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COVID-19

Diabetes and COVID-19

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Summary According to previous reports, diabetes seems to be a risk factor which worsens the serious clinical events caused by COVID-19. But is diabetes *per se* a risk factor that increases the probability of getting the virus? This paper will discuss this point. There are not many research data on antidiabetic drugs in this context. The potential influence of glucose-lowering agents on the severity of COVID-19 has not been described yet. Dipeptidylpeptidase-4 (DPP-4) is a cell surface protein ubiquitously expressed in many tissues and it is also a soluble molecule found in serum/plasma fluids. DPP-4 is involved in infection of cells by some viruses. This paper reviews data about the use of DPP-4 inhibitors and others diabetes drugs on COVID-19 patients. As such, no available evidence has yet suggested that glucose-lowering drugs — including those targeting DPP4-related pathways — produce any significant harm or benefit in the context of human infections. However, insulin must remain the first-choice agent in the management of critically ill-hospitalized patients, while it is recommended to suspend other agents in unstable patients. This paper provides related French and international recommendations for people with diabetes who got infected by COVID-19 and upholds that infections may alter glucose control and may require additional vigilance.

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Abbreviations

ACEi	angiotensin-converting enzyme inhibitors
ARB	angiotensin II receptor blockers
DPP-4	dipeptidylpeptidase-4
GLP-1R	glucagon-like-peptide-1 receptor
HAS	French High Authority for Health (*Hauteautoritéde santé*)
ICU	intensive care unit
IL-6	interleukin-6
MERS-CoV	Middle East Respiratory Syndrome Coronavirus
NSAIDs	non-steroidal anti-inflammatory drugs
SGLT-2	sodium-glucose-transporter-2
TNF-α	tumor necrosis factor-α

Introduction

The global COVID-19 pandemic has resulted in a large body of literature on the risk factors which worsen the clinical events associated with the virus. Indeed, all patients do not face the disease with the same severity, and some patients are not symptomatic. Diabetes has rapidly become one of the potential risk factors, but is it so? Is diabetes a susceptibility factor and/or a severity factor? If it is, then could antidiabetic drugs, in particular dipeptidylpeptidase-4 (DPP-4) inhibitors, play a role in the occurrence of infections? This paper aims at discussing these issues.

Prevalence

At the very beginning of the COVID-19 pandemic, it was suggested that diabetes was one of the susceptibility factors for the infection along with advanced age, high blood pressure, smoking, overweight and obesity. Thus, in one of the first short series in Wuhan, a city heavily affected by the virus, out of 41 patients, 20% had diabetes and 15% had hypertension [1]. In another series of 140 infected and hospitalized patients, 12% were diabetic [2]. However, the lack of a control group makes this possible increase in the prevalence of infected and hospitalized diabetic patients uncertain. In addition, a lower prevalence of 3% of diabetic patients presenting symptoms for more than 10 days was also reported, but there was only a small number of patients concerned here, which has been an obstacle to correctly estimating this prevalence [3]. Thus, in a meta-analysis of 12 studies in China, out of 2018 confirmed infected patients, the prevalence of diabetes was 10.3%, which was similar to the prevalence of diabetic patients in China in 2013, meaning 10.9% for all ages combined [4,5]. However, since the average age of infected diabetic patients was 49.6 years, this prevalence must be compared to the one of a corresponding age group, estimated at 12.3%. Thus, the prevalence of diabetics among patients with COVID-19 was even lower than in the general population [5]. Consistent with these observations, the same trend was described in Italy, a country heavily affected by COVID-19. In the epicenter of the epidemic in Padua, 8.9% of infected patients aged 65 years old in average were diabetics, while the prevalence of diabetic patients in this region for the same age group was higher, described as 11% [6]. Therefore, based on these Chinese and Italian data, there may not be more diabetic patients affected by COVID-19 and a diabetic patient would not be put at a greater risk of contracting the disease if one compares to a non-diabetic patient. Nonetheless, among 5700 patients hospitalized with COVID-19 in the New York City area in April (median age 63 years; 40% female), the proportion of diabetic patients was higher as 34% of the patients included suffered from diabetes, 57% had hypertension and 42% were obese [7]. In a large worldwide observational study of 8910 patients with COVID-19, 14.3% had diabetes mellitus [8].

To date, no study has been able to distinguish between type 1 and type 2 diabetic patients, but the advanced age of the patients with diabetes suggests that there is a high rate of type 2 diabetic patients.

A selection bias is not excluded since not all patients with COVID-19 were tested with the virus and the proportion of patients with diabetes may be overestimated. The rate of diabetic patients varies, depending of the patient's location, the age and the method of testing. Similarly, it depends on the hospitalization criteria, which have changed over time, meaning that patients having one of the moderate forms of the disease have been decreasingly hospitalized, compared with the practice followed at the beginning of the pandemic. Nevertheless, pursuant to various studies, individuals with diabetes seem to be at similar risk of getting COVID-19 as patients without diabetes.

Diabetes, COVID-19 and disease severity

While diabetes would not systematically increase the likelihood of being infected with COVID-19, once infected, patients with diabetes are likely to develop a severe form of the disease. A meta-analysis of 6 studies in China reported that the relative risk of having a severe form was 2.26 (95% CI: 1.47—3.49); it ranged from 0.31 (a lesser risk in one study) to 4.06 (higher risk in five studies) [4].

For example, in a Chinese observational study of 1000 patients with a confirmed infection, the prevalence of diabetes in those with a severe form was 16% and only 5.5% in those with a lower severity of illness [9]. In another study on 1043 Italian patients infected and hospitalised in Lombardy in intensive care units, two third had a comorbidity factor, 49% had hypertension and 17% had diabetes [10]. In Italy, in a systematic review of 1362 patients, diabetic patients resulted to have a significant increased risk of intensive care unit admission (OR 2.79, 95% CI: 1.85—4.22, $P < 0.0001$) and a higher mortality risk (OR 3.21, 95% CI: 1.82—5.64, $P < 0.0001$) [11]. They were more likely to have unfavorable outcomes (OR = 3.10, 95% CI: 1.16—8.37, $P = 0.025$) in a Chinese retrospective study on 323 patients [12]. Finally, in Seattle, out of 24 patients admitted to intensive care units, 58% were diabetic [13]. Consistent with these reports, a meta-analysis on 6452 patients with diabetes revealed that diabetes was associated with composite poor outcome (including mortality, severe COVID-19, acute respiratory distress syndrome, need for intensive care unit care, and disease progression) [RR 2.38, 95% CI: 1.88—3.03, $P < 0.001$], severe COVID-19 (RR 2.45, 95% CI: 1.79—3.35, $P < 0.001$), acute respiratory distress syndrome (RR 4.64, 95% CI: 1.86—11.58, $P = 0.001$), and

disease progression (RR 3.31, 95% CI: 1.08—10.14, $P = 0.04$). Meta-regression showed that the association with composite poor outcome was influenced by age ($P = 0.003$) and hypertension ($P < 0.001$) [14]. In the worldwide observational study of 8910 patients with COVID-19 in Asia, Europe, and North America, non-survivors had a greater prevalence of diabetes mellitus. However, in a multivariate analysis, diabetes mellitus was not an independent predictor of hospital death [8].

Diabetic patients with COVID-19 are at high risk of severe pneumonia and present a marked pro-inflammatory and pro-thrombotic state compared to infected non-diabetic patients. Inflammation markers such as CRP, interleukin-6, ferritin and D-dimers are increased compared to non-diabetic patients while a marked inflammatory or cytokine storm is thought to be associated with a more pejorative prognosis [15]. In a review and meta-analysis of 15 studies including 51,845 patients with COVID-19 of whom 9066 were severe cases, high age was independently associated with a severe form [16]. In this review, diabetes was also associated with the occurrence of a severe form with an RR of 2.81 (95% CI: 2.01—3.93), and this association persisted in a study with multivariate analysis taking into account age (RR 2.21, 95% CI: 1.33—3.66, $P = 0.002$) [17]. The risk of severe form was also increased by the presence of unbalanced or complicated diabetes in studies of patients with H1N1 viruses in 2009 and with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 [13—15]. In a retrospective observational study from March 1st to April 6th, 2020 and despite several limitations, the mortality rate was 28.8% in patients with diabetes and/or uncontrolled hyperglycemia, compared with 6.2% in patients without diabetes or hyperglycemia ($P < 0.001$). In a cohort of 7336 COVID-19 patients with or without diabetes from 19 hospitals in Hubei Province, China, people admitted to the hospital with COVID-19 and diabetes required more medical interventions. Despite these interventions, they also had significantly higher mortality: 7.8% versus 2.7% as well as a greater incidence of multiple organ injury. Patients with well-controlled blood glucose (glycemic variability within 3.9 to 10.0 mmol/L) had a markedly lower mortality compared to individuals with poorly controlled blood glucose (upper limit of glycemic variability exceeding 10.0 mmol/L) [adjusted HR, 0.14; 95% CI, 0.03—0.60, $P = 0.008$] during hospitalisation [18]. These COVID-19 patients with uncontrolled hyperglycemia had a particularly high mortality rate. A variety of immune system abnormalities has been postulated to explain the association between hyperglycemia and immune dysfunction, including impairment in polymorphonuclear and monocytic white blood cell chemotaxis and phagocytosis, complement function, and cytokine dysregulation [19]. The fact that acute hyperglycemia plays a role which can be improved through effective glycemic management remained to be proved. In another study among over 500 patients with coronavirus, hyperglycemia was often transient and generally resolved after discharge from hospital in the majority of subjects [20]. The authors suggest that clinicians should treat hyperglycemia to achieve BG targets <180 mg/dL for most patients [19]. Klonoff et al. proposed four risk factors which can increase the risk of poor outcomes: a susceptibility to hyperglycemia from corticosteroid therapy, an inadequate glucose monitoring, a lack of contact with healthcare professionals and an inappropriate discontinuation of angiotensin receptor blockers [21]. CORONADO is an ongoing French study aiming to determine the risk factors of severe forms of the disease throughout the country [22].

Which hospitalised patients require an intensive care unit?

In China, intensive care unit (ICU) patients were more likely to have diabetes, were older (66 years vs. 51 years), and had twice as many co-morbidities (72% vs. 37%) compared to those who did not need to go to the ICU [23]. Male sex was more frequent in infected vs non-infected patients, with a described proportion ranging from 56% to 82%; men also appeared to be over-represented in ICU patients (61% vs. 52%), but this difference was not statistically significant [3,10,23].

Diabetes and COVID-19 mortality

Among 44,672 infected patients, the mortality rate reported in China was 2.3%; it was 7.3% in the presence of diabetes and 6% in hypertensive patients [24]. In Italy, 35% of the fatal cases had diabetes compared to 20% in the general population for this age group: diabetic patients were therefore over-represented among deceased patients, 70% were men with an average age of 80 years [4]. A meta-analysis confirmed that diabetes was associated with a higher mortality rate (RR 2.12) [14].

COVID-19 and diabetes drugs

This paper does not discuss the potential association between COVID-19 and hypertension or the prescription of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB) already reported [25]. We just remind that except in acute situations where a case-by-case analysis is recommended, the European Society of Cardiology as well as the French and American associations have published position papers which advocate for maintaining treatments with ACEi or ARB for patients infected by the virus. Similarly, it appears that corticosteroid therapies aggravate the patient's condition (although retrospective analysis is difficult because these therapies are generally used when the patient is in a very serious condition) and that non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen increase the risk of developing a serious form of the disease [26]. Therefore, fever should be treated with paracetamol only.

DPP-4 inhibitors

Regarding drugs which are specific to type 2 diabetes, the increase risk of infection is an issue which arises with dipeptidyl peptidase-4 (DPP-4) inhibitors. Indeed, in addition to its role in incretin metabolism and glucose regulation, DPP-4, also known as CD26, is a membrane glycoprotein which can be found on the surface of many cells with non-specific

exopeptidase enzyme activity. It stimulates inflammatory immune responses by modifying the production of several cytokines and chemokines [27—30]. Several studies have therefore focused on the role of DPP-4 inhibitors in the development of infections. Data from clinical trials suggested an increase in upper respiratory and lower urinary tract infections with DDP-4 inhibitors, particularly with sitagliptin [31,32].

In 2011, an analysis of the international pharmacovigilance database VigiBase indicated higher reporting of infections associated with DPP-4 inhibitors with a higher signal for upper respiratory infections [33] but a case-control study nested in a cohort of nearly 50,000 diabetic patients in the UK found no association between DDP-4 inhibitors use and hospitalization for community-acquired pneumonia [34], and the most recent meta-analysis including 74 clinical trials of more than 12 weeks of duration also did not suggest an increase in the overall risk of infection with DDP-4 inhibitors [35].

In patients with diabetes, sitagliptin is believed to reduce levels of pro-inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) [36,37]. Thus, DPP-4 inhibitors could, via this anti-inflammatory effect, play a role in the course of the infection or in the occurrence of its complications. It is currently shown that, in patients with COVID-19, significantly elevated IL-6 levels are associated with an increased risk of respiratory failure [38,39].

In addition, human DPP-4 has been identified as a functional receptor for the spicule protein of the coronavirus which caused the Middle East Respiratory Syndrome (MERS) in Saudi Arabia in 2012 [40,41]. Antibodies directed against DPP-4 inhibited MERS-CoV infection. Studies on transgenic mice suggested that the complication rate in people with type 2 diabetes infected with MERS-CoV may be associated with a DPP-4 related disturbance of the immune response [42]. Although to date no direct consequences can be drawn for the current COVID-19 epidemic (whose gateway is the angiotensin-converting enzyme 2, ACE2), more studies on the links between DPP-4 and coronavirus infection have to be carried on [41].

Other glucose-lowering drugs

Similarly, concerning other antidiabetic medications, there is no established evidence supporting any clinical benefit in COVID-19 patients but potential risks must be carefully kept in mind. Indeed, while metformin, glucagon-like-peptide-1 receptor (GLP-1R) agonists, thiazolidinediones and insulin have all been associated with anti-inflammatory effects [43—48] which could be potentially beneficial in the context of a cytokine storm, no association was observed for insulin or other glucose-lowering therapy among survivors and non-survivors of COVID-19 [8]. However, it is suggested that the use of metformin, sodium-glucose-transporter-2 (SGLT-2) inhibitors, GLP-1R agonists, pioglitazone and insulin may increase the expression of ACE2 and therefore be potentially associated with a more severe condition [47—49]. In critically ill COVID-19 patients, the risk of metabolic acidosis associated with metformin might be exacerbated as well as the consequences of volume depletion with SGLT-2 inhibitors. Hence, insulin remains the drug of choice in these situations.

What can we learn from pharmacovigilance data in France?

Pharmacovigilance data in France were provided by the National Network of Pharmacovigilance Centers [50] which monitors on a daily basis the adverse drug reactions associated with the drugs used in COVID-19. As of mid-April 2020, nearly 3 months after the first case in the territory, there were 47 reported cases of adverse drug reactions occurring in the context of COVID-19 in patients with diabetes. The median age of the patients was 67 years (min-max: 34-88 years), 66% were male, 85% ($n = 40$) of the cases were serious and 7 (14%) died. One third of these cases (16 patients) presented with heart rhythm disorders related mainly to the use of hydroxychloroquine with or without azithromycin. Of these, 94% had high blood pressure and 38% had a history of heart disease. Eight cases (17%) exposed to the lopinavir/ritonavir (Kaletra®) combination presented a hepatic disorder ($n = 4$) or exacerbation of renal failure ($n = 4$). Eleven other cases (23%) had respiratory complications (90% were hypertensive and 18% had a pulmonary history). Of these cases, 4 patients treated with long-term sitagliptin required admission in ICU (one case died). They were 3 women and 1 man, 65 to 88 years old, 2 were obese, all were hypertensive. In none of the cases was sitagliptin the only drug suspected of worsening the infection: 2 cases were also treated with ARB and 2 had received an NSAID. These data show that patients with diabetes are also subject to serious adverse reactions to the drugs used in COVID-19. Patients with adverse reactions often have comorbidities, especially hypertension.

What are the recommendations?

The Francophone Society of Diabetology took up very early on the issue of how to manage diabetes on a daily basis in a COVID-19 situation without distinguishing between the management of type 1 or type 2 diabetes, but providing advice that applies in both situations. Thus, among 10 key messages, the over-risk of serious forms in diabetic patients with co-morbidities, the importance of protectives behaviours, the value of providing a 2-week supply of drugs and sensors and the increased risk of ketoacidosis in type 1 diabetics are highlighted [51]. The French High Authority for Health (*Haute autorité de santé*) provides recommendations to manage diabetes and points out that patients must take care of themselves and manage their glycemic control [52]. Then, during the period of COVID-19 infection, patients with diabetes should avoid close contact with others when indicated, should wear masks and apply protective behaviours. Glycaemia should be closely monitored and, if it is not the case, they must attend a practitioner visit.

In the ICU, practical sheets for management of diabetic patients have been drawn up (not exclusively regarding COVID-19 infection); they are similar to the recommendations for management in the perioperative period [53]. They also aim to standardise management by avoiding hyperglycemia, which could be harmful in this infectious context, but also hypoglycemia, whose negative impact is regularly recalled in particular in the case of ischemic heart

disease. It is mentioned that initial insulin resistance is frequently observed. The use of infusion pump insulin therapy is recommended to achieve glycemic targets and non-insulin treatments for type 2 diabetes should be stopped until the patient's clinical condition (renal, cardiac and respiratory function) is improved. Conversely, insulin should never be discontinued in patients with type 1 diabetes who are at increased risk of ketoacidosis in this context. Blood glucose monitoring should be carried out with classic blood glucose levels (arterial > venous > capillary blood), since glucose sensors may give erroneous measurements or may not be validated in resuscitation (distorted by high doses of vitamin C or by paracetamol).

The French Society of Pharmacology and Therapeutics has provided on its website answers on medication management in the context of COVID-19 [54]. The American Diabetes Association is pulling resources relevant to diabetes and COVID-19 for professionals treating patients with diabetes and there is also a forum accessible for free on this topic [50].

Conclusion

This paper highlights that while there have been no major safety concerns related to COVID-19 and the use of glucose-lowering drugs in patients with diabetes, there is only little information about the potential benefits or risks of these agents in the context of COVID-19 infections. This paper upholds that, upon admission to hospital of unstable patients and critically ill patients, DPP4 inhibitors, GLP-1R agonists, SGLT2 inhibitors and metformin should be used with caution or discontinued. In general, insulin is extensively used in critically ill hospitalized diabetic patients, as well as in patients with concomitant sepsis. Therefore, insulin is the most relevant treatment in these situations, particularly for patients who are hospitalized in intensive care units where other glucose lowering drugs should be discontinued. Careful attention must be paid to avoid hyperglycemia. The lack of physical activity and diet caused by the lockdown, and infection due to COVID-19 are two situations that may worsen glycemic control. Both hospitalized and ambulatory patients with diabetes are advised to ensure a careful monitoring of blood glucose and to maintain a regular communication with their health care provider.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel Coronavirus in Wuhan, China. Lancet Lond Engl 2020;395(10223):497—506, http://dx.doi.org/10.1016/S0140-6736(20)30183-5.

[2] Zhang JJ, Dong X, Cao YY, Yuan YD, Yang YB, Yan YQ, et al. Clinical characteristics of 140 patients infected with SARS-CoV-2 in Wuhan, China. Allergy 2020, http://dx.doi.org/10.1111/all.14238 [Epub ahead of print].

[3] Xu XW, Wu XX, Jiang XG, Xu KJ, Ying LJ, Ma CL, et al. Clinical findings in a group of patients infected with the 2019 novel Coronavirus (SARS-Cov-2) outside of Wuhan, China: retrospective case series. BMJ 2020;368:m606, http://dx.doi.org/10.1136/bmj.m606.

[4] Fadini GP, Morieri ML, Longato E, Avogaro A. Prevalence and impact of diabetes among people infected with SARS-CoV-2. J Endocrinol Invest 2020;43(6):867—9, http://dx.doi.org/10.1007/s40618-020-01236-2.

[5] Wang L, Gao P, Zhang M, Huang Z, Zhang D, Deng Q, et al. Prevalence and ethnic pattern of diabetes and prediabetes in China in 2013. JAMA 2017;317(24):2515—23, http://dx.doi.org/10.1001/jama.2017.7596.

[6] Longato E, Di Camillo B, Sparacino G, Saccavini C, Avogaro A, Fadini GP. Diabetes diagnosis from administrative claims and estimation of the true prevalence of diabetes among 4.2 million individuals of the Veneto region (North East Italy). Nutr Metab Cardiovasc Dis 2020;30(1):84—91, http://dx.doi.org/10.1016/j.numecd.2019.08.017.

[7] Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalised with COVID-19 in the New York City area. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.6775 [Epub ahead of print].

[8] Mehra MR, Desai SS, Kuy S, Henry TD, Patel AN. Cardiovascular disease, drug therapy, and mortality in COVID-19. N Engl J Med 2020:1—8, http://dx.doi.org/10.1056/NEJMoa2007621.

[9] Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of Coronavirus disease 2019 in China. N Engl J Med 2020;382(18):1708—20, http://dx.doi.org/10.1056/NEJMoa2002032.

[10] Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy region, Italy. JAMA 2020:1574—81, http://dx.doi.org/10.1001/jama.2020.5394 [Epub ahead of print].

[11] Roncon L, Zuin M, Rigatelli G, Zuliani G. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. J Clin Virol 2020;127:104354, http://dx.doi.org/10.1016/j.jcv.2020.104354.

[12] Hu L, Chen S, Fu Y, Gao Z, Long H, Wang JM, et al. Risk factors associated with clinical outcomes in 323 COVID-19 hospitalised patients in Wuhan, China. Clin Infect Dis 2020, http://dx.doi.org/10.1093/cid/ciaa539, pii: ciaa539, [Epub ahead of print].

[13] Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. COVID-19 in critically ill patients in the Seattle region — case series. N Engl J Med 2020, http://dx.doi.org/10.1056/NEJMoa2004500 [Epub ahead of print].

[14] Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia — a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14(4):395—403.

[15] Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab Res Rev 2020:e3319, http://dx.doi.org/10.1002/dmrr.3319 [Epub ahead of print].

[16] Matsushita K, Ding N, Kou M, Hu X, Chen M, Gao Y, et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: a systematic review and meta-analysis. medRxiv 2020, http://dx.doi.org/10.1101/2020.04.05.20054155, https://www.medrxiv.org/content/10.1101/2020.04.05.20054155v2. [Accessed May 12, 2020].

[17] Liang W, Guan W, Chen R, Wang W, Li J, Xu K, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. Lancet Oncol 2020;21(3):335—7.
[18] Zhu L, She ZG, Cheng X, Qin JJ, Zhang XJ, Cai J, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020, http://dx.doi.org/10.1016/j.cmet.2020.04.021, https://www.sciencedirect.com/science/article/pii/S1550413120302382?via%3Dihub [Epub ahead of print, Accessed May 12, 2020].
[19] Bode B, Garrett V, Messler J, McFarland R, Crowe J, Booth R, et al. Glycemic characteristics and clinical outcomes of COVID-19 patients hospitalised in the United States; 2020. https://glytecsystems.com/wp-content/uploads/Sage.Glycemic-Characteristics-and-Clinical-Outcomes-of-Covid-19-Patients.FINAL_.pdf [Accessed May 12, 2020 (17 pp.)].
[20] Yang JK, Lin SS, Ji XJ, Guo L-M. Binding of SARS Coronavirus to its receptor damages islets and causes acute diabetes. Acta Diabetol 2010;47(3):193—9.
[21] Klonoff DC, Umpierrez GE. COVID-19 in patients with diabetes: risk factors that increase morbidity. Metabolism 2020:154224.
[22] Société Francophone du Diabète. L'étude CORONADO : CORONAvirus disease 2019 and Diabetes Outcomes; 2020. https://www.sfdiabete.org/actualites/medical/letude-coronado-coronavirus-disease-2019-and-diabetes-outcomes [Accessed May 12, 2020].
[23] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalised patients with 2019 novel Coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;7, http://dx.doi.org/10.1001/jama.2020.1585 [Epub ahead of print].
[24] Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Centre for Disease Control and Prevention. JAMA 2020, http://dx.doi.org/10.1001/jama.2020.2648 [Epub ahead of print].
[25] Alexandre J, Cracowski JL, Richard V, Bouhanick B. Do we need to stop angiotensin converting enzyme inhibitors or angiotensin II receptor blockers in COVID-19 patients? Therapies 2020;75, http://dx.doi.org/10.1016/j.therap.2020.05.009 [in press].
[26] Micallef J, Soeiro T, Jonville-Bera AP. Non-steroidal anti-inflammatory drugs, pharmacology, and COVID-19 infection. Therapies 2020, http://dx.doi.org/10.1016/j.therap.2020.05.003. https://www.sciencedirect.com/science/article/pii/S0040595720300925 [Accessed May 12, 2020].
[27] Mentlein R. Dipeptidyl-peptidase IV (CD26)-role in the inactivation of regulatory peptides. Regul Pept 1999;85(1):9—24.
[28] Ou X, O'Leary HA, Broxmeyer HE. Implications of DPP4 modification of proteins that regulate stem/progenitor and more mature cell types. Blood 2013;122(2):161—9.
[29] Reinhold D, Biton A, Goihl A, Pieper S, Lendeckel U, Faust J, et al. Dual inhibition of dipeptidyl peptidase IV and aminopeptidase N suppresses inflammatory immune responses. Ann N Y Acad Sci 2007;1110:402—9.
[30] Steinbrecher A, Reinhold D, Quigley L, Gado A, Tresser N, Izikson L, et al. Targeting dipeptidyl peptidase IV (CD26) suppresses autoimmune encephalomyelitis and up-regulates TGF-beta 1 secretion in vivo. J Immunol 2001;166(3):2041—8.
[31] Richter B, Bandeira-Echtler E, Bergerhoff K, Lerch CL. Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetes mellitus. Cochrane Database Syst Rev 2008;2:CD006739.
[32] Monami M, Lacomelli I, Marchionni N, Mannucci E. Dipeptydil peptidase-4 inhibitors in type 2 diabetes: a meta-analysis of randomised clinical trials. Nutr Metab Cardiovasc Dis 2010;20(4):224—35.
[33] Willemen MJ, Mantel-Teeuwisse AK, Straus SM, Meyboom RH, Egberts TC, Leufkens HG. Use of dipeptidyl peptidase-4 inhibitors and the reporting of infections: a disproportionality analysis in the World Health Organisation VigiBase. Diabetes Care 2011;34(2):369—74.
[34] Faillie JL, Filion KB, Patenaude V, Ernst P, Azoulay L. Dipeptidyl peptidase-4 inhibitors and the risk of community-acquired pneumonia in patients with type 2 diabetes. Diabetes Obes Metab 2015;17(4):379—85.
[35] Yang W, Cai X, Han X, Ji L. DPP-4 inhibitors and risk of infections: a meta-analysis of randomised controlled trials. Diabetes Metab Res Rev 2016;32(4):391—404.
[36] Satoh-Asahara N, Sasaki Y, Wada H, Tochiya M, Iguchi A, Nakagawachi R, et al. A dipeptidyl peptidase-4 inhibitor, sitagliptin, exerts anti-inflammatory effects in type 2 diabetic patients. Metabolism 2013;62(3):347—51.
[37] Matsubara J, Sugiyama S, Akiyama E, Iwashita S, Kurokawa H, Ohba K, et al. Dipeptidyl peptidase-4 inhibitor, sitagliptin, improves endothelial dysfunction in association with its anti-inflammatory effects in patients with coronary artery disease and uncontrolled diabetes. Circ J 2013;77(5):1337—44.
[38] Coomes EA, Haghbayan H. Interleukin-6 in COVID-19: a systematic review and meta-analysis. medRxiv 2020, http://dx.doi.org/10.1101/2020.03.30.20048058 [2020.03.30.20048058].
[39] Herold T, Jurinovic V, Arnreich C, et al. Level of IL-6 predicts respiratory failure in hospitalised symptomatic COVID-19 patients. medRxiv 2020, http://dx.doi.org/10.1101/2020.04.01.20047381 [2020.04.01.20047381].
[40] Raj VS, Mou H, Smits SL, Dekkers DH, Müller MA, Dijkman R, et al. Dipeptidyl peptidase 4 is a functional receptor for the emerging human Coronavirus-EMC. Nature 2013;495(7440):251—4.
[41] Drucker DJ. Coronavirus infections and type 2 diabetes-shared pathways with therapeutic implications. Endocr Rev 2020;41(3) [pii: bnaa011].
[42] Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role? Diabetes Res Clin Pract 2020;162:108125.
[43] Cameron AR, Morrison VL, Levin D, Mohan M, Forteath C, Beall C, et al. Anti-inflammatory effects of metformin irrespective of diabetes status. Circ Res 2016;119(5):652—65.
[44] Drucker DJ. Mechanisms of action and therapeutic application of glucagon-like peptide-1. Cell Metab 2018;27(4):740—56.
[45] Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den Berghe G. Intensive insulin therapy exerts anti-inflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. J Clin Endocrinol Metab 2003;88(3):1082—8.
[46] Ceriello A. Thiazolidinediones as anti-inflammatory and anti-atherogenic agents. Diabetes Metab Res Rev 2008;24(1):14—26.
[47] Carboni E, Carta AR, Carboni E. Can pioglitazone be potentially useful therapeutically in treating patients with COVID-19? Med Hypotheses 2020;140:109776.
[48] Ursini F, Ciaffi J, Paola Landini M, Meliconi R. COVID-19 and diabetes: is metformin a friend or foe? Diabetes Res Clin Pract 2020:108167.
[49] Pal R, Bhadada SK. Should anti-diabetic medications be reconsidered amid COVID-19 pandemic? Diabetes Res Clin Pract 2020;163:108146.
[50] Réseau français des centres régionaux de pharmacovigilance. https://www.rfcrpv.fr/.[Accessed May 12, 2020].
[51] Société francophone du diabète. Diabète et COVID-19 ? : 10 messages clés; 2020. https://www.sfdiabete.org/files/files/Divers/diabete_et_covid-19_messages_cles.pdf [Accessed May 12, 2020 (2 pp.)].

[52] Haute autorité de santé. Diabète ? : poursuivre ses soins et faire face au COVID-19; 2020. https://www.has-sante.fr/jcms/p_3182187/fr/diabete-poursuivre-ses-soins-et-faire-face-au-covid-19 [Accessed May 12, 2020].
[53] Société francophone du diabète — Société française d'anesthésie et de réanimation. Prise en charge des patients diabétiques à la phase aiguë d'une infection en réanimation; 2020. https://www.sfdiabete.org/files/files/Divers/diabete_covid_et_reanimation_mars_2020.pdf [Accessed May 12, 2020 (8 pp.)].
[54] Société française de pharmacologie et de thérapeutique. Réponses d'experts à vos questions sur les médicaments et le COVID-19; 2020. https://www.pharmacol-fr.org/covid19-foire-aux-questions [Accessed May 12, 2020].