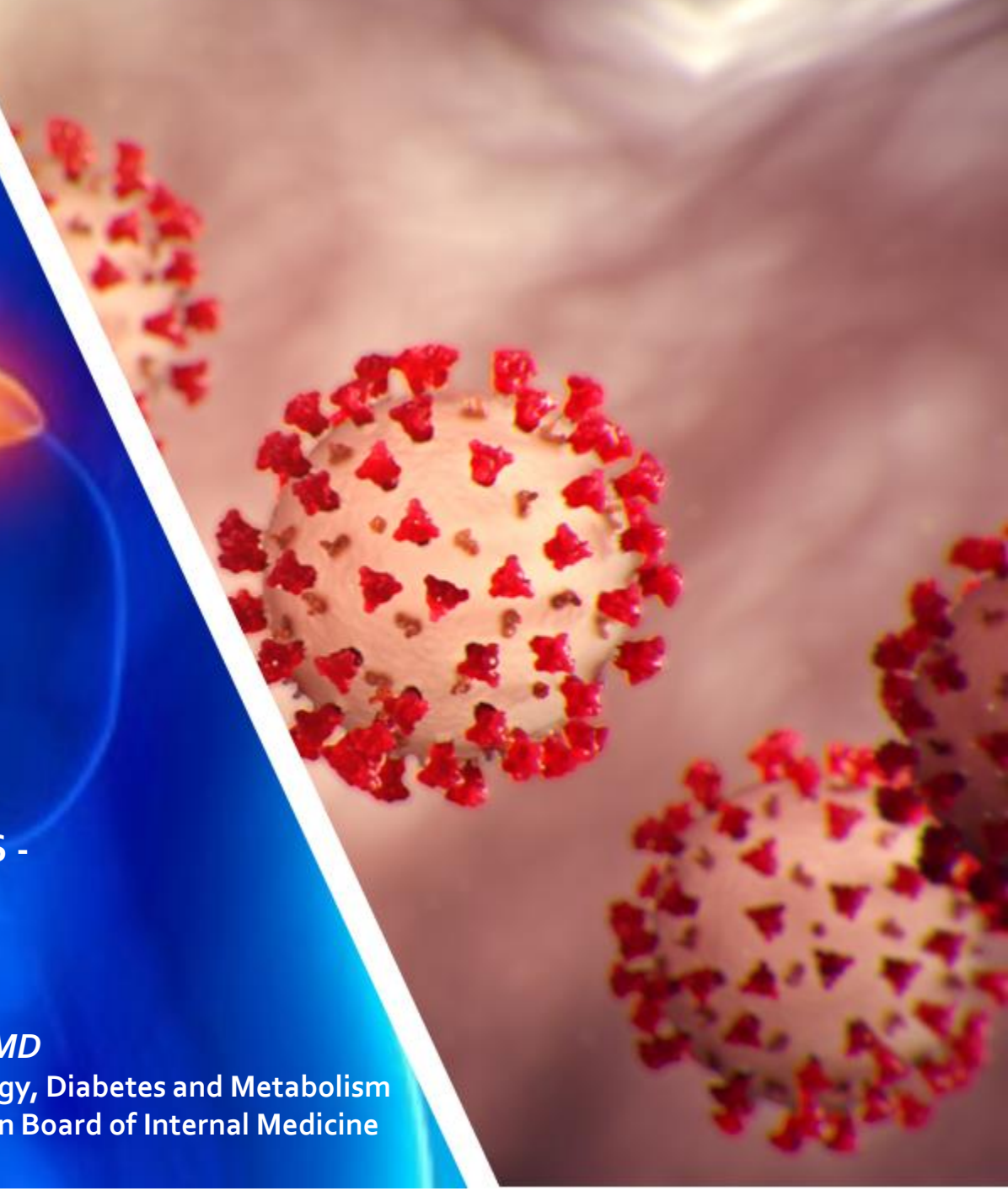
ENDOCRINE SYSTEM EXPRESSION OF SARS COV-2 INFECTION



SPED SEMI-ANNUAL MEETING:
UPDATE IN THE MANAGEMENT OF ENDOCRINE DISORDERS -
MAY 22, 2021

Paula Jeffs-González, MD
Diplomate of Endocrinology, Diabetes and Metabolism
Diplomate of the American Board of Internal Medicine

DISCLOSURE

- **No Conflicts of Interest to Disclose**

Learning Objectives

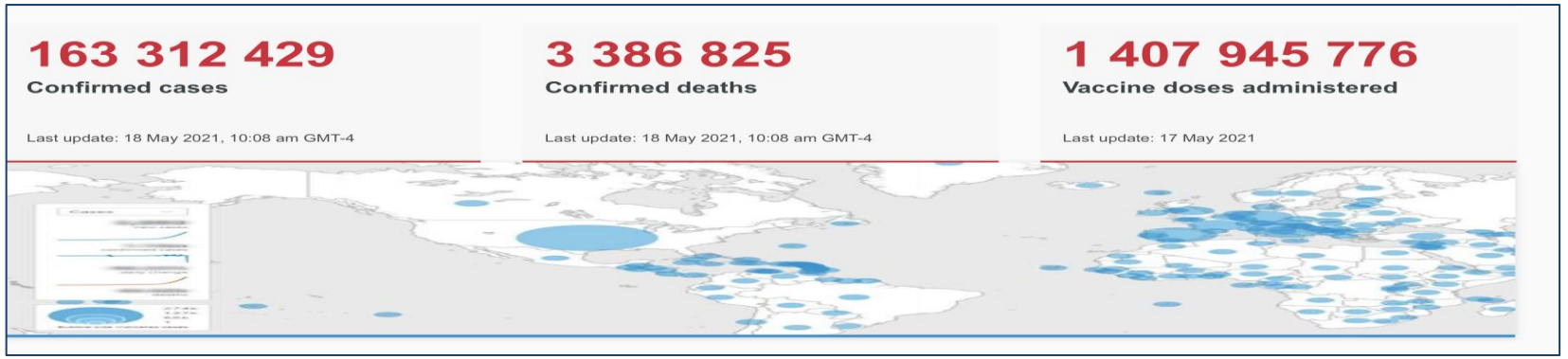
- Review Epidemiology, virology and the pathophysiology of SARS-CoV-2
- Analyze the potential effect of hormones on the susceptibility to COVID-19 infection
- Discuss about the relationships between COVID-19 infection and the endocrine system.
- Asses the recommendations for management of endocrine diseases during COVID19 era.

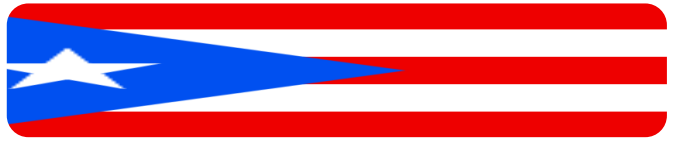
News


Coronavirus COVID-19
1 million deaths
BBC NEWS
CORONAVIRUS LATEST
CASES: 31,521
DEATHS: 638
TRANSIT
el Vocero de Puerto Rico
WWW.ELVOCERO.COM
ALERTA POR PRIMER CASO SOSPECHOSO DE CORONAVIRUS
La gobernadora Wanda Vázquez informa que una mujer y su esposo que llegaron en crucero italiano se mantienen bajo observación.
Gobierno defiende haber usado el protocolo adecuado y espera por la confirmación de las pruebas enviadas al CDC. >P3/4
COVID-19 RESPONSE
BREAKING NEWS
CDC DIRECTOR: EXTREMELY CONCERNED ABOUT U.S. COVID TRAJECTORY
CNBC
WH.GOV

Epidemiology

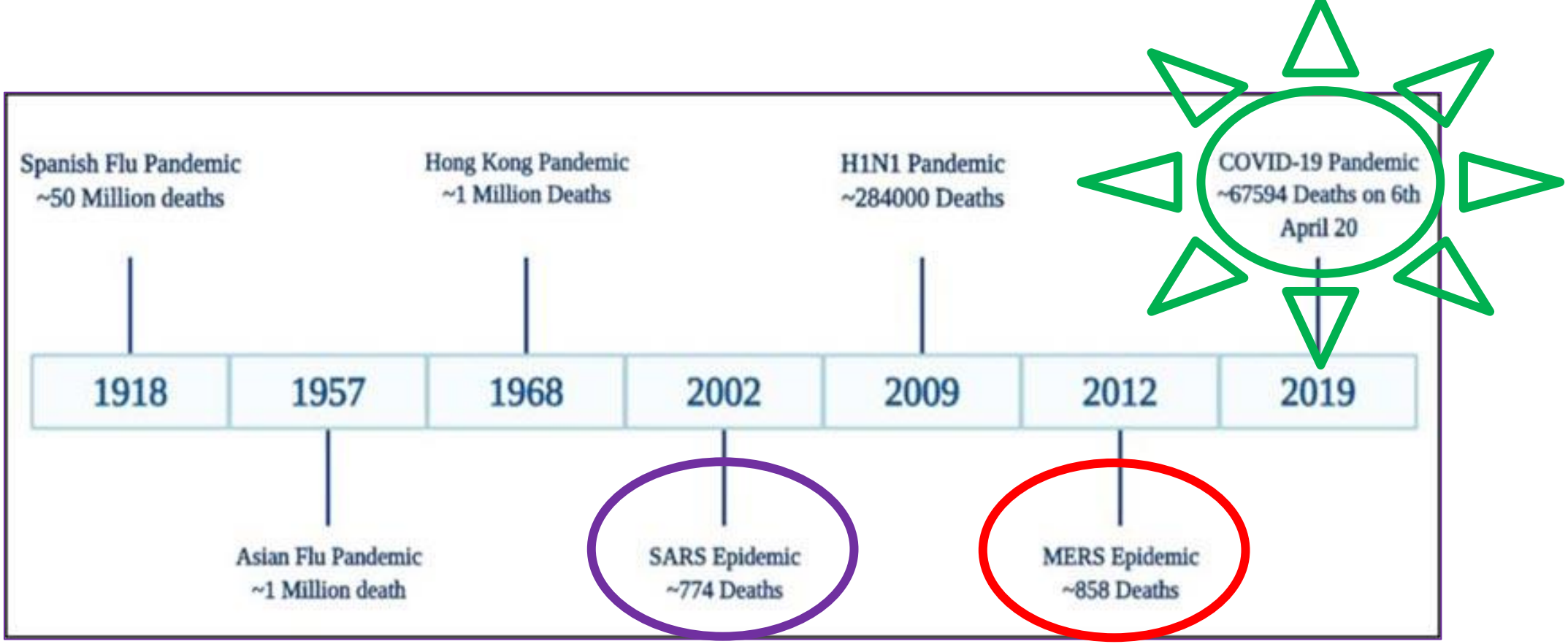
World Health Organization





Confirmed cases: 121,047

Confirmed cases: 2,466


Spanish Flu Pandemic
~50 Million deaths
Hong Kong Pandemic
~1 Million Deaths
H1N1 Pandemic
~284000 Deaths
COVID-19 Pandemic
~67594 Deaths on 6th
April 20
1918
1957
1968
2002
2009
2012
2019
Asian Flu Pandemic
~1 Million death
SARS Epidemic
~774 Deaths
MERS Epidemic
~858 Deaths

Timeline

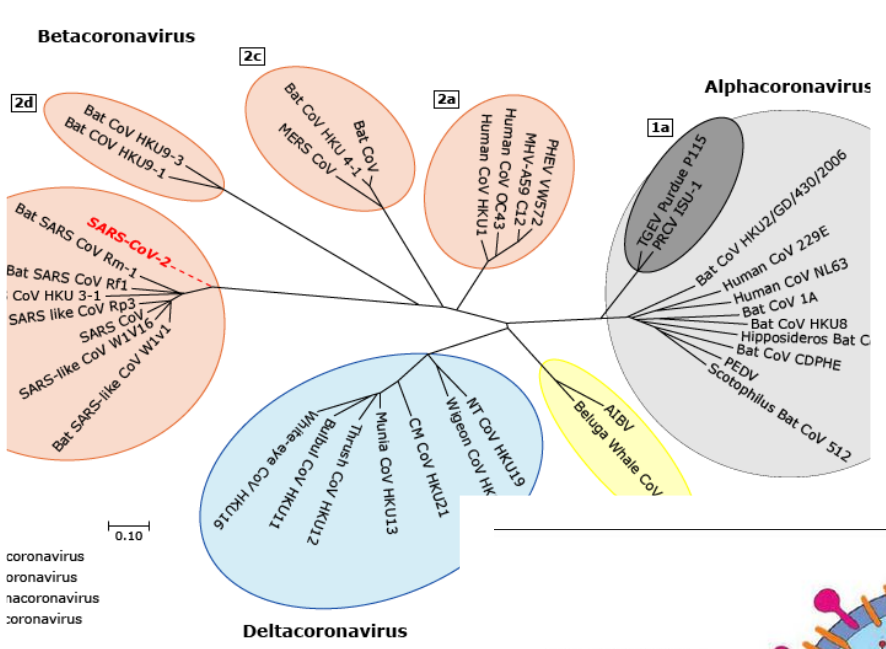
Virology

A novel coronavirus, identified at the end 2019 as the cause of cluster of severe pneumonia cases in Wuhun, a city in the Hubei Province of China.

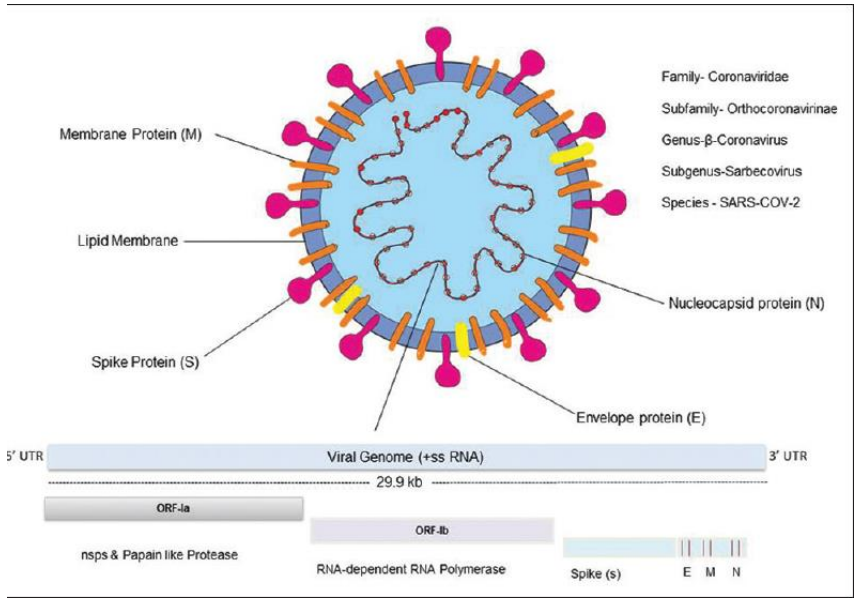
Belongs to the betacoronavirus genus, including SARS-CoV-1 and MERS-CoV.

The seventh coronavirus that is know cause disease in human. And in 6 months , the numbers of death globally have exceeded >400,000.

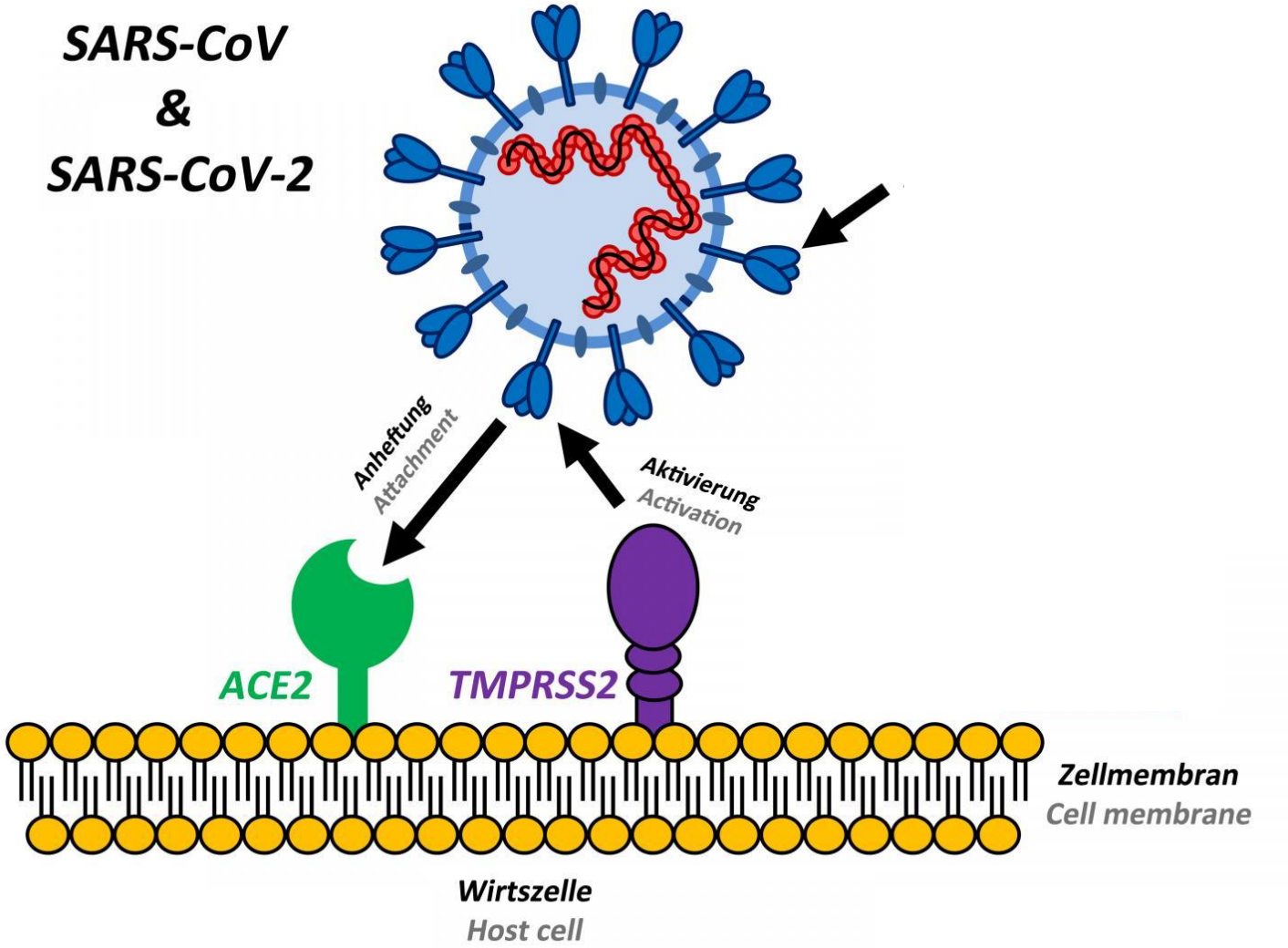
It appears that bats are primary source, transmitted directly by bats or intermediate hosts.



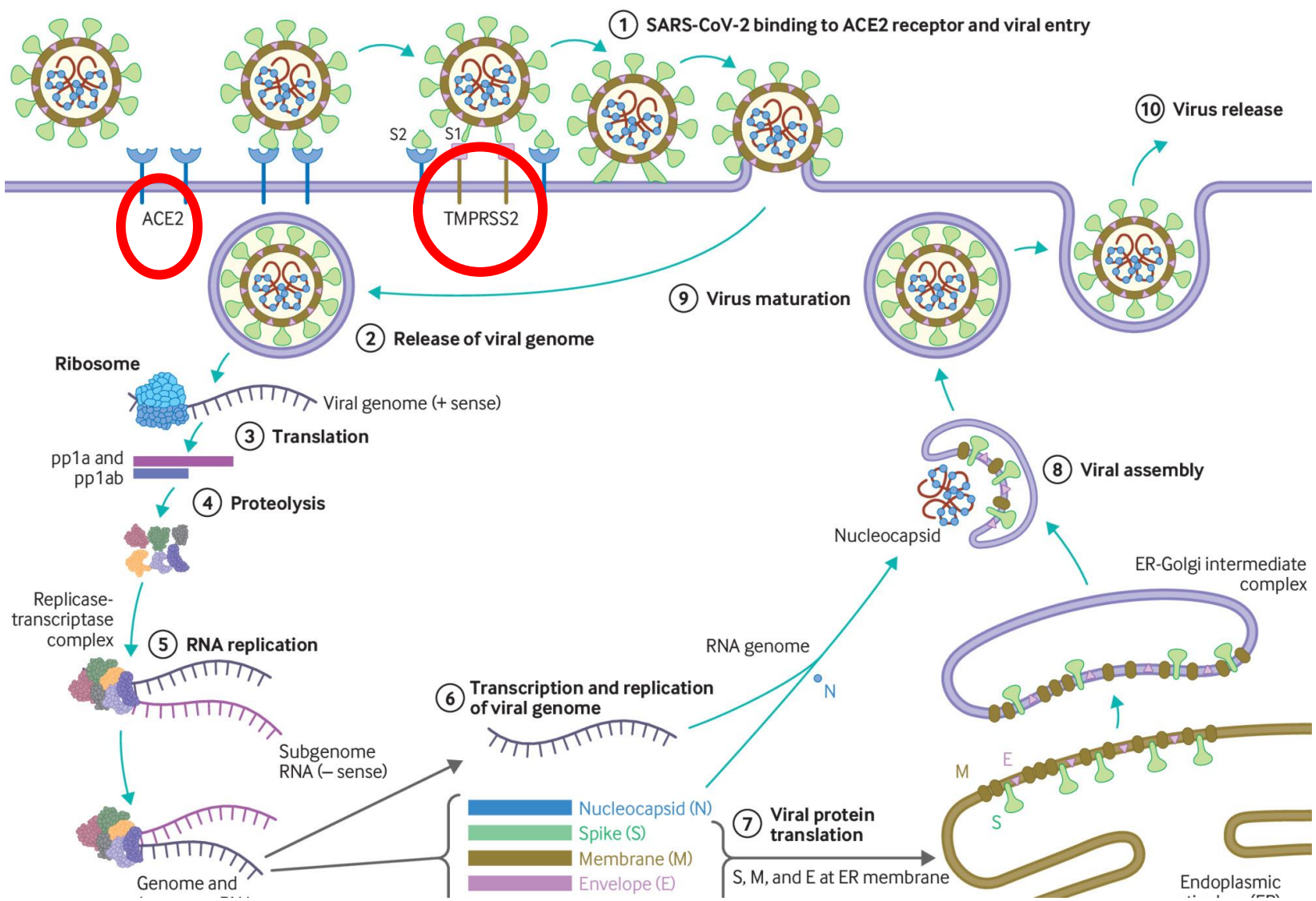
STRUCTURE



Virulence

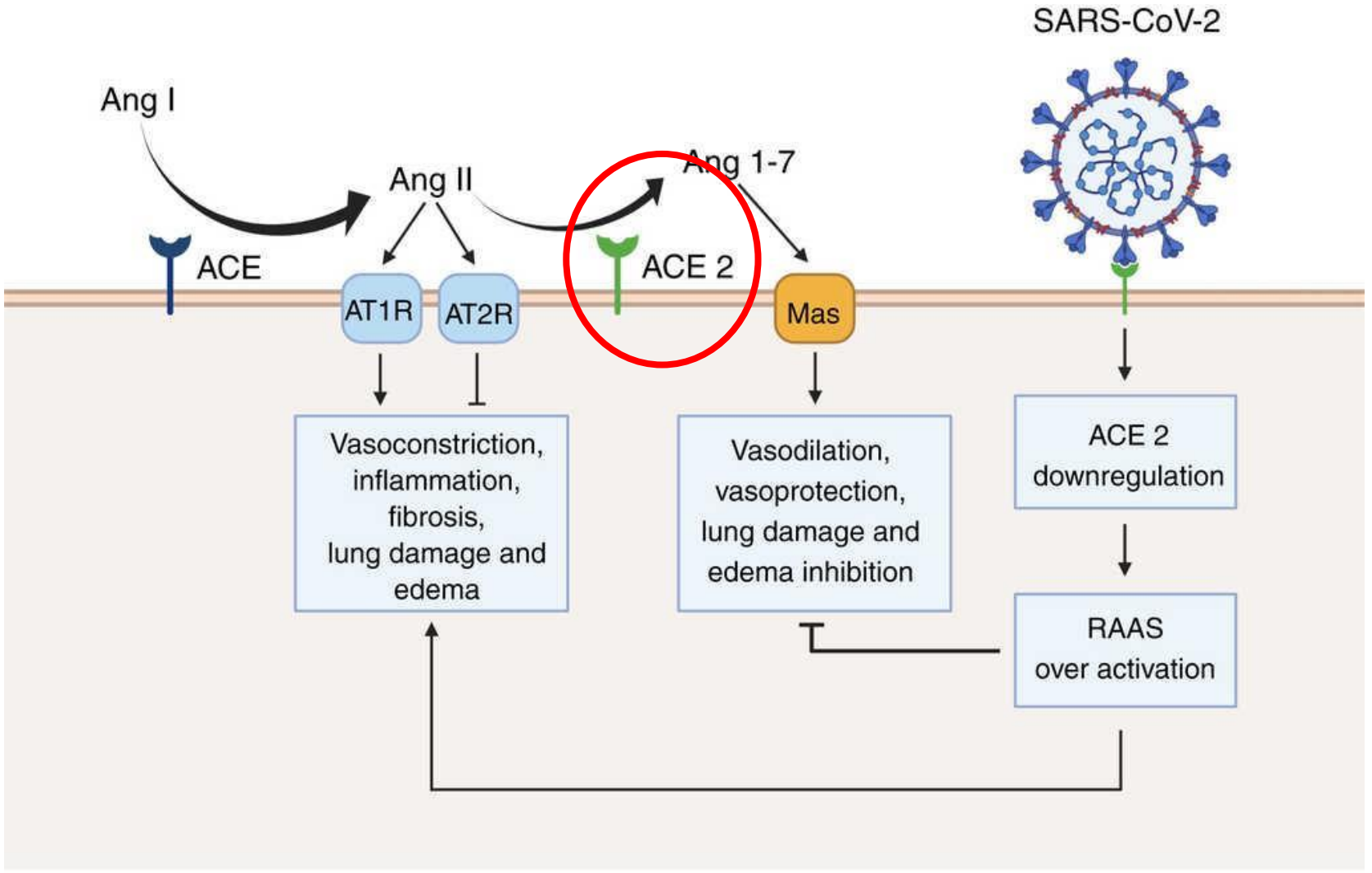

SARS-CoV
&
SARS-CoV-2
Anheftung
Attachment
Aktivierung
Activation
ACE2
TMPRSS2
Zellmembran
Cell membrane
Wirtszelle
Host cell

Mechanism of Transmission



Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2 *BMJ* 2020; 371 :m3862 doi:10.1136/bmj.m3862

ACE-2
Renin-Angiotensin-Aldosterone System



Rev Col Cardiol. 2020;27:129–31

LUNG ACE/TMPRSS2 expression

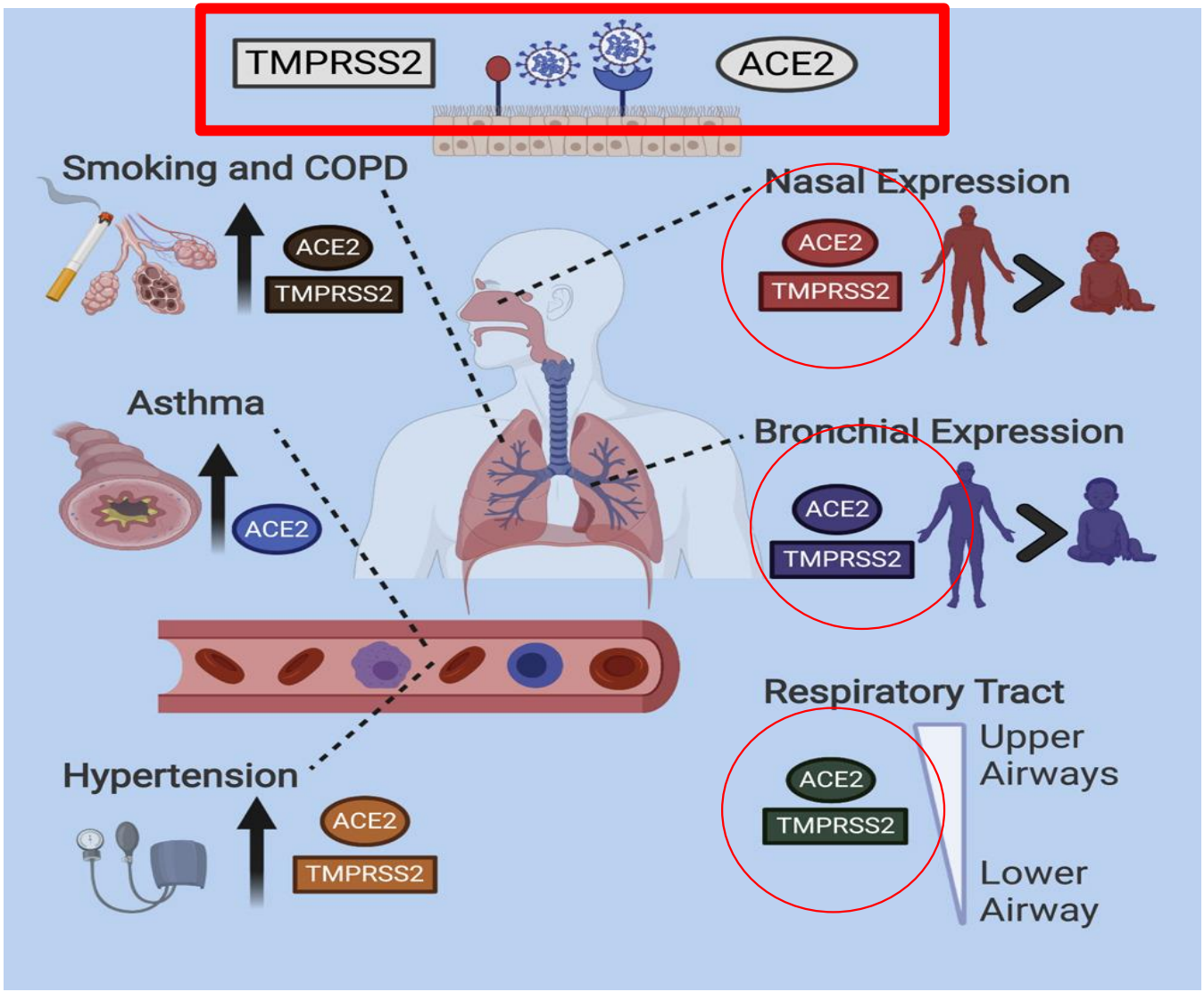
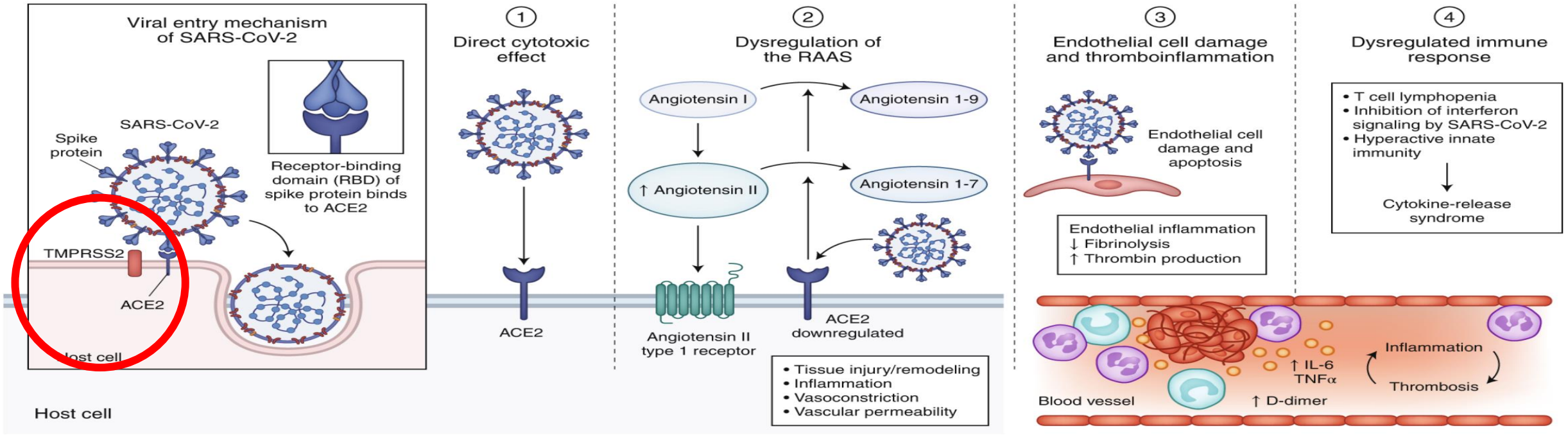


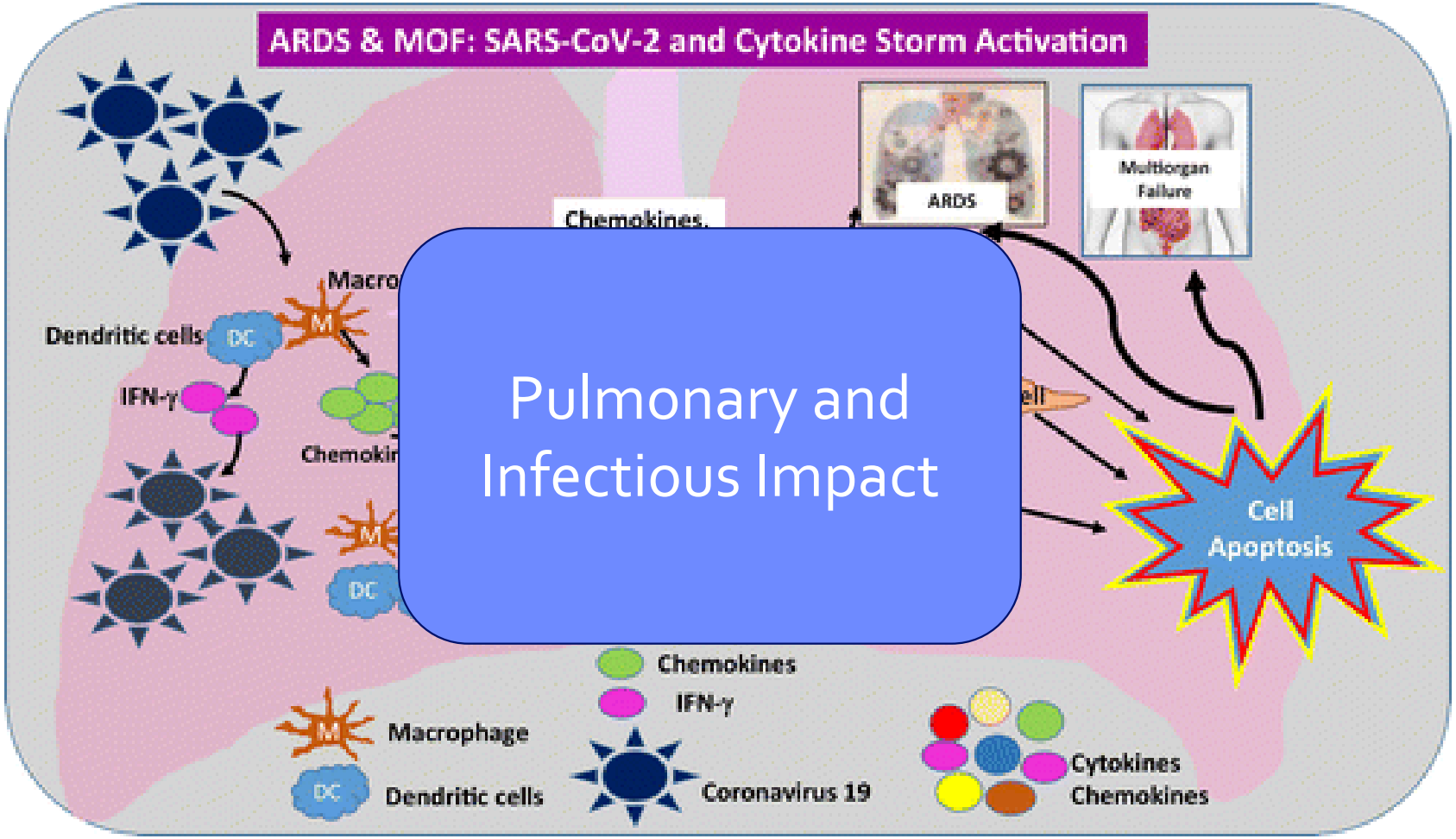
Fig. 1: Pathophysiology of COVID-19.

From: Extrapulmonary manifestations of COVID-19



Gupta, A., Madhavan, M.V., Sehgal, K. *et al.* Extrapulmonary manifestations of COVID-19.*Nat Med* **26,** 1017–1032 (2020). https://doi.org/10.1038/s41591-020-0968-3

SARS-CoV-2 Pathogenesis



Endocrine Impact

COVID-19 in people with diabetes: understanding the reasons for worse outcomes

Matteo Apicella, Maria Cristina Campopiano*, Michele Mantuano*, Laura Mazoni*, Alberto Coppelli, Stefano Del Prato*

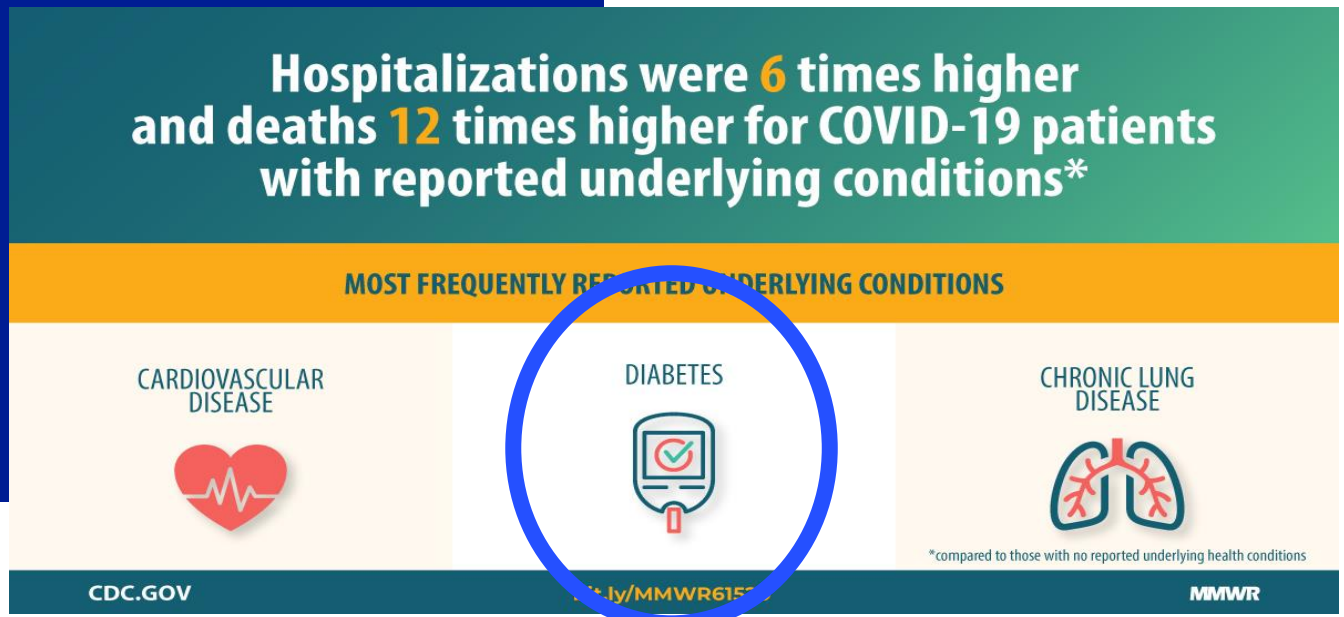
Lancet Diabetes Endocrinol
2020; 8: 782–92
Published Online
July 17, 2020

Since the initial COVID-19 outbreak in China, much attention has focused on people with diabetes because of poor prognosis in those with the infection. Initial reports were mainly on people with type 2 diabetes, although recent surveys have shown that individuals with type 1 diabetes are also at risk of severe COVID-19. The reason for worse prognosis in people with diabetes is likely to be multifactorial, thus reflecting the syndromic nature of diabetes. Age

Obesity and impaired metabolic health in patients with COVID-19

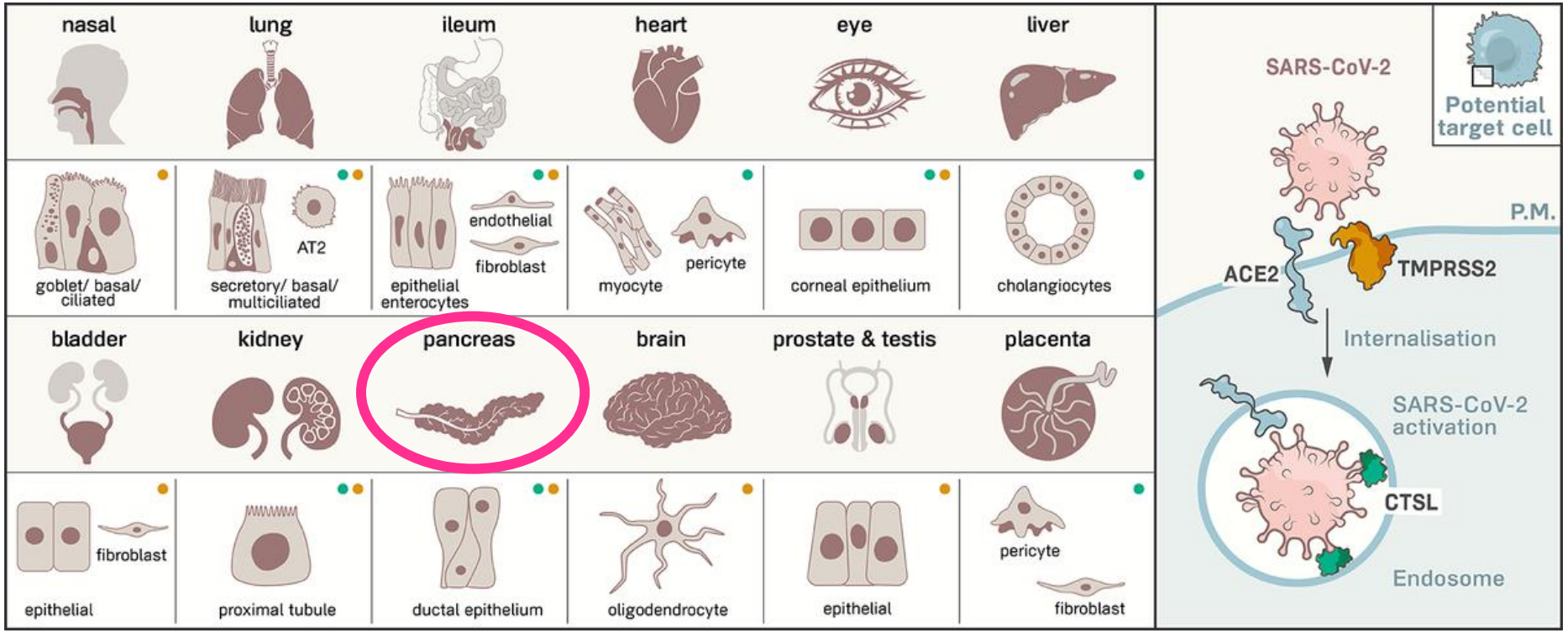
Norbert Stefan[1,2,3,4]✉, Andreas L. Birkenfeld[1,2,3,5], Matthias B. Schulze[3,6] and David S. Ludwig[4,7,8]

Preliminary data suggest that people with obesity are at increased risk of severe COV



	Article type	Study population	Prevalence of diabetes	Outcome	Risk
Zhang et al[3]	Retrospective	258	24%	Mortality	3·64 (1·08–12·21)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Severe disease	2·75 (2·09–3·62)*
Kumar et al[4]	Meta-analysis	16 003	9·8%	Mortality	1·90 (1·37–2·64)*
Guan et al[10]	Retrospective	1590	NA	Composite†	1·59 (1·03–2·45)‡
Li et al[11]	Meta-analysis	1525	9·7%	ICU admission§	2·21 (0·88–5·57)¶
Fadini et al[12]	Meta-analysis	1687	NA	Severe disease	2·26 (0·98–4·82)‖
Fadini et al[12]	Meta-analysis	355	35·5%	Mortality	1·75‖
Petrilli et al[13]	Retrospective	5279	22·6%	Hospital admission	2·24 (1·84–2·73)*
Roncon et al[14]	Meta-analysis	1382	NA	ICU admission	2·79 (1·85–4·22)*
Roncon et al[14]	Meta-analysis	471	NA	Mortality	3·21 (1·82–5·64)*
Zhou et al[15]	Retrospective	191	19%	Mortality	2·85 (1·35–6·05)*
Zhu et al[16]	Retrospective	7337	13%	Mortality	1·49 (1·13–1·96)‡
Yan et al[17]	Retrospective	193	25%	Mortality	1·53 (1·02–2·3)‡
Sardu et al[18]	Retrospective	59	44%	Survival	0·172 (0·051–0·576)‡
Yang et al[19]	Meta-analysis	4648	NA	Severe disease	2·07 (0·88–4·82)*
Barron et al[20]	Cohort study	61 414 470	0·4% type 1 diabetes	Mortality	3·50 (3·15–3·89)*
Barron et al[20]	Cohort study	61 414 470	4·7% type 2 diabetes	Mortality	2·03 (1·97–2·09)*

ICU=intensive care unit. NA=not given. *Odds ratio (95% CI). †ICU admission, or invasive ventilation, or death. ‡Hazard ratio (95% CI). §Calculated for 1056 patients (in three of six studies). ¶Risk ratio (95% CI). ‖Rate ratio (95% CI not given).

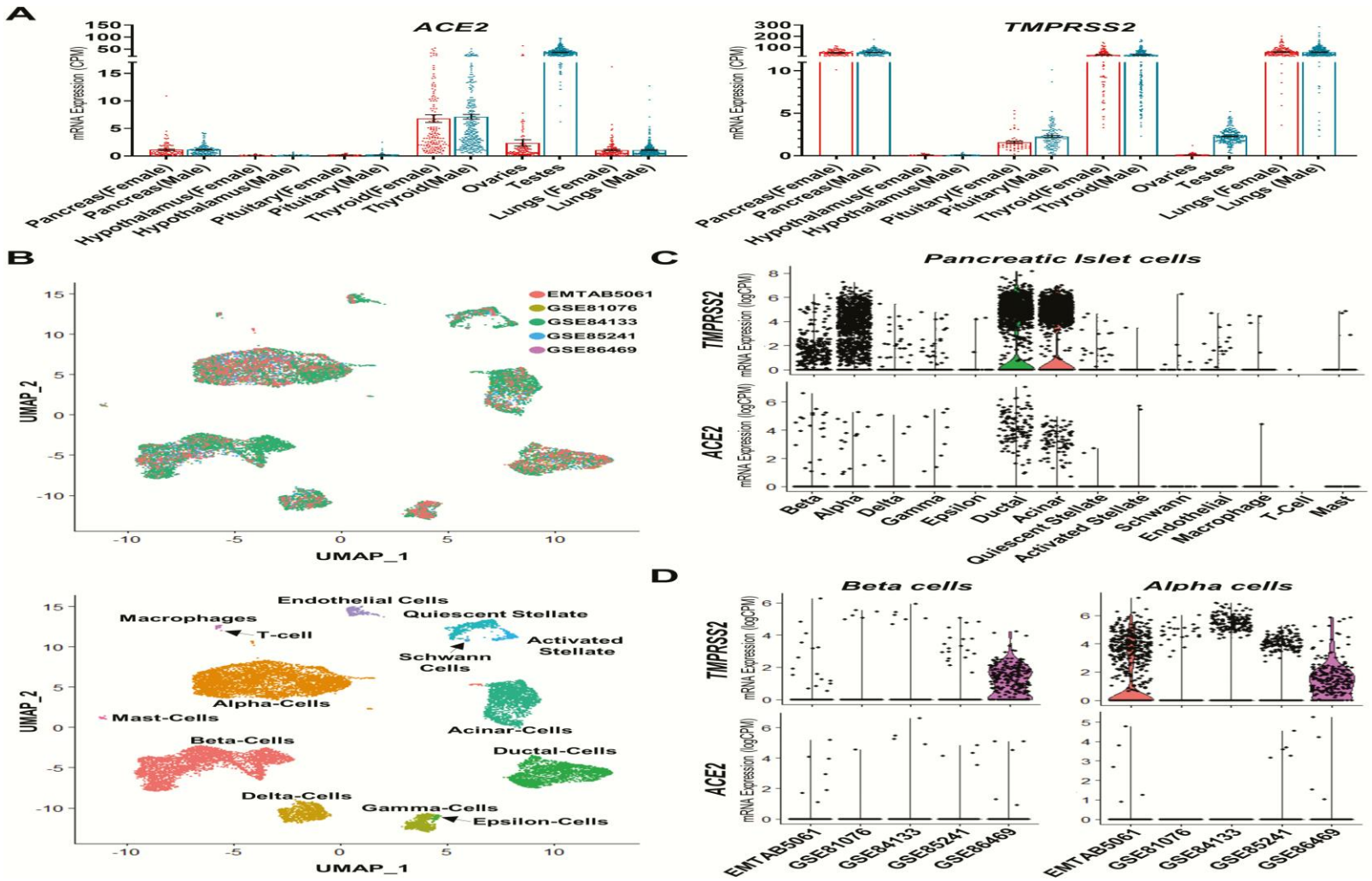


Human cell types within corresponding organs that express the genes for both ACE2 and CTSL (green dot) or both ACE2 and TMPRSS2 (orange dot).
ANNA HUPALOWSKA

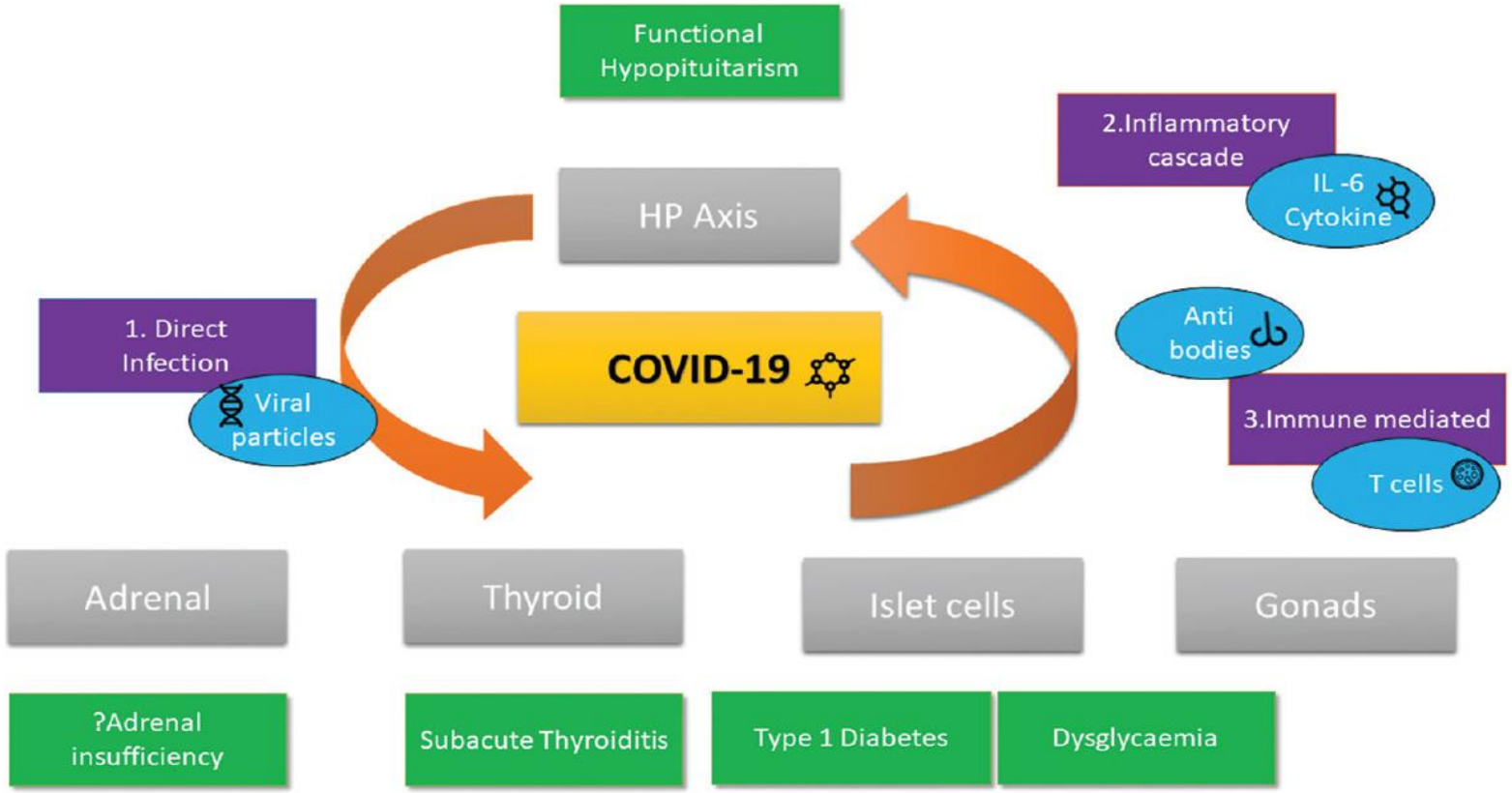
ACE2 / TMPRSS2 expression

Endocrine Expression

Gene expression for ACE2 and TMPRSS2 across select human tissues are widely distributed in human body, with a relevant expression in endocrine tissues including testicle, thyroid, adrenal and pituitary



Endocrinology, Volume 161, Issue 9, September 2020, bqaa108,
Eric Lazartigues, Mirza Muhammad Fahd Qadir, Franck Mauvais-Jarvis, Endocrine Significance of SARS-CoV-2's Reliance on ACE2, *Endocrinology*, Volume 161, Issue 9, September 2020, bqaa108,



COVID-19 and Endocrinopathy

Marazuela, M., Giustina, A. & Puig-Domingo, M. Endocrine and metabolic aspects of the COVID-19 pandemic. *Rev Endocr Metab Disord* **21,** 495–507 (2020).

Diabetes and Covid 19

Inpatient hyperglycemia during the COVID-19 pandemic has been associated with worse outcomes, but improvement of glycemic control can reduce complications

Diabetes and Covid19

Diabetes is a primary risk factor for the development of severe pneumonia and a septic course due to virus infections and occurs in around 20% of patients

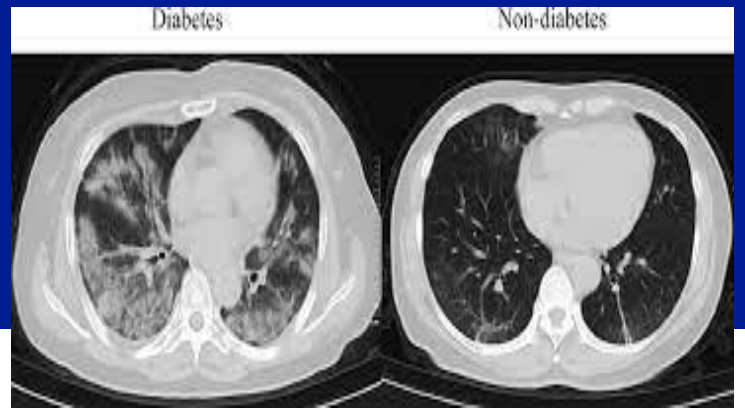


Table 2 Laboratory and Radiologic Findings of Patients on Admission

Variables	Normal Range	Total (n = 584)	Diabetes (n = 84)	Nondiabetes (n = 500)	*P* Value
Blood routine					
White blood cells, × 10^9/L	3.5-9.5	5.15 (3.95, 6.97)	5.63 (4.31, 7.47)	5.08 (3.89, 6.94)	.167
Neutrophils, × 10^9/L	1.8-6.3	3.39 (2.39, 5.04)	3.86 (2.91, 6.31)	3.29 (2.35, 4.94)	.014
Lymphocytes, × 10^9/L	1.1-3.2	1.02 (0.66, 1.51)	0.84 (0.59, 1.42)	1.04 (0.67, 1.54)	.032
Platelets, × 10^9/L	125-350	192 (149, 250)	181 (139, 242)	193 (150, 254)	.196
Hemoglobin, × 10^9/L	130-175	127 (116,137)	126 (112, 134)	127 (116, 137)	.432
Biochemical					
Alanine aminotransferase, IU/L	9-50	21 (13, 35)	22 (16, 40.5)	20 (13, 35)	.122
Aspartate aminotransferase, IU/L	15-40	26 (18, 38)	26 (21, 38.5)	25 (18, 38)	.191
Total bilirubin, μmol/L	2-23	7.9 (5.7, 11)	9.7 (7.4, 13.05)	7.5 (5.5, 10.7)	< .01
Albumin, g/L	40-55	37.3 (33.3, 41.5)	35.5 (30.9, 41.5)	37.5 (33.7, 41.5)	.035
Blood urea nitrogen, mmol/L	3.6-9.5	4.38 (3.43, 5.79)	5.09 (3.68, 6.59)	4.3 (3.41, 5.61)	.001
Serum creatinine, μmol/L	57-111	63 (53, 74)	66 (55, 79.5)	63 (52.7, 73)	.169
Cardiac troponin I, ng/mL	0-0.014	0.008 (0.006, 0.014)	0.012 (0.008, 0.02)	0.008 (0.005, 0.013)	< .01
Creatine kinase-MB, ng/mL	0-6.22	1.19 (0.74, 2.20)	1.37 (0.78, 3.32)	1.17 (0.74, 2.04)	.068
Infection-related biomarkers					
C-reactive protein, mg/L	0-3	18 (2.3, 57.4)	33.5 (6.1, 84.3)	15.45 (2.0, 51.7)	.008
Procalcitonin, ng/mL	0-0.1	0.05 (0.03, 0.13)	0.10 (0.04, 0.23)	0.05 (0.03, 0.11)	< .01
Coagulation function					
Prothrombin time, s	9.3-12.9	12.3 (11.5, 13.3)	12.85 (11.6, 13.62	12.3 (11.5, 13.2)	.063
D-dimer, μg/L	0-0.243	0.21 (0.10, 0.61)	0.31 (0.13, 1.06)	0.19 (0.09, 0.52)	.033
Imaging features					
Unilateral pneumonia	NA	67/584 (11.5%)	6/84 (7.1%)	61/500 (12.2%)	.200
Bilateral pneumonia	NA	450/584 (77.1%)	73/84 (86.9%)	377/500 (75.4%)	.020

NA = not available.
Data are median (IQR) or n/N (%). *P* values were calculated by chi-squared test, Fisher's exact test, or Mann-Whitney *U* test, as appropriate.

CLINICAL RESEARCH STUDY

THE AMERICAN JOURNAL of MEDICINE®

The Relationship Between Diabetes Mellitus and COVID-19 Prognosis: A Retrospective Cohort Study in Wuhan, China

Jian Shang, MD, PhD,[a,b,1] Qian Wang, MD,[a,b,1] Haiping Zhang, MD,[c,1] Xiaoyue Wang, MD,[a,b] Jing Wan, MD, PhD,[d] Youqin Yan, MD,[e] Yadong Gao, MD, PhD,[f] Jie Cheng, MD,[a,b] Ziang Li, MD,[a,b] Jun Lin, MD, PhD[a,b]

[a]Department of Gastroenterology/Hepatology, Zhongnan Hospital of Wuhan University, Wuhan, P.R. of China; [b]The Hubei Clinical Center

Hyperglycemia

- Higher mortality
- Increase severity and frequency of ARDS
- Higher inflammatory markers
- Higher complications AKI, Septic Shock, DIC.

Diabetes Care Volume 43, October 2020 2345

Hyperglycemia at Hospital Admission Is Associated With Severity of the Prognosis in Patients Hospitalized for COVID-19: The Pisa COVID-19 Study

*Alberto Coppelli,[1] Rosa Giannarelli,[1] Michele Aragona,[1] Giuseppe Penno,[1,2] Marco Falcone,[2] Giusy Tiseo,[2] Lorenzo Ghiadoni,[2] Greta Barbieri,[2] Fabio Monzani,[2] Agostino Virdis,[2] Francesco Menichetti,[2] and Stefano Del Prato,[1,2] on behalf of the Pisa COVID-19 Study Group**

Diabetes Care 2020;43:2345–2348 | https://doi.org/10.2337/dc20-1380

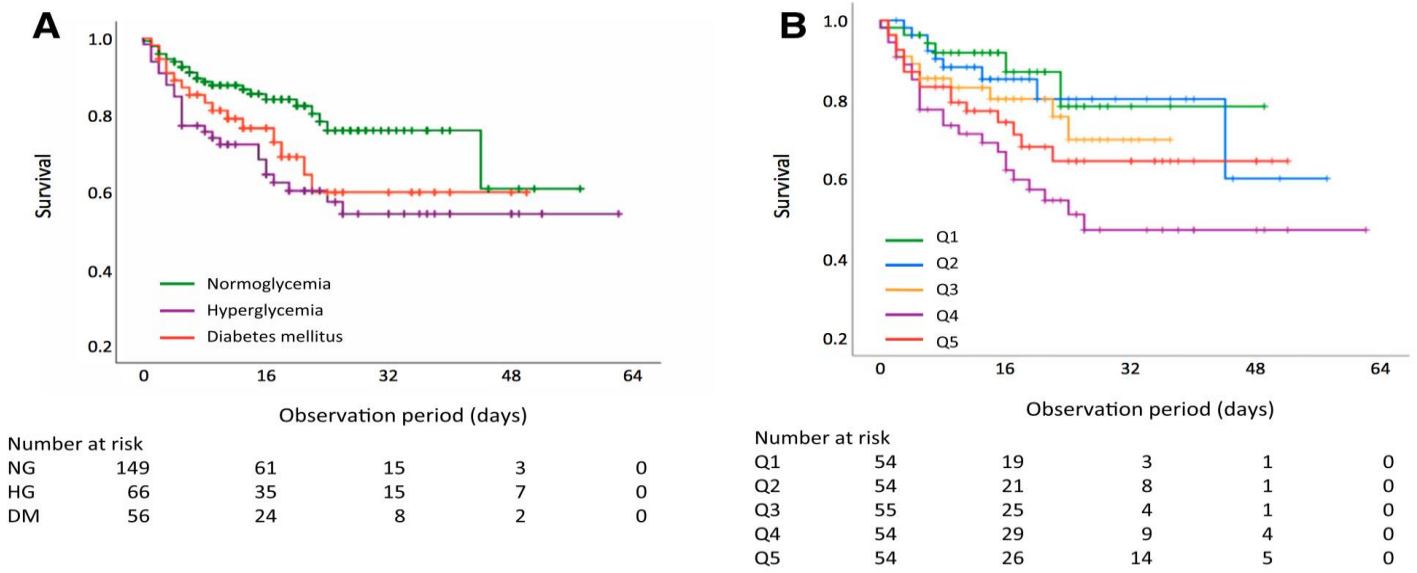
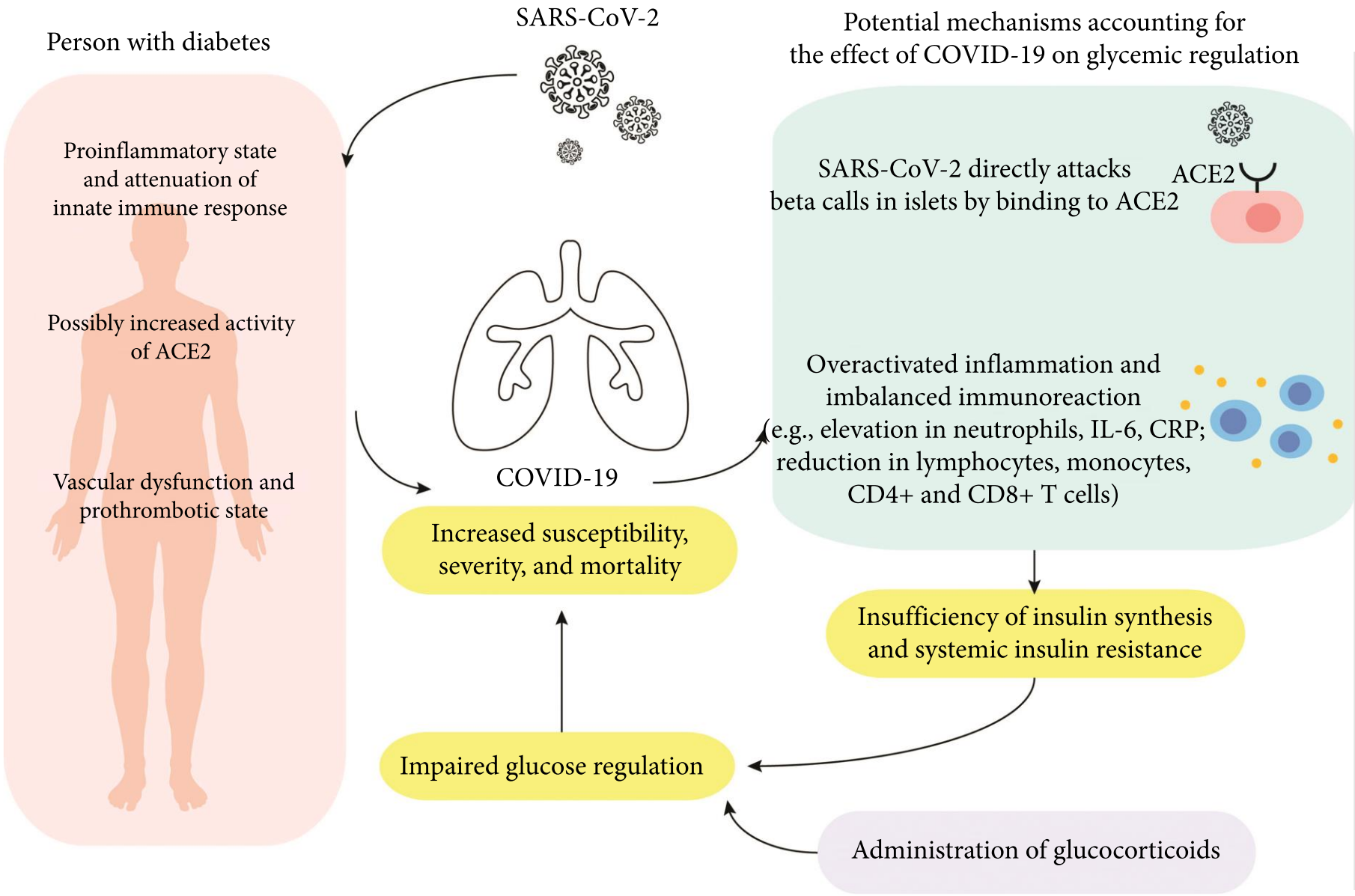


Figure 1—*A*: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients. *B*: Kaplan-Meier analysis showing survival during hospitalization in COVID-19 patients stratified by quintiles of at-admission plasma glucose levels.

Pancreas Effects

- SARS directly affects beta cells causing hyperglycemia or new onset diabetes
- Increase ACE 2 glycosylation and facilitating viral entry.
- Delay in the initiation of adaptive immunity and dysregulation of the cytokine response in DM



COVID-19 pandemic, coronaviruses, and diabetes mellitus
Ranganath Muniyappa and Sriram Gubbi
American Journal of Physiology-Endocrinology and Metabolism 2020 318:5, E736-E741

Mechanism

Sustained hyperglycemia, the ACE2 expression is reduced and its anti-inflammatory effect restrained, contributing to the severity of the infection.

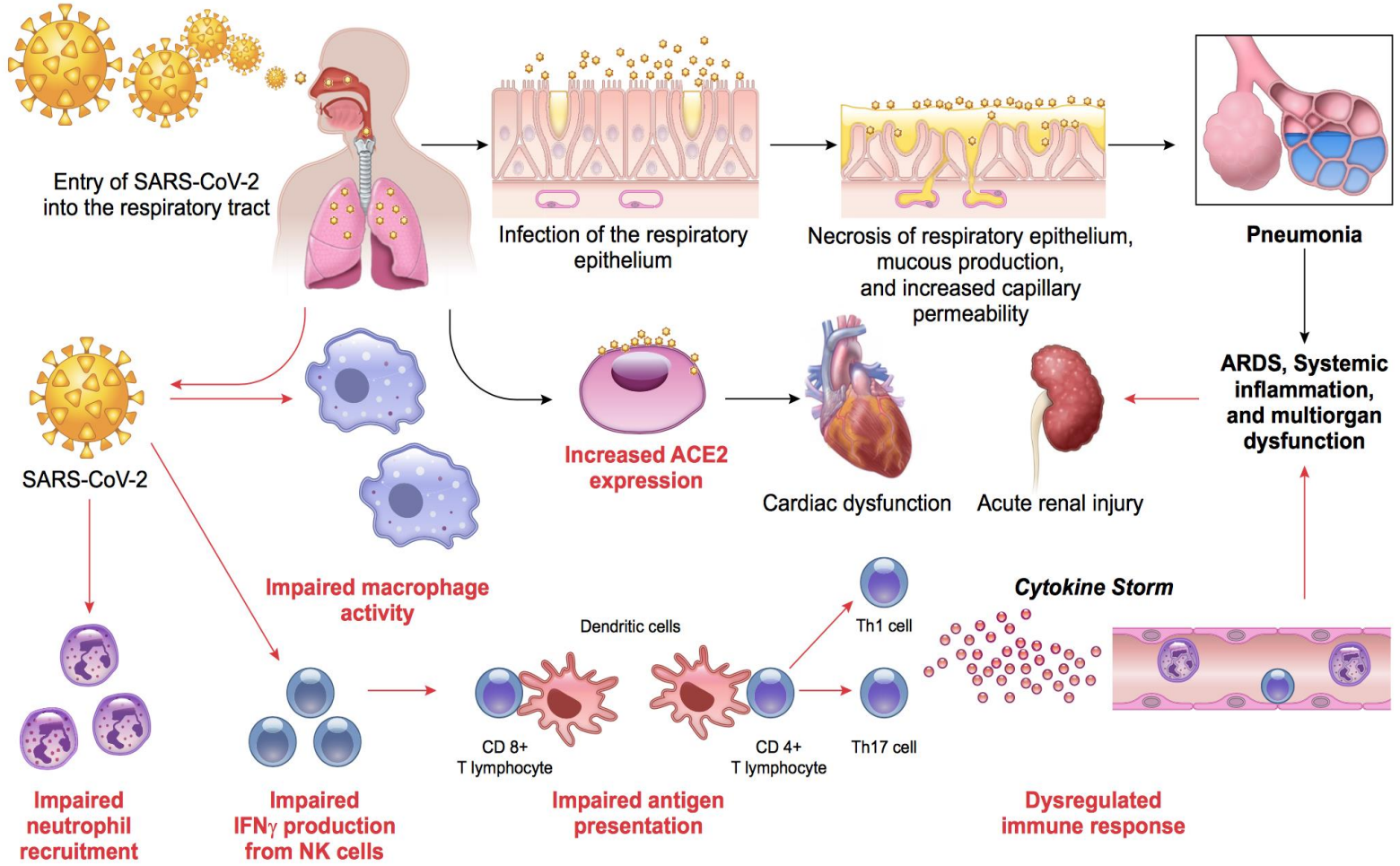
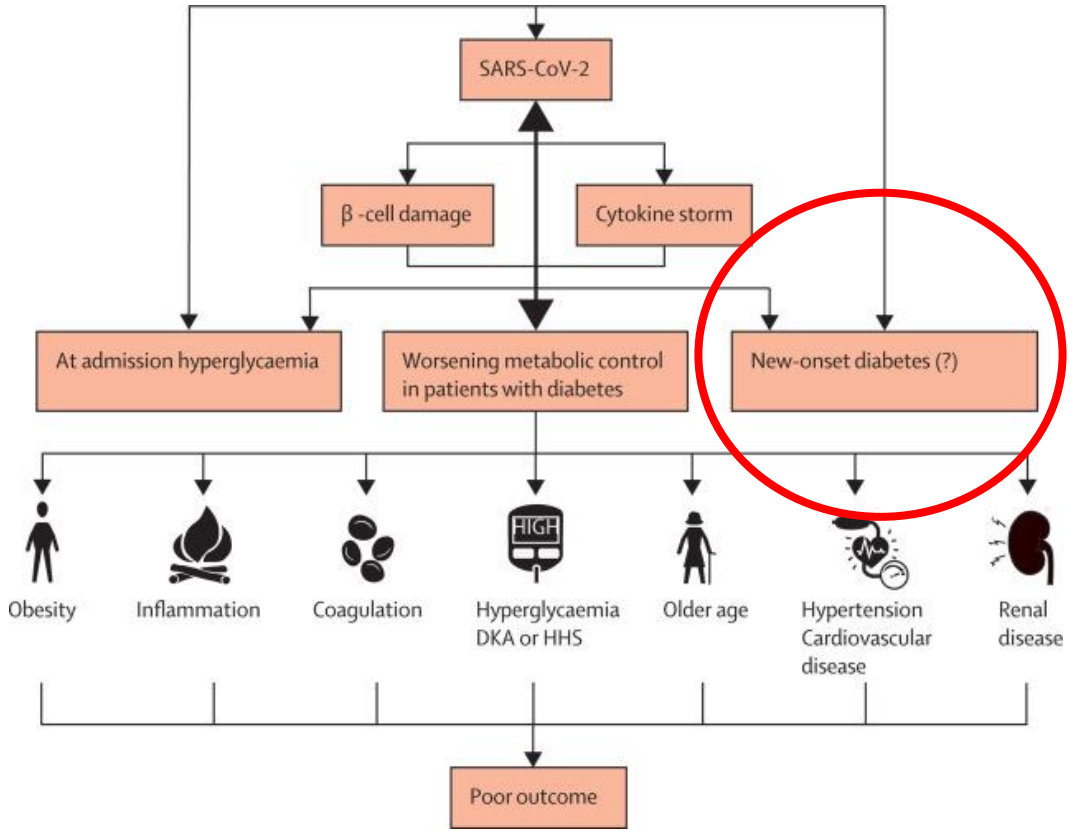


Fig. 2. Putative mechanisms contributing to increased susceptibility for coronavirus disease (COVID-19) in patients with diabetes mellitus (DM). Following aerosolized uptake of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), invasion of the respiratory epithelium and other target cells by SARS-CoV-2 involves binding to cell surface angiotensin converting enzyme 2 (ACE2). Increased expression of ACE2 may favor more efficient cell binding and entry into cells. Early recruitment and function of neutrophils and macrophages are impaired in DM. Delay in the initiation of adaptive immunity and dysregulation of the cytokine response in DM may lead to the initiation of cytokine storm.

COVID-19 pandemic, coronaviruses, and diabetes mellitus
Ranganath Muniyappa and Sriram Gubbi
American Journal of Physiology-Endocrinology and Metabolism 2020 318:5, E736-E741

New Onset Diabetes

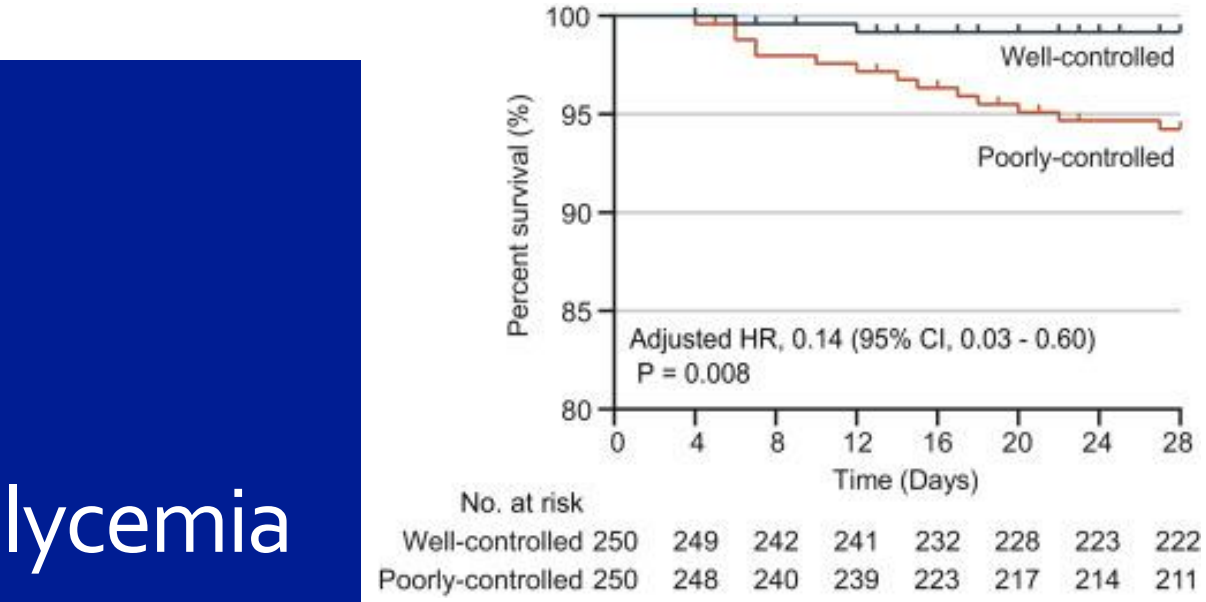


Viral Infections are known to cause Type 1 Diabetes.

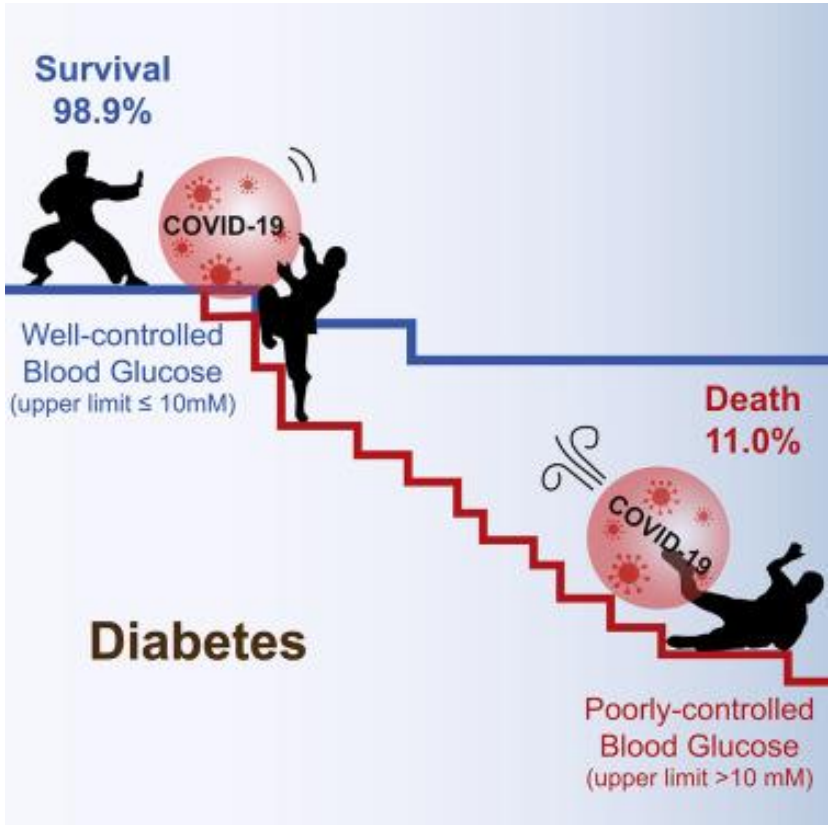
However, a bidirectional relationship between COVID-19 and hyperglycemia may be postulated.

Trigger inflammatory and stress responses and inducing insulin resistance.

Normoglycemia



Well controlled required less usage of antibiotherapy, steroids, vasopressors, intubation and lower death rate



L. Zhu, Z.G. She, X. Cheng, J.J. Qin, X.J. Zhang, J. Cai, F. Lei, H. . Yuan, X. Huang, J. Guo, B.H. Zhang, H. Li, Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab. **31**(6), 1068–1077.e3 (2020).

Management of diabetes in patients with COVID -19

THE LANCET
Diabetes & Endocrinology

Practical recommendations for the management of diabetes in patients with COVID-19

Stefan R Bornstein, Francesco Rubino, Kamlesh Khunti, Geltrude Mingrone, David Hopkins, Andreas L Birkenfeld, Bernhard Boehm, Stephanie Amiel , Richard IG Holt, Jay S Skyler, J Hans DeVries, Eric Renard, Robert H Eckel, Paul Zimmet, Kurt George Alberti, Josep Vidal, Bruno Geloneze, Juliana C Chan, Linong Ji, Barbara Ludwig

Consensus recommendations for COVID-19 and metabolic disease

Out-patient care

Prevention of infection in diabetes

- Sensitisation of patients with diabetes for the importance of optimal metabolic control
- Optimisation of current therapy if appropriate
- Caution with premature discontinuation of established therapy
- Utilisation of Telemedicine and Connected Health models if possible to maintain maximal self containment

In-patient or intensive care unit

Monitor for new onset diabetes in infected patients (in-patient care)

- Plasma glucose monitoring, electrolytes, pH, blood ketones, or β-hydroxybutyrate
- Liberal indication for early intravenous insulin therapy in severe courses (ARDS, hyperinflammation) for exact titration, avoiding variable subcutaneous resorption, and management of commonly seen very high insulin consumption

Management of infected patients with diabetes (intensive care unit)

Therapeutic aims

- Plasma glucose concentration: 4–8 mmol/L (72–144 mg/dL)*
- HbA_{1c}:† less than 53 mmol/mol (7%)
- CGM/FGM targets
  - TIR (3·9–10 mmol/L): more than 70% (>50% in frail and older people)
  - Hypoglycaemia (<3·9 mmol/L): less than 4% (<1% in frail and older people)

- Plasma glucose concentration: 4–10 mmol/L (72–180 mg/dL)*

Inpatient Management during COVID9 Pandemic

A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic

Mary Korytkowski,[1] Kellie Antinori-Lent,[2] Andjela Drincic,[3] Irl B. Hirsch,[4] Marie E. McDonnell,[5] Robert Rushakoff,[6] and Ranganath Muniyappa[7]

doi:10.1210/clinem/dgaa342

Table 2. Initiating Insulin Therapy in the Acute Care Setting[a]

	Basal Insulin	Prandial Insulin	Correction Insulin
Patients who are eating	Glargine U100 Starting dose: 0.1-0.2 units/kg/day[b]	Rapid-acting analog 0.1 unit/kg/day in divided doses before meals	Administered prior to meals Reduce dose by 50% if given at bedtime
Patients who are NPO	Glargine U100 Dose: 0.1-0.2 units/kg/day	None	Administered every 4-6 hours as a rapid-acting insulin analog or regular insulin, respectively
Patients receiving parenteral nutrition	Start if BG >180 mg/dL despite use of insulin in TPN solution	1 unit/10-15 grams of carbohydrate in parenteral solution	Administered every 4-6 hours as a rapid-acting insulin analog or regular insulin, respectively
Patients receiving continuous enteral nutrition[d]	NPH insulin administered every 8-12 hours with rapid-acting or regular insulin administered every 4-6 hours Or Human 70/30 insulin administered every 8-12 hours Starting dose: 0.1-0.2 units/kg/day[b]		
	Alternative regimen: Glargine U100 Starting dose: 0.1-0.2 units/kg/day	Administer as rapid-acting insulin analog or regular insulin every 4-6 hours according to duration of enteral nutrition[c]	Administered as a rapid-acting insulin analog or regular insulin every 4-6 hours, respectively
Patients receiving bolus enteral nutrition[d]	Administer rapid-acting or regular insulin prior to administration of enteral nutrition (similar to patients eating meals) Some patients may also require basal insulin		Administered prior to bolus

Inpatient Hyperglycemia Management

Diabetes Ther (2021) 12:121–132
https://doi.org/10.1007/s13300-020-00966-z

REVIEW

Inpatient Hyperglycemia Management and COVID-19

Virginia Bellido · Antonio Pérez

	Glycemic targets	Clinical situation		Insulin regimen	BG monitoring
Critically ill patients	140–180 mg/dL* (7.8–10.0 mmol/L)	Hemodynamically unstable Parenteral nutrition Unstable insulin requirements Corticosteroid therapy		Continuous intravenous insulin infusion	Every hour
		Hemodynamically stable Stable insulin requirements		Subcutaneous insulin Basal-correction or basal-bolus-correction	Every 4–6 h
Noncritically ill patients	110–180 mg/dL** (6.1–10.0 mmol/L)	T1D T2D on oral agents ± insulin	Not oral intake	Basal-correction	Every 4–6 h##
			Oral intake	Basal-bolus-correction	Before meals and at bedtime##
		T2D on diet Unknown DM	Glycemia at admission < 180 mg/dL (10.0 mmol/L)	Correction insulin before meals or every 6 h#	Before meals and at bedtime or every 6 h##
			Glycemia at admission > 180 mg/dL (10.0 mmol/L)	Basal-bolus-correction	Before meals and at bedtime##

BG blood glucose, *T1D* type 1 diabetes, *T2D* type 2 diabetes, *DM* diabetes mellitus

*110–140 mg/dL (6.1–7.8 mmol/L) may be reasonable for selected patients, as long as it can be achieved without significant hypoglycemia

**110–140 mg/dL (6.1–7.8 mmol/L) may be reasonable for stable patients with mild disease and previous tight glycemic control. BG levels > 180 mg/dL (7.8 mmol/L) might be acceptable for patients who are at high risk of hypoglycemia or who have limited life expectancy

#To calculate insulin requirements during the first 24 h. Then intensify to a basal-correction or basal-bolus regimen

##Consider the use of continuous glucose monitoring if feasible to limit fingersticks

Table 1. Considerations for Noninsulin Therapies in the Hospital Setting for COVID-19 Patients

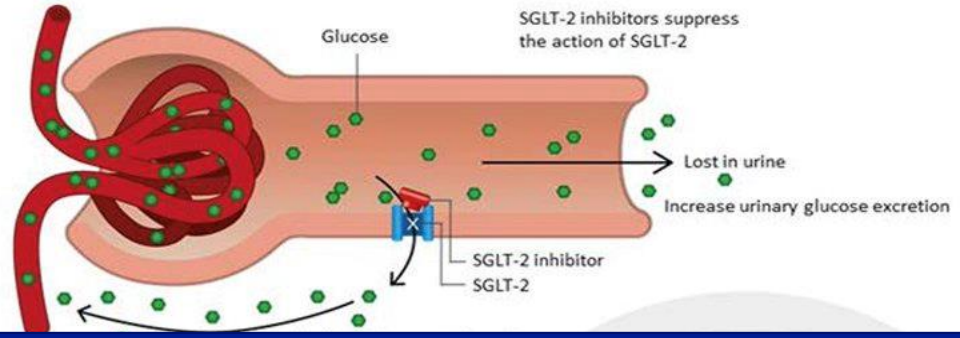
Drug Class	Concerns for Hospital Use	Relevance to COVID-19 Patients
Sulfonylureas Insulin secretagogues	High risk for hypoglycemia particularly in patients ≥65 years of age, with eGFR ≤30 mL/min, or receiving insulin therapy	The occurrence of any hypoglycemic event increases need for interaction with hospital personnel.
Metformin	Contraindicated for patients with respiratory problems and hypoxia, hemodynamic instability, and unstable renal or hepatic function	Hospitalized patients with COVID-19 can experience sudden and rapid deteriorations in clinical status which contraindicates continued use of metformin in these patients when hospitalized
DPP-4 inhibitors	DPP-4 enzyme has been identified as a co-receptor for the coronavirus which has potential to either favorably or unfavorably affect the binding of the virus to cell membranes. Majority of inpatient studies with these agents used these in combination with correction or basal insulin.	Generally not recommended in acute phase of COVID-19 due to concerns for abrupt deteriorations in clinical status. Saxagliptin and alogliptin should not be used as they are associated with higher risk for HF.
SGLT2 inhibitors	Increases risk for euglycemic DKA, UTI, genital infections, and volume depletion	Discontinuation of these agents recommended at time of hospitalization.
GLP1 receptor agonists	Nausea and vomiting, particularly in patients who are not eating meals on a regular basis	Patients treated with long-acting agents will have these onboard at time of hospital admission. Continued use not currently recommended during acute hospitalizations.
Thiazolidinediones	Delay in glucose lowering effect, increase risk for fluid retention in insulin treated patients	These agents should not be used in this population.

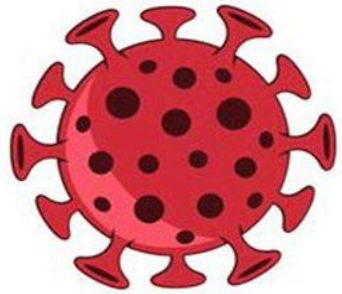
Abbreviations: DKA, diabetic ketoacidosis; DPP-4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; HF, heart failure; SGLT2, sodium-glucose transport protein 2; UTI, urinary tract infection.

Use Noninsulin Therapies

Mary Korytkowski, Kellie Antinori-Lent, Andjela Drincic, Irl B Hirsch, Marie E McDonnell, Robert Rushakoff, Ranganath Muniyappa, A Pragmatic Approach to Inpatient Diabetes Management during the COVID-19 Pandemic, *The Journal of Clinical Endocrinology & Metabolism*, Volume 105, Issue 9, September 2020, Pages 3076–3087,

Update on the DARE-19 Phase III trial for Farxiga in COVID-19





The trial did not achieve statistical significance for the primary endpoint of prevention measuring organ dysfunction and all-cause mortality, and the primary endpoint of recovery measuring a change in clinical status (from early recovery to death), at 30 days.

Pituitary Effects

Forty percent of patients had evidence of central hypocortisolism, the majority of which (62.5%) resolved within a year .

Thus, monitoring of HPA and thyroid function will likely be justified in the first year following recovery from COVID-19.

TRANSIENT HYPOPHYSITIS

- Central hypocortisolism
- Central Hypothyroidism

DIRECT HYPOTHALAMIC EFFECT

- Focal damage with reduction of TSH, ACTH and GH positive cells.
- Detention of SARS RNA in hypothalamus and pituitary , CSF
- Increase of PRL, LH,FSH positive cells

MOLECULAR MIMICRY OF SARS TO ACTH

HYPERPROLACTENEMIA

- Stress/Infection
- Increase of PRL, LH,FSH positive cells

Clinical Features

Pathology	Possible Mechanism	Effect on Hormonal Axis	Clinical Features	Management Issues and Solutions
Pituitary				
Central hypocortisolism and hypothyroidism	Hypophysitis resulting from infiltration by virus [41] Hypothalamic involvement [41] Destruction of ACE2 in hypothalamus [43, 44] Molecular mimicry of SARS-CoV-1 to ACTH and subsequent host defense mechanisms [46]	Impaired ACTH/cortisol production Low thyroid hormones sometimes with low TSH	Postviral syndromes [41]	Cosyntropin/ Synacthen test TSH and free T4 If deficient, hormone replacement in physiological doses [41]
Hyperprolactinemia	Dopaminergic stress response [48]	Transient hyperprolactinemia	Asymptomatic	Prolactin levels may be high during acute illness. Caution on interactions of DRA with CYP450 inducing antivirals and amine based pressors/inotropes [55, 56]

Drug Interaction

Noel Pratheepan Somasundaram, Ishara Ranathunga, Vithiya Ratnasamy,, The Impact of SARS-Cov-2 Virus Infection on the Endocrine System, *Journal of the Endocrine Society*, Volume 4, Issue 8, August 202

Dysnatremias

Electrolytes and water disturbances may develop in COVID-19 patients in ICU, due to insensible water losses from pyrexia, GI losses, increased respiration rate and use of diuretics.

Clinical Practice Guidance | M Christ-Crain and others | DI and hypontraemia in times of COVID-19 | 183:1 | G9–G15

ENDOCRINOLOGY IN THE TIME OF COVID-19

Management of diabetes insipidus and hyponatraemia

Mirjam Christ-Crain[1], Ewout J Hoorn[2], Mark Sherlock[3], Chris J Thompson[3] and John A H Wass[4]

Table 1 Risks and protective measures in DI and hyponatremia in times of COVID-19.

	Risks	Protective measures
Diabetes insipidus	**Dilutational hyponatraemia** as side effect of desmopressin therapy	Delay desmopressin dose once or twice weekly; Advise to regularly control body weight Drink to thirst
	High risk for dysnatraemia if admitted to the hospital due to missed desmopressin dose, reduced fluid intake, increased insensible losses and the potential need for diuretic therapy	Endocrine consultation for every patient with DI to reduce prescribing errors and to advise with fluid management Patient empowerment Appropriate stress dosing of corticosteroids in patients with additional ACTH deficiency
Hyponatraemia	**New diagnosis of SIAD** after neurosurgical interventions, brain injury or subarachnoid hemorrhage	Advise to limit fluid intake for two weeks following surgery / injury Measure body weight daily and aim to stay at eunatraemic weight Drink only to thirst Know the early symptoms of hyponatraemia

Christ-Crain, M., Hoorn, E. J., Sherlock, M., Thompson, C. J., & Wass, J. A. H. (2020). ENDOCRINOLOGY IN THE TIME OF COVID-19: Management of diabetes insipidus and hyponatraemia, *European Journal of Endocrinology*, *183*(1), G9-G15. Retrieved May 5, 2021,.

Diabetes insipidus	Titrate the dose of desmopressin according to serum sodium, and osmolality. Convert to parenteral form (IV/IM) if intranasal route is not feasible [52]
	Desmopressin dose equivalents [138]

Tablets	Spray	Injections
100 µg	2.5 µg	NA
200 µg	5.0 µg	<0.5 µg
400 µg	10.0 µg	<1.0 µg

Hyperprolactinemia	Bromocriptine: may need dose adjustment because of interactions between lopinavir/ritonavir, which increase bromocriptine levels [55]
	Cabergoline: dose adjustment is not required
GH deficiency	Continue on the same dose of growth hormone in those with established GH deficiency

Management

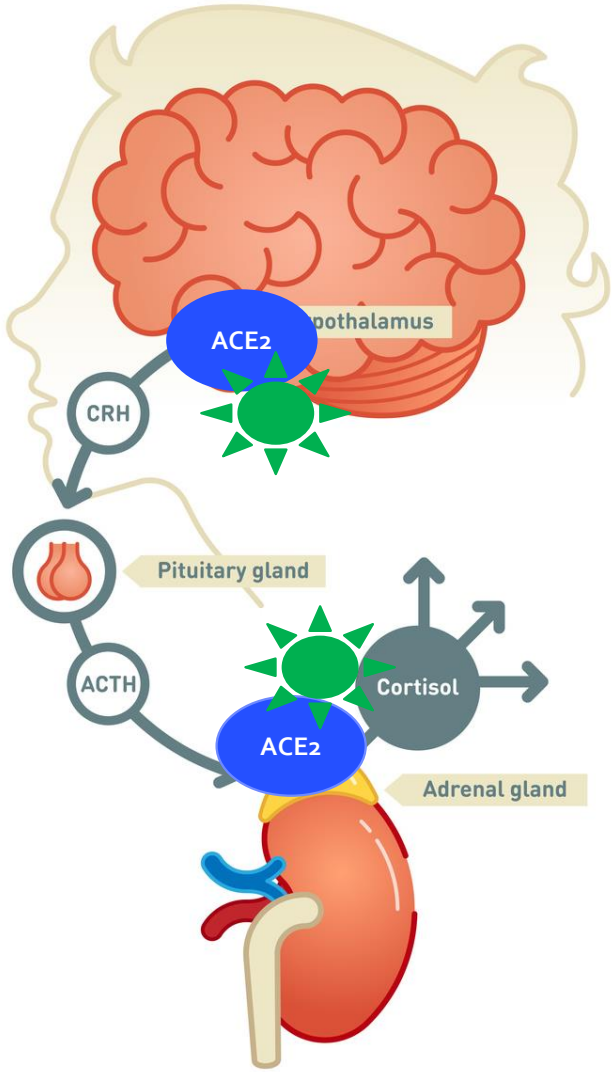
PREEXTING PITUITARY CONDITION

Noel Pratheepan Somasundaram, Ishara Ranathunga, Vithiya Ratnasamy, Piyumi Sachindra Alwis Wijewickrama, Harsha The Impact of SARS-Cov-2 Virus Infection on the Endocrine System, *Journal of the Endocrine Society*, Volume 4, Issue 8, August 2020.

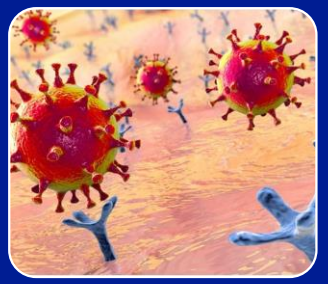
Adrenal Effects

Primary Adrenal insufficiency

- SARS RNA has been identified in hypothalamic autopsies of patients with COVID-19
- **Degeneration and necrosis of the adrenal cortical cells**
- **Vasculitis of small veins of adrenal medulla**
- **Adrenal infiltrates with monocytes and lymphocytes**



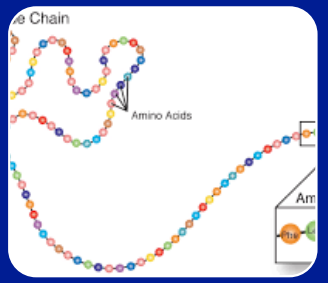
SARS-CoV-2-related Adrenal Insufficiency



The cytokine storm caused by this coronavirus provides negative feedback toward the hypothalamic-pituitary-adrenal axis

Relative AI is a common condition in critically ill patients

patients with severe COVID-19 may be more prone to develop critical illness-related corticosteroid insufficiency (CIRCI) .



SARS viruses produce certain amino acid sequences mimicking the host ACTH, thus the production of the corresponding antibodies may contribute toward the development of central AI

AACE Position Statement: Coronavirus (COVID-19) and People with Adrenal Insufficiency and Cushing's Syndrome

March 24, 2020

European Society of Endocrinology
The voice for endocrinology

Società Italiana Endocrinologia

Expert Opinion

Management "Sick Day Rule"

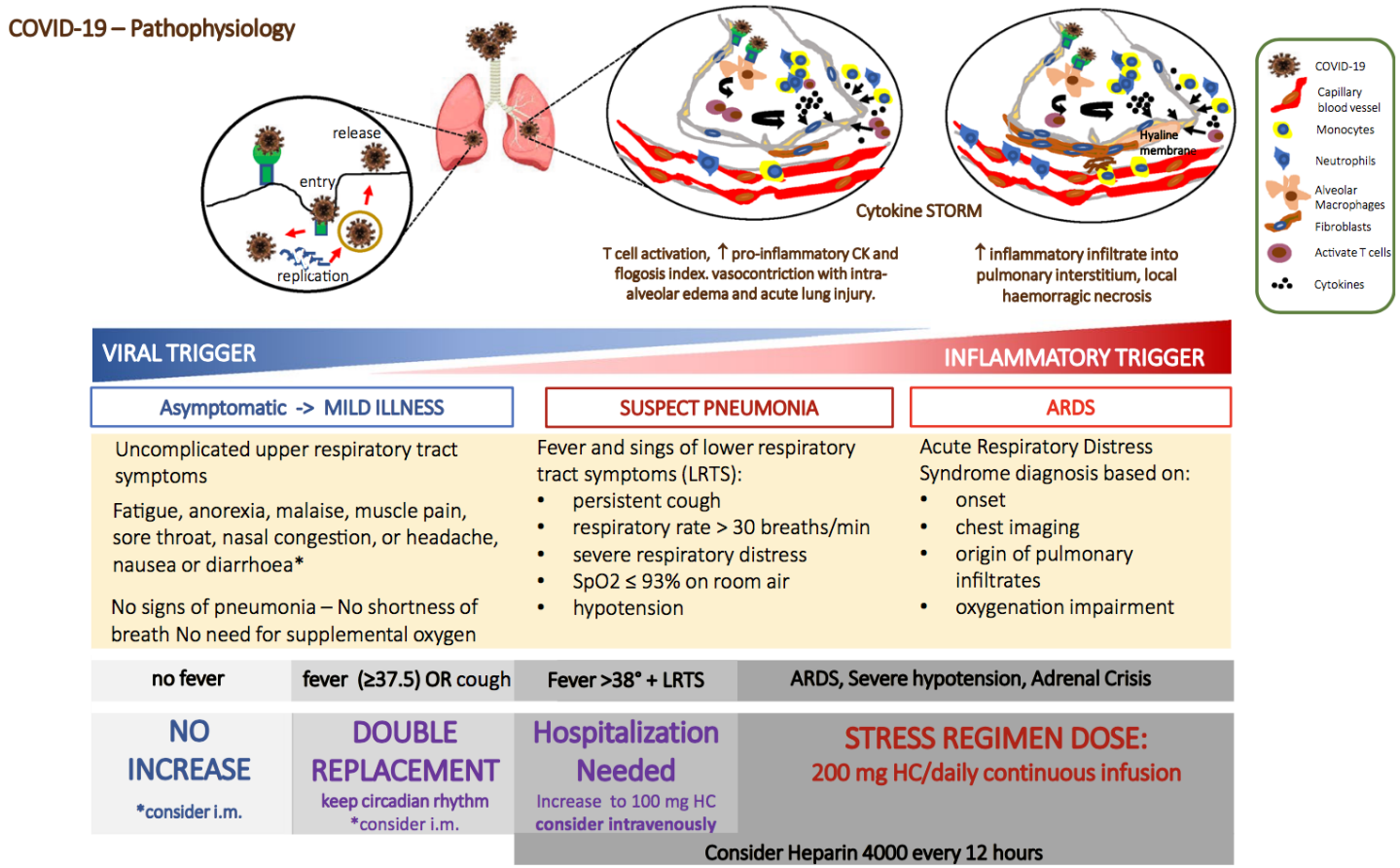


Fig. 1 Proposal for a stage-specific adjustment of glucocorticoid therapy in adrenal insufficient patients with COVID-19 infection

Cushing's Syndrome

Poor prognosis with Increase mortality, AMI, venous thromboembolism, stroke, and infections.

ENDOCRINOLOGY IN THE TIME OF COVID-19

Management of Cushing's syndrome

John Newell-Price[1], Lynnette K Nieman[2], Martin Reincke[3] and **Antoine Tabarin[4]**

nt

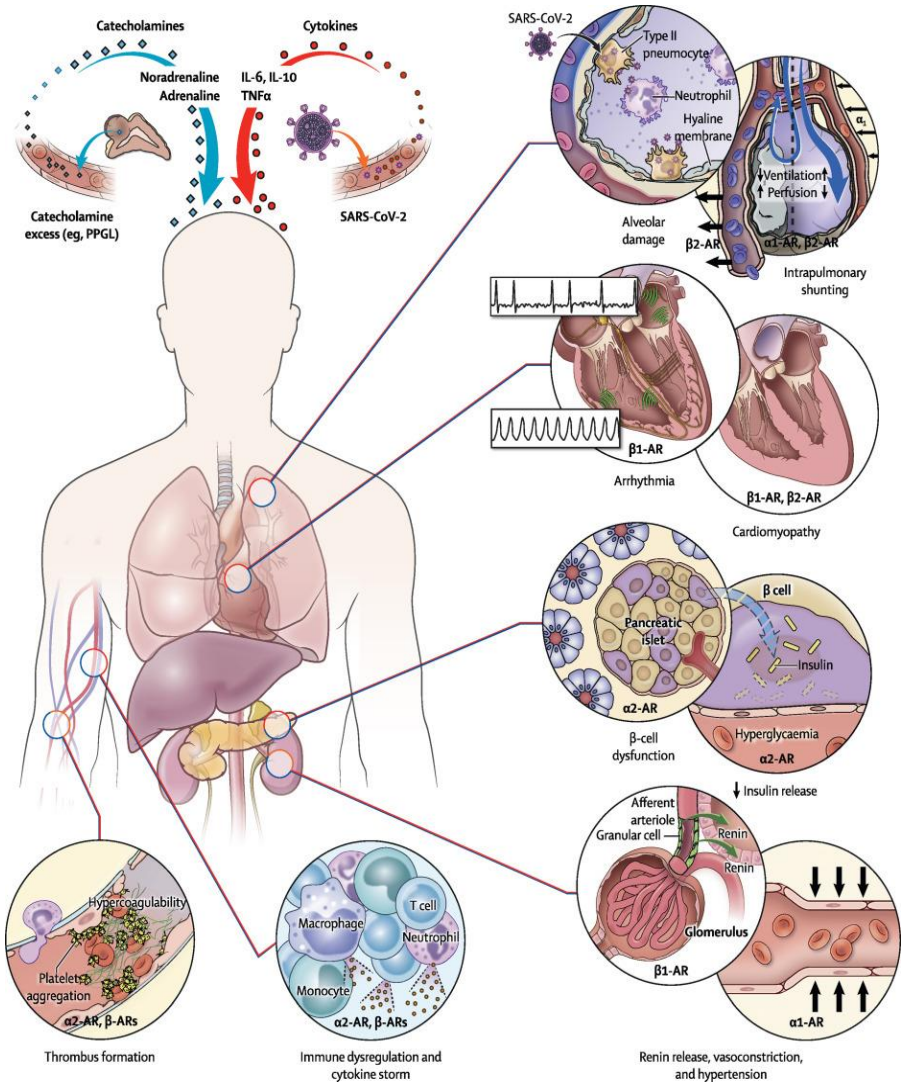
Medical Therapies – Active disease, IV etomidate for severe illness and no TSS due high risk for aerosol formation.

Pheochromocytoma and Paraganglioma

Catecholamines cause dysregulation of physiological cascades.

If infected with SARS- CoV-2, plasma and urinary metanephrines can be elevated from the associated stress response and measurement during illness will give false-positive results .

Treatment with initial alpha blockers followed by beta blokers



Sriram Gubbi, Matthew A Nazari, David Taieb, Joanna Klubo-Gwiezdzinska, Karel Pacak, Catecholamine physiology and its implications in patients with COVID-19,The Lancet Diabetes & Endocrinology,Volume 8, Issue 12,2020,Pages 978-986,SSN 2213-8587.

Thyroid Effect

Patients with baseline thyroid diseases are not at higher risk of contracting or transmitting SARS-CoV-2, and baseline thyroid dysfunction does not foster a worse progression of COVID-19

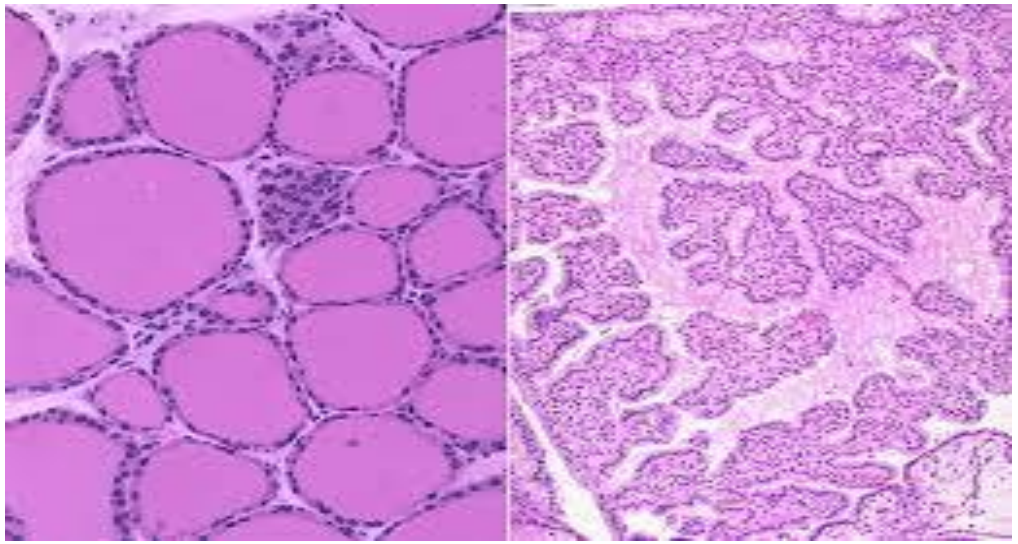
Thyroid hormones modulate innate and adaptive immune responses.

Physiological concentrations of L- thyroxine (T_4) and (T_3) stimulate the production and release of cytokines, which are also components of "cytokine storm" potentially characterizing systemic viral infections .

Decrease activity D1 (cortisol, cytokines, endogenous FFA and drugs) and increase clearance T_3 by increase activity D3.

Scappaticcio, L., Pitoia, F., Esposito, K. *et al.* Impact of COVID-19 on the thyroid gland: an update. *Rev Endocr Metab Disord* (2020). https://doi.org/10.1007/s11154-020-09615-z

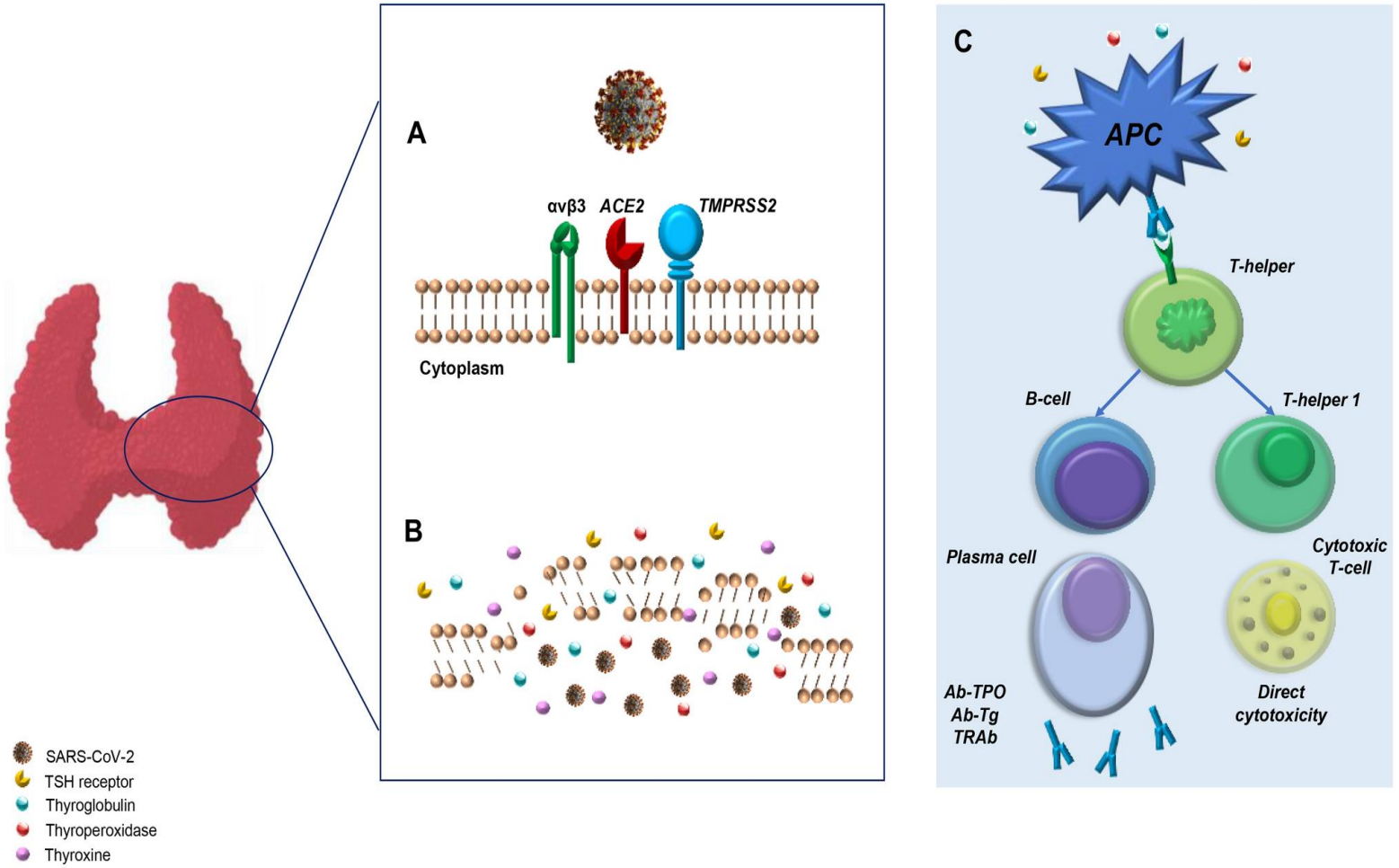
Thyroid Histology



SARS	Derangement of the follicular architecture High levels of apoptosis Interfollicular fibrosis Absence of calcitonin positive cells
SARS COv2	Interstitial Lymphocytic infiltration

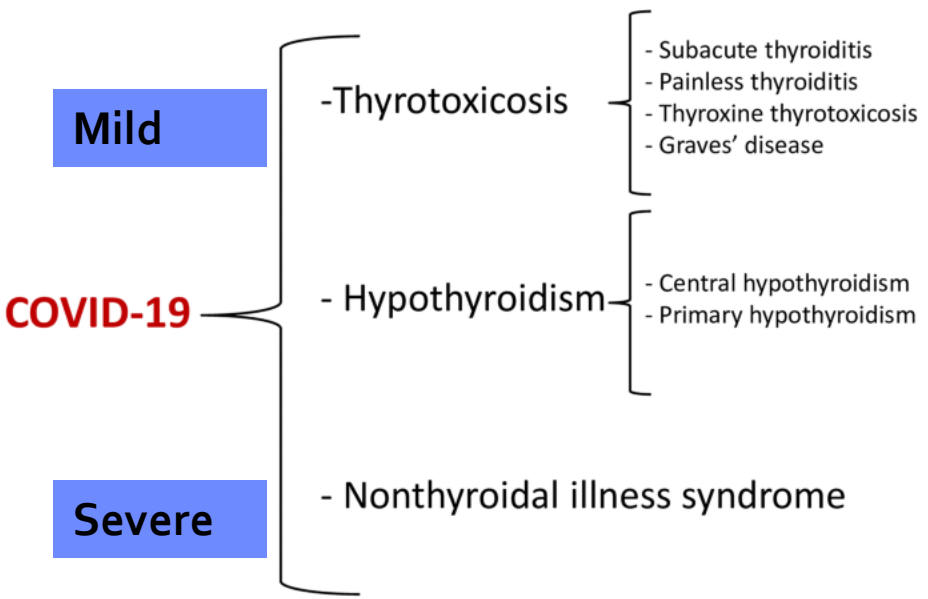
Piticchio, T., Le Moli, R., Tumino, D. *et al.* Relationship between betacoronaviruses and the endocrine system: a new key to understand the COVID-19 pandemic—A comprehensive review. *J Endocrinol Invest* (2021). https://doi.org/10.1007/s40618-020-01486-0

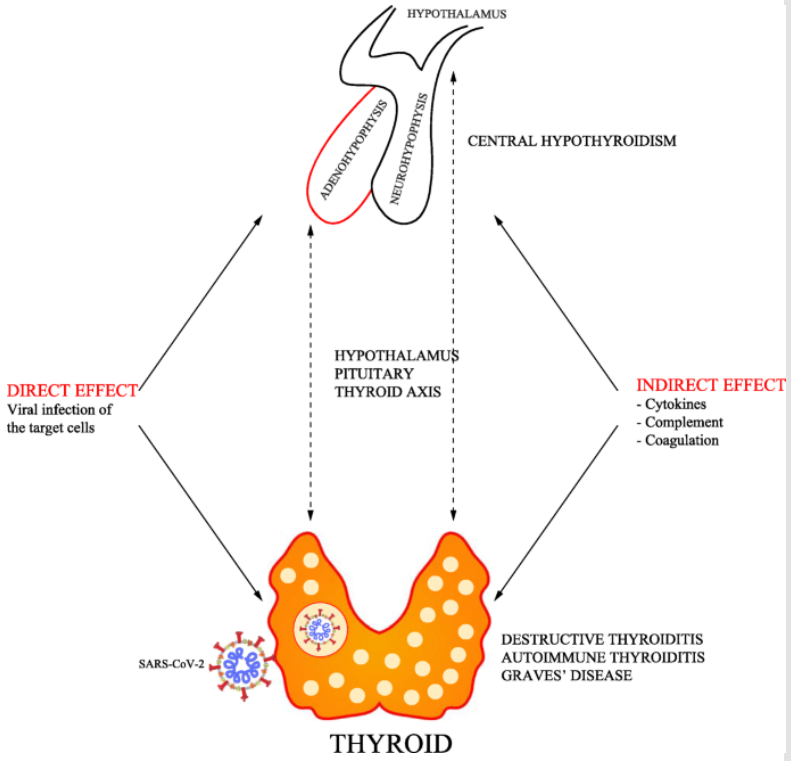
Direct Effects



Lisco, G., De Tullio, A., Jirillo, E. *et al.* Thyroid and COVID-19: a review on pathophysiological, clinical and organizational aspects. *J Endocrinol Invest* (2021).

Thyroid Diseases and Severity of cOVID19





Giovanella, L., Ruggeri, R.M., Petranović Ovčariček, P. *et al.* SARS-CoV-2-related thyroid disorders: a synopsis for nuclear medicine thyroidologists. *Eur J Nucl Med Mol Imaging* (2021)

Subacute Thyroiditis

Rev Endocr Metab Disord

Table 1 Analysis of cases of COVID-19-related subacute thyroiditis (SAT) reported in the literature to date

Case, (ref.)	1, (35)	2, (36)	3, (36)	4, (36)	5, (36)	6, (38)	7, (39)	8, (40)	9, (41)
Sex	F	F	F	F	F	F	F	F	M
Age (yr)	18	38	29	29	46	69	41	43	34
Thyroid disease before Covid-19	no	no	no	no	no	nodules	no	no	no
Covid-19 test	swab	swab	swab, sIg	swab, sIg	swab	swab	swab	swab, sIg	swab
Covid-19 manifestations	mild	mild	mild	mild	mild	pneumonia	mild	mild	mild
Time from Covid-19 to SAT onset (days)	17	16	30	36	20	during Covid-19	during Covid-19	40	during Covid-19
Doctor's visit	outpatient, in-person	outpatient, in-person	outpatient, in-person	outpatient, in-person	outpatient, in-person	inpatient	inpatient	outpatient, in-person	inpatient
SAT manifestations	typical, neck pain, fever (37.5 °C)	typical, neck pain, fever (38.5 °C), AF	typical, neck pain	typical, neck pain	typical, neck pain, fever (37.2 °C)	typical, no neck pain	typical, neck pain, fever (38.5 °C)	typical, neck pain, fever (37.5 °C)	typical, neck pain
Biochemical profile	TSH 0.004 FT4 27.2 FT3 8.7 TgAb+ TPOAb- TRAb-	TSH 0.1 FT4 29.3 FT3 8.0 TgAb- TPOAb- TRAb-	TSH 0.01 FT4 31.8 FT3 8.9 TgAb+ TPOAb- TRAb-	N.A.	TSH 0.01 FT4 27.8 FT3 6.9 TRAb-	TSH 0.08 FT4 31.6 FT3 7.0 TgAb- TPOAb- TRAb-	TSH 0.08 FT4 25.7 FT3 7.7 TgAb- TPOAb- TRAb-	TSH 0.006 FT4 34.6 FT3 9.0 TgAb- TPOAb- TRAb-	TSH 0.01 FT4 41.8 FT3 13.4 TPOAb- TRAb-
Inflammatory markers	WBC 11.2, CRP 6.9	CRP 11.2	CRP 7.9	N.A.	CRP 8	N.A.	WBC 15.6, CRP 101	WBC 6.6, CRP 8.8	WBC 11.6, CRP 122
Thyroid US features	typical	typical	typical	typical	typical	typical	typical	typical	typical
Thyroid scintigraphy uptake	N.A.	N.A.	absent	N.A.	N.A.	absent	N.A.	markedly reduced	N.A.
Resolutive therapy	prednisone	prednisone	prednisone, propanolol	ibuprofen	prednisone	prednisone	prednisolone	prednisone	prednisolone atenolol
Thyroid function after SAT	normal	normal	hypothyroidism	hypothyroidism	normal	N.A.	N.A.	normal	normal
Relapse of Covid-19	no	no	no	no	no	swab+	N.A.	no	N.A.

Scappaticcio, L., Pitoia, F., Esposito, K. *et al.* Impact of COVID-19 on the thyroid gland: an update. *Rev Endocr Metab Disord* (2020)

Parathyroid and Bone Effects

No data exist on ACE2 expression, viral invasion or inflammation of the gland.

No evidence of PHPT or Hypoparathyroidism are risk factors for COVID19.

Hypocalcemia associated to severity and worse prognosis.

Hypocalcemia

Lower calcium levels were found strongly correlated with a more pronounced inflammatory response in COVID-19 patients

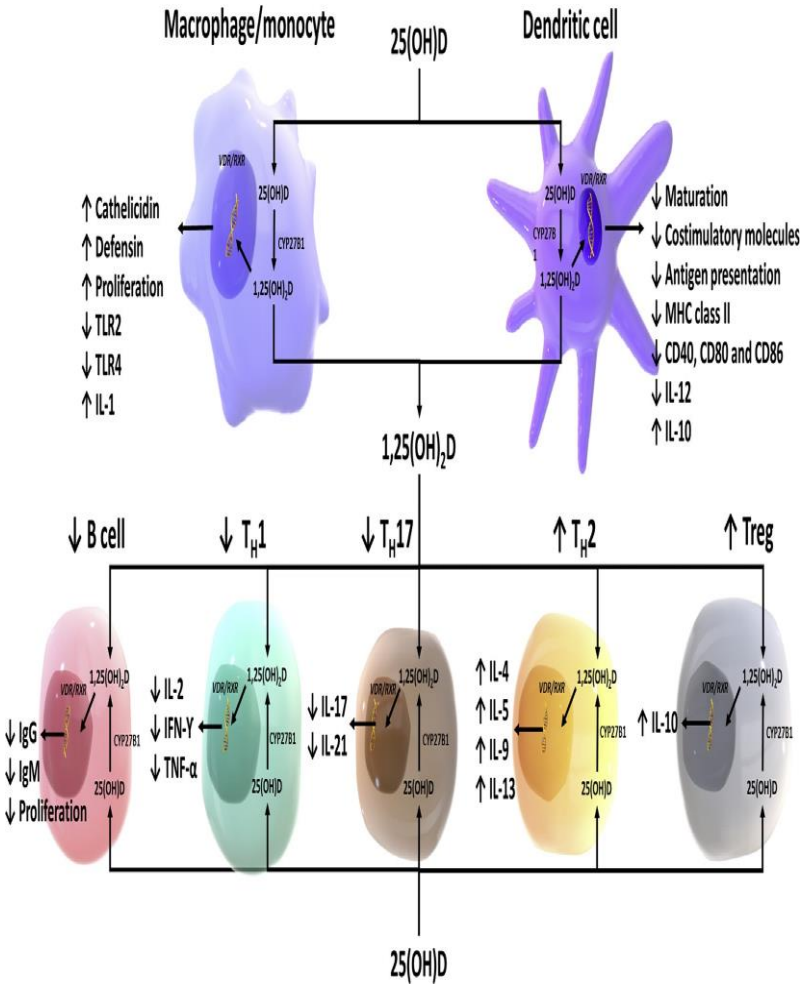
- Calcium dependent viral mechanisms of action
- High prevalence of hypovitaminosis D in general population,
- Chronic and acute malnutrition during critical illness
- High levels of unbound and unsaturated fatty acids (UFA) in inflammatory responses.

Vitamin D Effects

Experimental studies have shown that vitamin D exerts several actions that are thought to be protective against (COVID-19) infectivity and severity

Vitamin D is considered an immunomodulatory agent that regulates both innate and adaptive immune systems

Supplementation is beneficial in protecting against risk of respiratory viral infection and may improve outcomes in sepsis and critically ill patients .



Vitamin D Deficiency

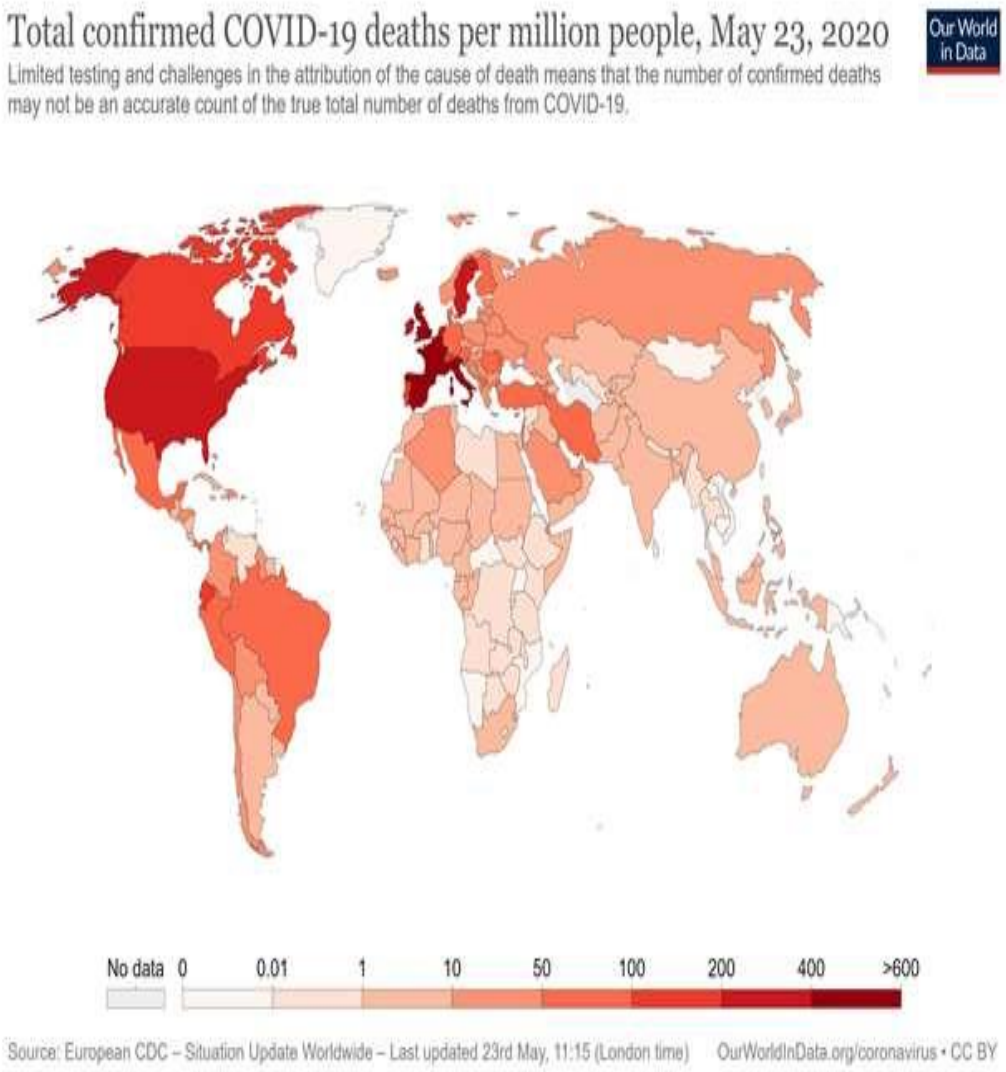
Deficiency of vitamin D is a common problem in ARDS and inflammation of alveolar epithelial cells.

The effect were more pronounced when vitamin D were less than 25 ng/mL.

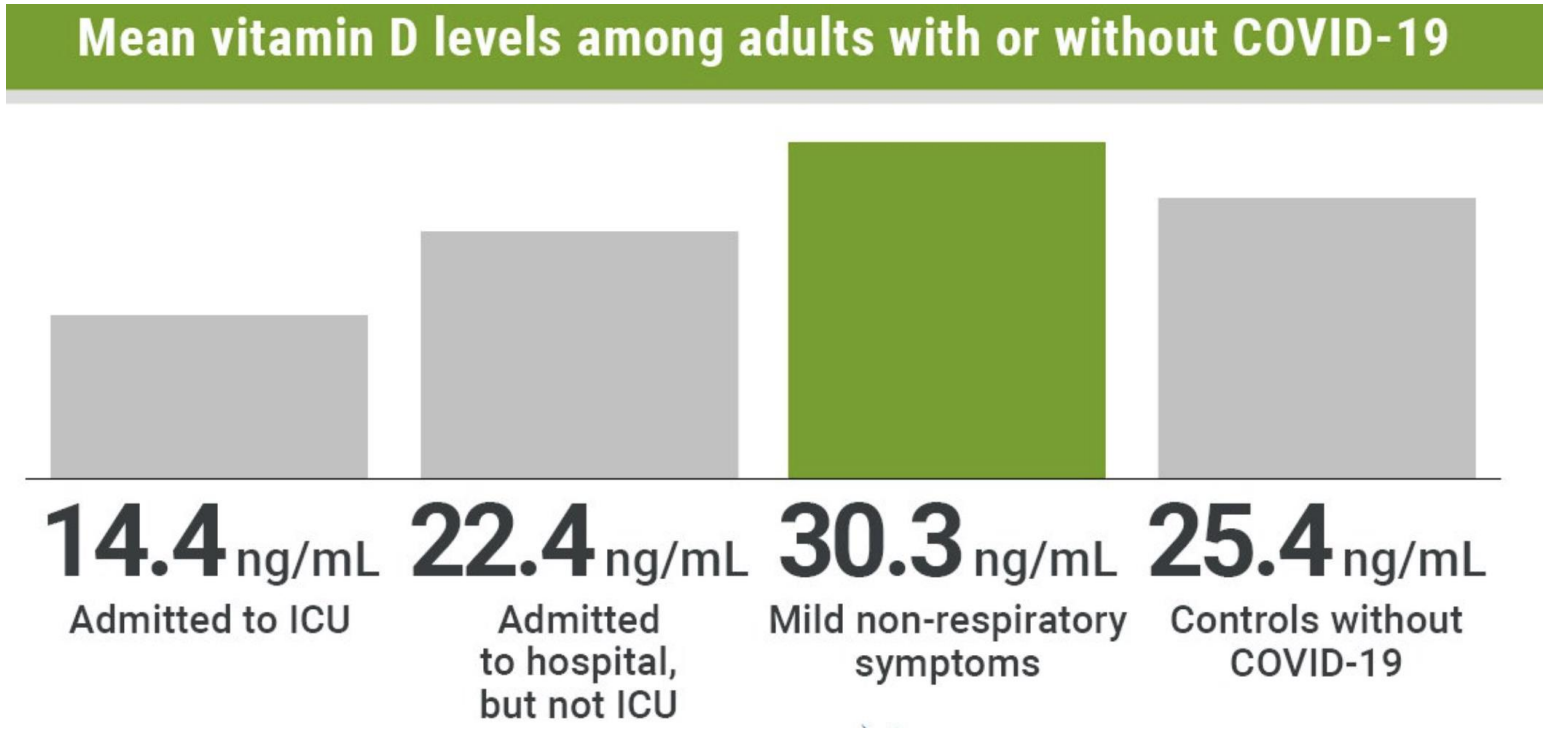
Chronic illness, smoking, increase age and dark skinned ethnicities.

Geographic Locations

Northern latitude locations with higher rates of vitamin D Deficiency , be it Europe and USA, have had higher rates of related mortality.



Vitamin D Levels Impact



Gennari L, et al. Vitamin D deficiency is independently associated with COVID-19 severity and mortality. Presented at: American Society for Bone and Mineral Research Annual Meeting; Sept. 11-15, 2020

Mechanism of Vitamin D in prevention of Covid 19

Inhibit T-helper cells 1 (Th1)

Induced T-helper 2 (Th2)

Inhibits viral binding to the receptor ACE2

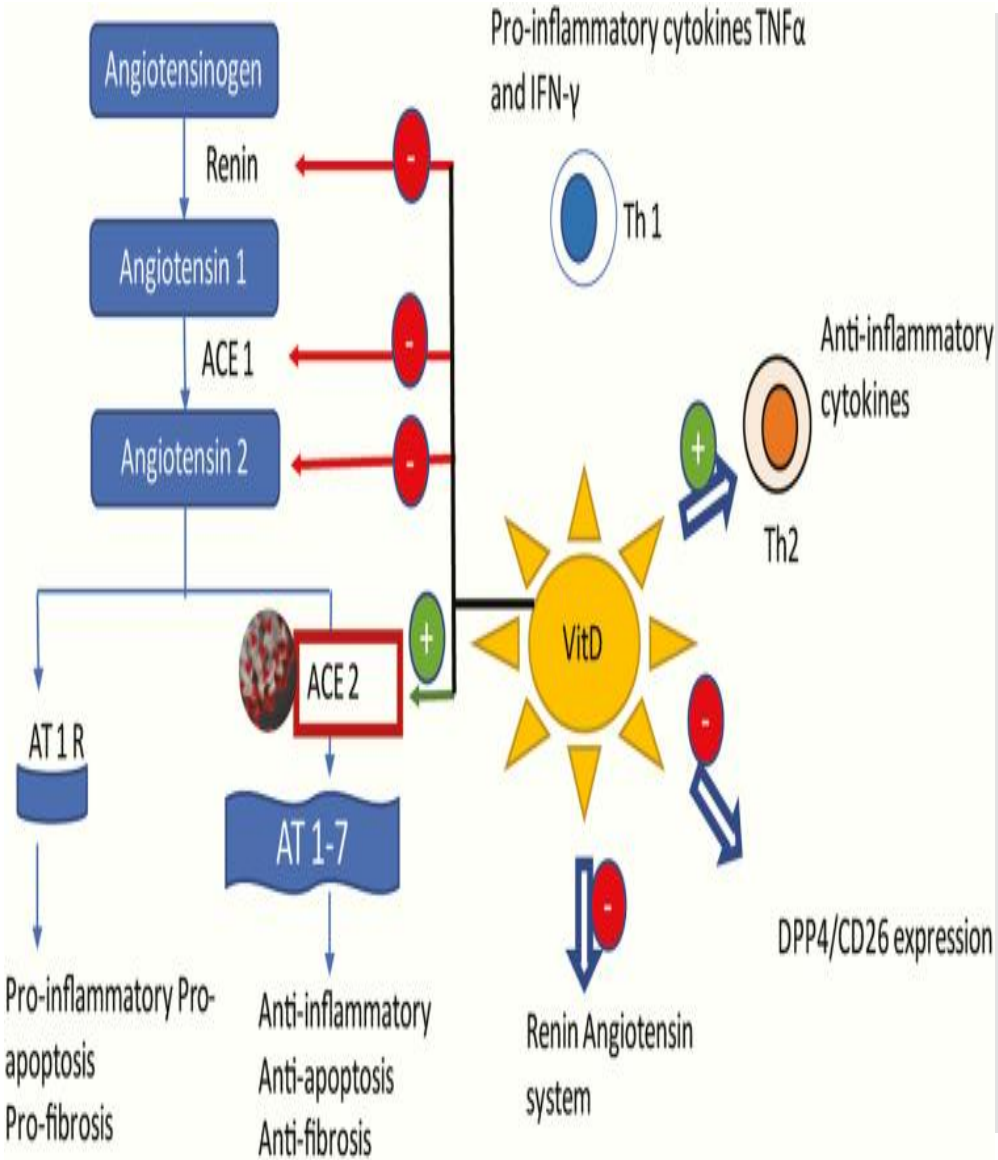
Interact with DPP4/D26 expression (block virulence)

Downregulated RAAS system by suppressing renin, ACE, ANGII expression

Induced ACE2 levels

Inhibit ACE2 expression in the renal tubular cells

May mitigate vascular leakage secondary to systemic inflammatory response and prevent COVID-associated arterial and venous thrombosis.



Vitamin D Supplementation

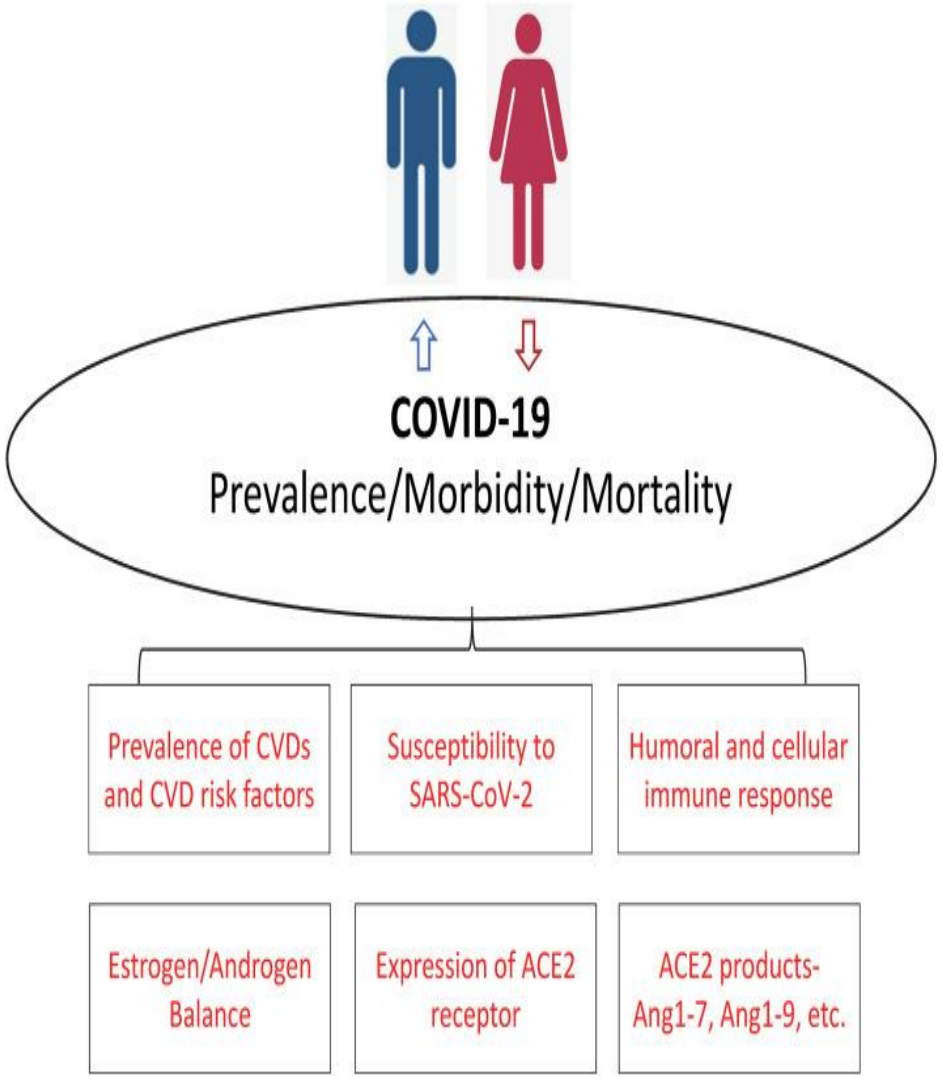
- Vitamin D threshold >50 is thought to be adequate for the prevention of acute respiratory tract infections.
- The degree of protection appears to be optimal in the range of 40-60.
- A daily dose 2000 to 5000 IU was required to achieve this level during winter
- Daily doses of vitamin D up to 10 000 IU/day are generally safe and not associated with any adverse effects
- Endocrine Society recommends supplementation with 1000-4000IU of vitamin and maintain Vitamin 25 oh levels >30 ng/ml or higher.

Grant WB, Lahore H, McDonnell SL, Baggerly CA, French CB, Aliano JL, Bhattoa HP. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. *Nutrients*. 2020; 12(4):988. https://doi.org/10.3390/nu12040988

Sex Hormones Effects

Men and women have a similar susceptibility to SARS-CoV-2, men appear to be prone to a more severe disease and mortality.

Meta-analysis of over 3.1 million global cases reported odds ratios of 2.8 and 1.4 for ICU admission and death in men compared to women



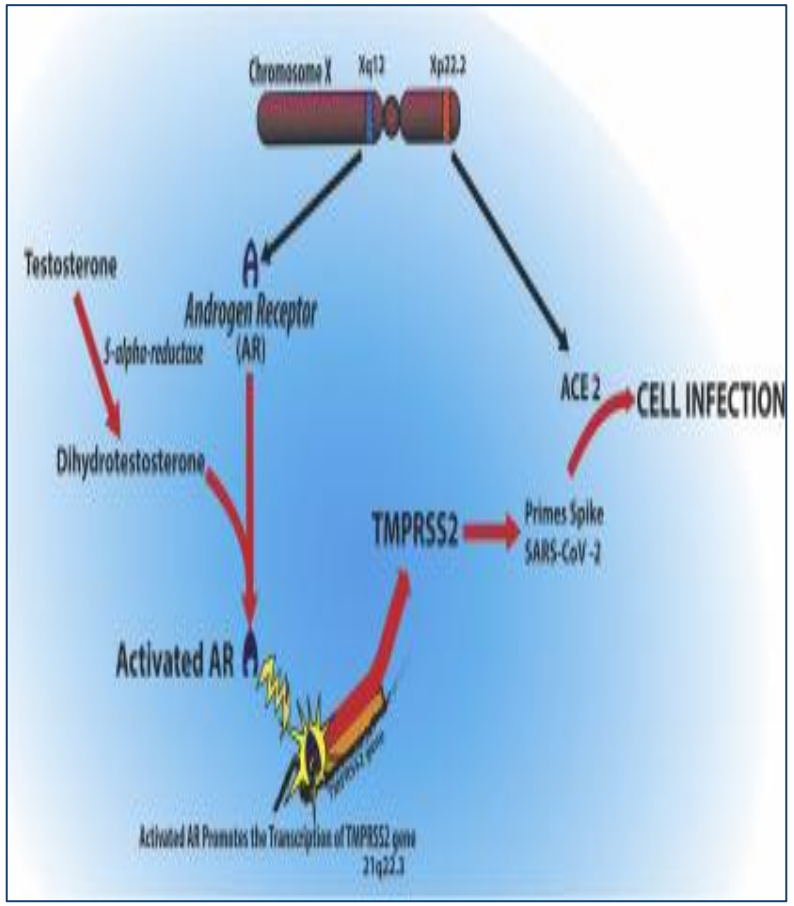
H. Peckham, N.M. de Gruijter, C. Raine, A. Radziszewska, C. Ciurtin, L.R. Wedderburn, E.C. Rosser, K. Webb, C.T. Deakin, Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. Nat. Commun. **11**(1), 6317 (2020)

Androgen Receptor Activity

The gene for ACE-2 receptors is on the X chromosome, which raises the possibility of different gender-specific activity due to X chromosome inactivation and parental imprinting

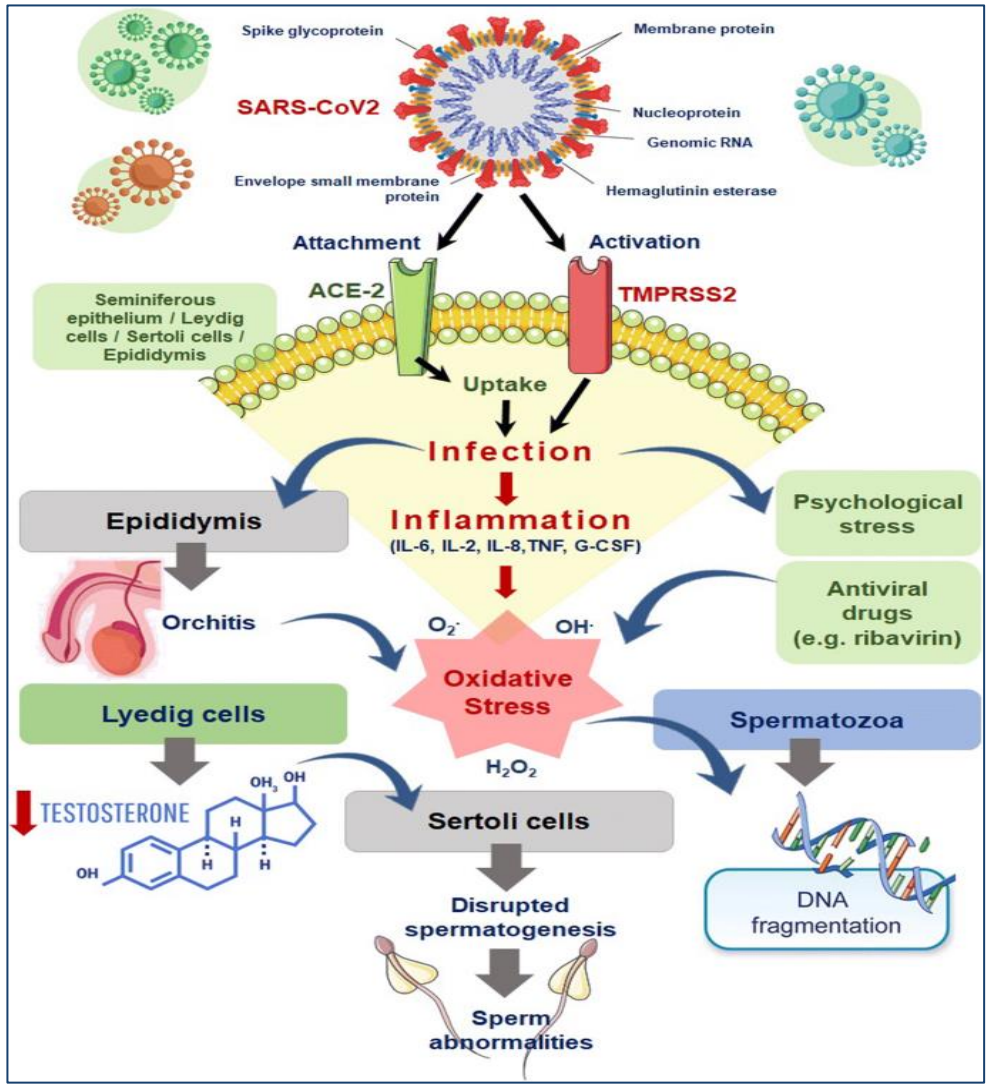
There several evidences indicate that TMPRSS2 expression in human tissues is regulated by androgen receptor activity.

The protein expression of ACE2 /TMPRSS2 in the testis is almost the highest in the human body.



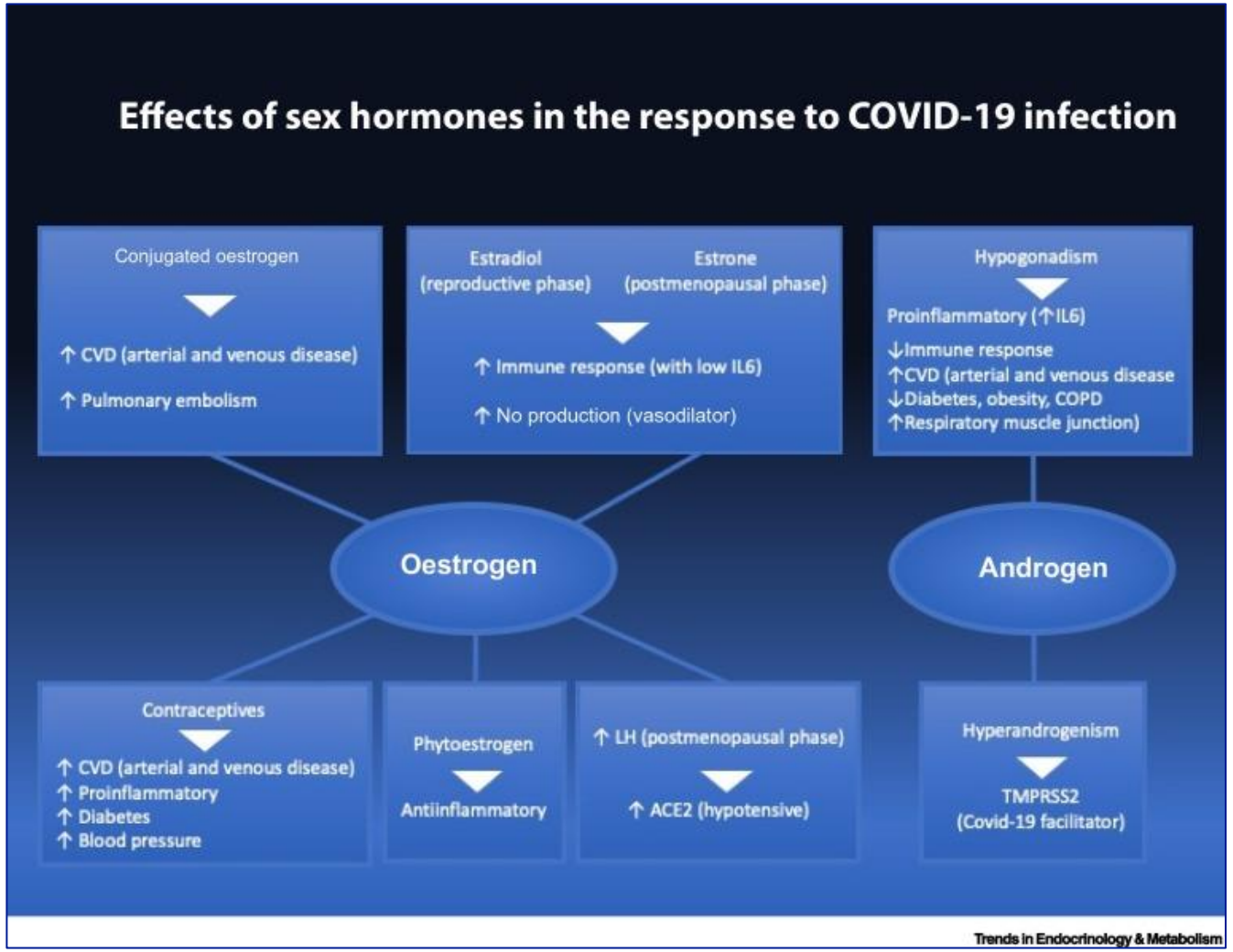
Direct Male Gonads Effects

- Germ cell Destruction
- Reduced spermatozoan in seminiferous tube
- Thikening basement membrane
- Leukoytes infiltration



Sex Hormones Effects

Androgens and estrogens may influence immune response against viral infection in an opposite way and adverse reaction rates

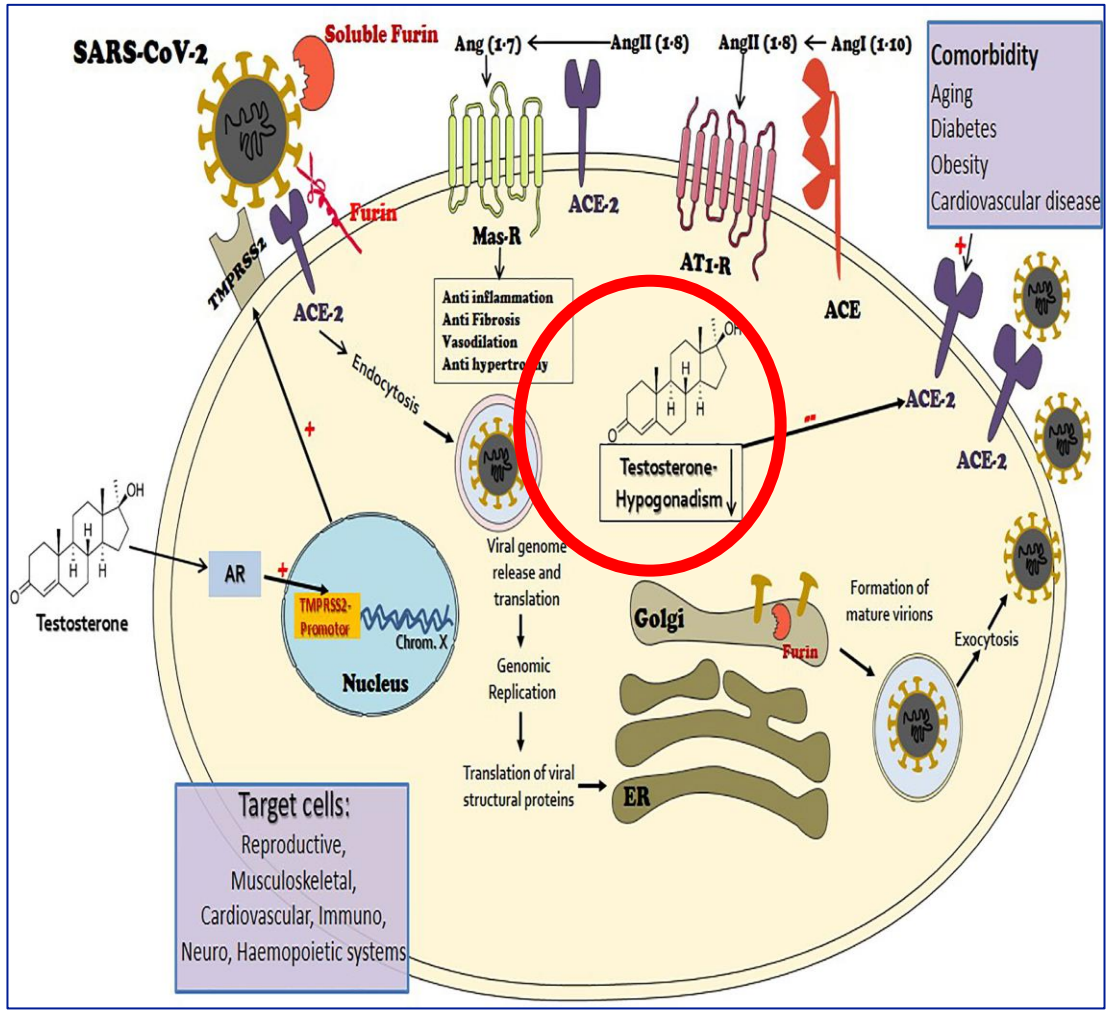


Sexual Dimorphism of Coronavirus 19 Morbidity and Lethality
Trends in Endocrinology & Metabolism, December 2020, Vol. 31, No. 12 https://doi.org/10.1016/j.tem.2020.09.003

Male Hypogonadism And Subfertility

Development of acute stage hypogonadism which has been linked with increased levels of pro-inflammatory cytokines,

Elevated serum LH in men with COVID-19 hints toward primary Leydig cell damage.



Female Gonads Effects

ACE-2 expression

Female mount a stronger innate and adaptive immune response than males.

Table 2
Angiotensin-converting enzyme 2 receptor and SARS-CoV-2 RNA detection in the nonpregnant female reproductive tract

	ACE2 receptor		SARS-CoV-2 RNA	
Reproductive tract locus	Positive	Negative	Positive	Negative
Vagina	Jing et al.[20]	–	Scorzolini et al.[91]	Qiu et al.[99] Cui et al.[100]
Uterus	Jing et al.[20]	Goad et al.[98]	–	–
Endometrium	Henarejos-Castillo et al.[97]	–	–	–
Endometrial epithelial cells	Vaz-Silva et al.[22]	–	–	–
Endometrial stromal cells	Vaz-Silva et al.[22]; Chadchan et al.[23]	–	–	–
Myometrium	–	Goad et al.[98]	–	–
Fallopian tube	–	Goad et al.[98]	–	–
Ovary	Reis et al.[19]; Jing et al.[20]	Goad et al.[98]	–	–
Oocyte	Jing et al.[20]	–	–	–
Follicular fluid	Reis et al.[19]	–	–	–
Cumulus cells	Stanley et al.[21]	–	–	–

ACE2 = angiotensin-converting enzyme 2.

Estrogen Therapy

J Pharm Pharm Sci (www.cspsCanada.org) 23, 75-85, 2020

Prevention and Therapy of COVID-19 *via* Exogenous Estrogen Treatment for Both Male and Female Patients; An Opinion Paper

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Estrogen and 17-β-estradiol can act on cellular subsets of the immune system resulting in modulation of lymphocyte activity.

Several clinical trials for the use of estrogen and androgen deprivation therapies in reducing the severity of COVID-19 are ongoing.

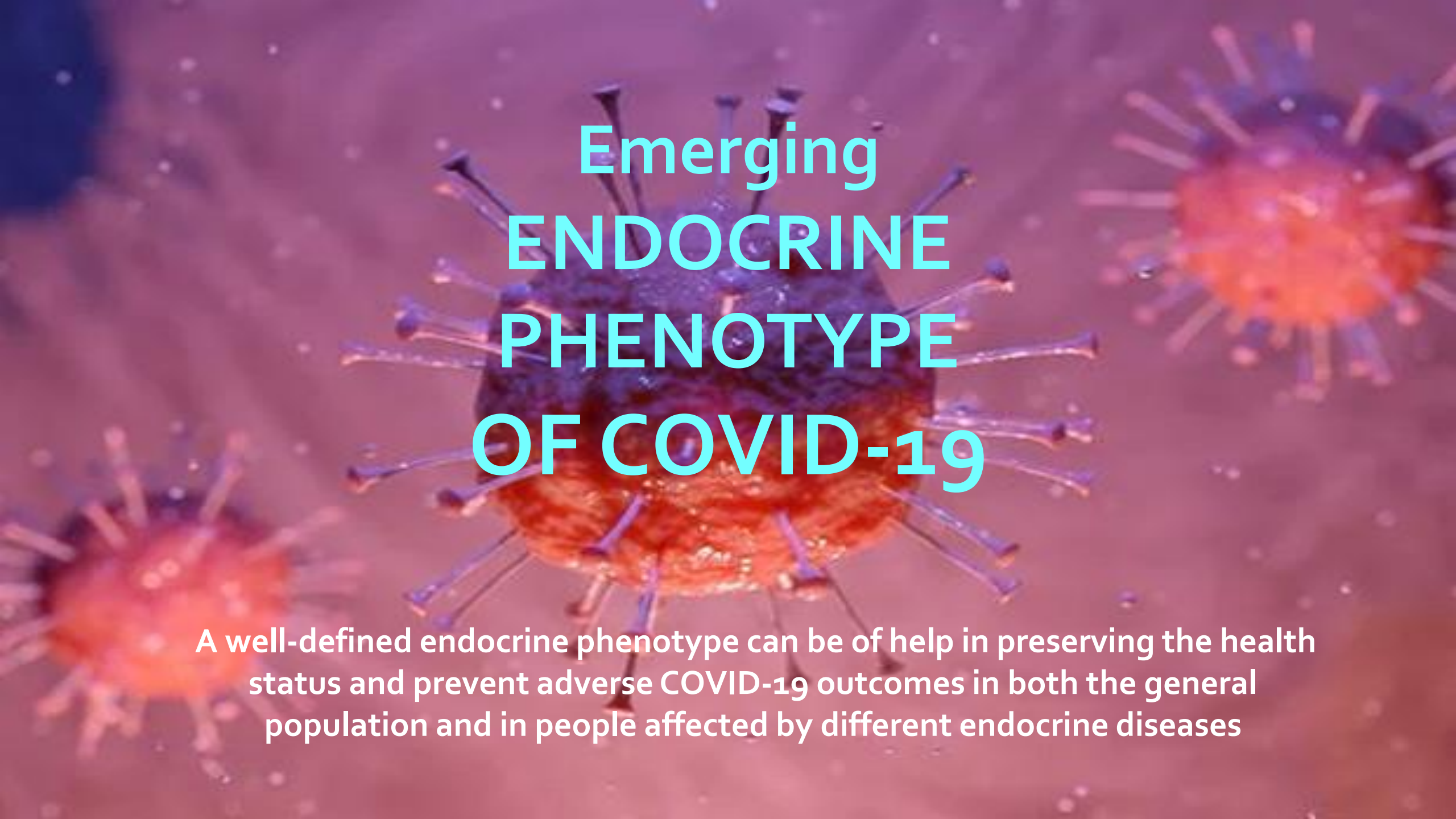
	ACE2 Expression	Patological finding of histological alterations		Finding of hormonal alterations		Expression of Virus RNA polymerase through in situ hybridization		Finding of viral particles with electron microscopy		Finding of Virus genome sequences through RT-PCR	
		SARS	COVID-19	SARS	COVID-19	SARS	COVID-19	SARS	COVID-19	SARS	COVID-19
HIPOTALAMUS / PITUITARY	✓	○		✓	✓	○		○		○	
THYROID	✓	○	○	✓	✓						
ADRENAL	✓	○	✓		○	○					
OVARY	✓/✗										
TESTIS	✓	✓	✓	✓	✓	✓/✗					✓/✗
SEMEN											✓/✗

○ : Evidence suggested by one or more studies on a total number of samples < 10

✓ : Evidence suggested by one or more studies on a total number of samples ≥ 10

✓/✗ : Controversial evidence

Piticchio, T., Le Moli, R., Tumino, D. *et al.* Relationship between betacoronaviruses and the endocrine system: a new key to understand the COVID-19 pandemic—A comprehensive review. *J Endocrinol Invest* (2021).



Emerging ENDOCRINE PHENOTYPE OF COVID-19

A well-defined endocrine phenotype can be of help in preserving the health status and prevent adverse COVID-19 outcomes in both the general population and in people affected by different endocrine diseases

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COVID-19 in people with diabetes: understanding the reasons for worse outcomes.The Lancet Diabetes & Endocrinology, ISSN: 2213-8587, Vol: 8, Issue: 9, Page: 782-792. 2020


It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is the most adaptable to change.
CHARLES DARWIN

Gracias