an individual is impacted with COVID-19 and when poor, increased the likelihood of a severe presentation compared to those with no diabetes. Their study also revealed that T2DM patient required more time in intensive care units compared to non-diabetic patients. A gender difference was identified with males with T2DM at higher risk than females. Paland Bhadada [2] discussed the interaction between the two diseases and reviewed how T2DM placed individuals at a disadvantage. They found a clear relationship between

the two conditions and on how they combine to precipitate a severe outcome in response to the COVID-19 infection. They hypothesized that the interaction occurs because of the “*exaggerated pro-inflammatory cytokine response and low expression of angiotensin-converting enzyme 2 (ACE2)*” enhancing the severity of the symptoms caused by the virus. They also explain how SARS-Cov-2 causes worsening glycemic control. This is postulated to be due to SARS-Cov-2 mediated damage to pancreatic beta cells causing “*augmentation of insulin resistance through cytokines and ferritin A and hypokalemia*” [2]. The study by Singh and Singh [16] supported Banerjee et al [17] who focused on the relationship between poor glycemic control and the increased risk of severe presentation of COVID-19 symptoms.

Huang et al [4] concluded that COVID-19 pneumonia was both more severe and more often fatal in T2DM patients than in non-diabetic patients. They described how other risk factors alongside T2DM such as hypertension, particularly when influenced by age, could further worsen the patient outcomes [4]. Zhang et al [9] also reported that patients with uncontrolled T2DM were more susceptible to COVID-19 infection, with higher mortality and severity of symptoms.

Bouhanick et al [18] stated that “*whilst diabetes would not systemically increase the likelihood of being infected with COVID-19, once infected patients with diabetes are likely to develop a severe form of the disease*”. The authors also highlighted the association of T2DM medication and how it may impact the severity in symptoms of COVID-19. They explain how dipeptidylpeptidase-4 inhibitors can “*via the inflammatory effect, play a role in the course of the infection or in the occurrence of its complications*” [18]. The authors highlighted other T2DM medications that should be used with caution or discontinued in patients with COVID-19. These included ipeptidylpeptidase-4 inhibitors, glucagon like peptide-1 agonists, sodium-glucose co-transporter 2 inhibitor, and metformin [18]. Mukherjee et al [19] concluded that “*pioglitazone has more potential for benefit than harm and can be continued in people with T2DM and mild/moderate COVID-19*” unless contraindicated in the specific patient.

The pharmacology of the thiazolidinediones is said to play a vital role against COVID-19 through the moderation of host inflammatory responses that are driving hyperinflammation [19].

Bornstein et al [15] explained the nature and complexity of diabetes and how it is generally a primary risk factor for severe pneumonia in up to 50% in a diabetic patients compared to non-diabetic patients. The increased risk of infection is postulated to be due to “*defects in innate immunity affecting phagocytosis, neutrophil chemotaxis and cell mediated immunity*” [15]. In a meta-analysis, Kumar et al [7] described a strong correlation between diabetes and severe COVID-19 symptoms, from the pooled data of 16,003 patients, leading to a two-fold increase in mortality and severity of COVID-19 as compared to non-diabetics. Roncon et al [8] further explained that the diabetic patient is at higher risk of ICU admission, poor short-term outcome, and poor survival rate due to exhibiting deteriorating, disabling, severe symptoms. Raoufi et al [10] demonstrated that the chest computed tomography score did not show a statistically significant difference between the two groups.

Age is reported to impact outcome. Desai et al [11] pooled data on various age groups to understand the effect on patients with COVID-19 and T2DM. Their results revealed older patients showed an increased chance both of contracting COVID-19 and experiencing greater severity of symptoms. They reported that a patient, mean age <50 had a 9% chance of contracting COVID-19 compared to 13.2% for >50 years of age. They also considered comorbidities such as cardiovascular complications, and reported that increasing comorbidities alongside age may further impact T2DM / COVID-19 patients. The retrospective study of Guo et al [13] (n=174) found patients with T2DM were at a higher risk of severe pneumonia compared to patients without other comorbidities. Patients were screened with chest computed tomography (CT) alongside other treatment measures. They determined that 24 of their 174 patients were at higher risk of pneumonia and “*excessive uncontrolled inflammatory responses*” [13]. They concluded such patients required closer attention and were to be reviewed

accordingly due to their potential for rapid deterioration.

Zhou and Tan [12] reviewed the records of 881 patients concluding that diabetes and hyperglycemia can lead to higher secondary infection risks and mortality and therefore, tight glycemic control is essential in COVID-19 patients. Wang et al [14], in a retrospective study of 132 patients, found the mortality rate was higher in patients with T2DM by 27.7% and that high HbA_{1c} levels were associated with inflammation, hypercoagulability, and low oxygen saturations. They emphasized the importance of measuring HbA_{1c} levels post hospital admission to improve the prognosis of COVID-19 [14]. They also explained how COVID-19 potentially caused abnormal beta cell damage and insulin resistance causing blood glucose levels above their baseline in all patients.

Antidiabetic medication and COVID-19

Medications used to treat diabetes can lead to further deterioration in COVID-19 due to dehydration and renal injury. Banerjee et al [17] highlighted how the pandemic may have had an impact on glycemic control; reduced physical activity, more chance of eating at home and of consuming high energy take-away food affecting weight and consequently their diabetes [17].

Bouhanick et al [18] reviewed the pharmacological characteristics of T2DM treatment and the linkage to their effect on COVID-19. They discussed dipeptidyl peptidase-4 (DPP-4) inhibitors and the potential increased risk of infection through stimulating an 'inflammatory immune response through modifying the production of several cytokines and chemokines' [18]. They noted that other studies agreed that DPP-4 inhibitors in T2DM patients, particularly sitagliptin, increased the risk of upper respiratory tract and lower urinary tract infections.

Nakhleh and Shehadeh [20] agreed that T2DM medications may have deleterious effects on patients presenting with COVID-19. However, they also noted how some T2DM treatment may offer a protective role in COVID-19 related lung injury [20]. Insulin is an effective treatment to continue in diabetic patients positive

for COVID-19 as it inhibits the production of pro-inflammatory factors preventing acute lung injury. It also reduces the risk of developing diabetic ketoacidosis or hyperglycemic hyperosmolar states preventing further deterioration of any acute lung injury and acute respiratory distress [20].

Bornstein et al [15] stated that biguanides and SGLT-2 inhibitors should be withheld in patients with severe symptoms of COVID-19 to prevent the risk of metabolic decompensation [15]. They recommend that after cessation, insulin should be used for acute control. Conversely, regarding the DPP-4 inhibitors, Bornstein et al [15] differed from Bouhanick et al [18] by concluding they believed there was no convincing evidence to suggest DPP-4 inhibitors should be discontinued.

Ursini et al [21] focused on biguanides in COVID-19 patients. Their article on "COVID-19 and diabetes: Is metformin a friend or foe" describes how metformin and other medications such as pioglitazone and liraglutide may play a role in promoting the SARS-Cov-2 virus entry into host cells, they are said to 'work synergistically to increase the angiotensin converting enzyme-2 availability in the respiratory tract promoting SARS-Cov-2 infection' [21]. On the other hand, the author expounds how these medications may be advantageous in maintaining the optimal management of glycemic control and therefore need to be monitored to assess whether they are beneficial to be continued in patients who are positive COVID-19 [21].

A scoping review by Wicaksana et al [22] focused on the pharmacological management of T2DM patients during the pandemic. They also noted the importance of glycemic control and the prevention of hypoglycemia. They advised that adjustment of 'sulfonylurea and insulin dose may be necessary to prevent hypoglycemia' and should be handled with caution in elderly patients as they are more likely to have deteriorating glycemic control. They also explained the importance of close glycemic control during the COVID-19 pandemic due to the restrictions imposed; the social distancing and lockdown affecting individual weight, health, and mental state causing poorer glycemic control, and

pressure on staff in hospitals overloaded with Covid admissions [22].

Singh and Khunti [23] presented a concise table on anti-diabetic medications that may have a deleterious effect on patients diagnosed with COVID-19. The table showed that Metformin, Pioglitazone, Sulfonylurea, DPP-4 inhibitors, SGLT-2 inhibitors, and GLP-1 receptor agonists can all be continued in patients with mild to moderate COVID-19 disease but should be withheld in those presenting with severe symptoms, whilst insulin may be continued at any stage [23].

Mukherjee et al [19] analyzed the use of pioglitazone in patients with COVID-19. They explained how pioglitazone had potential for more benefit than harm and could be continued as advised also for mild/moderate COVID-19 disease.

It appears clear that tight glycaemic control appears advantageous, but must be weighed against the risk of precipitating hypoglycaemic episodes.

Limitations

COVID-19 is an extremely fast-moving field, and it is important to try to learn lessons as they emerge. However, most of the studies reported collected data in the early phase of the epidemic when many health services were overloaded and under pressure, whilst emerging data was constantly modifying policies and practices. It quickly became clear that T2DM is a major risk factor for severe presentations of COVID-19, and it is important that pharmacists learn the lessons of early experience in relation to diabetes and anti-diabetic drugs. This review presents and summarizes the information available at the time of submission.

Conclusion

Managing COVID-19 disease continues to follow emerging evidence which appears almost daily, but it is essential to pause and try to review the best information available to date in order to adapt and try to ensure our management reflect the

current evidence. Clearly diabetes and particularly T2DM are risk factors for worsening prognosis in COVID-19. Based upon the above we believe the current understanding of the evidence is:

1. Patients diagnosed with T2DM in lockdown need to the best of their ability, to maintain good weight, good glycaemic control, good hydration, and remain physically active.
2. Practitioners should provide information on the importance of early presentation to healthcare providers if COVID-19 symptoms are developing.
3. Following the treating practitioner's directions where possible, but taking note of the findings from previous studies. This suggests most patients with no symptoms or only mild symptoms of COVID-19 can maintain their normal therapy in T2DM patients.
4. Patients with severe COVID-19 symptoms, on presentation to hospital, most probably should have their oral therapy withheld and replaced by insulin while hydration and metabolic parameters are monitored until the patient has recovered.
5. This, like all other aspects of COVID-19 management, remains a fast-moving field and advice may change as more information emerges.

Conflict of interest

The authors declare no conflict of interest.

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Ethics clearance

This is a review article based on data already published in other research and does not include any new real life data; so it is exempted under the university and the UK health research approval requirement.

Authors' contributions

The 1st and 2nd authors conducted the review, 3rd and 4th authors completed the paper.

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