

The Use of Insulin Negatively Impacts the Mortality of Severe COVID-19 in Patients with Type 2 Diabetes—A Systematic Review

Caio F. Biolcatti^{1#}, Marcela R. Simoes^{1#}, Thais P. Prado¹, Milena Monfort-Pires², Licio A. Velloso^{1,3*}

¹Obesity and Comorbidities Research Center, Campinas, Brazil

²Turku PET Centre, University of Turku, Turku, Finland

³National Institute of Science and Technology on Neuroimmunomodulation, Campinas, Brazil

Email: *lavellos@unicamp.br

How to cite this paper: Biolcatti, C.F., Simoes, M.R., Prado, T.P., Monfort-Pires, M. and Velloso, L.A. (2024) The Use of Insulin Negatively Impacts the Mortality of Severe COVID-19 in Patients with Type 2 Diabetes—A Systematic Review. *Journal of Diabetes Mellitus*, **14**, 166-176.
<https://doi.org/10.4236/jdm.2024.143014>

Received: June 4, 2024

Accepted: August 3, 2024

Published: August 6, 2024

Copyright © 2024 by author(s) and Scientific Research Publishing Inc. This work is licensed under the Creative Commons Attribution International License (CC BY 4.0).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Obesity and type 2 diabetes are among the most important risk factors for severe coronavirus disease-19. Some studies have suggested that the use of insulin as a therapeutic agent to treat hyperglycemia and the metabolic abnormalities associated with type 2 diabetes during the acute phase of severe coronavirus disease-19 could have a negative impact on the disease's progression; however, there is no consensus on this issue. Here, we performed a systematic review in an attempt to answer this important question. We included 29 articles published from December 2019 to August 2023, which reported the outcomes of 3,070,657 patients with severe coronavirus disease-19 that had the diagnosis of diabetes and were treated with either insulin or other glucose-reducing agents. The results show that using insulin as a pharmacological intervention to treat type 2 diabetes in patients with severe coronavirus disease-19 increases the likelihood of mortality by 193%.

Keywords

SARS-CoV2, Obesity, Inflammation, Metabolism, Glucose

1. Introduction

As of March 2024, coronavirus disease-19 (COVID-19) has claimed the lives of over 7 million people worldwide [1]. In the early reports on the emergence and clinical aspects of COVID-19, obesity and type 2 diabetes (T2D) were cited as important risk factors for the development of severe forms of the disease [2] [3].

*Corresponding Author.

#Contributed equally as first author of this study.

Several mechanisms have been described as potentially being involved in the overlap of COVID-19, obesity, and T2D, suggesting that it results from multiple factors, including genetic, epigenetic, and environmental [4] [5].

Regardless of the mechanisms behind these common epidemiological associations, the severity of the disease has imposed therapeutic puzzles, as warranting metabolic stability directly impacts COVID-19 outcomes [4] [6]. An important therapeutic question that emerged early during the COVID-19 pandemic was whether the use of insulin to control glucose levels and metabolic abnormalities in T2D patients who developed COVID-19 would be safer and more effective than other glucose-lowering agents [7]-[9]. After the first year of the pandemic, a review published in *Nature Reviews Endocrinology* [9] proposed that insulin was the best option as compared to inhibitors of sodium-glucose cotransporter 2 (iSGLT2), and inhibitors of dipeptidyl peptidase 4 (iDPP4). A similar recommendation was published in a review in *The Lancet: Diabetes & Endocrinology* [10]. However, at about the same time, a study reported that the use of insulin was associated with increased mortality in patients with COVID-19 and T2D, and suggested that this outcome was due to increased systemic inflammation and aggravated injuries of vital organs [11]. The publication of this study initiated an important debate in the field, and after three years, we are still uncertain about the impact of insulin use on T2D patients with COVID-19.

In 2022, a large meta-analysis evaluated the outcomes of treating T2D in COVID-19 patients with iSGLT2, iDPP4, metformin, glucagon-like-1 receptor antagonists (GLP1-RA), thiazolidinediones (TZD), inhibitors of alpha-glucosidase, secretagogues and insulin [12]. The study showed that iSGLT2 and GLP1-RA were the drugs with the lowest, whereas insulin was the drug with the highest risk of adverse outcomes [12]. However, the study included articles published until September 2022, which means that it was representative of a very particular phase of the pandemic when mortality was high and there was no vaccine available. At present, the spectrum of patients developing severe COVID-19 has changed as compared to the early days of the pandemic, and this could impact the responsiveness and complications attributed to insulin. Therefore, we hypothesized that the use of insulin to treat patients with T2D and COVID-19 could represent a risk for increased mortality. Thus, we conducted a systematic review to determine the current status of the outcomes associated with the use of insulin in T2D patients who develop severe COVID-19. Our results indicate that the use of insulin increases the mortality of severe COVID-19 patients with T2D.

2. Methods

This was a systematic review that explored the clinical impact of using insulin in hospitalized T2D patients with COVID-19 (in four articles, highlighted in **Table 1**, the patients were already using insulin prior to hospitalization). Two authors (CFB and MRS), independently, identified studies published until August 31, 2023, which contained data on COVID-19 patients with T2D using or not using

insulin. The search was conducted separately in four databases: PubMed-NCBI, Scopus, Web of Science, and Google Scholar. English was the chosen language for search and articles.

The selected keywords and their synonymous terms, which were selected from the MeSH database, were: 1) “insulin” OR “regular insulin” OR “soluble insulin”; 2) “diabetes mellitus, type 2” OR “diabetes mellitus type 2” OR “diabetes mellitus type II” OR “type 2 diabetes” OR “diabetes mellitus, non-insulin-dependent”; iii, “covid-19” OR “SARS CoV 2” OR “2019 novel coronavirus” OR “2019 nCoV” OR “covid-19” OR “severe acute respiratory syndrome coronavirus 2 infection” OR “coronavirus disease 2019”. All these synonyms were combined using “AND”, and the search was performed in the title and/or abstract. The search was conducted similarly in all databases.

From all the articles found in the four databases, the researchers independently excluded duplicates and selected the relevant articles, based on the title and abstract—those directly or indirectly related to the correlation of favorable and unfavorable outcomes with the use or non-use of insulin in patients T2D and with COVID-19. Once this process was concluded, the authors compared their findings (cross-reference), resulting in the final pre-selected list of 543 articles.

From this list, 480 articles were screened for one or more of the following exclusion criteria, previously defined by the researchers: editorials, meta-analyses, systematic reviews, experimental studies, comments, letters to the Editor, studies without descriptions of patients’ clinical characteristics and/or current therapeutic regimens, studies that did not follow the selected clinical criteria, duplicated articles, and texts in languages other than English. After exclusions, 63 articles remained for the study analysis. Finally, the authors independently and carefully analyzed each of the 63 articles to determine those with the necessary and accessible data, which means, the articles presented in detail the pharmacological interventions for each group of patients and the respective clinical outcomes. In case of discrepancies, a third author (LAV) was consulted. As a result, 29 articles were included in the final analysis (**Figure 1**). Risk of bias was evaluated by three authors, independently (CFB, MRS and LAV).

For the statistical analysis, the assumption was that the use of insulin to treat T2D in patients with COVID-19 could increase mortality. It was determined the probability of the outcome, under analysis, to occur, using the odds ratio. This analysis was made for all the study designs, together and separately. The outcome under analysis was death. Patients using insulin were considered the intervention group, and patients without insulin were considered the control group. In addition, an unpaired student’s t-test was used to determine the statistical difference of the percentage of alive patients, between patients using insulin and those not using insulin. The significant difference was defined as $p < 0.05$. The software employed for statistical analysis was StatView for Windows.

3. Results

This systematic review evaluated the outcomes of 3,070,657 patients with severe

COVID-19 and T2D that required pharmacological intervention to treat hyperglycemia (**Table 1**).

Table 1. Articles included in the final analysis.

Articles	Type of Study	T2D Patients With Covid-19										
		Number of Patients			T2D Treatment		Outcomes With Insulin			Outcome Without Insulin		
		Male	Female	Total Patients	Insulin	Non-insulin	Alive	Deceased	Total	Alive	Deceased	Total
10.1016/j.jcte.2021.100265	Retrospective Study	166	82	248	171	77	94	74	168	54	23	77
10.1002/edm.2.301	Retrospective Study	74	57	131	48	83	40	8	48	68	15	83
0.1016/S2213-8587(21)00050-4	Observational Cohort Study	159,3730	1,257,735	2,851,465	350,960	2,500,505	338,180	2825	341,005	2,446,340	10,654	2,456,994
10.1080/07435800.2020.1856865 *	Retrospective Study	86	80	166	88	78	57	31	88	64	14	78
10.1016/j.cmet.2020.11.014	Retrospective Study	364	325	689	346	343	252	94	346	231	12	243
10.2337/dc20-0660	Retrospective Study	—	—	120	71	49	55	16	71	46	3	49
10.7196/SAMJ.2021.v111i10.15779	Cross-Sectional Descriptive Study	304	370	674	421	253	395	26	421	243	10	253
10.7759/cureus.14223	Case Report Article	4	1	5	2	3	1	1	2	2	1	3
10.1007/s00125-020-05351-w *	Observational Cohort Study	1782	1014	2796	1039	1757	762	277	1039	1457	300	1757
10.1016/j.diabres.2021.108925	Retrospective Study	2121	3598	5708	2073	2735	1661	412	2073	3119	516	3635
10.1016/j.amjmed.2020.05.033	Retrospective Study	42	42	84	29	55	14	15	29	53	2	55
10.2147/DMSO.S385646	Retrospective Study	1150	773	1923	170	286	93	77	170	119	167	286
10.2337/dc22-0357	Retrospective Study	1910	1157	3067	924	1827	565	359	924	1132	695	1827
10.3389/fendo.2022.909874	Retrospective Study	70,617	153,573	224,190	58,271	165,899	47,112	11,159	58,271	142,866	23,033	165,899
10.1007/s13300-022-01259-3	Case-Control Study	7749	6058	13,807	1714	12,093	1497	217	1714	11248	845	12,093
10.1155/2022/8030765	Retrospective Study	65	48	113	39	74	28	11	39	53	21	74
10.1155/2022/9322332	Retrospective Study	—	—	108	43	65	29	14	43	63	2	65
10.1136/bmjopen-2021-052310	Retrospective Study	—	—	901	273	628	241	32	273	606	22	628
10.1007/s40200-021-00833-z	Observational Cohort Study	155	89	244	140	104	84	56	140	70	34	104
10.2337/dc20-1340	Case Report (Series) Article	65	25	90	29	61	10	19	29	42	19	61
10.15277/bjd.2021.319	Retrospective Study	—	—	84	39	45	21	18	39	28	17	45
10.1002/hsr.2.889	Cross-Sectional Descriptive Study	46	24	70	39	31	6	33	39	29	2	31

Continued

10.1136/bmjdr-2021-002252	Retrospective Study	12,970	893	13,863	3508	10,355	2592	916	3508	7673	2682	10,355
10.2337/dc20-1543 *	Retrospective Study	630	649	1279	531	748	246	285	531	639	109	748
10.1186/s13098-022-00857-2 *	Case-Control Study	476	220	696	227	469	194	33	227	416	53	469
10.1016/j.eprac.2023.06.001	Retrospective Study	279	250	529	377	152	314	63	377	126	26	152
10.2337/dc22-0357	Retrospective Study	—	—	2751	924	1827	565	359	924	1132	695	1827
10.1002/hsr.2.889	Cross-Sectional Descriptive Study	46	24	70	39	31	33	6	39	29	2	31
10.5114/hpc.2022.122344	Cross-Sectional Descriptive Study	76	82	158	111	47	44	67	111	30	17	47

*Home-use insulin.

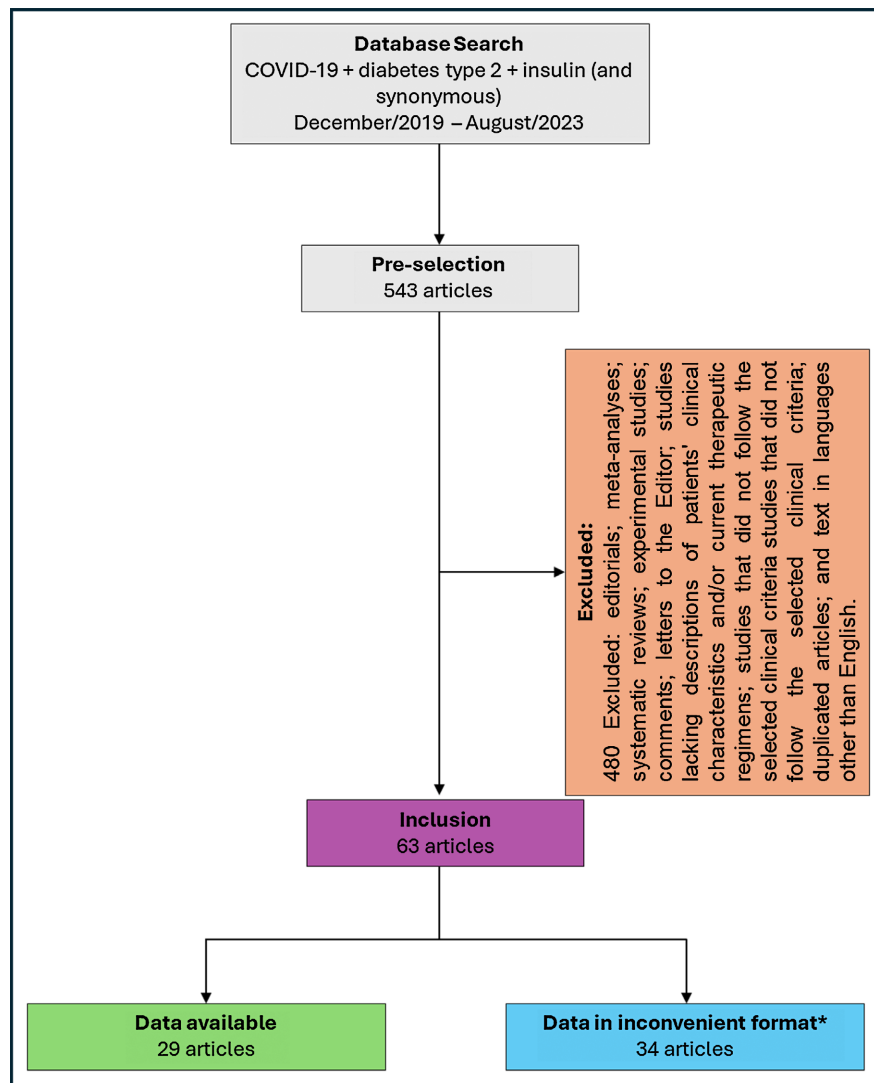


Figure 1. Systematic review flowchart. *Data in inconvenient format: refers to data without raw number for analysis.

The outcomes of the patients were reported in 29 articles published between December 2019 and August 2023, and included detailed information about the medication that was used and the final outcome, as deceased or alive (Figure 1).

First, we analyzed the results separately, in each type of study. Two case-control studies reported the outcomes of 14,503 patients (Table 2); 1,941 under insulin therapy and 12,562 under other modalities of intervention except for insulin.

In these studies, there was increased mortality in the insulin group with an odds ratio of 1.92. In two case report articles that included 95 patients (31 treated with insulin and 64 with no insulin), there was increased mortality in the insulin group with an odds ratio of 4.0 (Table 3).

In four cross-sectional studies, there were 972 patients (610 treated with insulin and 362 with no insulin), and there was an increased mortality in the insulin group with an odds ratio of 2.94 (Table 4).

Three observational cohort studies reported the outcomes of 2,801,039 patients (Table 5); 342,184 were under insulin therapy and 2,458,855 were under

Table 2. Odds ratio in case-control studies.

	Deceased	Alive	Odds
With Insulin	250	1691	$250/1691 = 0.148$
Without Insulin	898	11,664	$898/11,664 = 0.077$
Totals	<i>1148</i>	<i>13,355</i>	<i>$0.148/0.077 = 1.92$</i>

Table 3. Odds ratio in case report articles.

	Deceased	Alive	Odds
With Insulin	20	11	$20/11 = 1.818$
Without Insulin	20	44	$20/44 = 0.455$
Totals	<i>40</i>	<i>55</i>	<i>$1.818/0.455 = 4.00$</i>

Table 4. Odds ratio in cross-sectional descriptive studies.

	Deceased	Alive	Odds
With Insulin	132	478	$132/478 = 0.276$
Without Insulin	31	331	$31/331 = 0.094$
Totals	<i>163</i>	<i>809</i>	<i>$0.276/0.094 = 2.94$</i>

Table 5. Odds ratio in observational cohort studies.

	Deceased	Alive	Odds
With Insulin	3158	339,026	$3158/339,026 = 0.009$
Without Insulin	10,988	2,447,867	$10988/2,447,867 = 0.004$
Totals	<i>14,146</i>	<i>2,786,893</i>	<i>$0.009/0.004 = 2.25$</i>

other modalities of intervention except for insulin. In these studies, there was increased mortality in the insulin group with an odds ratio of 2.25.

Finally, 18 retrospective studies evaluated 254,048 patients; 67,922 were treated with insulin, and 186,126 were treated with other modalities of intervention except for insulin (Table 6). In these studies, there was increased mortality in the insulin group with an odds ratio of 1.46.

Table 6. Odds ratio in retrospective studies.

	Deceased	Alive	Odds
With Insulin	13,943	53,979	$13,943/53,979 = 0.258$
Without Insulin	28,054	158,072	$28,054/158,072 = 0.177$
Totals	<i>41,997</i>	<i>212,051</i>	<i>$0.258/0.177 = 1.46$</i>

Next, we used two approaches to evaluate the whole sample: the determination of the odds ratio, and a direct comparison of the two groups using unpaired Student's t-test. In the evaluation of all 3,070,657 patients included in this study (412,688 treated with insulin and 2,657,969 treated with another approach except for insulin) there was an odds ratio of 2.93 indicating greater mortality in the insulin group. This was further confirmed by the determination of the percentage of alive patients in either group (Figure 2).

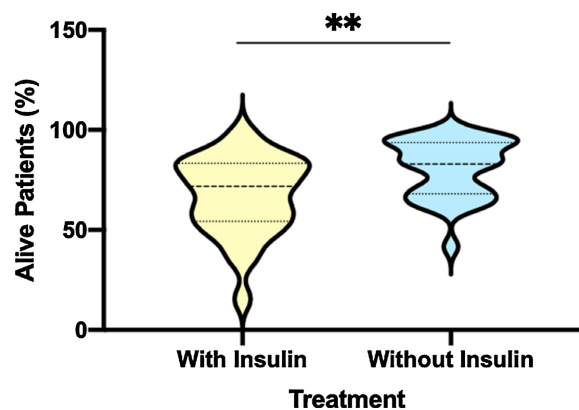


Figure 2. Percentage of alive patients in all studies, comparing the use or non-use of insulin in patients with T2D and with COVID-19. Values are expressed as violin plot, ** $p < 0.01$, Unpaired Student's t-test.

4. Discussion

In this study, we show that using insulin as a therapeutic intervention to treat hyperglycemia and metabolic abnormalities in patients with T2D who develop severe COVID-19, increases the probability of death by almost 200%, which is similar to a previous publication [12]. While deaths related to COVID-19 are also closely related to the clinical condition of the disease, the more severe forms of the illness are strongly associated with the presence of comorbidities [13]. Among these, T2D plays an important role due to its high prevalence in the

population and its impact on several organs and systems that play important roles in whole-body homeostasis. As a chronic disease that is frequently poorly controlled, T2D impacts several clinical parameters that negatively influence the prognosis of COVID-19, such as the functional impairment of phagocytes, and the abnormal expression of the SARS-CoV2 receptor, ACE2, both of which directly interfere with the pathogenesis of COVID-19 [14]-[16].

Given the high prevalence and the pathophysiological complexity of diabetes mellitus, it is not a surprise that up to 58% of all COVID-19 patients have diabetes [17]. Moreover, infected patients with diabetes have an increased 8% risk of death and are nearly 15% more likely to require intensive care as compared to individuals without this comorbidity [18]. Thus, these patients need special attention in the treatment of COVID-19, as well as rigorous management of diabetes.

Despite recent advances in the pharmacological treatment of diabetes, a considerable fraction of patients use insulin as monotherapy or in conjunction with other drugs. In addition, when patients with diabetes develop severe infectious diseases or other medical conditions that require intensive care, insulin is commonly used to maintain metabolic stability, and this is recommended in the most important guidelines for diabetes management [19] [20]. Thus, it was not a surprise that in the early days of the COVID-19 pandemic, important journals published reviews, editorials, commentaries, and expert opinions recommending insulin as the drug of choice for the treatment of hyperglycemia in severe COVID-19 [9] [10]. However, in early 2021, a study reported for the first time that using insulin to treat severely ill COVID-19 patients with diabetes resulted in increased mortality [11]. The study retrospectively evaluated 689 patients with COVID-19 and T2D and showed an increased mortality in the insulin-treated group with a hazard ratio of 5.38. The authors suggested that mortality could be due to increased inflammatory activity and increased damage to vital organs [11].

The publication of that study [11] triggered a series of questions regarding the optimal pharmacological intervention to treat diabetes in patients with COVID-19. In addition, it stimulated the search for the mechanisms behind this putative adversity. As a whole, we found seven articles [12] [21]-[26] that performed systematic reviews/meta-analyses to determine the impact of using insulin to treat hyperglycemia in patients with severe COVID-19. In all of them, the results indicated that using insulin resulted in increased complications and/or mortality. However, the studies were all published between July 2021 and October 2022; thus, they are representative of a phase of the pandemic with high mortality rates, and when most patients had not been submitted to vaccination.

In the present study, we revisited the theme, incorporating articles published in late 2022 and 2023, thus expanding the analysis for a new phase when COVID-19 is no longer a pandemic, and when the number of people fully vaccinated is much greater than when the prior studies were performed. In addition, the selection of articles was very strict, including only those with a clear

description of therapeutic interventions for the treatment of hyperglycemia, and the relation of such interventions with one out of two outcomes: alive or deceased. Our results reinforce the concept that using insulin in patients with severe COVID-19 increases mortality and have a broad impact on clinical science, which goes much beyond diabetology and endocrinology. In addition, it calls for actions aimed at defining the mechanisms that contribute to the increased rate of mortality in insulin-treated patients.

Author's Contribution Statement

CFB and MRS performed an article search and the first round of inclusions. LAV performed the second round of inclusion. MRS and MM-P performed statistics analysis. LAV, MRS, TPP and CFB wrote the manuscript. All authors read the manuscript and provided approval.

Funding

This research received funding from the São Paulo Research Foundation (2022/00956-6 and 2021/09662-2). The study was also supported by FAPESP (2013/07607-8).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

- [1] Msemburi, W., Karlinsky, A., Knutson, V., Aleshin-Guendel, S., Chatterji, S. and Wakefield, J. (2022) The WHO Estimates of Excess Mortality Associated with the COVID-19 Pandemic. *Nature*, **613**, 130-137. <https://doi.org/10.1038/s41586-022-05522-2>
- [2] Chen, N., Zhou, M., Dong, X., Qu, J., Gong, F., Han, Y., *et al.* (2020) Epidemiological and Clinical Characteristics of 99 Cases of 2019 Novel Coronavirus Pneumonia in Wuhan, China: A Descriptive Study. *The Lancet*, **395**, 507-513. [https://doi.org/10.1016/s0140-6736\(20\)30211-7](https://doi.org/10.1016/s0140-6736(20)30211-7)
- [3] Richardson, S., Hirsch, J.S., Narasimhan, M., Crawford, J.M., McGinn, T., Davidson, K.W., *et al.* (2020) Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA*, **323**, 2052-2059. <https://doi.org/10.1001/jama.2020.6775>
- [4] Steenblock, C., Schwarz, P.E.H., Ludwig, B., Linkermann, A., Zimmet, P., Kulebykin, K., *et al.* (2021) COVID-19 and Metabolic Disease: Mechanisms and Clinical Management. *The Lancet Diabetes & Endocrinology*, **9**, 786-798. [https://doi.org/10.1016/s2213-8587\(21\)00244-8](https://doi.org/10.1016/s2213-8587(21)00244-8)
- [5] Sudhakar, M., Winfred, S.B., Meiyazhagan, G. and Venkatachalam, D.P. (2022) Mechanisms Contributing to Adverse Outcomes of COVID-19 in Obesity. *Molecular and Cellular Biochemistry*, **477**, 1155-1193. <https://doi.org/10.1007/s11010-022-04356-w>
- [6] Bornstein, S.R., Rubino, F., Khunti, K., Mingrone, G., Hopkins, D., Birkenfeld, A.L.,

- et al.* (2020) Practical Recommendations for the Management of Diabetes in Patients with COVID-19. *The Lancet Diabetes & Endocrinology*, **8**, 546-550. [https://doi.org/10.1016/s2213-8587\(20\)30152-2](https://doi.org/10.1016/s2213-8587(20)30152-2)
- [7] Sardu, C., D'Onofrio, N., Balestrieri, M.L., Barbieri, M., Rizzo, M.R., Messina, V., *et al.* (2020) Outcomes in Patients with Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control? *Diabetes Care*, **43**, 1408-1415. <https://doi.org/10.2337/dc20-0723>
- [8] Solerte, S.B., D'Addio, F., Trevisan, R., Lovati, E., Rossi, A., Pastore, I., *et al.* (2020) Sitagliptin Treatment at the Time of Hospitalization Was Associated with Reduced Mortality in Patients with Type 2 Diabetes and COVID-19: A Multicenter, Case-Control, Retrospective, Observational Study. *Diabetes Care*, **43**, 2999-3006. <https://doi.org/10.2337/dc20-1521>
- [9] Lim, S., Bae, J.H., Kwon, H. and Nauck, M.A. (2020) COVID-19 and Diabetes Mellitus: From Pathophysiology to Clinical Management. *Nature Reviews Endocrinology*, **17**, 11-30. <https://doi.org/10.1038/s41574-020-00435-4>
- [10] Pasquel, F.J., Lansang, M.C., Dhatariya, K. and Umpierrez, G.E. (2021) Management of Diabetes and Hyperglycaemia in the Hospital. *The Lancet Diabetes & Endocrinology*, **9**, 174-188. [https://doi.org/10.1016/s2213-8587\(20\)30381-8](https://doi.org/10.1016/s2213-8587(20)30381-8)
- [11] Yu, B., Li, C., Sun, Y. and Wang, D.W. (2021) Insulin Treatment Is Associated with Increased Mortality in Patients with COVID-19 and Type 2 Diabetes. *Cell Metabolism*, **33**, 65-77.E2. <https://doi.org/10.1016/j.cmet.2020.11.014>
- [12] Zhu, Z., Zeng, Q., Liu, Q., Wen, J. and Chen, G. (2022) Association of Glucose-Lowering Drugs with Outcomes in Patients with Diabetes before Hospitalization for COVID-19: A Systematic Review and Network Meta-Analysis. *JAMA Network Open*, **5**, e2244652. <https://doi.org/10.1001/jamanetworkopen.2022.44652>
- [13] Wu, Z. and McGoogan, J.M. (2020) 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 Center for Disease Control and Prevention. *JAMA*, **323**, 1239-1242. <https://doi.org/10.1001/jama.2020.2648>
- [14] Sidarta-Oliveira, D., Jara, C.P., Ferruzzi, A.J., Skaf, M.S., Velander, W.H., Araujo, E.P., *et al.* (2020) SARS-CoV-2 Receptor Is Co-Expressed with Elements of the Kinin-Kallikrein, Renin-Angiotensin and Coagulation Systems in Alveolar Cells. *Scientific Reports*, **10**, Article No. 19522. <https://doi.org/10.1038/s41598-020-76488-2>
- [15] D'Onofrio, N., Scisciola, L., Sardu, C., Trotta, M.C., De Feo, M., Maiello, C., *et al.* (2021) Glycated ACE2 Receptor in Diabetes: Open Door for SARS-COV-2 Entry in Cardiomyocyte. *Cardiovascular Diabetology*, **20**, Article No. 99. <https://doi.org/10.1186/s12933-021-01286-7>
- [16] Codo, A.C., Davanzo, G.G., Monteiro, L.D.B., de Souza, G.F., Muraro, S.P., Virgilio-da-Silva, J.V., *et al.* (2020) Elevated Glucose Levels Favor SARS-CoV-2 Infection and Monocyte Response through a HIF-1 α /Glycolysis-Dependent Axis. *Cell Metabolism*, **32**, 437-446.e5. <https://doi.org/10.1016/j.cmet.2020.07.007>
- [17] Bhatraju, P.K., Ghassemieh, B.J., Nichols, M., Kim, R., Jerome, K.R., Nalla, A.K., *et al.* (2020) Covid-19 in Critically Ill Patients in the Seattle Region—Case Series. *New England Journal of Medicine*, **382**, 2012-2022. <https://doi.org/10.1056/nejmoa2004500>
- [18] Chen, T., Wu, D., Chen, H., Yan, W., Yang, D., Chen, G., *et al.* (2020) Clinical Characteristics of 113 Deceased Patients with Coronavirus Disease 2019: Retrospective Study. *BMJ*, **368**, m1091. <https://doi.org/10.1136/bmj.m1091>
- [19] ElSayed, N.A., Aleppo, G., Bannuru, R.R., Bruemmer, D., Collins, B.S., Ekhlaspour,

- L., *et al.* (2023) 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes—2024. *Diabetes Care*, **47**, S158-S178.
<https://doi.org/10.2337/dc24-s009>
- [20] Silver, B., Ramaiya, K., Andrew, S.B., Fredrick, O., Bajaj, S., Kalra, S., *et al.* (2018) EADSG Guidelines: Insulin Therapy in Diabetes. *Diabetes Therapy*, **9**, 449-492.
<https://doi.org/10.1007/s13300-018-0384-6>
- [21] Hariyanto, T.I., Lugito, N.P.H., Yanto, T.A., Siregar, J.I. and Kurniawan, A. (2022) Insulin Therapy and Outcome of Coronavirus Disease 2019 (COVID-19): A Systematic Review, Meta-Analysis, and Meta-Regression. *Endocrine, Metabolic & Immune Disorders—Drug Targets*, **22**, 481-489.
<https://doi.org/10.2174/1871530321666210709164925>
- [22] Yang, Y., Cai, Z. and Zhang, J. (2021) Insulin Treatment May Increase Adverse Outcomes in Patients with COVID-19 and Diabetes: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology*, **12**, Article 696087.
<https://doi.org/10.3389/fendo.2021.696087>
- [23] Wang, W., Sun, Y., Wang, S. and Sun, Y. (2021) The Relationship between Insulin Use and Increased Mortality in Patients with COVID-19 and Diabetes: A Meta-Analysis. *Endocrine Research*, **47**, 32-38.
<https://doi.org/10.1080/07435800.2021.1967376>
- [24] Kan, C., Zhang, Y., Han, F., Xu, Q., Ye, T., Hou, N., *et al.* (2021) Mortality Risk of Antidiabetic Agents for Type 2 Diabetes with COVID-19: A Systematic Review and Meta-Analysis. *Frontiers in Endocrinology*, **12**, Article 708494.
<https://doi.org/10.3389/fendo.2021.708494>
- [25] Chen, Y., Lv, X., Lin, S., Arshad, M. and Dai, M. (2022) The Association between Antidiabetic Agents and Clinical Outcomes of COVID-19 Patients with Diabetes: A Bayesian Network Meta-Analysis. *Frontiers in Endocrinology*, **13**, Article 895458.
<https://doi.org/10.3389/fendo.2022.895458>
- [26] Zhan, K., Weng, L., Qi, L., Wang, L., Lin, H., Fang, X., *et al.* (2022) Effect of Antidiabetic Therapy on Clinical Outcomes of COVID-19 Patients with Type 2 Diabetes: A Systematic Review and Meta-Analysis. *Annals of Pharmacotherapy*, **57**, 776-786.
<https://doi.org/10.1177/10600280221133577>