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.

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JACC FOCUS SEMINAR

Coronavirus and Cardiometabolic Syndrome

JACC Focus Seminar

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic exposes unexpected cardiovascular vulnerabilities and the need to improve cardiometabolic health. Four cardiometabolic drivers—abnormal adiposity, dysglycemia, dyslipidemia, and hypertension—are examined in the context of COVID-19. Specific recommendations are provided for lifestyle change, despite social distancing restrictions, and pharmacotherapy, particularly for those with diabetes. Inpatient recommendations emphasize diligent and exclusive use of insulin to avert hyperglycemia in the face of hypercytokinemia and potential islet cell injury. Continuation of statins is advised, but initiating statin therapy to treat COVID-19 is as yet unsubstantiated by the evidence. The central role of the renin-angiotensin system is discussed. Research, knowledge, and practice gaps are analyzed with the intent to motivate prompt action. An emerging model of COVID-related cardiometabolic syndrome encompassing events before, during the acute phase, and subsequently in the chronic phase is presented to guide preventive measures and improve overall cardiometabolic health so future viral pandemics confer less threat. (J Am Coll Cardiol 2020;76:2024–35) © 2020 by the American College of Cardiology Foundation.

Cardiometabolic-based chronic disease (CMBCD) results from primary (genetic, environmental, behavioral) and metabolic drivers (abnormal adiposity, dysglycemia, metabolic syndrome traits) (1,2). Epidemiological/mechanistic associations of CMBCD with coronavirus disease 2019 (COVID-19) substantiate a postulated coronavirus disease-related cardiometabolic syndrome (CIRCS) (**Table 1**). The role of healthy lifestyles and pharmacotherapy targeting metabolic drivers to reduce cardiovascular risk is well established (1,2). However, lessons learned from the COVID-19 pandemic support shorter-term benefits of these interventions, similar to observed benefits on acute cardiovascular disease (CVD) outcomes (3). Therefore, a prevention program for patients of all ages should be developed to create a healthy culture, reduce chronic disease risks, and mitigate unforeseen acute insults, such as COVID-19.

Listen to this manuscript's audio summary by Editor-in-Chief Dr. Valentin Fuster on JACC.org.

From the Zena and Michael A. Wiener Cardiovascular Institute/Marie-Josée and Henry R. Kravis Center for Cardiovascular Health, Icahn School of Medicine at Mount Sinai, New York, New York. Dr. Mechanick has received honoraria for lectures and program development from Abbott Nutrition. Dr. Rosenson has received research grants to institution from Amgen, The Medicines Company, Novartis, and Regeneron; has served on consulting/advisory boards for Amgen, C5, Corvidia, CVS Caremark, and The Medicines Company; has received honoraria from Angen, Kowa, Pfizer, and Regeneron; has received royalties from UpToDate; and has stock holdings in MediMergent, LLC. Dr. Pinney has received consulting fees from Abbott, CareDx, Medtronic, and Procyrion. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Muthiah Vaduganathan, MD, served as Guest Editor for this paper. Deepak L. Bhatt, MD, MPH, served as Guest Editor-in-Chief for this paper.

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HIGHLIGHTS

- COVID-19 exposes epidemiological and mechanistic relationships with cardiometabolic links (abnormal adiposity, dysglycemia, dyslipidemia, and hypertension).
- Lifestyle, glycemic control, and regulation of the RAS have important implications for management of patients with COVID-19.
- CIRCS applies to all stages of COVID-19 illness, including prevention, acute management, and long-term outcomes.
- Further research should address gaps in current knowledge and clinical implementation of available strategies to mitigate the adverse consequences of CIRCS.

CARDIOMETABOLIC TARGETS

ABNORMAL ADIPOSITY. Obesity is a major global problem. According to the World Health Organization, over 1.9 billion people age ≥18 years were overweight (39%) or obese (13%) in 2016, with 40 million children age <5 years overweight/obese in 2018 (4). Obesity is defined by the body mass index (BMI), which despite adjustments based on ethnicity, remains inadequate as a cardiovascular risk stratifier (5). Consequently, adiposity-based chronic disease has been developed as a new framework incorporating abnormal adiposity amount, distribution, and function, along with clinical complication severity (5). Not surprisingly, abnormal adiposity is a key driver, not only for obesity-related complications, but also insulin resistance, inflammation, type 2 diabetes (T2D), and CVD (1,2,5,6). A principal mechanism of abnormal adiposity leading to CVD is the accumulation of inflammatory pericardial/epicardial fat (1). This ectopic adipose tissue secretes more type II phospholipase A2 with ischemia, leading to more phospholipid hydrolysis, local free fatty acids, nerve impulse disruption, and arrhythmia; vascular inflammation, atherosclerosis, and arterial stiffness; cardiomyocyte fibrosis/apoptosis and left ventricular hypertrophy; and aortic valve sclerosis (1,7). Because this pathological adiposity results, in part, from unhealthy lifestyles, and is poorly detected with conventional anthropometrics, many people are at increased risk for cardiac injury.

Initial reports of COVID-19 in Italy (8) and China (9–14) point to those age >50 years at higher risk for infection and hospitalization, and >80 years at higher risk for mortality. As of June 2020 in the United States, those age >85 years accounted for the highest mortality numbers (31,778), but there was a disproportionately younger age associated with mortality among those with obesity (652 [ages 55 to 64 years] and 605 [65 to 74 years], compared with only 109 [≥85 years]) (15). One explanation relates to abnormal adiposity and its sequelae, based on prior experiences with various respiratory viruses (16). The 2017 to 2018 U.S. obesity prevalence rate was 42.4%, with 40.0% age 20 to 39 years (17). Moreover, 71.6% of adults age ≥20 years were overweight/obese in 2015 to 2016 (18). In several studies (19–22), patients with COVID-19 and obesity were more likely to be admitted to the intensive care unit (ICU) and have higher mortality rates than those without obesity. In 1 study of 3,615 patients with COVID-19, hospitalization and ICU admissions of patients with obesity were higher in those age <60 years, compared with those age ≥60 years (20). Possible mechanisms for this observation include dysregulated immunity with high leptin/adiponectin ratios (23) and sedentariness (24), increased angiotensin-converting enzyme 2 (ACE2) expression in epicardial adipose tissue (25), concurrent cardiopulmonary disease (1,26), and lipotoxic adiposity (1). This phenomenon not only applies to Americans who have greater BMIs and risk for visceral/ectopic fat, but also Asians who are more prone to visceral/ectopic fat accumulation and dysglycemia at milder BMI elevations (1,5,6). A common link is unhealthy "Western" lifestyles. Taken together, the increasingly "sick" nature of populations with increased cardiometabolic risk factors, particularly at younger ages and below detection thresholds, amplifies effects of any acute insult, particularly one that subverts the immune-cardiopulmonary system, such as COVID-19 (27).-

DYSGLYCEMIA. Diabetes is characterized by abnormally high blood glucose levels sufficient to cause end-organ damage (**Table 2**). Diabetes is a global problem affecting approximately 463 million people worldwide in 2019, expected to increase 51% to 700 million by 2045, with about 90% having T2D (28). T2D falls within a "dysglycemia-based chronic disease" spectrum consisting of insulin resistance, pre-diabetes, T2D, and vascular complications (1,6). There are higher prevalence rates of obesity, hypertension (HTN), and CVD with diabetes, intensifying risks for CMBCD. Of note, 50.1% of those with diabetes and 88.4% with pre-diabetes are unaware of

ABBREVIATIONS AND ACRONYMS

BMI = body mass index

CIRCS = coronavirus disease-related cardiometabolic syndrome

CMBCD = cardiometabolic-based chronic disease

COVID-19 = coronavirus disease 2019

HCP = health care professional

ICU = intensive care unit

RAS = renin-angiotensin system

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

TABLE 1 Components of a Postulated COVID-Related Cardiometabolic Syndrome

Pre-CIRCS	Acute CIRCS	Chronic CIRCS
Prior to COVID-19 diagnosis	From COVID-19 diagnosis to resolution or 3 months	≥ 3 months from COVID-19 diagnosis
Unhealthy lifestyle	Hypercytokinemia and inflammation	Preparedness for theoretical post-viral syndrome
Unfavorable social determinants of health	Severe acute respiratory syndrome	Implement chronic care model
Transcultural factors	Severe insulin resistance and hyperglycemia	Intensive lifestyle change
Cardiometabolic-based chronic disease	Abnormal adiposity	Address social determinants of health
Preventive care	Cardiovascular disease	Novel therapies for preventive care
	Hypercoagulable state and thromboemboli	Infrastructural change in healthcare system
	High insensible water losses and hypernatremia	
	Acute kidney injury	
	Hyperphosphatemia and hypocalcemia	
	High nutritional risk	
	Encephalopathy	
	Prolonged acute and chronic critical illness	
	Intensive metabolic support	

This postulated model will require validation (research gap), with particular focus on whether and how chronic CIRCS (with or without antecedent critical illness) differs from chronic critical illness.

CIRCS = coronavirus disease–related cardiometabolic syndrome; COVID-19 = coronavirus disease 2019.

their condition (28,29), necessitating case finding for dysglycemia in all hospitalized patients.

COVID-19 is associated with worse outcomes in patients with T2D, but less so when the hyperglycemia is better controlled (30). Specifically, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rates and disease severity markers are increased in patients with diabetes (14,31–38). Potential mechanisms include: cytokine-mediated aggravation of insulin resistance (39) and hypercoagulability (40); increased expression of the SARS-CoV-2 receptor (ACE2) with renin-angiotensin system (RAS) agents (41); effects of SARS-CoV-2 on pancreatic ACE2 with decreased β-cell insulin reserve (42); immunosuppression; glycosylation of viral spike protein and ACE2 with increased viral binding/entry (43); decreased viral clearance and increased viral replication (44,45); and comorbidities (38). Adverse outcomes with diabetes have also been reported with pandemic influenza A 2009 and Middle-East respiratory syndrome coronavirus (46).

DYSLIPIDEMIA. In 2015 to 2016, over 12% of adults age ≥20 years and about 7% of children/adolescents ages 6 to 19 years had high cholesterol (47). Statin therapy is indicated as CVD preventive therapy for high-risk patients. Statins have cholesterol-lowering and anti-inflammatory properties that mitigate the risk of CVD events. Multiple prospective population studies and randomized clinical trials involving patients at risk, and with established atherosclerotic CVD, have attributed risk reduction with statins to both low-density lipoprotein cholesterol and high-sensitivity C-reactive protein lowering (48). Statins also diminish inflammatory responses and possibly improve survival in a hyperinflammatory subphenotype of acute respiratory distress syndrome (49).

COVID-19 associated cardiac injury and mortality is higher in patients with older age and certain comorbidities: HTN, diabetes, chronic kidney disease, atherosclerotic cardiovascular disease, and chronic heart failure (38,50). Thus, most patients with cardiac injury are identified as very high risk for CVD events (51). Viral illnesses incite a profound systemic inflammatory response leading to tissue injury and organ failure. Among patients with COVID-19, cardiac injury is associated with higher leukocyte counts and elevated procalcitonin and C-reactive protein levels (50). This immune response involves activation/proliferation of lymphocytes/macrophages, with increased pro-inflammatory cytokines: monocyte chemoattractant protein-1; macrophage inflammatory protein-1α; tumor necrosis factor-α; and interleukin-2, -7, and -10 (52). Although many patients with COVID-19 take a statin, the use of statins to specifically manage viral illnesses remains unclear. In cell culture studies with human alveolar epithelial cells, H5N1 (influenza A) infection induced cytokine production (53). Moreover, suppression of sterol biosynthesis with simvastatin reduced viral replication and cytokine production at a farnesylation step (54). Nevertheless, combined treatment with simvastatin did not enhance the efficacy of oseltamivir in mice (55). Also, atorvastatin mediates epigenetic histone modifications and ACE2 up-regulation in a rabbit atherosclerosis model (56). Patients with

TABLE 2 Diabetes Types, Cardiometabolic Context, and COVID-Related Cardiometabolic Syndrome Relevance

Diabetes Type	Description	Cardiometabolic Context	CIRCS Relevance
T1D			
	Generally younger age at onset*	Increased CVD risk	Insulin only while in hospital†
	Primary destruction of ß-cells	Increased CRD risk	Consider using CGM technology
	Autoimmune	Increased hypoglycemia risk	Avoid SGLT2 during acute COVID-19 and consider stopping SGLT2i in patients at risk for COVID-19
	Increased risk for DKA	Consider SGLT2i, especially with HF	Arrange telemedicine contacts
	Lifestyle and insulin treatment‡		Reassure about prescriptions/supplies
	Diabetes complications		Avoid overprescribing
	Management per guidelines		Restructure routines at home
	Insulin on-board at all times		
T2D			
	Generally older age at onset	Metabolic driver in CMBCD	Insulin only while in hospital†
	Primary insulin resistance	Hypoglycemia risk	Avoid SGLT2 during acute COVID-19 and consider stopping SGLT2i in patients at risk for COVID-19
	Subsequent destruction of ß-cells	Consider SGLT2i and/or GLP1ra with CMBCD	Arrange telemedicine contacts
	Associated with CVD risk factors	Emphasis on healthy weight	Reassure about prescriptions/supplies
	Preceded by milder hyperglycemia		Avoid overprescribing
	May develop DKA		Restructure routines at home
	Multimodality treatments§		Greater emphasis on healthy weight
	Diabetes complications		
	Management per guidelines		

*Some adults may develop autoimmune ß-cell destruction and a T1D picture, possibly with DKA, at later ages (latent autoimmune diabetes in adults); this state may persist as T1D, revert to T2D, or resolve. †Insulin drips should be used judiciously to avoid unnecessary exposures of personnel to COVID+ patients. Alternatives include more aggressive subcutaneous insulin dosing (e.g., q6h NPH + correction rapid-acting insulin), use of intravenous chromium, and permissive underfeeding until glycemic target achieved (140 to 180 mg/dl). ‡Some patients with T1D are treated with SGLT2i. §Patients with T2D may be treated with lifestyle change, oral medications, noninsulin injectables, insulin, and/or metabolic procedures.

CIRCS = coronavirus disease–related cardiometabolic syndrome; CKD = chronic kidney disease; CMBCD = cardiometabolic-based chronic disease; CVD = cardiovascular disease; DKA = diabetic ketoacidosis; GLP1ra = glucagon-like peptide-1 receptor agonist; SGLT2i = sodium-glucose co-transporter 2 inhibitor; T1D = type 1 diabetes; T2D = type 2 diabetes.

familial hypercholesterolemia represent another challenge with COVID-19 due to increased risk for premature coronary heart disease, low-density lipoprotein receptor variants modulating the immune response to SARS-CoV-2, and higher lipoprotein(a) and risk for atherothrombosis (57,58).

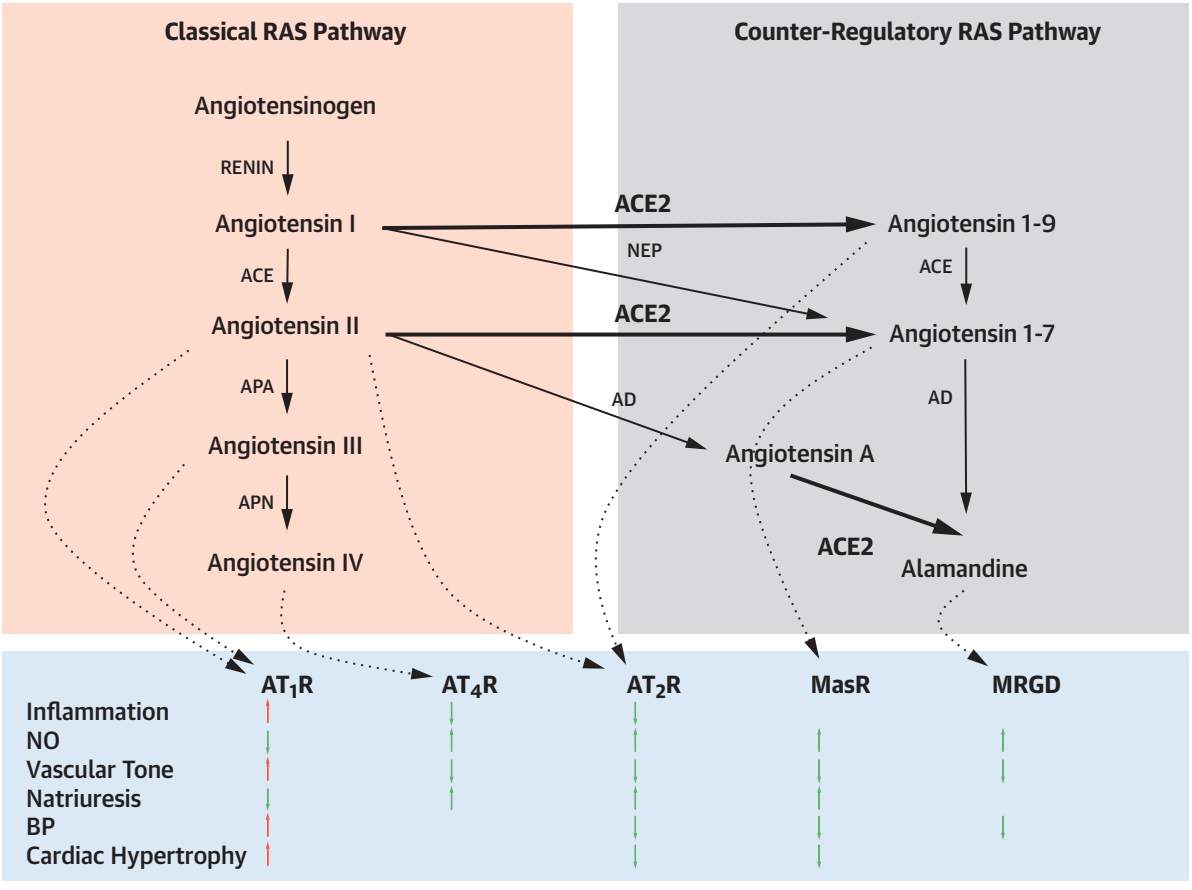
HYPERTENSION. The age-adjusted prevalence of HTN among U.S. adults in 2015 to 2016 was 44.1% based on 2017 American College of Cardiology/American Heart Association criteria (compared with 29.0% [JNC7] and 32.4% [self-reported]) (59–61), with high population-attributable risks of coronary heart disease, heart failure, stroke, chronic renal disease, and dementia, as well as increasing HTN-related CVD mortality from 2007 to 2017 (62–64). Among patients with HTN, 49.5% had obesity, 63.2% hypercholesterolemia, and 27.2% diabetes (63). There are multiple drivers of HTN: genetic; environmental; behavioral; and abnormalities in the cardiovascular, autonomic nervous, renal, and endocrine systems. Central to the RAS is ACE2, a master regulator that converts angiotensin I and II into angiotensin 1-9 and 1-7, respectively (**Figure 1**) (65). Based on this schematic, down-regulation of ACE2 with SARS-CoV-2 binding impairs cardioprotection via the counter-regulatory RAS pathway.

Widely expressed, ACE2 mediates SARS-CoV-2 entry in epithelium. The viral spike protein is primed for viral entry by different host proteases, including transmembrane protease serine 2 (TMPRSS2) (45). The risk of SARS-CoV-2 infection does not appear affected with RAS inhibitors (66,67). Among patients with COVID-19, HTN was associated with frequent cardiovascular morbidities (24.3%), diabetes (15.2%), cardiac disease (6.2%), and high mortality risk (68). In another study, HTN was associated with a ~2.5-fold increased risk of COVID-19 severity and mortality, mainly in those patients over age >60 years (69).

CARDIOMETABOLIC INTERVENTION

ABNORMAL ADIPOSITY. Prudent recommendations can be made based on the high prevalence of overweight/obesity and unhealthy lifestyle in the general population. Formal lifestyle medicine programs should be implemented in the context of social distancing. Specifically, with school and lunch

FIGURE 1 **The Role of ACE2 in the RAS**



ACE2 figures prominently in the RAS, mediates cardioprotection, and is a receptor for SARS-CoV-2. Loss of ACE2 function with SARS-CoV-2 binding can lead to CIRCS. **Bold arrows** correspond to ACE2 pathways. In the **bottom panel, red arrows** correspond to adverse and **green arrows** to beneficial effects on cardioprotection. Adapted from Paz Ocaranza et al. (65). ACE = angiotensin-converting enzyme; AD = aspartate decarboxylase; APA = aminopeptidase A; APN = aminopeptidase N; AT_1R = type 1 angiotensin II receptor; AT_2R = type II angiotensin II receptor; AT_4R = angiotensin IV receptor; BP = blood pressure; MasR = proto-oncogene Massey receptor; MRGD = Mas-related G protein-coupled receptor member D; NEP = neprilysin; NO = nitric oxide; RAS = renin-angiotensin system.

program closings (70), and new work or stay-at-home routines (71), the risks of undernutrition, weight gain, and deconditioning in children/adults need to be countered by planned home physical activities. Social distancing foments a culture of ordering in and over-consuming "comfort foods." Simple instructions should be provided to promote a healthy lifestyle (**Table 3**) (72). Health care professionals (HCPs) should be trained in lifestyle medicine using printed materials, web-based learning tools, and practical experiences. At a systems level, a network of lifestyle medicine programs forges a new culture of healthy living.

The "gaps" in research evidence, knowledge dissemination, and practical implementation are wide with respect to obesity and COVID-19. Research gaps correspond to unanswered scientific questions (73). Epidemiological studies are needed to capture associations of COVID-19 risks with adiposity and short-term benefits of lifestyle change on body composition. Subsequent basic research studies, clinical trials, and targeted interventions should be designed. Simple technologies that detect abnormal adiposity should be developed. Knowledge gaps correspond to the nonuniform dissemination of information to HCPs, patients, and policymakers (74). New information should be well-communicated to HCPs in live educational activities and in printed and web-based materials. Practice gaps correspond to failures converting information into action (75). The

TABLE 3 Healthy Lifestyle During and After Social Distancing

Healthy Lifestyle Component	During Social Distancing	After Social Distancing
Nutrition	Arrange home delivery of healthy foods/meals Consume >5–7 daily servings of plants Minimize starchy, sugary, salty, and fried foods Prepare and consume high-fiber breakfasts Have high fiber between meal snacks Avoid fad diets/supplements unless advised by your HCP Learn/practice how to cook/prepare healthy foods	Continue same healthy eating recommendations When food shopping, adhere with lists, created after meal consumption In restaurants, order healthy dishes without a menu Create healthy eating culture at home, work, and school
Physical activity	Consider ordering home exercise equipment Engage in home aerobic and strength training Judicious outdoor walking/running Create/execute realistic daily exercise program	Increase exercise time at home Increase physical activity at work and school Engage in organized sports
Behavior	Innovate new home routines for healthy lifestyle* Reassure family members about preparedness Re-message healthy lifestyle and short-term protection Continue message healthy lifestyle and long-term benefits	Adapt routines to "normal" schedules Continue positive attitudes Increase outdoor fun activities with family/friends
Sleep	Restructure routines for about 7 h sleep per night Implement new routines for better quality of sleep	Adapt sleep routines to "normal" schedule
Alcohol	Abstinence preferred Otherwise limit to <1 (women), <2 (men) drinks/day Use telemedicine for counseling	Continue same recommendation
Tobacco	No tobacco products Use telemedicine for counseling	Continue same recommendation
Community engagement	Contact local charities, houses or worship, schools, and so on Engage to help others remotely (phone, internet, and so on)	Continue same recommendation
Technology	Prepare for telemedicine visits with your HCP Download smartphone lifestyle applications Consider purchase of wearable technologies	Continue same recommendation

*Innovation results from organizational change at the micro (individuals), meso (guidelines), and macro levels (organizations, government, policies) (72).
HCP = health care professional.

identification of champions and team members, adequate funding, administrative support from sponsoring organizations, and innovative leveraging of technology can optimize lifestyle medicine programs.

DYSGLYCEMIA. Because many patients with CVD have T2D, healthy lifestyle changes are encouraged in the context of social distancing. Patients should restructure their routines due to potential disruptions in work, sleep, and meal times. Diabetes practice preparedness includes patient access to telemedicine technology. Overprescribing is dissuaded to avoid hoarding, and patients are reassured about ready accessibility to medications and supplies. Continuous glucose monitoring should be considered in patients checking levels multiple times a day, especially with type 1 diabetes (T1D), to alleviate burdens of maintaining supplies. Notwithstanding secondary CVD prevention goals, HCPs should: 1) avoid sodium-glucose cotransporter-2 inhibitors (SGLT2i) in patients with acute COVID-19; and 2) consider holding outpatient SGLT2i in patients at risk for COVID-19, especially with poor or variable oral intake, to lower the risk for diabetic ketoacidosis (euglycemic and hyperglycemic) and avoidable non-COVID hospitalizations. Of note, the SGT2i dapagliflozin is being evaluated as a potential treatment of COVID-19 for organ protection (NCT04350593 and NCT04393246). Urinary glucose losses resulting from SGLT2i create a physiological state mimicking starvation, with elevated glucagon/insulin ratios, ketone production and reabsorption, and risk for ketoacidosis at lower-than-anticipated glucose levels (76).

Physicians should determine if patients have diabetes or take a "sugar medicine." The glucose and hemoglobin A1c levels should be checked in all patients upon presentation. All oral and noninsulin injectable diabetes medication are stopped in the hospital, and only insulin is used. Inpatient monitoring and therapeutics must be protocolized.

TABLE 4 Association of Cardiometabolic Risk Factors With Degrees of COVID-19 Severity

General Population (% With Risk Factor)	COVID-19 Positive Total (% With Risk Factor)	COVID-19 Positive Not Severe (% With Risk Factor)	COVID-19 Positive Severe (% With Risk Factor)		
			Hospitalization	Intensive Care Unit	Mortality
Obesity*					
China (6.2)	ND	ND	**22**	**25.5–27.0**	**88.2**
France (21.6–25.8)	ND	ND	ND	**47.6**	ND
United States (34.0–42.4)	ND	14.4	14–**53.7**	**19.0–45.7**†	ND
Diabetes					
China (9.2–10.9)	2–**22**	4.5–**11**	7.4–**19**	**13.8–34.6**	**7.3–31**‡
Italy (5–9)	**33.9–35.5**	ND	ND	**17**	**33.9–35.5**
Spain (6.9)	ND	ND	ND	ND	**12**
United States (9.8–10.8)	5.4–**10.9**	5.3–**24.0**	**15.0–37.8**	**58**	ND
Dyslipidemia					
United States (12.0)	ND	10.5	**25.9**	**26.6**	ND
Hypertension					
China (15.0–44.7)	9.5–34	ND	23.7–40.8	**58**	37.6
Italy (30)	ND	ND	ND	ND	**73.8**
United States (32.4–44.1)	ND	11.5	37.1–**63.0**	39.5–**66.9**	**73.5**
CVD					
China (43)	1.6–40.0	ND	15.7	9.6–25.0	9.4–11.8
Italy (36)	36.0–**42.5**	ND	ND	ND	24.5–30.1
United States (30–37.4)	ND	16.3	27.8–**44.6**	30.6–**47.1**	**45.6**

Percentage ranges correspond to the proportion of patients in a country's general population and at varying levels of COVID-19 severity (column), with a particular cardiometabolic risk factor (row). These percentages are synthesized based on existing published data covering a wide range of surveillance dates, denominators, definitions, and populations, limiting the validity of comparisons and representing research gaps. However, the pattern of increased proportions of these cardiometabolic risk factors with COVID-19 severity compared with the respective general population support a COVID-Related Cardiometabolic Syndrome (figures with increased proportions in **bold**). See references: China (9,32–34,37,40,88–98); France (19); Italy (8,99,100); Total (4,31,101–104); United States (15,20,29,38,47,59,61,105–111). *Obesity defined by body mass index >30 kg/m^2. †Increased risk for intensive care unit with increased BMI >35 kg/m^2 with age <60 years (20). ‡In largest retrospective study to date in China (n = 72,314), only 0.9% of mortality without any comorbidities, compared with 7.3% with diabetes (66).

COVID-19 = coronavirus disease 2019; CVD = cardiovascular disease; ND = no data (represents epidemiological research gap).

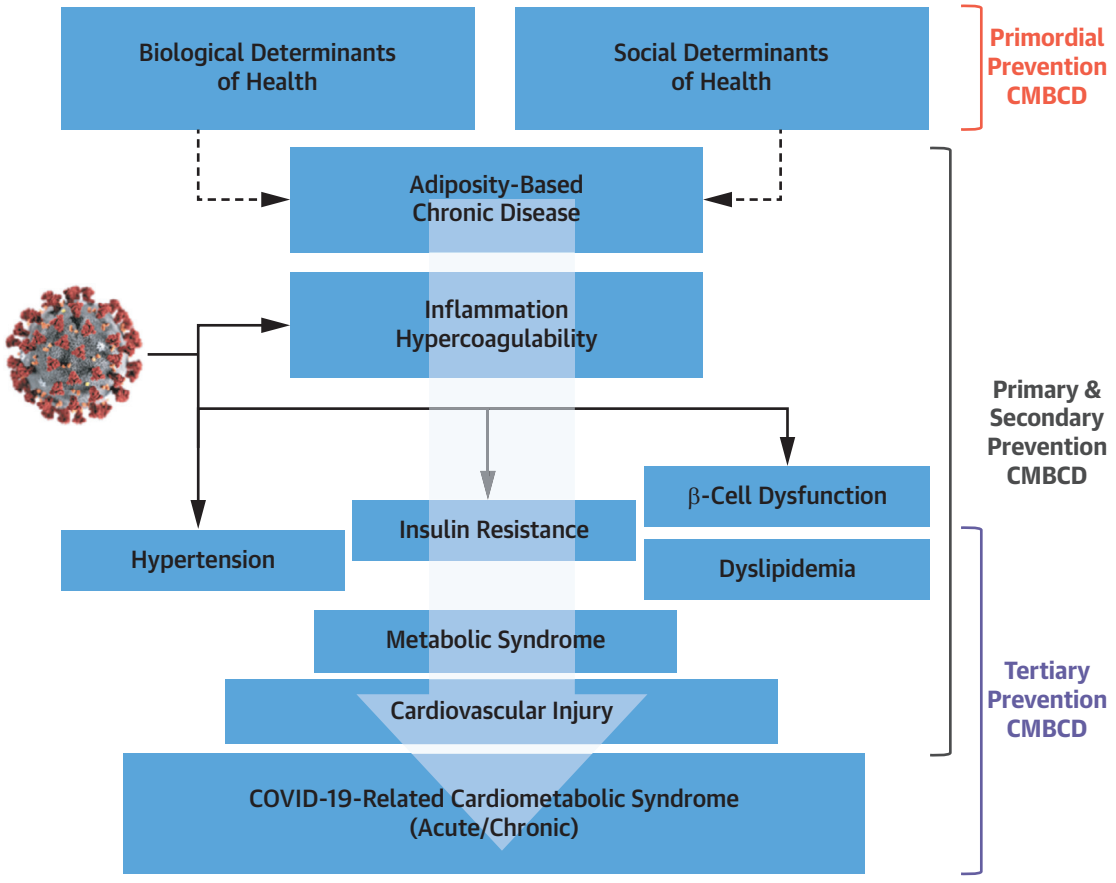
Because all patients with COVID-19 and significant hyperglycemia will require insulinization, a correction insulin protocol must be started immediately. In addition, a guideline-directed, standing subcutaneous insulin protocol must be started based on the nutritional regimen and in all patients with T1D. Endocrinologists should be consulted for all patients with T1D or those with recalcitrant hyperglycemia. In the ICU, hyperglycemia is managed with guidelines-directed insulin protocols. Both ICU and non-ICU glycemic targets are 140 to 180 mg/dl, prioritizing the avoidance of severe hyperglycemia and hypoglycemia. Despite the adverse effects of undernutrition in COVID-19 (77), nutrition support should not be started until severe hyperglycemia is controlled, especially with concurrent or planned glucocorticoid use. If hyperglycemia is recalcitrant on nutrition support, then hold (or significantly reduce) the nutrition support until glycemic control is re-established. Also, to limit HCP exposures, it may be necessary to manage patients without intravenous insulin and/or with less frequent monitoring; in this case, subcutaneous NPH was administered every 6 to 8 h for basal insulinization, and rapid-acting insulin every 3 to 6 h for correction depending on when personnel are already in the room. Last, insulin requirements need to be preemptively increased when steroids are administered, and decreased as steroids are tapered.

Research gaps exist in epidemiology, mechanisms, and clinical trials. Knowledge gaps are related to decreased awareness about the impact of diabetes and hyperglycemia on COVID-19 outcomes, nuances in diabetes and nutrition management in the ICU, and adaptive protocols with resource limitations. Finally, practice gaps involve optimal use of telemedicine to prevent hospitalizations and early insulinization once in hospitals.

DYSLIPIDEMIA. Continuation of statin therapy is recommended in high-/very high-risk patients who have increased susceptibility to a CVD event with hypercytokinemia. The safety of continued statin therapy must be considered as 5% to 20% of patients taking a statin report adverse muscle events (78), mimicking viral-induced muscle symptoms. In addition, drug interactions and tissue organ failure may adversely impair statin elimination, increasing the risk of muscle injury.

Research is needed on the anti-inflammatory effects of statins in patients with COVID-19. Before

CENTRAL ILLUSTRATION **Effects of Severe Acute Respiratory Syndrome Coronavirus 2 on the Development of a Coronavirus Disease-Related Cardiometabolic Syndrome**



Mechanick, J.I. et al. J Am Coll Cardiol. 2020;76(17):2024–35.

The coronavirus disease 2019 (COVID-19)–related cardiometabolic syndrome is triggered by severe acute respiratory syndrome coronavirus 2 infection in susceptible hosts. Primordial prevention focuses on societal/infrastructural changes and social determinants of cardiometabolic health to decrease cardiometabolic-based chronic disease (CMBCD) risk and COVID-19 severity in a population. Primary prevention focuses on specific CMBCD risk factors to decrease severity of abnormal adiposity, dysglycemia, dyslipidemia, and hypertension. Secondary prevention focuses on specific CMBCD components that have progressed to early disease states to decrease COVID-19 severity. Tertiary prevention focuses on advanced CMBCD states associated with severe COVID-19. Severe acute respiratory syndrome coronavirus 2 image adapted from the Centers for Disease Control and Prevention (113).Courtesy of CDC/Alissa Eckert, MS; Dan Higgins, MAMS.

considering a clinical trial, this multidimensional effort requires: 1) establishing the efficacy of statins in reducing viral replication and inflammatory responses in human alveolar cells and experimental COVID-19 models; and 2) assessment of inflammatory responses, myocardial damage, and event rates in patients with COVID-19 treated with/without statin therapy. Certain immunomodulatory bioactive lipids (arachidonic acid and other unsaturated fatty acids) may confer anti-SARS-CoV-2 activity and should be investigated (79). Ongoing clinical trials are investigating anti-inflammatory effects of statins. RuxoSim-20 is an open-label, randomized trial investigating whether combined ruxolitinimb with simvastatin has a synergistic effect on viral entry and reduced inflammation with confirmed SARS-Cov-2 (NCT04348695). C-19 ACS is a prospective, multicenter clinical trial investigating multiple cardioprotective therapies on all-cause mortality at 30 days after admission with acute coronary syndrome (NCT04333407). The intervention includes aspirin 75 mg or clopidogrel 75 mg, rivaroxaban 2.5 mg for patients not receiving an anticoagulant, atorvastatin 40 mg if not taking a statin, and

TABLE 5 Actions to Address Research, Knowledge, and Practice Gaps in COVID-Related Cardiometabolic Syndrome

Research Gaps	Knowledge Gaps	Practice Gaps
Optimize cardiac imaging for epi/pericardial adiposity	Educate about CIRCS	Formulate and implement clinical practice algorithms and protocols
Clarify roles of DPP4i, GLP1ra, RAS antagonists, and TZD	Update on abnormal adiposity, dysglycemia, hypertension, and prior CVD effects on risk	Address social determinants of health, including structural racism
Clarify glucocorticoid and hydroxychloroquine roles	Emphasize importance of prevention and lifestyle change	Plan, build, and operate a lifestyle medicine program
Formalize management in children, adolescents, and pregnancy (including gestational diabetes)	Increase use of webinars, teleconferences, and rapid publication of position papers and guidelines for education	Identify champions, team members, funding sources, administrative allies, and appropriate technologies
Design and implement clinical trials on molecular/metabolic targeting (e.g., ACE2)	Communicate effectively with media and policy-makers	Optimize telemedicine and use of wearable technologies
Clarify roles of specific nutrients (e.g., vitamins B, C, D; chromium, zinc; and fatty acids)	Develop and distribute public service announcements	Create formal preventive care plans to apply before, during, and after COVID-19 infection
Continue epidemiological studies on associations of metabolic syndrome traits with COVID-19	Collaborate with public and private entities to create a culture of awareness	Use a chronic care model for post-COVID-19 follow-up

See text for definitions of gaps. Gaps need to be addressed promptly to create successful prevention plans.

ACE2 = angiotensin-converting enzyme 2; CIRCS = COVID-related cardiometabolic syndrome; COVID-19 = coronavirus disease 2019; CVD = cardiovascular disease; DPP4i = dipeptidyl peptidase-4 inhibitor; GLP1ra = glucagon-like peptide-1 receptor agonist; TZD = thiazolidinedione.

omeprazole 20 mg daily. Knowledge gaps include the evidence-based role of lipid-lowering therapies in patients with COVID-19. Practice gaps include algorithms and policies to implement relevant clinical protocols.

HYPERTENSION. Manipulation of ACE2 activity in patients with COVID-19 decreases pulmonary and vascular injury, pulmonary hypertension, lung fibrosis, and systemic inflammation, with arterial remodeling, improved right ventricular function, and cardioprotective effects (80–82). Although still controversial, there is consensus among professional medical societies to continue RAS antagonists in those currently prescribed these agents (83,84). Of note, inpatient use of angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB) in patients with hypertension and COVID-19 was associated with lower disease severity and interleukin-6 levels, peak viral load, and increased CD3 and CD8 T-cell counts in peripheral blood, compared with other antihypertensive drugs (85). In another inpatient study, there was lower mortality with ACE inhibitor/ARB use compared with those not on ACE inhibitor/ARB therapy (86). Spironolactone has also been proposed as an alternative therapy due to theoretical advantages of avoiding ACE inhibitor/ARB withdraw (87).

Research gaps focus on the role of RAS antagonists in patients with COVID-19, including the role of dual receptor (androgen and mineralocorticoid) antagonism with spironolactone. Besides the role of intensive lifestyle change in the routine management of HTN, knowledge gaps in the context of COVID-19 are focused on guideline-directed use of RAS antagonists. Practice gaps for HTN can be addressed with greater use of home BP monitoring, telemedicine visits with HCPs, and wearable technologies to increase physical activity.

CIRCS AND BEYOND

The current imperative to aggressively address key metabolic drivers of CVD in patients with COVID-19 is supported by epidemiological evidence implicating a nexus of cardiometabolic risks with disease severity (**Table 4**) (4,8,19,20,29,32–34,37,38,40,47,59,61,88–111). For example, in a case series of 5,700 patients admitted to 12 hospitals in the New York metropolitan area, the most common comorbidities were hypertension (56.6%), obesity (41.7%), and diabetes (33.8%) (109). In a meta-analysis, CVD (odds ratio [OR]: 2.93; $p < 0.001$), diabetes (OR: 2.47; $p < 0.001$), and hypertension (OR: 2.29; $p < 0.001$) were identified as predictors of COVID-19 symptoms or ICU admission (112). Many patients and HCPs are unaware of this interconnection among a cluster of metabolic drivers, CVD, and COVID-19, representing a CIRCS framework, and the downstream risks, representing research, knowledge, and practice gaps that must be expeditiously addressed (**Central Illustration, Table 5**). Clinical actions range from preventive care before CIRCS, to acute care during CIRCS, to chronic care after CIRCS (**Table 1**). The anticipation of a chronic CIRCS should alert the health care system to avoid another wave of acute and chronic illnesses. Starting points include addressing research, knowledge, and practice gaps now: planning and implementing lifestyle

medicine and cardiometabolic programs for people of all ages; improving infrastructure for comprehensive prevention plans to reduce CMBCD burden before, during, and after CIRCS; addressing potential post-CIRCS phenomena; and improving preparedness for future pandemics.

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