Addressing the Bidirectional Link Between COVID-19 and Diabetes

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NYSCHP Diabetes Miniseries

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Objectives

1. Review the pathophysiology of metabolic disturbances in COVID-19.
2. Describe the bidirectional interplay between COVID-19 and diabetes.
3. Discuss outcomes associated with glycemic control in COVID-19 patients.
4. Apply glycemic control strategies to patients with COVID-19.

1

Metabolic Disturbances in COVID-19

The COVID-19 Pandemic

- Global pandemic declared in March 2022
- Disease ranges from mild acute respiratory illness to severe pneumonia with respiratory failure
    - Severe disease mainly occurs in older adults and those with comorbidities

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)

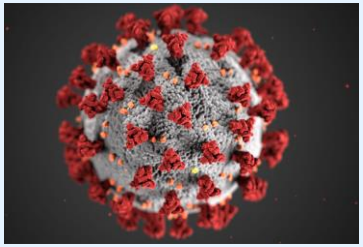


Image from: https://www.cdc.gov/dotw/covid-19/index.html

COVID-19 disease

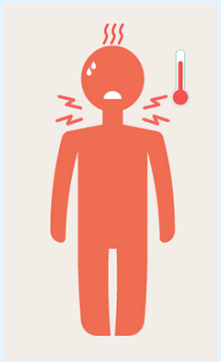
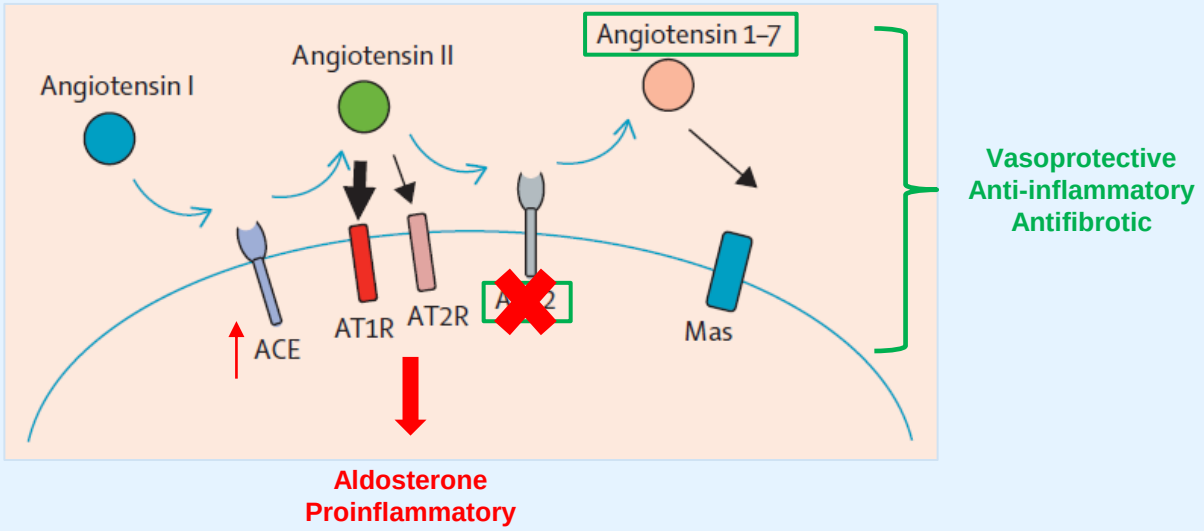


Image from: https://www.hopkinsmedicine.org/health/conditions-and-diseases/coronavirus/how-rates-produce-data-spikes

Papadokostaki E, et al. Prim Care Diabetes. 2020 Oct;14(5):558-563.

RASS System in COVID-19

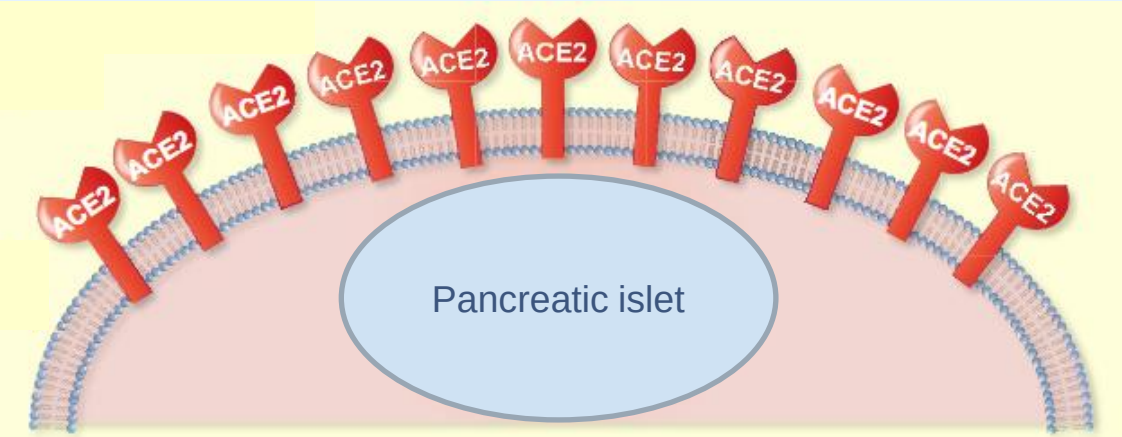
- Deregulation of angiotensin-converting enzyme (ACE) or angiotensin-converting enzyme 2 (ACE2) balance causes an exaggerated inflammatory response



Steenblock C, et al. Lancet Diabetes Endocrinol. 2021 Nov;9(11):786-798.

Role of ACE2 Receptor

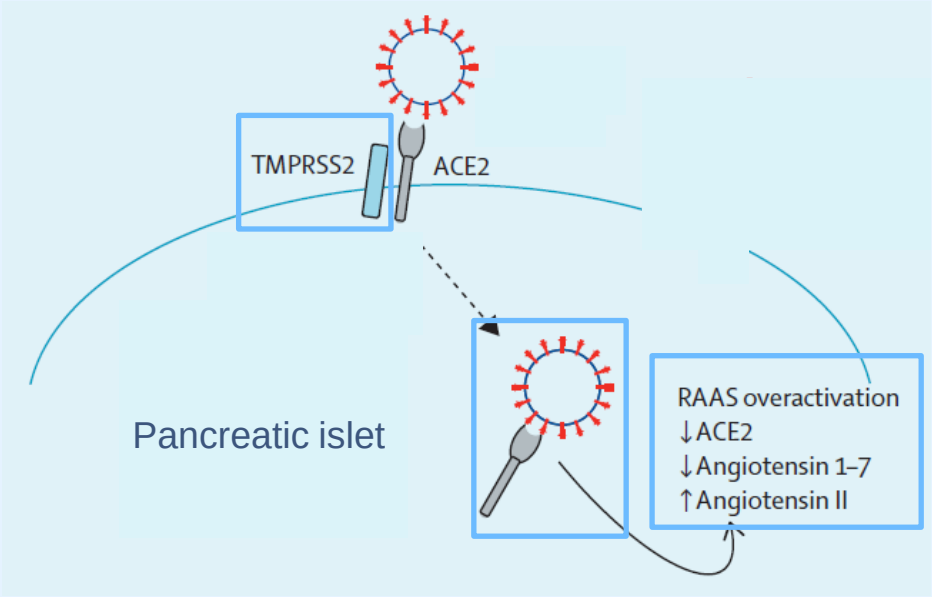
- ACE2 receptor serves as a cellular entry point for SARS coronavirus
- ACE2 receptors expressed on pancreatic beta cells facilitate entrance of coronaviruses, including SARS-CoV-2



Yang JK, et al. Acta Diabetol. 2010 Sep;47(3):193-9.
Memon B, et al. Acta Physiol (Oxf). 2021 Dec;233(4):e13733.

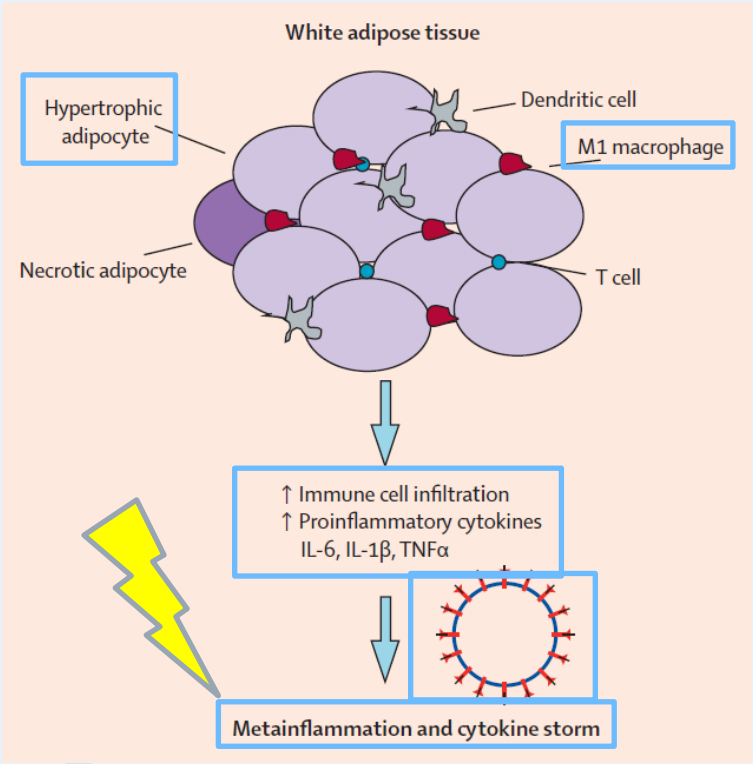
RASS Overactivation in Islets

- Following binding of the SARS-CoV-2 virus, the ACE2 receptor is internalized, leading to a decrease in ACE2 expression and overactivation of ACE



Liao YH, et al. J Clin Med. 2020 Dec 7;9(12):3962.
Memon B, et al. Acta Physiol (Oxf). 2021 Dec;233(4):e13733.
Steenblock C, et al. Lancet Diabetes Endocrinol. 2021 Nov;9(11):786-798.

Metabolic Complications: Adipose Tissue



- Common complications of inflammatory state:
  - Damaged blood vessels and nerves
  - Stroke
  - Heart failure
  - Myocardiopathy
  - Proteinuria
  - Coagulopathies
  - Insulin resistance
  - Endothelial dysfunction

Steenblock C, et al. Lancet Diabetes Endocrinol. 2021 Nov;9(11):786-798.

Metabolic Reprogramming

- The SARS-CoV-2 virus induces alterations in metabolic pathways involved in energy production and regulation of immune response

Metabolic Pathway Altered	Clinical Effect(s)
Amino acid	Dysregulated immune response and assembly of progeny virus
Glucose	Enhanced glycolysis → inflammation, T cell impairment, lung epithelial cell death
Cholesterol & Fatty Acids	Consumption to facilitate viral entry into cells → impaired cellular function

Shen T, et al. Int J Mol Sci. 2021 Oct 25;22(21):11475.

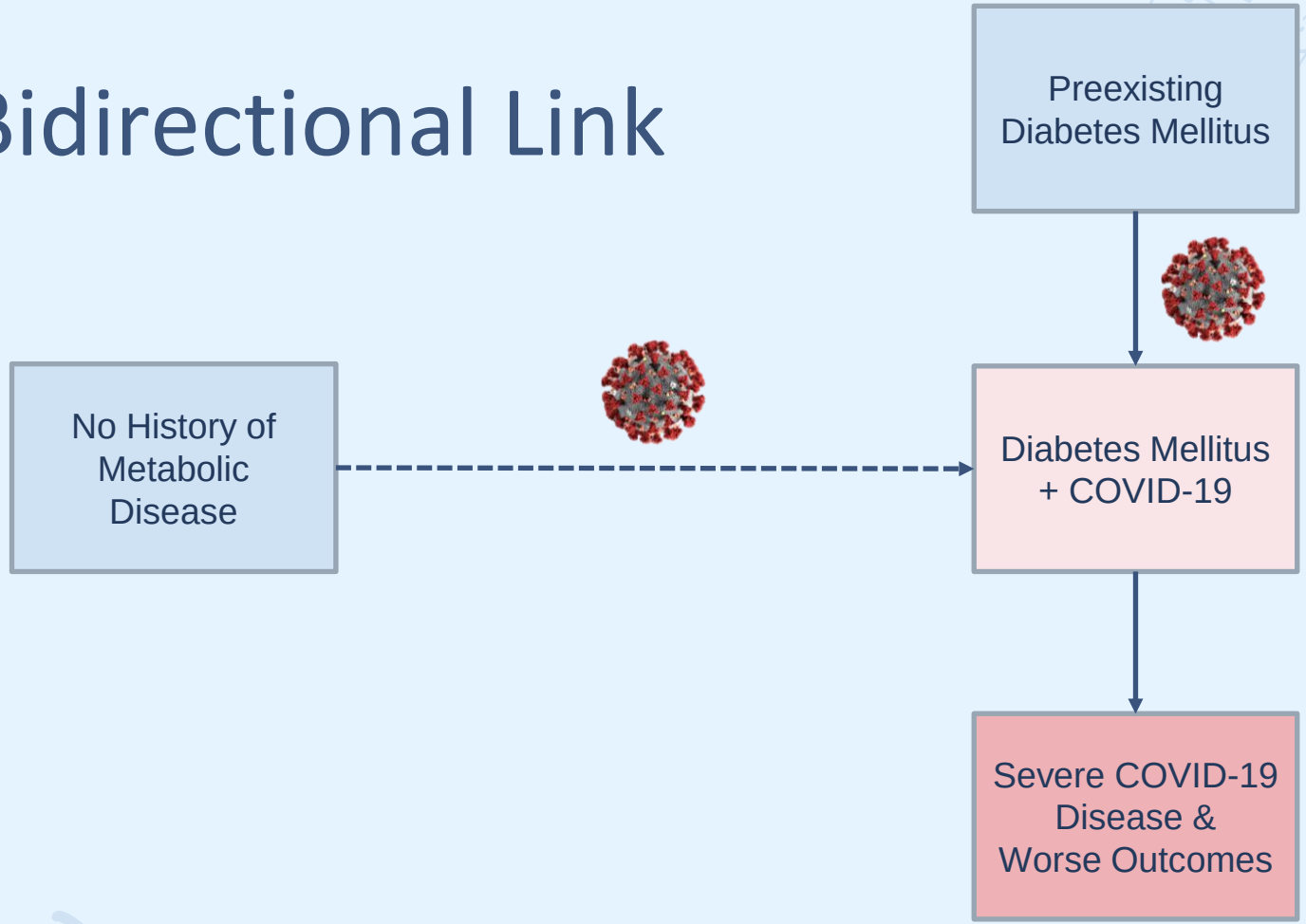
Polling Question #1

1. Which is the primary receptor implicated in COVID-19-induced metabolic derangements?
    a) ACE
    b) ACE2
    c) AT1R
    d) AT2R

2

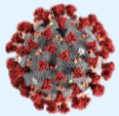
COVID-19 and Diabetes

Bidirectional Link



Mazzone J, et al. Hosp Pharm. 2022 Apr;57(2):205-210.

Preexisting Diabetes Mellitus



Diabetes Mellitus + COVID-19

Severe COVID-19 Disease & Worse Outcomes

Mazzone J, et al. Hosp Pharm. 2022 Apr;57(2):205-210.

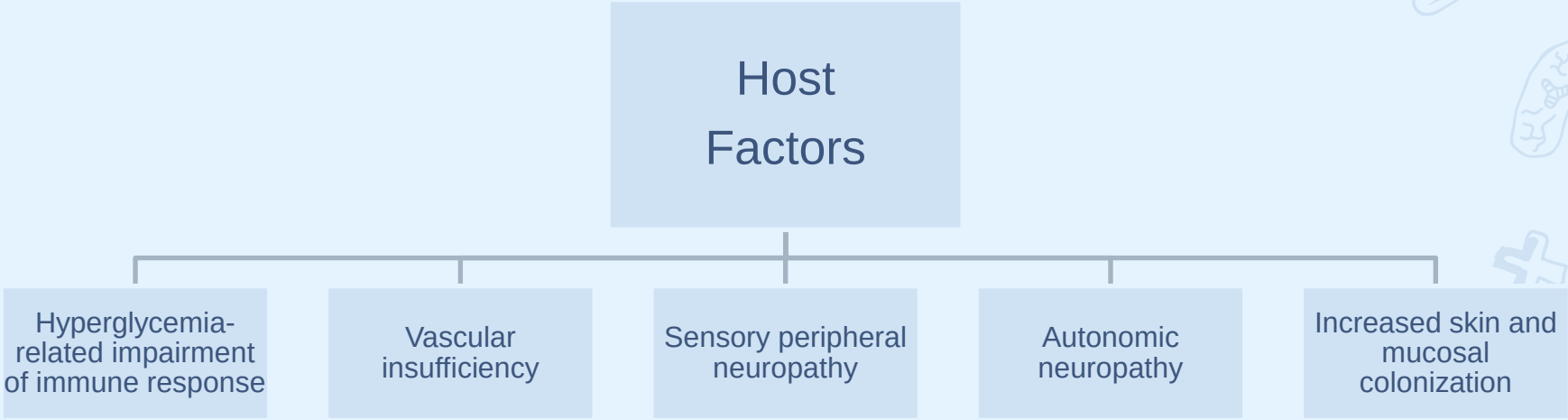
Increased Infection Risk in Diabetes

- Several studies suggest an increased risk of infection among patients with diabetes, although the magnitude of this risk is uncertain

Study	Design	Findings in DM Patients Compared with Matched Controls	Infection Types
Abu-Ashour et al, 2018	Matched cohort study of Canadian medical records (n=12,845)	• Odds of any infection: adjusted OR 1.21, 95% CI 1.07-1.37	• Skin and soft tissue, followed by genitourinary, gastrointestinal, and respiratory
Carey IM et al, 2018	Retrospective cohort study of primary care database in England (n=102,493)	• IRR for any infection: 1.47, 95% CI 1.46-1.49	• Bone and joint infections, followed by candidiasis, sepsis, and cellulitis

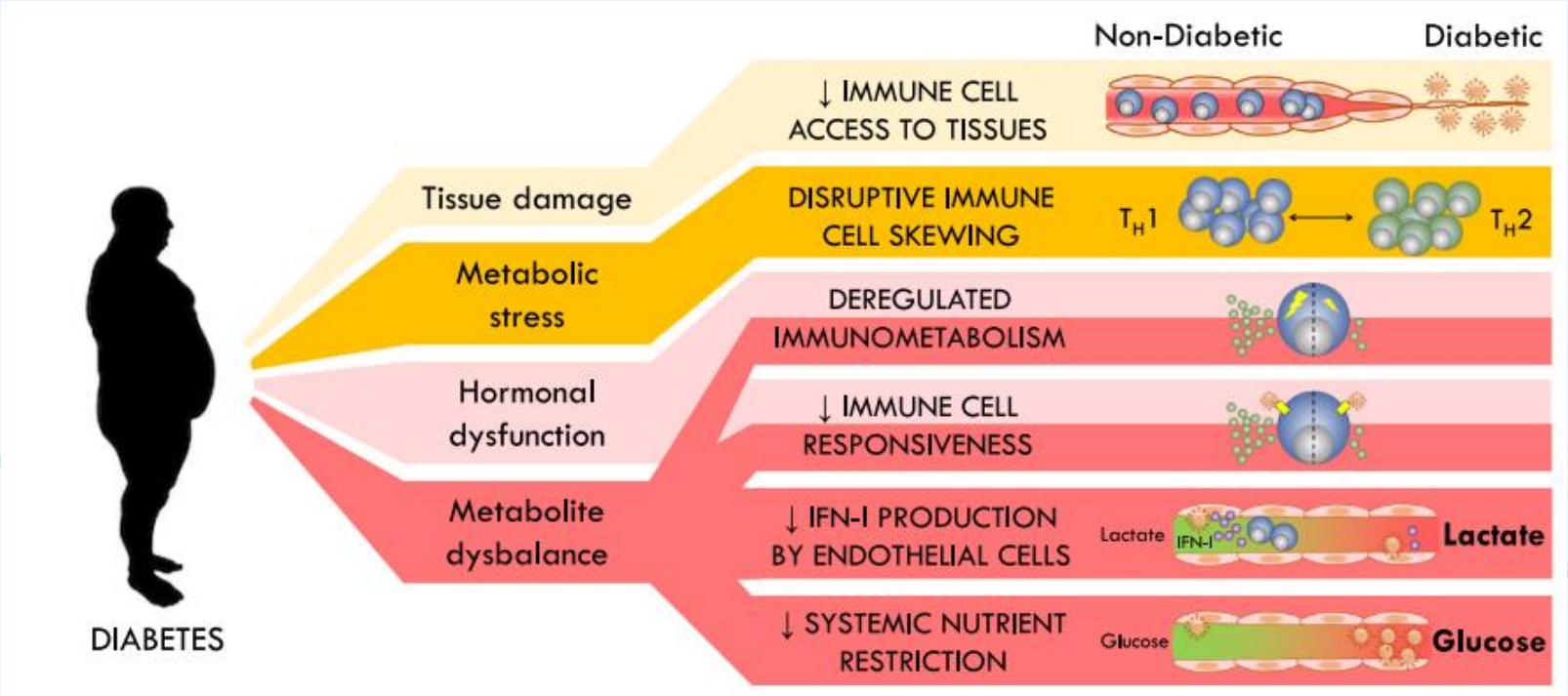
Carey IM, et al. Diabetes Care. 2018 Mar;41(3):513-521.
Abu-Ashour W, et al. BMC Infect Dis. 2018 Feb 5;18(1):67.

Susceptibility to Infection in Diabetes



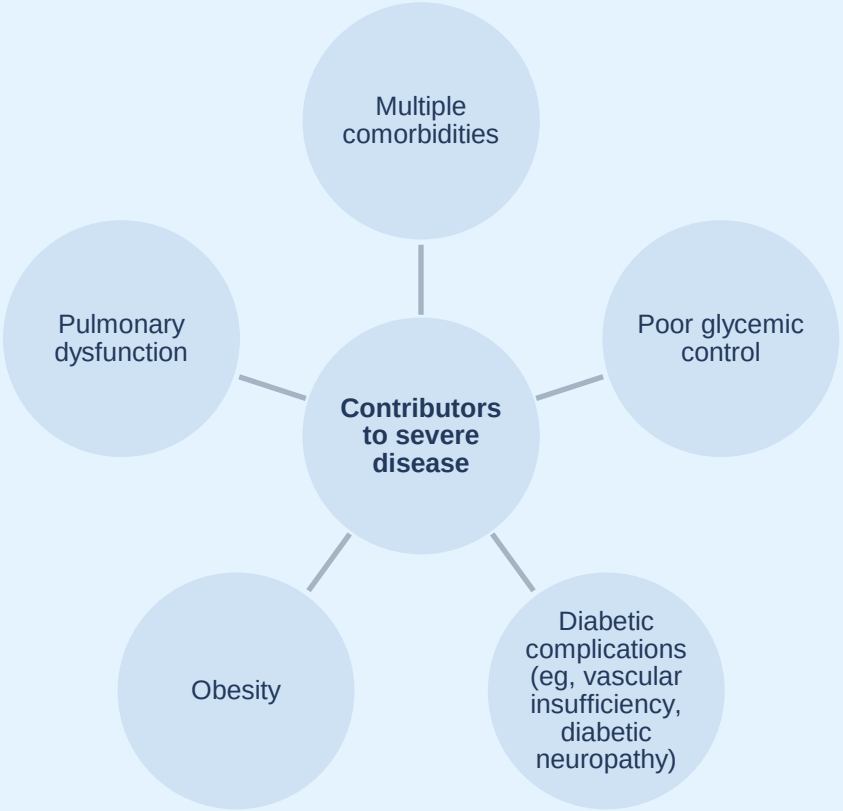
Casqueiro J, et al. Indian J Endocrinol Metab. 2012 Mar;16 Suppl 1(Suppl1):S27-36.

Viral Infections in Diabetes



Turk Wensveen T, et al. Diabetes Res Clin Pract. 2021 Feb;172:108637.

Severe Disease in Diabetic Patients



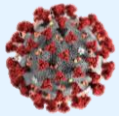
Papadokostaki E, et al. Prim Care Diabetes. 2020 Oct;14(5):558-563.

Hyperinflammatory State of Diabetes

		Median (IQR)		
	Normal Range	**Non-Diabetic COVID-19 Patients (n=137)**	**Diabetic COVID-19 Patients (n=37)**	**P value**
C-reactive protein (mg/L)	< 8	7.43 (3.14-13.45)	76.4 (12.4-93)	< 0.01
D-dimer (mcg/L)	< 0.5	0.25 (0.22-0.31)	1.16 (0.74-1.89)	< 0.01
Serum ferritin (ng/mL)	21.8-275	128.9 (57.25-193.15)	764.8 (164-1496)	< 0.01
Erythrocyte sedimentation rate (mm/h)	< 15	8 (7-26)	76 (59-85)	< 0.01
IL-6 (pg/mL)	0.1-2.9	4.13 (3.14-10.61)	13.73 (7.28-28.31)	< 0.01
Fibrinogen (g/L)	2.0-4.0	3.75 (3.04-4.75)	5.01 (4.48-6.25)	< 0.01

Guo W, et al. Diabetes Metab Res Rev. 2020 Mar 31;36(7):e3319.

No History of Metabolic Disease



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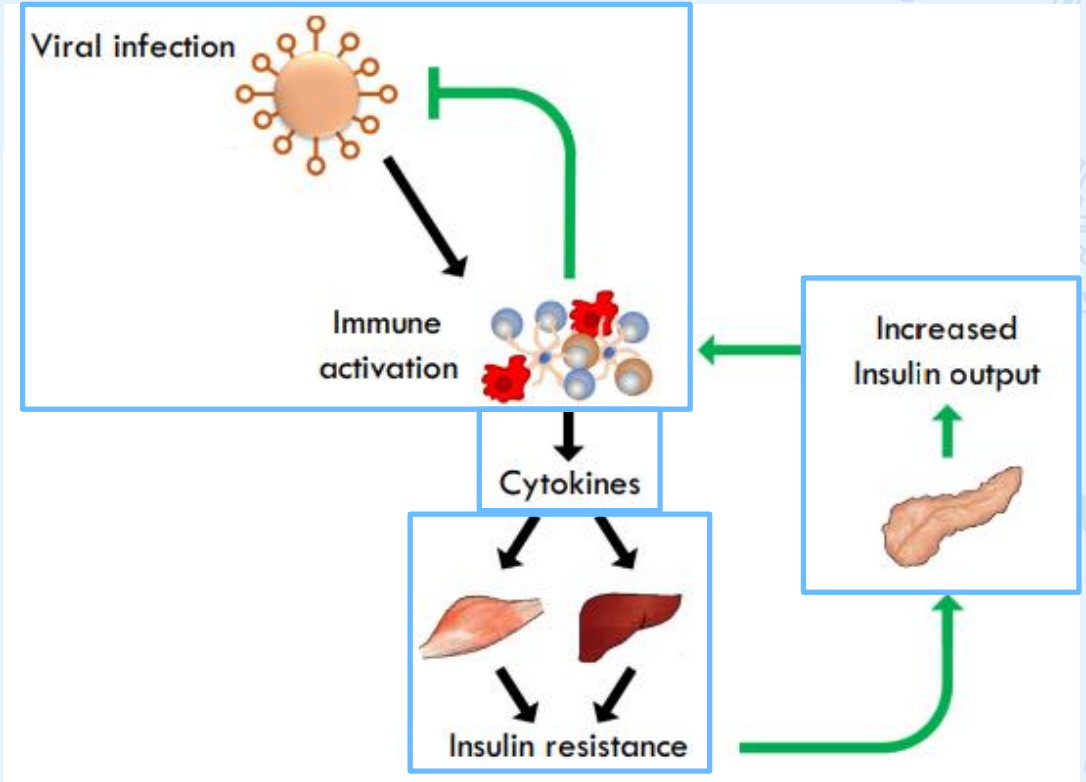
Mazzone J, et al. Hosp Pharm. 2022 Apr;57(2):205-210.

Insulin Resistance in Viral Infections

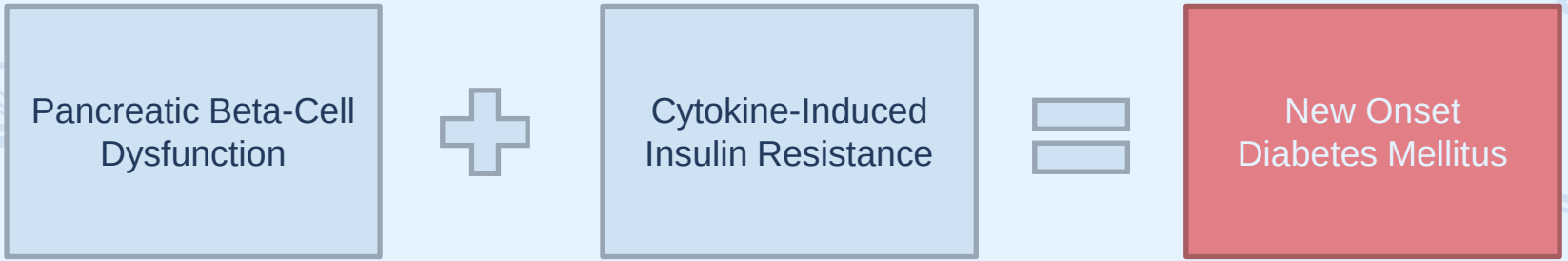
- Physiological changes in metabolism in response to infection may be a trigger for permanent dysregulation of blood glucose levels
- Infection-associated inflammation induces insulin resistance



Turk Wensveen T, et al. Diabetes Res Clin Pract. 2021 Feb;172:108637.

New Onset Diabetes in Viral Infections

- New-onset diabetes has been documented in chronic viral infections including:
  - Cytomegalovirus
  - Hepatitis C
- Several recent studies have reported new-onset diabetes associated with COVID-19
  - Many patients present with complications, including diabetic ketoacidosis
  - Phenotypically described as both T1DM and T2DM



Khunti K, et al. Diabetes Care. 2021 Dec;44(12):2645-2655.
Turk Wensveen T, et al. Diabetes Res Clin Pract. 2021 Feb;172:108637.

Polling Question #2

2. True/False: COVID-19 disease may induce new-onset diabetes in a healthy individual with no history of metabolic disease.

a) True

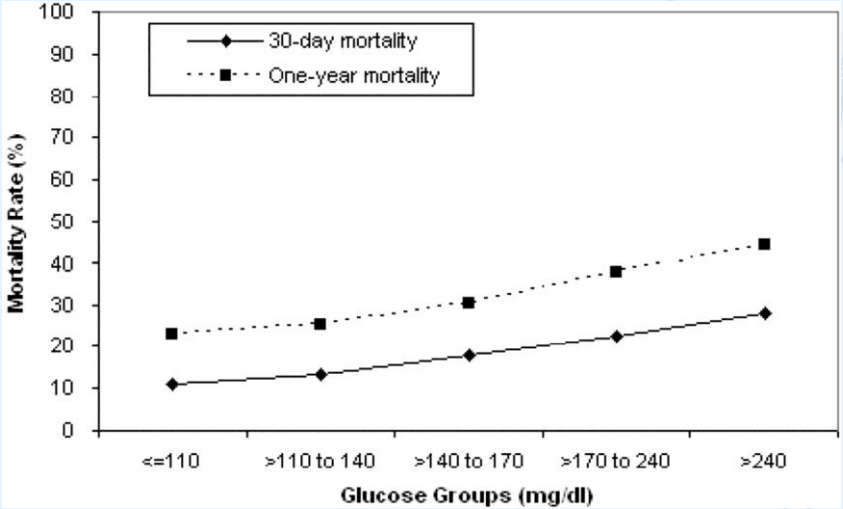
b) False

3

Glycemic-Related Outcomes in COVID-19

Consequences of Inpatient Hyperglycemia

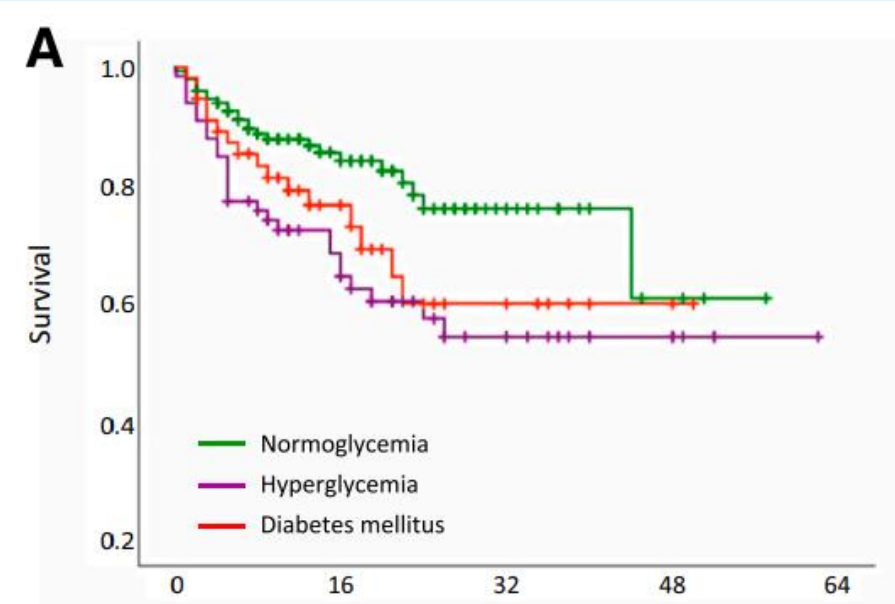
- Uncontrolled blood glucose associated with:
  - Impaired wound healing
  - Increased risk of infection
  - Decreased neurologic recovery
  - Higher mortality after acute MI
  - Delays in procedures or discharge



Kosiborod M, et al. Circulation. 2005; 111: 3078–3086.
Kodner C, et al. Am Fam Physician. 2017 Nov 15;96(10):648-654.

Hyperglycemia in COVID-19

- In patients with no history of diabetes, hyperglycemia in COVID-19 was an independent predictor of mortality (HR 1.80, 95% CI 1.03–3.15, P = 0.04)

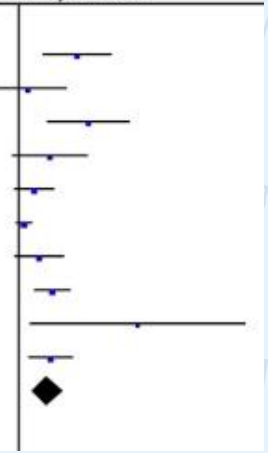


Coppelli A, et al. Diabetes Care. 2020 Oct;43(10):2345-2348.

Pre-Existing Diabetes + COVID-19

- In a meta-analysis of 6,452 patients with COVID-19, DM was associated with increased risk of death (RR 2.12, P < 0.001)

	Diabetes Mellitus (+)		Diabetes Mellitus (-)			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
6.1.1 Mortality							
Akbari 2020	4	13	29	423	3.6%	4.49 [1.85, 10.91]	
Bai T 2020	5	36	10	91	3.1%	1.26 [0.46, 3.44]	
Cao J 2020	6	17	5	85	2.9%	6.00 [2.07, 17.43]	
Chen 2020	6	31	8	92	3.2%	2.23 [0.84, 5.91]	
Chen T 2020	24	113	23	161	5.3%	1.49 [0.88, 2.50]	
Fu L 2020	26	34	111	166	6.6%	1.14 [0.92, 1.42]	
Li K 2020	7	15	24	87	4.7%	1.69 [0.89, 3.21]	
Luo XM 2020	25	100	32	303	5.5%	2.37 [1.48, 3.79]	
Yuan M 2020	6	10	0	17	0.7%	21.27 [1.32, 341.84]	
Zhou 2020	17	54	19	137	5.0%	2.27 [1.28, 4.03]	
Subtotal (95% CI)		**423**		**1562**	**40.6%**	**2.12 [1.44, 3.11]**	
Total events	126		261				



Huang I, et al. Diabetes Metab Syndr. 2020 Jul-Aug;14(4):395-403.

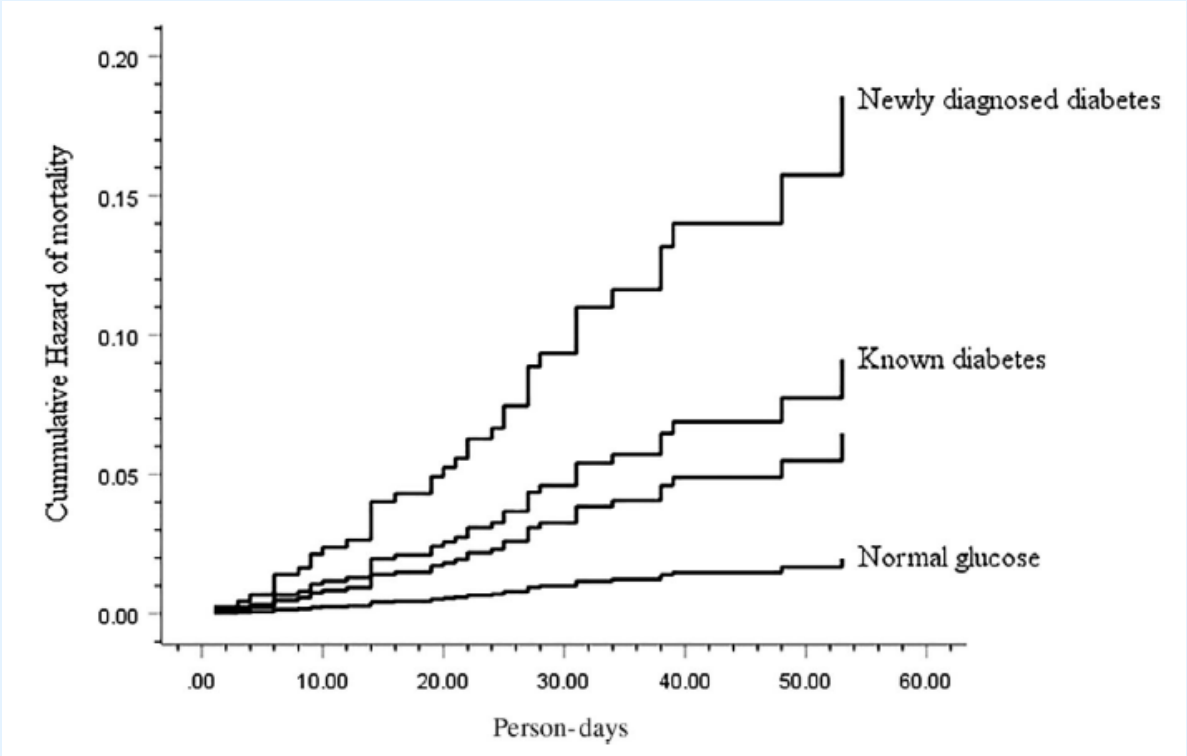
Newly Diagnosed DM + COVID-19

- Retrospective study of 453 patients in Wuhan, China

Categories	Fasting blood glucose (mg/dL) and/or HbA1c	Mortality
Normal glucose	Not defined	1.00
Hyperglycemia	101-124 and/or 5.7%-6.4%	3.29 (95% CI, 0.65-16.6)
Known diabetes	--	4.63 (95% CI, 1.02-21.0)
Newly diagnosed diabetes	126 and/or $\geq$ 6.5%	9.42 (95% CI, 2.18-40.7)

Li H, et al. Diabetes Obes Metab. 2020 Oct;22(10):1897-1906.

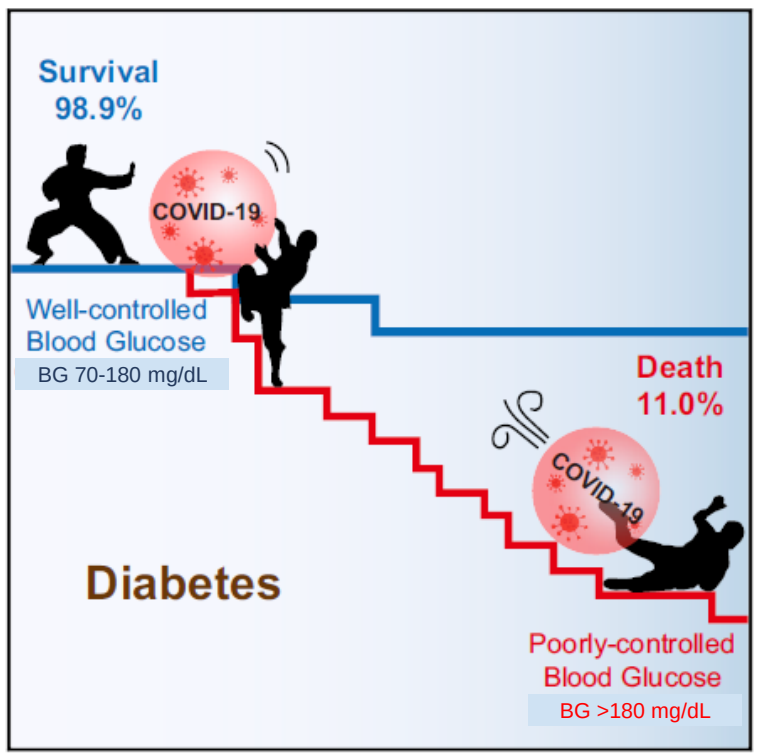
Mortality by Diabetes Status



Li H, et al. Diabetes Obes Metab. 2020 Oct;22(10):1897-1906.

Glycemic Control = Reduced Mortality

- Among patients with COVID-19 and pre-existing T2DM, patients with well-controlled blood glucose had markedly reduced mortality compared to patients with poorly controlled blood glucose (adjusted HR 0.14, 95% CI, 0.03-0.60, P = 0.008)



Zhu L, et al. Cell Metab. 2020 Jun 2;31(6):1068-1077.e3.

Polling Question #3

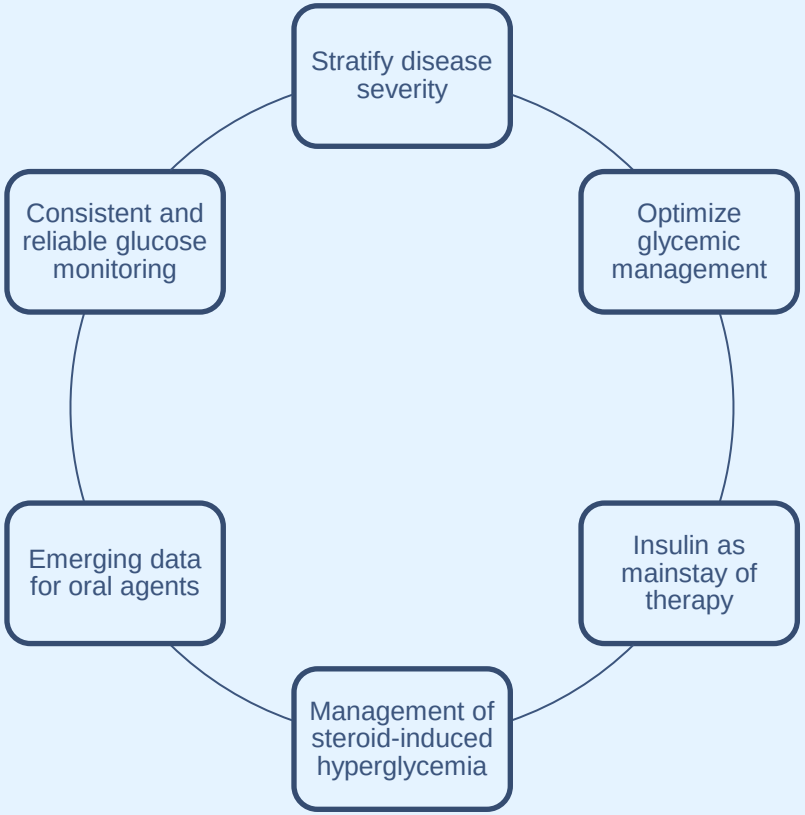
3. Which of the following populations has the highest mortality rates in COVID-19 disease?

a) Normal glucose
b) Transient hyperglycemia
c) History of DM
d) New-onset DM

4

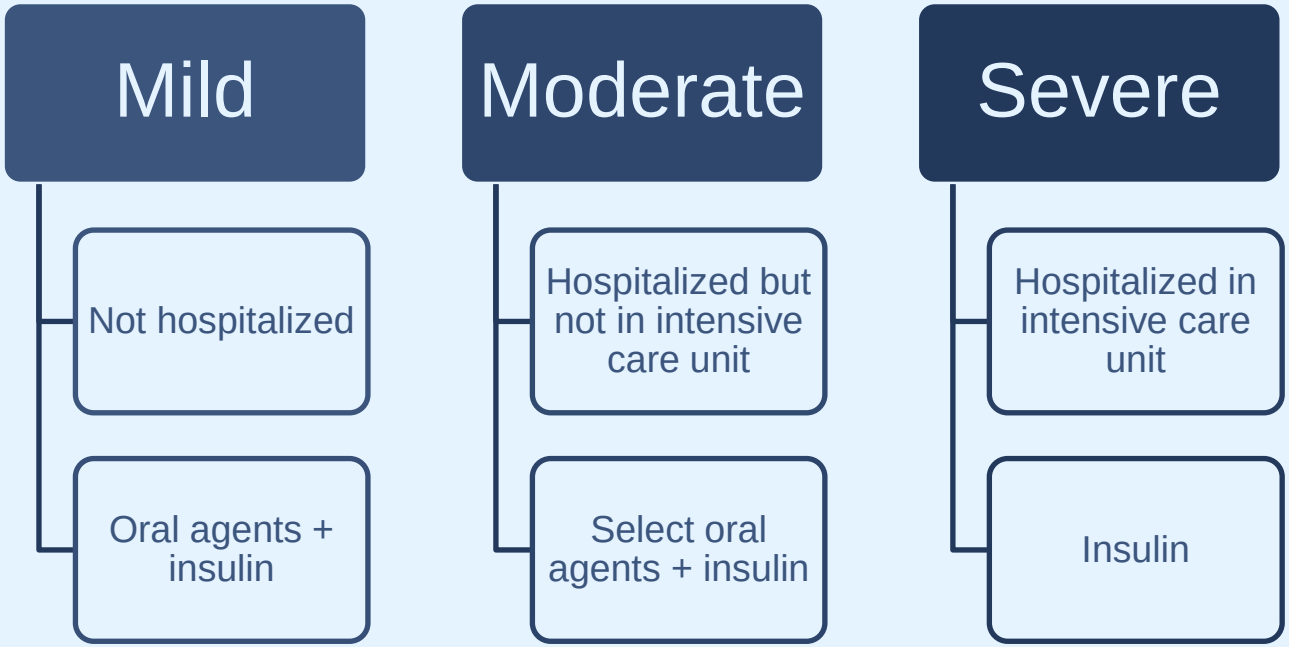
Glycemic Control in COVID-19

COVID-19 Guideline Recommendations



Bornstein SR, et al. Lancet Diabetes Endocrinol. 2020 Jun;8(6):546-550.

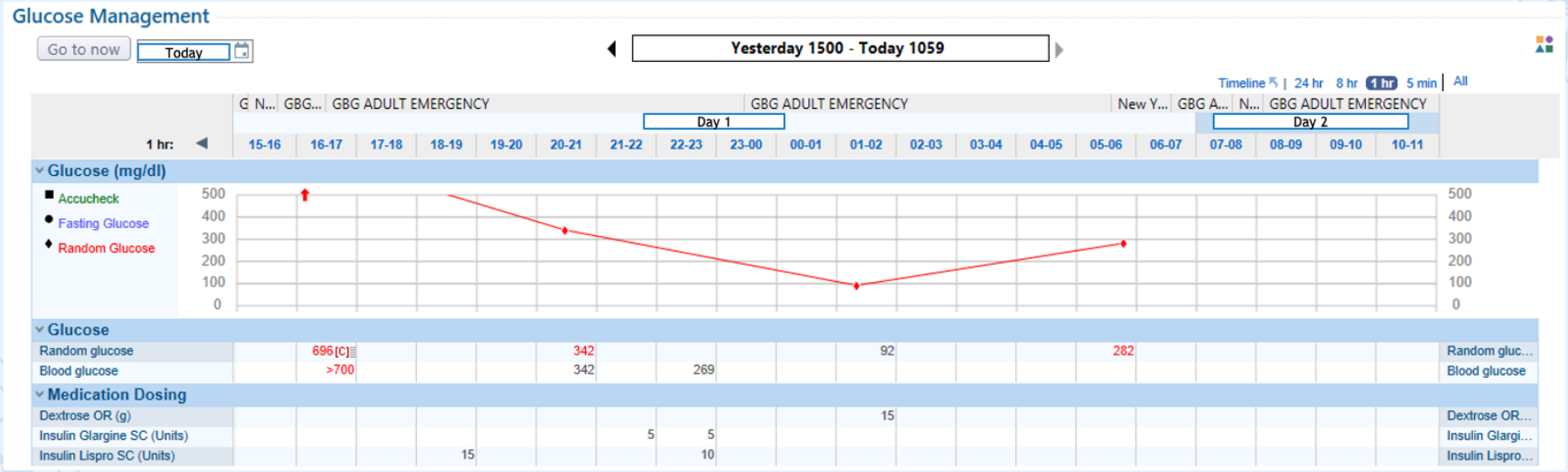
Stratifying Disease Severity



Czupryniak L, et al. Cardiovasc Diabetol. 2021 Oct 1;20(1):198.

Inpatient Glycemic Targets

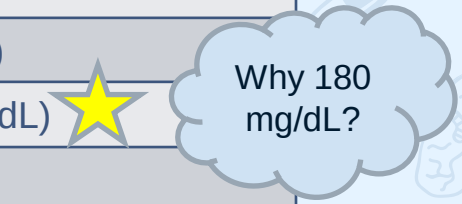
- 2021 ADA Guidelines: **140-180** mg/dL
  - 110-140 mg/dL for select patients



ADA. Diabetes Care. (Suppl. 1):S211-S220. 2022.

Moderate Vs Tight Glycemic Control

Population	Medical & surgical ICU patients
Intervention	Intensive glycemic control (target 81-108 mg/dL)
Comparator	Conventional glycemic control (target ≤ 180 mg/dL)
Outcomes	• Primary: 90-day mortality • Adverse Events: hypoglycemia (blood glucose ≤ 40 mg/dL)
Results	• 27.5% vs. 24.9% (OR 1.14; 95% CI 1.02-1.28; p=0.02) • 6.8% vs. 0.5% (OR 14; 95% CI 9.0-25.9; p < 0.001)
Conclusion	• Conventional glycemic control (target ≤ 180 mg/dL) results in lower mortality and lower rates of hypoglycemia for ICU patients.



Finfer S, et al. N Engl J Med. 2009 Mar 26;360(13):1283-97.

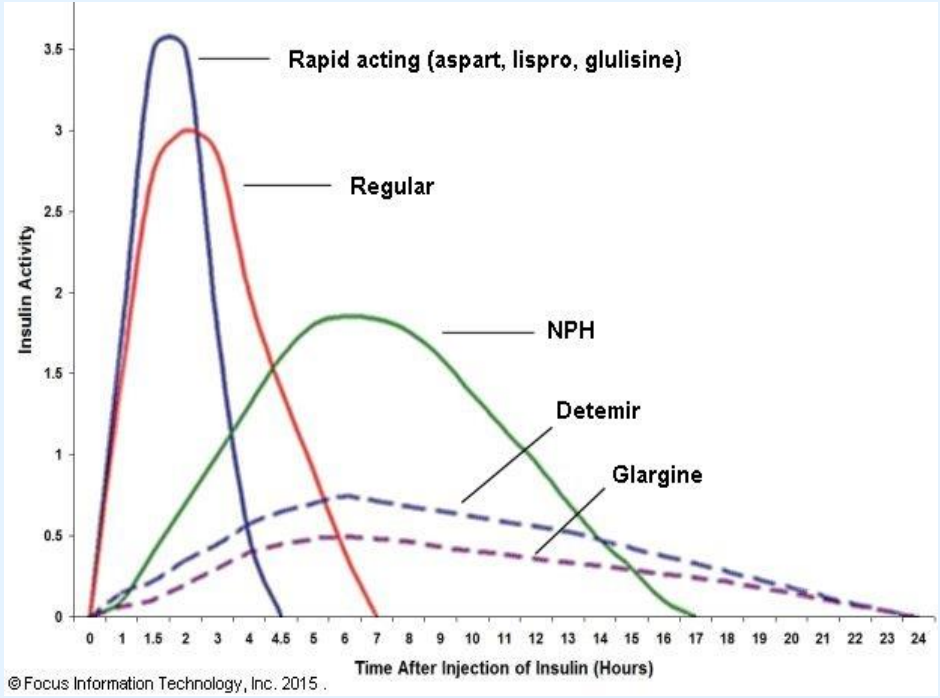
Choice of Therapy: Insulin

- Insulin is the preferred glycemic control agent for critically ill hospitalized COVID-19 patients
- Individualized insulin therapy to achieve glycemic targets

- Goals of insulin regimen:
  - Reduce contact frequency
  - Reduce glucose variability
  - Minimize risk of hypoglycemia
  - Improve overall glycemic control

Bellido V, et al. Diabetes Ther. 2021 Jan;12(1):121-132.
Bornstein SR, et al. Lancet Diabetes Endocrinol. 2020 Jun;8(6):546-550.

Time-Action Profiles of Insulin Analogs



Hirsch IB. N Engl J Med. 2005 Jan 13;352(2):174-83.

Dosing Insulin: Weight & Insulin Sensitivity

Weight-Based Total Daily Starting Dose: ~0.4-0.6 units/Kg
Divide Total Daily Dose into: ½ Basal, ½ Bolus

Total Daily Dose: 0.4----------0.6----------0.8 units/kg

INSULIN SENSITIVE:
T1DM, Thin, Elderly
Renal Insufficiency,
Pancreatectomy

Basal dose: 0.1 units/kg

INSULIN AVERAGE:
Overweight
T2DM

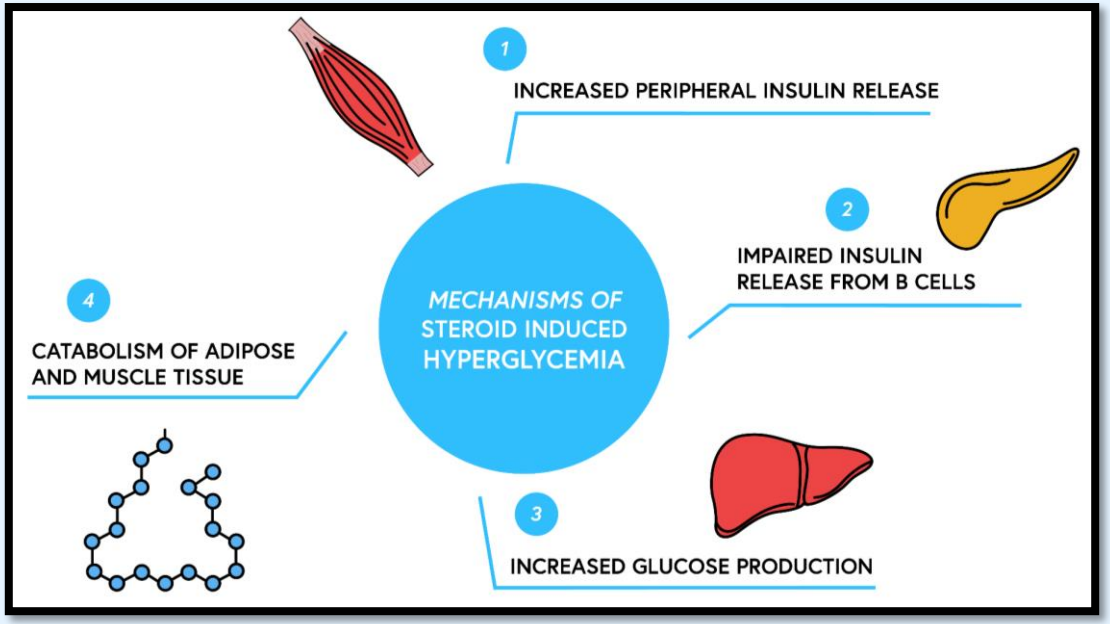
Basal dose: 0.2 units/kg

INSULIN RESISTANT:
Infection, Steroids
Pregnancy
Morbid Obesity

Basal dose: 0.3 units/kg

Steroid-Induced Hyperglycemia (SIHG)

- New-onset hyperglycemia or exacerbation of pre-existing DM
- Glucose targets same as general DM population

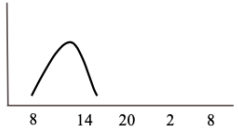
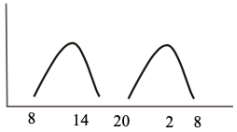
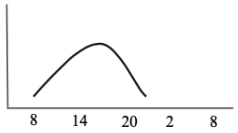
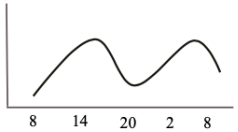
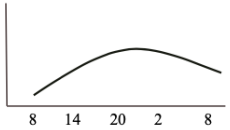


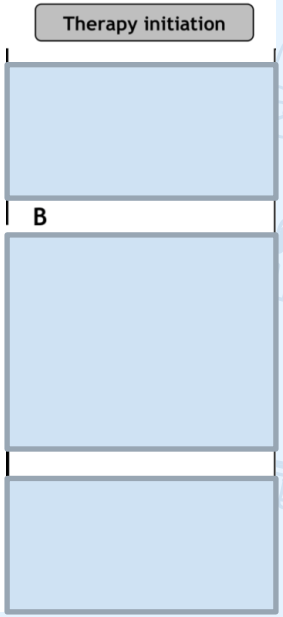
Aberer F, et al. J Clin Med. 2021 May 16;10(10):2154.

Management of SIHG

- Insulin is treatment of choice
- Tailor insulin therapy to PK profile of corticosteroid

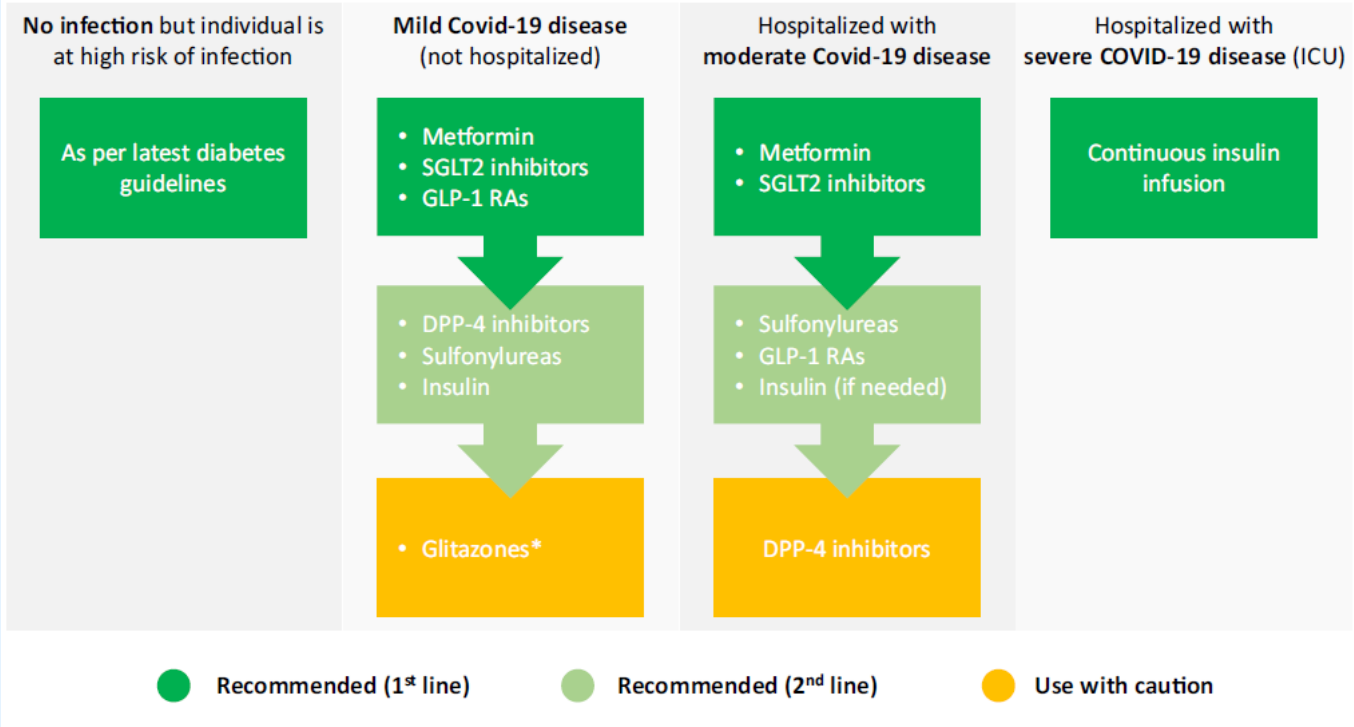
Which insulin analog is appropriate?

Glucocorticoids		Hyperglycaemic Effects (hours)			Glucose Profiles (GC Given Once Daily [8 a.m.])	Glucose Profiles (GC Given Twice Daily [8 a.m. and 20 p.m.])
		Onset	Peak	Resolution		
Short-acting	Hydrocortisone	1	3	6		
Intermediate-acting	Predniso(lo)ne	4	8	12–16		
	Methylprednisolone	4	8	12–16		
Long-acting	Dexamethasone	8	variable	24–36		n.a.



Aberer F, et al. J Clin Med. 2021 May 16;10(10):2154.

Antihyperglycemics in COVID-19



Czupryniak L, et al. Cardiovasc Diabetol. 2021 Oct 1;20(1):198.

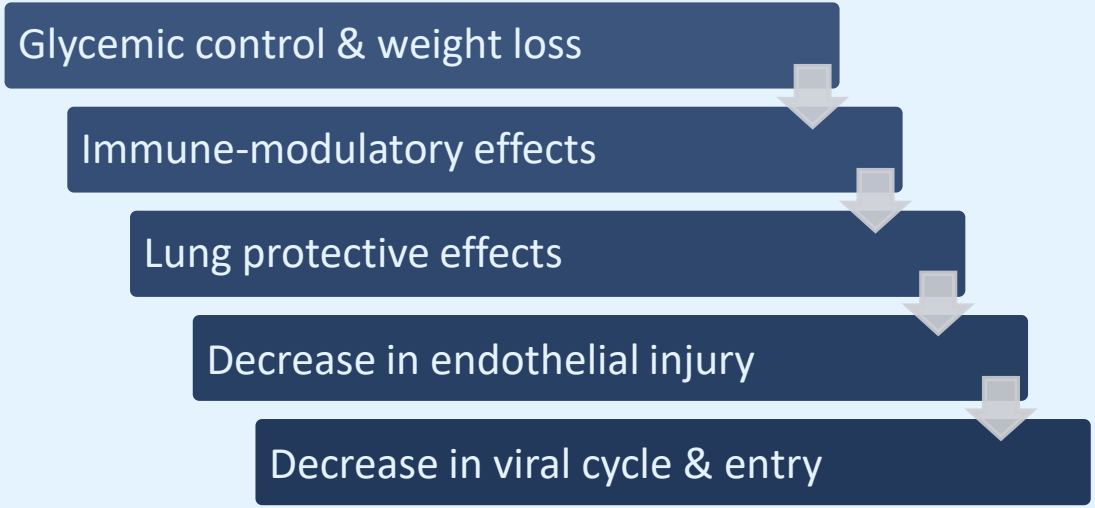
Antihyperglycemics in COVID-19

	Potential Positive Effects	Potential Negative Effects
Metformin	Stabilizes ACE2; inhibits host-virus binding; protects vasculature; decreases virus maturation	Risk of dehydration, lactic acidosis, and acute kidney injury
SGLT2 inhibitors	Reduces viral load; positive effects on cardiovascular and renal functions	Risk of dehydration, diabetic ketoacidosis, and acute kidney injury
GLP-1 receptor agonists	Anti-inflammatory effects; improves endothelial dysfunction; improves cardiovascular and renal functions	Increases satiety; gastrointestinal symptoms
DPP-4 inhibitors	Blocks virus uptake; reduces inflammatory response; well tolerated	Increases mortality in older patients in one study (likely due to confounding by indication)

Steenblock C, et al. Lancet Diabetes Endocrinol. 2021 Nov;9(11):786-798.

Metformin in COVID-19

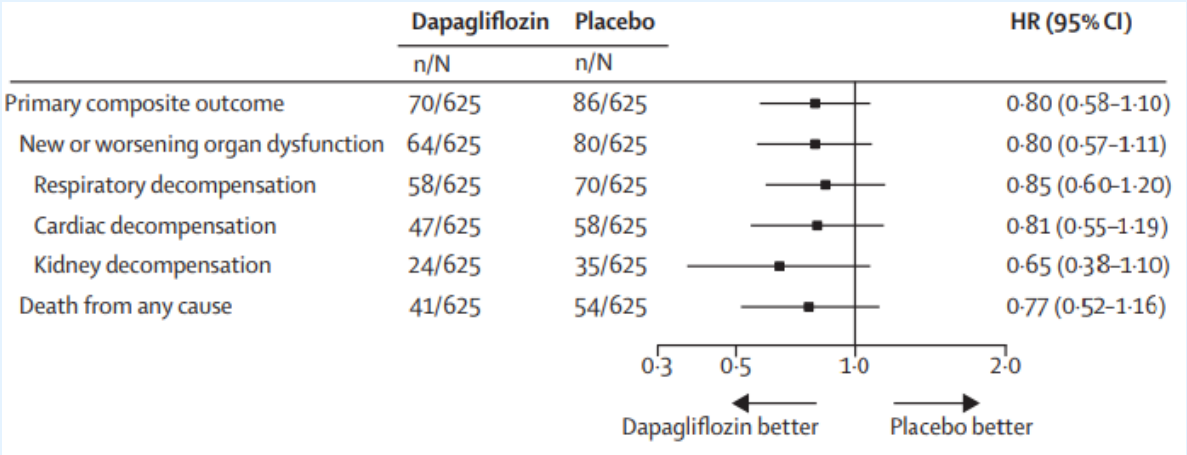
- 4 observational studies have shown decreased mortality among individuals with home metformin use
- Mechanisms of benefit in COVID-19:



Ibrahim S, et al. Front Endocrinol (Lausanne). 2021 Jul 22;12:587801.

SGLT2 Inhibitors in COVID-19

- DARE-19 Trial: Dapagliflozin in Respiratory Failure in Patients with COVID-19
  - Excluded critically ill patients
  - SGLT2 inhibitor well tolerated
  - No significant difference in clinical outcomes



Kosiborod MN, et al. Lancet Diabetes Endocrinol. 2021 Sep;9(9):586-594.

Inpatient Glucose Monitoring

- Guidelines recommend continuous and reliable glycemic monitoring every 2 to 4 hours
- Emerging role for continuous glucose monitoring (CGM)
    - Potential to limit staff exposure
    - Reduced hypoglycemic episodes, improved glycemic control in hospitalized patients
    - Limited experience in COVID-19 patients

Image from: https://www.umassmed.edu/dcoe/news/umass-diabetes-news/2019/08/diabetes-cgm/

Ehrhardt N, Hirsch IB. Diabetes Care. 2020 Nov;43(11):2628-2630.
Bornstein SR, et al. Lancet Diabetes Endocrinol. 2020 Jun;8(6):546-550.

Future Directions: CoviDIAB Project

COVIDIAB REGISTRY

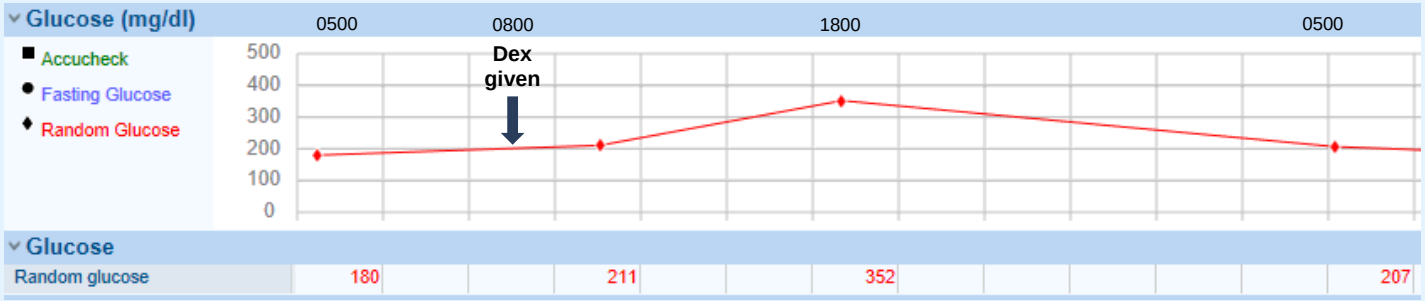
An international group of leading diabetes researchers are establishing a Global Registry of COVID-19-related diabetes.

This registry is specifically designed to establish the extent and characteristics of new-onset, COVID-19-related diabetes, and to investigate its pathogenesis, management and outcomes. The Registry also collects data about presentations with severe metabolic disturbance in pre-existing diabetes (DKA, hyperosmolarity; severe insulin resistance).

Rubino F, et al. N Engl J Med. 2020 Aug 20;383(8):789-790.

Polling Question #4

- KS is a 58-year-old female with a past medical history of HTN, HLD, COPD, and obesity who is admitted to the MICU for management of COVID-19 infection requiring ventilatory support. She is Day 5/10 of dexamethasone 6 mg IV daily and the team is concerned for SIHG.



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4. Which insulin analog would you recommend?

a) Glargine daily
b) Glargine BID
c) Lispro correction scale
d) NPH BID

Conclusions

- The SARS-CoV-2 virus induces significant metabolic disturbances through the RAAS system and ACE2 receptor.
- Patients with diabetes are at an increased risk of severe COVID-19 disease, whereas patients with COVID-19 and no known history of diabetes may also present with new onset diabetes.
- Although diabetes and hyperglycemia are independent predictors of mortality in COVID-19, these risks can be significantly reduced through glycemic control.
- Insulin, in combination with select oral agents, are the mainstays of therapy for hyperglycemia management in COVID-19.

Addressing the Bidirectional Link Between COVID-19 and Diabetes

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