

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.

FISEVIER

Contents lists available at ScienceDirect

## Metabolism Clinical and Experimental

journal homepage: www.metabolismjournal.com



COVID-19 in Metabolism

# COVID-19 editorial: mechanistic links and therapeutic challenges for metabolic diseases one year into the COVID-19 pandemic



Accumulating evidence has clearly suggested that cardiometabolic risk factors such as obesity, hypertension, dyslipidemia and diabetes mellitus (DM) are associated with a more severe disease course and worse clinical outcomes of coronavirus disease 2019 (COVID-19) [1].

COVID-19 severity is predicted by the presence of older age and a variety of obesity-related comorbidities [2]. Patients with obesity are at increased risk for developing severe pneumonia and requiring mechanical ventilation due to impaired respiratory mechanics and the concomitant presence of comorbidities such as DM, cardiovascular and renal disease, which further increase their vulnerability to multi-organ dysfunction [2].

Black, Latinos and Native Americans suffer disproportionate rates of severe acute respiratory syndrome-coronavirus 2 (SARS-CoV2) infections, hospitalizations and deaths [3]. Socioeconomic factors including racial discrimination, food insecurity, limited availability of healthy food, poor access to health care facilities, low level of education and socioeconomic status, and lack of job flexibility may all contribute to this disparity. These social determinants of health, combined with underlying health inequities in obesity-related chronic diseases, may inevitably culminate in severe COVID-19 outcomes in these socioeconomically deprived populations.

DM is characterized by enhanced susceptibility to infections due to inherent neutrophil dysfunction, reduced T-cell responses and disordered humoral immunity [4]. Furthermore, there seems to be a direct underlying endocrine/metabolic link between DM and severe COVID-19 [5]. In patients at metabolic risk, hyperglycemia, metabolic inflammation, enhanced cytokine release and endothelial dysfunction have been all implicated in the COVID-19-associated multi-organ dysfunction. [4,5]. SARS-CoV2 utilizes host angiotensin converting enzyme 2 (ACE2) to facilitate viral fusion and cell entry. ACE2 is highly expressed in the lungs, heart, endothelium, kidneys and pancreatic beta cells. The acute infection of beta cells by SARS-CoV2 has been associated with subsequent dysfunction and hyperglycemia due to diminished insulin secretion. The resultant acute hyperglycemia seems to upregulate ACE2 expression in other tissues, possibly enhancing viral entry into additional host cells. The downstream effects of angiotensin (1-9) and (1-7), resulting from the conversion of angiotensin I and II respectively by ACE2, include anti-inflammatory and anti-proliferative actions which are thought to limit acute inflammatory injury. Chronic hyperglycemia due to DM down-regulates the anti-inflammatory effects of ACE2 [4,5]. This vulnerability, coupled with the inherent underlying inflammatory milieu and immune defects seen in obesity and DM, provides SARS-CoV2 a pathway for causing exaggerated and prolonged lung injury and severe multi-system disease.

In the absence of randomized clinical trials, the optimal strategy for achieving metabolic control in patients with COVID-19 remains unknown. Relevant recommendations have been published last year [4–6], but have not yet been updated in 2021 in view of novel scientific evidence. In Fig. 1, we summarize the major principles of optimal care for patients with metabolic risk and COVID-19 based on the currently available evidence.

The adherence to lifestyle interventions can be challenging amidst the pandemic given the limited access to healthy foods and the impact of social distancing and facility closures on regular exercise. This is particularly salient in areas of the world where governments have implemented generalized lockdowns to halt the spread of SARS-CoV2. The amelioration of such barriers will require systemic social programs to be implemented so that this therapeutic modality can be fully accessed.

Optimizing nutrition may produce a tangible impact upon COVID-19 risk. The Mediterranean diet, mostly composed of whole grains, vegetables, fruits, fish, mono- and polyunsaturated fatty acids (PUFA), has significant anti-inflammatory properties and confers multiple cardiometabolic benefits in patients with DM. Omega-3 PUFA, polyphenols, flavonoids, and vitamin D have been all shown to reduce inflammation and improve immune response in respiratory infections. A Mediterranean-style diet rich in these anti-inflammatory components has been hypothesized to blunt the severity of COVID-19 in people with DM [7]. Investigation into the immunomodulatory role of vitamin D has suggested that serum 25hydroxyvitamin D levels >30 ng/ml are associated with lower rates of in-hospital mortality and mechanical ventilation in COVID-19 [8]. Given the high prevalence of vitamin D deficiency, especially in socioeconomically deprived populations, further study into the role of vitamin D is warranted. Exercise training improves a variety of physiological processes including cardiovascular function, insulin sensitivity, skeletal muscle mass and immune function, and is a cornerstone in the treatment of DM and metabolic diseases. However, mandatory restrictions on fitness facilities and recommendations for individuals to shelter-in-place to reduce SARS-CoV2 exposure, have had unintended consequences promoting sedentary behaviours and physical deconditioning. Thus, homebased training modules and outdoor activities to maintain aerobic capacity and physical strength are highly recommended. For individuals recovering from COVID-19, early mobilization and exercise rehabilitation programs are vital to restore pulmonary, cardiovascular and physical function.

The optimal pharmacologic strategy to address the various components of cardiometabolic risk in the setting of COVID-19 is an area of intense debate. Regarding hypertension, current evidence suggests the continuation of ACE inhibitors/angiotensin receptor blockers unless

### Major Principles of Optimal Care for Patients with Metabolic Risk

#### Primary prevention of infection







Minimize exposure to SARS-CoV2

- Emphasize social distancing, hand hygiene, face masks and home confinement
- · Avoid non-urgent medical visits and overcrowding in hospitals
- · Consult with treating physicians per telephone, email, videocall
- · Coordinate home drug delivery



(balanced nutrition, regular physical activity, adequate hydration, smoking abstinence, high sleep quality, psychological stress management)

Promote routine vaccinations as clinically recommended (SARS-CoV2, seasonal influenza, pneumococcus)



For patients with DM: Sensitize about the importance of optimal glycemic control

- Regular glucose monitoring
  - Appropriate adjustment of antidiabetic treatment

programs, monitor therapy and assess treatment adherence

Target efficient control of DM-related comorbidities (HTN, dyslipidemia, CVD, NAFLD, CKD)



Avoid the premature withdrawal of any established antidiabetic or other treatment



Implement Connected Health Models and Telemedicine applications to maximize self-containment, promote self-management education



At the community level: address and mitigate disparities and inequalities in social determinants of health (i.e. racial discrimination, access to healthy foods and healthcare facilities, socioeconomic status and level of education)



#### In the setting of confirmed COVID-19









Patient-tailored therapeutic approach

Healthy eating patterns with putative anti-inflammatory and immunomodulating properties (Mediterranean Diet)

- ↑ Zinc, vitamins A, B, C, D, MUFA, omega-3 PUFA, unprocessed plant-derived foods
- $\bullet \ \downarrow \ \text{Refined carbohydrates, saturated fat, salt}$ Regular glucose monitoring



Optimal glycemic control

Optimal control of HTN

- Individualize glycemic targets according to age, comorbidities, complications, severity of infection
- Special considerations for DM pharmacotherapy:
- ➤ Continue insulin and adjust dose
- ➤ Discontinue sulfonylureas if regular oral food intake cannot be maintained to reduce hypoglycemia risk
- ➤ Cautiously continue SGLT2-inhibitors to take advantage of cardio- and renoprotective effects
- ➤ Continue DPP-4 inhibitors due to good safety profile and potential of use across a wide range of renal
- ➤ Cautiously continue GLP1RAs and maintain adequate fluid intake to prevent dehydration risk related to gastrointestinal side effects



 Continue ACE inhibitors and ARBs unless contraindicated Optimal control of dyslipidemia

 Continue statins with pleiotropic anti-inflammatory effects, discontinue in case of myositis or transaminitis Continue aspirin for secondary prevention of CVD

#### Critically ill hospitalized patients (possibly ICU setting)

Tight monitoring of plasma glucose (preferably by subcutaneous CGM remote devices), fluids, electrolytes, pH and blood ketones Careful consideration of potential drug interactions



Optimal glycemic control

- Goals: limit abnormal glycemic variability, minimize hypoglycemic episodes
- Special considerations for DM pharmacotherapy:
  - ➤ Administer insulin in high doses intravenously to allow for flexible titration (mind hypoglycemia and insulin-induced hypokalemia risk)
  - ➤ Discontinue metformin in case of hypoxia and hemodynamic instability to prevent lactic acidosis
  - ➤ Discontinue SGLT2-inhibitors due to ↑ risk of euglycemic DKA precipitated by dehydration and insulinopenia
  - ➤ Discontinue GLP1RAs
  - ➤ Discontinue pioglitazone due to ↑ risk of fluid retention and HF worsening

Fig. 1. Flowchart summarizing the major general principles of optimal management of patients at metabolic risk during the COVID-19 pandemic Abbreviations: ACE: angiotensin converting enzyme; ARBs: angiotensin II type 1 receptor blockers; CGM: continuous glucose monitoring; CKD: chronic kidney disease; COVID-19: coronavirus disease 2019; CVD: cardiovascular disease; DKA: diabetic ketoacidosis; DM: diabetes mellitus; DPP4: dipeptidyl-peptidase 4; GLP1RAs; glucagon-like peptide 1 receptor agonists; ICU: intensive care unit; MUFA: monounsaturated fatty acids; NAFLD: non-alcoholic fatty liver disease; PUFA: polyunsaturated fatty acids; SARS-CoV2: severe acute respiratory syndrome-coronavirus-2; SGLT2: sodium-glucose cotransporter 2.

contraindicated [4]. Further continuation of aspirin for secondary prevention of cardiovascular disease is also strongly recommended, given the higher risk of cardiovascular dysfunction during COVID-19 infection [4]. For dyslipidemia, statins with pleiotropic anti-inflammatory effects should generally be continued, as discontinuation might lead to a rebound in levels of interleukin (IL)-6 and IL-1B, which have been implicated in the so-called cytokine storm [4,6]. There may also be a role for approved anti-obesity medications such as phentermine-topiramate, naltrexone-bupropion and liraglutide. These agents may prove to be useful, especially when adherence to a healthy hypocaloric diet is limited, and when elective metabolic surgeries are commonly postponed. Thoughtful consideration should be given to the role of antidiabetic drugs in patients with COVID-19. For patients with mild infection, the usual outpatient antihyperglycemic therapy can be continued with the following precautions: A recent retrospective study has shown a beneficial effect of the prior treatment with metformin on COVID-19 mortality [9]. However, it should be discontinued in those who are severely ill with hypoxia or hemodynamic instability due to the risk of lactic acidosis, Sodium-glucose-co-transporter 2 inhibitors should be withdrawn in severe illness or diminished oral intake due to the increased risk of dehydration and euglycemic diabetic ketoacidosis. Patients taking glucagon-like peptide 1 receptor agonists (GLP1RAs) should be monitored for gastrointestinal symptoms and encouraged to maintain adequate fluid intake to avoid dehydration. Dipeptidyl peptidase-4 inhibitors (DPP4i) are generally well-tolerated and can be continued in non-critically ill patients. Sulfonylureas should be discontinued in those unable to maintain regular food intake and could predispose to hypoglycemia. Patients taking pioglitazone should be monitored for fluid retention and stopped if there is evidence of hemodynamic instability, hepatic or cardiac dysfunction. Insulin therapy requires frequent monitoring and dose adjustment to avoid hypoglycaemia and abnormal glycemic variability [4,6,10]. In the hospital setting, monitoring for new-onset diabetes, awareness of the high prevalence of severe diabetic ketoacidosis and high insulin requirements in severe infections is paramount. The early use of intravenous insulin in hospitalized patients with severe COVID-19 allows for rapid achievement of glycemic control [4,6,10].

Even as vaccine roll out occurs across the globe, COVID-19 will continue its siege for the foreseeable future. Impaired metabolic health identified by the presence of obesity, insulin resistance, DM, hypertension and dyslipidemia, indicates a proinflammatory state and represents an important determinant of COVID-19 severity. A thoughtful approach to the management of DM and other metabolic comorbidities may improve immune response, reduce inflammation and prevent metabolic decompensation during acute illness.

#### Role of funding source

None.

#### **Declaration of competing interest**

C.M.T.: None.

A.K. has received research support or served on advisory boards for Lilly, Sanofi, Novo Nordisk, MSD, Astra Zeneca, ELPEN Pharma, Boehringer-Ingelheim, Bausch Health, Ethicon, Galenica, and Epsilon Health.

G.M. has served as consultant of Novo Nordisk, Johnson and Johnson, Fractyl Inc., ReCor Inc.

C.K.: None. I.R.Z.: None.

C.S.M. reports grants, personal fees, and other from AltrixBio, Coherus Biosciences, and Novo Nordisk, personal fees and non-financial support from Ansh, Aegerion, California Walnut Commission, and personal fees

from Amgen, Lumos, GENFIT, Intercept, Regeneron, CardioMetabolic Health Conference and The Metabolic Institute of America.

#### References

- 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 Center for Disease Control and Prevention. JAMA. 2020;323: 1239–42.
- [2] Palaiodimos L, Kokkinidis DG, Li W, et al. Severe obesity, increasing age and male sex are independently associated with worse in-hospital outcomes, and higher in-hospital mortality, in a cohort of patients with COVID-19 in the Bronx, New York. Metabolism. 2020:108:154262.
- [3] Belanger MJ, Hill MA, Angelidi AM, Dalamaga M, Sowers JR, Mantzoros CS. Covid-19 and disparities in nutrition and obesity. N Engl J Med. 2020;383:e69.
- [4] Katulanda P, Dissanayake HA, Ranathunga I, et al. Prevention and management of COVID-19 among patients with diabetes: an appraisal of the literature. Diabetologia. 2020:63:1440–52.
- [5] Bornstein SR, Dalan R, Hopkins D, Mingrone G, Boehm BO. Endocrine and metabolic link to coronavirus infection. Nat Rev Endocrinol. 2020;16:297–8.
- [6] Stefan N, Birkenfeld AL, Schulze MB, Ludwig DS. Obesity and impaired metabolic health in patients with COVID-19. Nat Rev Endocrinol. 2020;16:341–2.
- [7] Angelidi AM, Kokkinos A, Katechaki E, Ros E, Mantzoros CS. Mediterranean diet as a nutritional approach for COVID-19. Metabolism. 2021;114:154407.
- [8] Angelidi AM, Belanger MJ, Lorinsky MK, et al. Vitamin D status is associated with inhospital mortality and mechanical ventilation: a cohort of COVID-19 hospitalized patients. Mayo Clin Proc. 2021 [in press].
- [9] Crouse AB, Grimes T, Li P, Might M, Ovalle F, Shalev A. Metformin use is associated with reduced mortality in a diverse population with COVID-19 and diabetes. Front Endocrinol. 2021;11:600439.
- [10] Koliaki C, Tentolouris A, Eleftheriadou I, Melidonis A, Dimitriadis G, Tentolouris N. Clinical Management of Diabetes Mellitus in the era of COVID-19: practical issues. Peculiarities and Concerns J Clin Med. 2020;9:2288.

Christopher M. Tessier Section of Endocrinology, VA Boston Healthcare System and Harvard Medical School, Boston, MA, USA

Alexander Kokkinos

First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

Geltrude Mingrone

Fondazione Policlinico A. Gemelli IRCCS University Cattolica S. Cuore Roma, Italy

Department of Diabetes and King's College London, United Kingdom

Chrysi Koliaki

First Department of Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital, Athens, Greece

Juleen R. Zierath

Department of Molecular Medicine and Surgery, Karolinska Institute, Stockholm, Sweden

Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Copenhagen, Denmark

Christos S. Mantzoros

Section of Endocrinology, VA Boston Healthcare System and Harvard Medical School, Boston, MA, USA

Corresponding author at: VA Boston Health Care System, 1400 VFW Parkway, West Roxbury, MA 02132, USA

E-mail address: cmantzor@bidmc.harvard.edu.