



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Contents available at [ScienceDirect](https://www.sciencedirect.com)
**Diabetes Research
and Clinical Practice**
journal homepage: www.elsevier.com/locate/diabres
**International
Diabetes
Federation**


Commentary

Diabetes and CoViD-19: Experience from the frontline of Internal Medicine wards in Italy



A. Montagnani^a, F. Pieralli^b, P. Gnerre^c, F. Pomero^d, M. Campanini^e, F. Dentali^f,
A. Fontanella^g, D. Manfellotto^h, on behalf of the FADOI CoViD-19 Observatory Group

^a Internal Medicine, Hospital of Pitigliano, Grosseto, Italy

^b Internal Medicine, Hospital "Careggi", Florence, Italy

^c Internal Medicine, Hospital "San Paolo", Savona, Italy

^d Internal Medicine, Hospital "San Lazzaro", Alba, Cuneo, Italy

^e Department of Medicine, Hospital "Maggiore della Carità", Novara, Italy

^f Department of Medicine, ASST "Sette Laghi", Varese, Italy

^g Department of Medicine, Hospital "Buon Consiglio Fatebenefratelli", Naples, Italy

^h Department of Internal Medicine, Hospital "Fatebenefratelli-AFaR", Rome, Italy

ARTICLE INFO

Article history:

Received 14 July 2020

Accepted 14 July 2020

Available online 18 July 2020

Keywords:

Type 2 diabetes

CoViD-19

Mortality

ABSTRACT

Available data suggest that the issue of CoViD-19 is particularly critical in patients with diabetes. In Italy, Internal Medicine (IM) wards have played a pivotal role in contrasting the spread of SARS-Cov2. During this pandemic, FADOI submitted a brief questionnaire to a group of its members acting as Head of IM units. Considering 38 units, 58% of beds dedicated to CoViD patients in CoViD Hospitals were in charge of IM, and globally cared for 6650 patients during a six-week period. Of these patients, 1264 (19%) had diabetes. Mortality rate in CoViD patients with or without diabetes were 20.5% and 14%, respectively ($p < 0.001$). Our survey seems to confirm that diabetes is a major comorbidity of CoViD-19, but it does not support an increased incidence of CoViD-19 infection in people with diabetes, if compared with the figures of patients with diabetes and hospitalized before the outbreak. On the other side, patients with diabetes appeared at a significantly increased risk of worse outcome. This finding underlines the importance of paying special attention to this patient population and its management.

© 2020 Published by Elsevier B.V.

From January 2020, the world has been facing a catastrophic outbreak of coronavirus disease 2019 (CoViD-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

Available epidemiologic data suggest that a significant association with worse outcomes was seen in people with comorbidities [2], the most prevalent of which are hypertension, cardiovascular disease, and diabetes.

<https://doi.org/10.1016/j.diabres.2020.108335>

0168-8227/© 2020 Published by Elsevier B.V.

Specifically, a couple of mechanisms have been hypothesized that might explain the link between CoViD-19 infection and diabetes, namely the regulation of expression of the Angiotensin-converting-enzyme 2 (ACE2) which has been identified as the receptor for the coronavirus spike protein, and the involvement of the dipeptidyl peptidase-4 (DPP-4) enzyme, which is commonly targeted pharmacologically in people with type 2 diabetes [3–5]. The clinical relevance of

these mechanisms is currently uncertain, but as a matter of fact diabetes is considered a risk factor for the development of severe pneumonia and a septic course due to virus infections [6], and the same findings have been reported in case of CoViD-19 [7]. This has led to a number of papers recently published and aimed at providing practical management recommendations for patients with diabetes during the CoViD-19 outbreak [8,9].

Italy has been one of the earliest and most heavily involved countries in the CoViD-19 pandemic. Internal Medicine (IM) wards, present in all Italian hospitals, have redesigned their healthcare delivery, and played a pivotal role in contrasting the spread of SARS-CoV2 [10]. Due to their ubiquitous distribution, the IM departments and the relevant scientific societies, such as The Federation of Hospital Internists (FADOI) with about 3000 members working in more than 500 departments all over Italy, represent an observatory of particular importance to describe the burden of diabetes in the context of CoViD-19.

To assess how internists contributed during the first two more intense months of the CoViD-19 outbreak, FADOI submitted a brief questionnaire to a group of its members acting as Head of IM units, from north to south Italy. The questionnaire included several questions investigating IM activities and its involvement in the pandemic, and particular attention was paid to patients with diabetes, the relevant comorbidities, the antidiabetic drugs used during hospitalization and patient outcome.

Fifty-two IM units participated to the survey, and 38 of them were placed in CoVid Hospitals. In this setting, fifty-eight percent of beds dedicated to CoViD patients in CoViD Hospitals were in charge of IM units, and globally cared for 6650 patients during the period March 15-April 30, 2020. Of these patients, 1264 (19%) had diabetes. The percentage distribution of the main comorbidities among patients with diabetes, and of the main categories of antidiabetic drugs used

is shown in Table 1. Mortality rate in CoViD patients with or without diabetes were 20.5% and 14%, respectively ($p < 0.001$).

Our survey seems to confirm that type 2 diabetes is a major comorbidity of CoViD-19. However, the percentage of patients with diabetes that we observed among those with CoViD-19 is not higher than figures of patients with diabetes hospitalized in IM wards in Italy before the outbreak. Therefore, this finding does not support an increased incidence of CoViD-19 infection in people with diabetes, as previously reported [8].

On the other side, in our cohort patients with diabetes appeared at a significantly increased risk of worse outcome if compared with patients without diabetes. There are several hypotheses to explain this finding: these include defects in innate immunity, and the fact the diabetes is often combined with cardiovascular disease and overweight/obesity, which per se could help to explain the association with fatal outcomes of CoViD-19 [8]. The role of cardiovascular comorbidities and obesity seems to be confirmed by the high percentages found in the population of diabetes patients considered in our survey.

The complex clinical condition of patients with diabetes diagnosed with SARS-CoV-2 infection may bear challenges for the use of most diabetes medications. For some of them, concerns have been raised that they could increase the number of ACE2 receptors on the cells utilized by SARS-CoV-2 for penetration, however no evidence presently exists that shows that any specific antidiabetic drugs may be harmful in terms of acquiring or worsening CoViD-19 [9].

Moreover, it is important to underline the high insulin requirement in patients with a severe course of the infection [8], and that achieving glycemic targets can improve outcomes in patients with CoViD-19 [11–13]. Our findings, and namely a significantly higher percentage of patients treated with insulin than previously reported in the setting of Italian IM wards before the outbreak [14], and a not negligible use of DPP4-i, seem coherent with some suggestions from literature [4,8].

In conclusion, the significant relative weight of the IM units in the management of patients with CoViD-19 and the number of patients considered in our analysis, probably make our observatory of interest and worth considering for the scientific community. Our experience seems to suggest that some aspects related to a possible greater predisposition of patient with diabetes to CoVid-19 should be furtherly elucidated. Moreover, confirmation that patients with diabetes and CoViD-19 have a more severe outcome than non-diabetic patients, underlines the importance of paying special attention to this patient population and its management [15].

Funding

The authors received no funding from an external source.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Table 1 – Comorbidities and drugs used in diabetic patients with CoViD-19.

Variable	Cohort
<i>Comorbidity:</i>	
Arterial hypertension	69.9%
Heart failure	47.0%
Obesity	32.5%
Renal insufficiency	25.3%
COPD	22.9%
<i>Drugs used:</i>	
Insulin	97.1%
Metformin	34.3%
DPP4-i	20.1%
GLP1-RA	14.3%
Sulphonylureas	5.7%
SGLT2-i	5.4%
Repaglinide	2.9%

REFERENCES

- [1] Harapan H, Itoh N, Yufika A, Winardi W, Keam S, Te H, et al. Coronavirus disease 2019 (COVID-19): a literature review. *J Infect Public Health* 2020;13:667–73.
- [2] Y Chen, X Gong, L Wang, J Guo. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. medRxiv 2020; published online March 30; DOI:10.1101/2020.03.25.20043133 (preprint).
- [3] Bindom SM, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol* 2009;302:193–202.
- [4] Iacobellis G. COVID-19 and diabetes: can DPP4 inhibition play a role?. *Diabetes Res Clin Pract* 2020;162 108125.
- [5] A Ceriello, V De Nigris, F Prattichizzo. Why is hyperglycaemia worsening COVID-19 and its prognosis? *Diabetes Obes Metab* 2020 May 28;10.1111/dom.14098. doi: 10.1111/dom.14098. Online ahead of print.
- [6] Zou Q, Zheng S, Wang X, et al. Influenza A-associated severe pneumonia in hospitalized patients: risk factors and NAI treatments. *Int J Infect Dis* 2020;92:208–13.
- [7] Remuzzi A, Remuzzi G. COVID-19 and Italy: what next?. *Lancet* 2020;395:1225–8.
- [8] Bornstein SR, Rubino F, Khunti K, Mingrone G, Hopkins D, Birkenfeld AL, et al. Practical recommendations for the management of diabetes in patients with COVID-19. *Lancet Diabetes Endocrinol* 2020;8:546–50.
- [9] Ceriello A, Standl E, Catrinoiu D, Itzhak B, Lalic NM, Rahelic D, et al. Issues of Cardiovascular Risk Management in People With Diabetes in the COVID-19 Era. *Dia Care* 2020;43(7):1427–32. <https://doi.org/10.2337/dc20-0941>.
- [10] Mazzone A, Mumoli N. Reorganizing Italian Internal Medicine wards for COVID 19. *Eur J Intern Med* 2020 Apr 30; S0953–6205(20):30180–1.
- [11] 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 preexisting type 2 diabetes. *Cell Metab* 2020 May 1;S1550–4131(20):30238–42.
- [12] Ceriello A. Hyperglycemia and the worse prognosis of COVID-19. Why a fast blood glucose control should be mandatory. *Diabetes Res Clin Pract*. 2020 May;163 108186.
- [13] Sardu C, D’Onofrio N, Balestrieri ML, Barbieri M, Rizzo MR, Messina V, et al. Outcomes in Patients With Hyperglycemia Affected by COVID-19: Can We Do More on Glycemic Control?. *Dia Care* 2020;43(7):1408–15. <https://doi.org/10.2337/dc20-0723>.
- [14] Gulli G, Frasson S, Borzì V, Fontanella A, Grandi M, Marengo C, et al. Effectiveness of an educational intervention on the management of type 2 diabetic patients hospitalized in Internal Medicine: results from the FADOI-DIAMOND study. *Acta Diabetol*. 2014;51(5):765–70.
- [15] Ceriello A, Stoian AP, Rizzo M. COVID-19 and diabetes management: What should be considered?. *Diabetes Res Clin Pract*. 2020 May;163.