NATIONAL LGBTQIA+ HEALTH EDUCATION CENTER
A PROGRAM OF THE FENWAY INSTITUTE

Brigham and Women's Hospital
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HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

COVID-19 and Diabetes

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Fenway Health

- Independent 501(c)(3) FQHC
- Founded 1971
- Mission: To enhance the wellbeing of the LGBTQIA+ community as well as people in our neighborhoods and beyond through access to the highest quality health care, education, research, and advocacy
- Integrated primary care model, including HIV and transgender health services

The Fenway Institute

- Research, Education, Policy

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The National LGBTQIA+ Health Education Center offers educational programs, resources, and consultation to health care organizations with the goal of providing affirmative, high quality, cost-effective health care for lesbian, gay, bisexual, transgender, queer, intersex, asexual, and all sexual and gender minority (LGBTQIA+) people.

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- Grand Rounds
- Online Learning
  - Webinars, Learning Modules
  - CE, and HEI Credit
- ECHO Programs
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www.lgbtqiahealtheducation.org

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COVID-19 and Diabetes

What have we learned?
What more do we need to know?

	Worldwide
Confirmed Cases	543,325,844
Deaths	6,328,556
Fully Vaccinated	4,787,404,327 (61.6%)

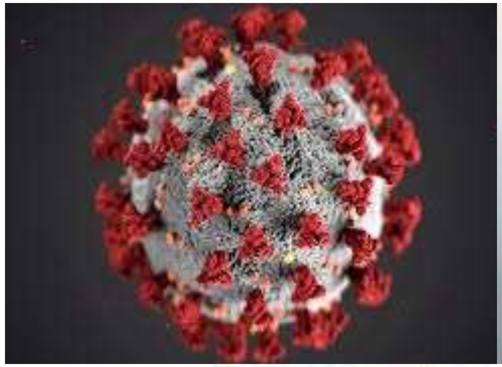
	USA
Confirmed Cases	86,881,533
Deaths	1,012,480
Fully Vaccinated	222,123,223 (67.4%)

Data as of 6.25.22

Disclosures

- Co-Investigator, Effectiveness and Safety of Dexcom G6 Continuous Glucose Monitoring System in Non-Critically Ill Patients in the Inpatient Setting [PTL-904283]

COVID Times…Looking Back on the Last 2 Years…

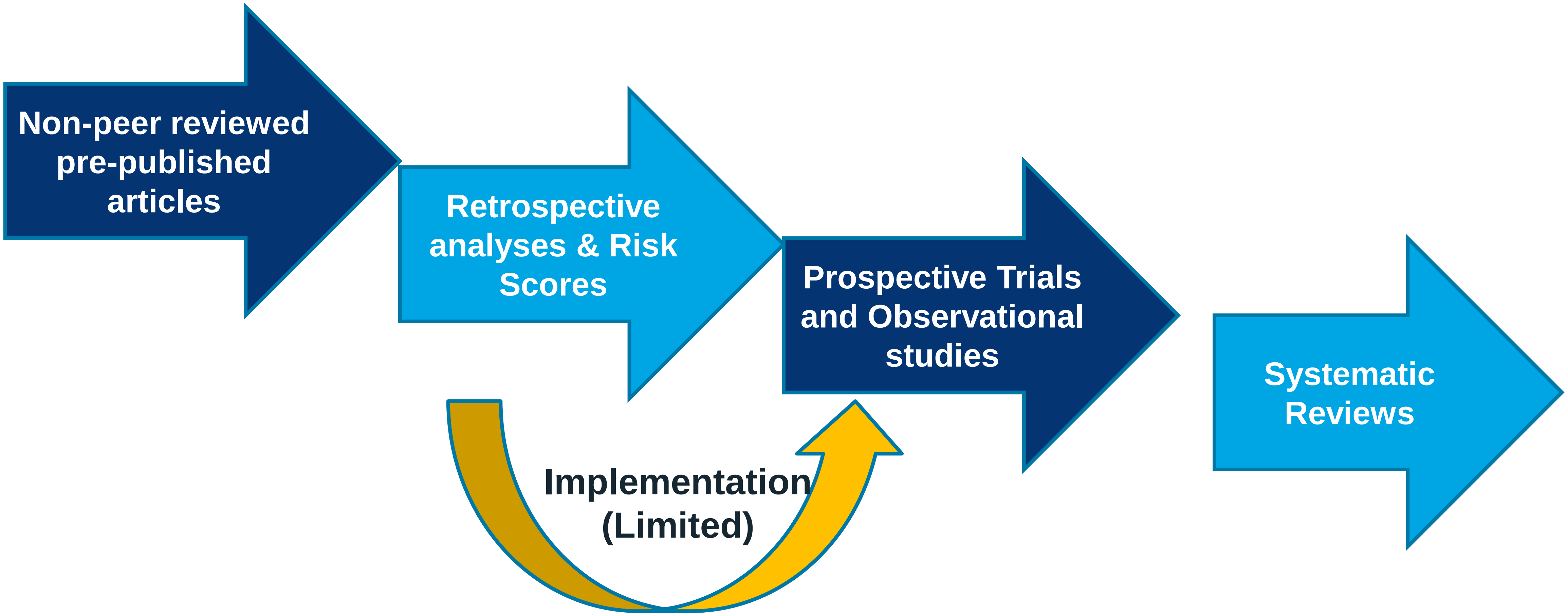
Cases	Deaths	Hospitalizations	Vaccinations
New Cases (Daily Avg)	New Deaths (Daily Avg)	New Admissions (Daily Avg)	% First Booster Dose
102,250	287	4,467	33.6%
Case Trends	Death Trends	Admission Trends	People Age 5+
May 2022 – Jun 2022	May 2022 – Jun 2022	May 2022 – Jun 2022	
Total Cases	Total Deaths	Current Hospitalizations	Total First Booster Dose
86,787,443	1,011,013	25,621	105,093,591

CDC | Data as of: June 25, 2022 1:50 PM ET. Posted: June 25, 2022 2:50 PM ET

Today's Discussion:

- Impact of COVID-19 on people with diabetes
  - Epidemiology
  - Outcomes of COVID-19 in patients with diabetes
  - Perspective on long term outcomes
- Understanding the pathophysiology of COVID-19 in diabetes
- Management of patients with diabetes in COVID-19
  - Acute Care
  - Ambulatory Care

COVID-19 data sources:
Rapid evolution in 24 months



Impact of COVID-19 on People with Diabetes

Hyperglycemia and Diabetes:
Is There a Link to Disease Severity?

- Diabetes has been identified as contributor in patients with Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS)
- Several studies have demonstrated increased risk of severe complications of infection and life threating illness from SARS-CoV-2 (COVID-19)

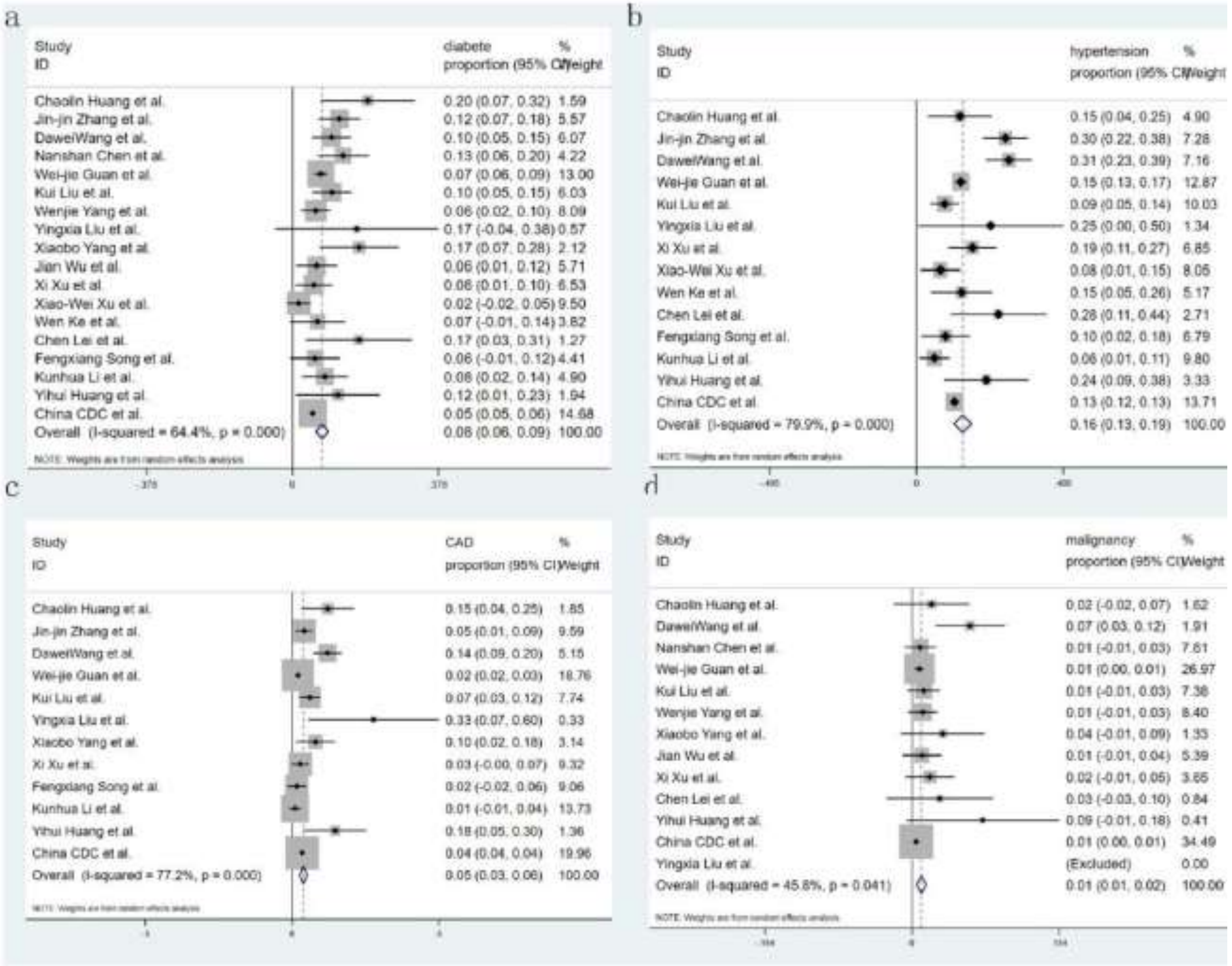
Table 2
Prevalence of non-severe versus severe COVID-19 in patients with diabetes.

Study	n	DM (n, %)	Non-severe/Non-ICU care [Mild/moderate] (%)*	ICU care [Severe/Critical] (%)*	p value between non-severe vs. severe COVID-19	Ref.
Liu et al.	61	5 (8.2%)	4.5%	17.6%	0.094	[16]
Guan et al.	1099	81 (7.4%)	5.7%	16.2%	NR	[17]
Wang et al.	138	14 (10.1%)	5.9%	22.2%	0.009	[20]
Wu et al.	201	22 (10.9%)	5.1%	19.0%	0.002	[24]
Zhang et al.	140	17 (12.1%)	11.0%	13.8%	0.615	[22]
Huang et al.	41	8 (15%)	8.0%	25.0%	0.16	[18]
CDC COVID-19 Response Team, USA	7162	784 (10.9%)	9.4%	32.0%	NR	[15]

DM-diabetes mellitus, NR-not reported, ICU- intensive care unit, Ref. References, CDC- Centers for Disease Control and Prevention. * % is calculated from total population having either Non-severe or Severe COVID-19 infection.

Yang JK et al. Diabet Med. 2006 Jun;23(6):623-8
Yang JK et al. Acta Diabetol. 2010 Sep;47(3):193-9
Bornstein SR et al.Nat Rev Endocrinol. 2020 Apr 2.
Singh AK et al. Metab Syndr 2020 Apr 9; 14(4):303-310

Prevalence of Diabetes and COVID-19



Meta-analysis 21 studies (n=47,344)

Hypertension and diabetes were most prevalent comorbidities

Hu Y et al. Clin Virol. 2020 Jun;127:104371.

Factors Associated with Poor Prognosis

Table 3—Univariable and multivariable logistic regression for risk factors associated with in-hospital death and poor prognosis in all patients with COVID-19 and in patients with diabetes and COVID-19

	All patients				Patients with diabetes			
	Risk factors associated with in-hospital death		Risk factors associated with poor prognosis*		Risk factors associated with in-hospital death		Risk factors associated with poor prognosis*	
	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value	Univariable OR (95% CI)	*P* value
Age, years	1.10 (1.08, 1.12)	<0.001	1.04 (1.03, 1.05)	<0.001	1.08 (1.03, 1.13)	0.001	1.03 (1.00, 1.06)	0.103
Sex, female vs. male	0.38 (0.24, 0.61)	<0.001	0.46 (0.35, 0.60)	<0.001	0.40 (0.16, 0.96)	0.041	0.36 (0.17, 0.77)	0.009
Diabetes	2.51 (1.53, 4.13)	<0.001	2.21 (1.50, 3.26)	<0.001	NA†	NA†	NA†	NA†
Hypertension	3.48 (2.24, 5.40)	<0.001	2.50 (1.86, 3.37)	<0.001	1.21 (0.50, 2.96)	0.673	1.25 (0.60, 2.61)	0.554
Cardiovascular disease	8.29 (5.02, 13.68)	<0.001	3.63 (2.17, 6.07)	<0.001	3.75 (1.48, 9.48)	0.005	3.59 (1.16, 11.06)	0.026
Chronic kidney disease	13.91 (7.23, 26.80)	<0.001	7.23 (2.82, 18.57)	<0.001	4.14 (1.37, 12.45)	0.012	8.08 (1.03, 63.29)	0.047
Chronic lung disease	4.38 (1.74, 11.03)	0.002	2.48 (0.96, 6.40)	0.060	NA‡	NA‡	NA‡	NA‡
Nervous system disease	19.14 (10.38, 35.30)	<0.001	7.63 (3.23, 18.06)	<0.001	10.79 (3.62, 32.14)	<0.001	9.40 (1.21, 73.10)	0.032
White blood cells, $\times 10^9$/L	1.17 (1.10, 1.25)	<0.001	1.10 (1.04, 1.16)	<0.001	1.39 (1.17, 1.65)	<0.001	1.07 (0.945, 1.23)	0.319
Neutrophils, $\times 10^9$/L	1.26 (1.19, 1.34)	<0.001	1.17 (1.10, 1.24)	<0.001	1.42 (1.19, 1.69)	<0.001	1.15 (0.97, 1.35)	0.105
Lymphocytes, $\times 10^9$/L	0.27 (0.17, 0.44)	<0.001	0.42 (0.34, 0.54)	<0.001	0.78 (0.37, 1.65)	0.520	0.48 (0.26, 0.86)	0.015
Albumin, g/L	0.82 (0.78, 0.86)	<0.001	0.91 (0.88, 0.93)	<0.001	0.91 (0.83, 1.00)	0.057	0.88 (0.80, 1.00)	0.003
ALT, units/L	1.00 (1.00, 1.00)	0.179	1.00 (1.00, 1.00)	0.404	1.00 (0.95, 1.01)	0.194	1.00 (0.98, 1.01)	0.603
AST, units/L	1.01 (1.00, 1.02)	0.031	1.01 (1.01, 1.02)	<0.001	1.01 (0.98, 1.03)	0.592	1.01 (0.98, 1.03)	0.657
LDH, units/L	1.00 (1.00, 1.01)	<0.001	1.01 (1.01, 1.01)	<0.001	1.00 (1.00, 1.01)	0.034	1.00 (1.00, 1.01)	0.248
Urea, mmol/L	1.16 (1.11, 1.21)	<0.001	1.14 (1.08, 1.21)	<0.001	1.07 (1.01, 1.14)	0.034	1.25 (1.07, 1.46)	0.005
Creatinine, μmol/L	1.00 (1.00, 1.00)	<0.001	1.01 (1.00, 1.01)	0.011	1.00 (1.00, 1.00)	0.613	1.01 (1.00, 1.02)	0.056
Creatine kinase, units/L	1.00 (1.00, 1.00)	0.014	1.00 (1.00, 1.00)	0.058	1.00 (1.00, 1.01)	0.325	1.00 (1.00, 1.00)	0.764
Glucose, mmol/L	1.16 (1.09, 1.24)	<0.001	1.17 (1.10, 1.25)	<0.001	1.05 (0.97, 1.14)	0.257	1.04 (0.96, 1.13)	0.330
CRP, mg/dL	1.22 (1.16, 1.28)	<0.001	1.29 (1.22, 1.37)	<0.001	1.02 (1.01, 1.04)	0.013	1.01 (0.99, 1.03)	0.324
D-dimer, mg/L	1.02 (1.01, 1.04)	0.007	1.06 (1.01, 1.10)	0.008	1.00 (0.97, 1.03)	0.852	1.00 (0.98, 1.03)	0.789
	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value	Multivariable OR (95% CI)	*P* value
Age, years	1.09 (1.07, 1.12)	<0.001	1.02 (1.01, 1.03)	<0.001	1.09 (1.04, 1.15)	0.001	1.02 (0.99, 1.05)	0.249
Albumin, g/L	0.91 (0.86, 0.97)	0.006	0.98 (0.95, 1.02)	0.302	0.94 (0.84, 1.05)	0.288	0.91 (0.83, 0.99)	0.030
Creatinine, μmol/L	1.00 (1.00, 1.00)	0.001	1.00 (1.00, 1.01)	0.064	1.00 (1.00, 1.00)	0.468	1.01 (1.00, 1.02)	0.154
CRP, mg/dL	1.14 (1.08, 1.21)	<0.001	1.20 (1.13, 1.28)	<0.001	1.12 (1.00, 1.24)	0.043	1.16 (1.01, 1.32)	0.033
Glucose, mmol/L	1.08 (1.01, 1.16)	0.033	1.06 (1.00, 1.13)	0.072	1.07 (0.97, 1.17)	0.181	1.06 (0.96, 1.17)	0.242

Among all patients with COVID-19, 92 (26 of whom had diabetes) died in the hospital; 473 (93 of whom had diabetes) had a poor prognosis. Laboratory findings tested in no more than half of the total cases were not included in regression models in order to avoid possible bias. Age, albumin, creatinine, CRP, and glucose were chosen as variables for the multivariate analysis of all patients with COVID-19 and all patients with diabetes and COVID-19. $P <$ 0.05 was considered significant. ALT, alanine aminotransferase; NA, not available. *Poor prognosis included progression to severe or critical illness, and in-hospital death. †No available result because diabetes is not included in the regression model for patients with diabetes and COVID-19. ‡No available result because only two patients with diabetes had chronic lung disease.

Wuhan, China

Retrospective (n=904)

- Older patients
- Male sex
- Comorbidities:
  - Diabetes Mellitus
  - Hypertension
  - Cardiovascular Disease
  - Chronic Kidney Disease

Chen Y et al. Diabetes Care. 2020 Jul;43(7):1399-1407

Patients with Diabetes Hospitalized for COVID-19: *The Early Data*

Table 1 The characteristics of patients with severe covid-19 with or without diabetes

	Total (n=193)	Diabetes (n=48)	Non-diabetes (n=145)	
	Number (%)	Number (%)	Number (%)	*P* value*
Age, median (IQR), years	64 (49 to 73)	70 (62 to 77)	60 (43 to 71)	<0.001
Sex				
Male	114 (59.1)	33 (68.8)	81 (55.9)	0.115
Female	79 (40.9)	15 (31.3)	64 (44.1)	
Symptoms				
Fever	173 (89.6)	43 (89.6)	130 (89.7)	0.989
Cough	135 (69.9)	37 (77.1)	98 (67.6)	0.214
Dyspnea	115 (59.6)	33 (68.8)	82 (56.6)	0.136
Pectoralgia	10 (5.2)	1 (2.1)	9 (6.2)	0.458
Diarrhea	51 (26.4)	10 (20.8)	41 (28.3)	0.311
Nausea	14 (7.3)	2 (4.2)	12 (8.3)	0.528
Vomiting	5 (2.6)	2 (4.2)	3 (2.1)	0.788
Anorexia	68 (35.2)	21 (43.8)	47 (32.4)	0.154
Headache	21 (10.9)	5 (10.4)	16 (11.0)	0.905
Fatigue	101 (52.3)	28 (58.3)	73 (50.3)	0.337
Comorbidities	94 (48.7)	29 (60.4)	65 (44.8)	0.061
Hypertension	73 (37.8)	24 (50.0)	49 (33.8)	0.045
Cardiovascular disease	31 (16.1)	13 (27.1)	18 (12.4)	0.016
Cerebrovascular disease	8 (4.1)	5 (10.4)	3 (2.1)	0.036
Chronic kidney disease	4 (2.1)	0 (0.0)	4 (2.8)	0.574
Chronic pulmonary disease	14 (7.3)	4 (8.3)	10 (6.9)	0.739
Chronic liver disease	1 (0.5)	0 (0.0)	1 (0.7)	1.000
Exposure to disease	76 (39.4)	17 (35.4)	59 (40.7)	0.517
ICU patients	92 (47.7)	32 (66.7)	60 (41.4)	0.002
Mechanical ventilation treatment†	110 (57.0)	39 (81.3)	71 (49.0)	<0.001
Length of hospital stay, median (IQR), days	13 (7 to 16)	10 (6 to 13)	13 (9 to 18)	0.001
Mortality	108 (56.0)	39 (81.3)	69 (47.6)	<0.001

- Single center, retrospective observational study
- Tongji hospital, Wuhan, China
- Patients with diabetes vs. non-diabetes:
  - Intensive care unit (ICU) admission (66.7% vs 41.4%); p 0.002
  - Mechanical ventilation (81.3% vs 49.0%): p<0.001
  - Mortality (81.3% vs. 47.6%); p<0.001

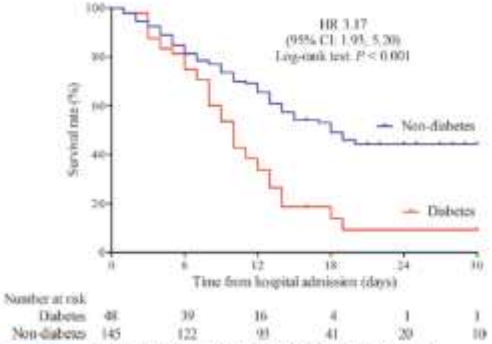
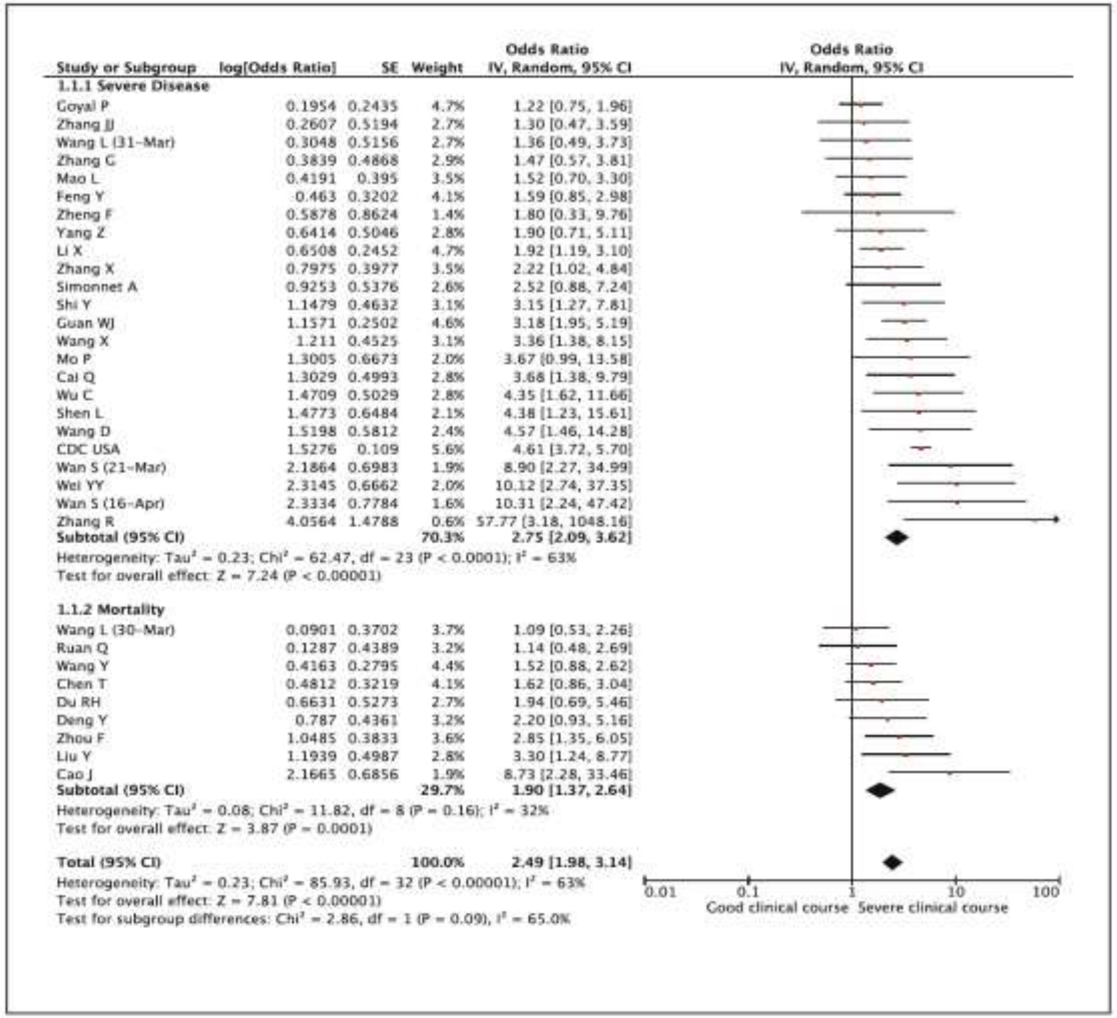


Figure 1 Kaplan-Meier survival curve for patients with severe covid-19 with and without diabetes.

Yan Y et al.BMJ Open Diabetes Res Care. 2020 Apr;8(1):e001343

Patients with Diabetes Hospitalized for COVID-19: *Similar Trends Worldwide*



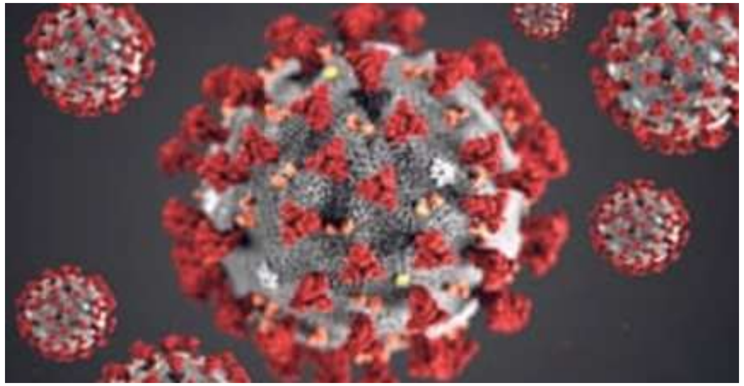
Meta-Analysis (n=16,003)
February 7,2020-April 17, 2020
33 centers: China, USA, France

- Diabetes is associated with 2-fold increase in mortality and severe COVID-19 infection
- Similar findings in other studies (Yang et al)
- 2.12-fold increase in mortality
- 2.4-fold increase in severe COVID infection
- 4.6-fold increase in ARDS
- 3.3 increase in disease progression from mild to severe illness

Yan Y et al. BMJ Open Diabetes Res Care. 2020
Yang J, et al. J Infect Dis. 2020 May;94:91-95.

COVID-19 and People with Diabetes

- Are there any factors in patients with diabetes that can predict poor prognosis?
  - Type of diabetes
  - Duration of diabetes
  - Long term glycemic control (HbA1c)
  - Diabetes-relates complications
  - Medications used for glycemic control
  - Glycemic control at time of COVID-19 infection



- High variability: 5.3%-58%
- Varied by country

Prevalence in Early Studies

First author	n	Smokers, %	HTN, %	Diabetes, %	CVD, %	COPD, %	CKD, %	CLD, %
COVID-19 in China								
Liu et al.	61	6.6	19.7	8.2	1.6	8.2	NR	NR
Guan et al.	1099	12.6	15.0	7.4	3.8	1.1	0.7	NR
Huang et al.	41	7.3	14.6	19.5	15.0	2.4	NR	2.4
Chen et al.	99	NR	NR	12.1	40.0	1.0	NR	NR
Wang et al.	138	NR	31.2	10.1	19.6	2.9	2.9	2.9
Zhou et al.	191	6.0	30	19.0	8.0#	3.0	1.0	NR
Zhang et al.	140	NR	30	12.1	8.6	1.4	1.4	NR
Yang et al.	52	4.0	NR	17.0	23.0	8.0	NR	NR
Wu et al.	201	NR	19.4	10.9	4.0	2.5	1.0	3.5
Guo et al.	187	9.6	32.6	15.0	11.2#	2.1	3.2	NR
Liu et al.	137	NR	9.5	10.2	7.3	1.5	NR	NR
Chen et al.	274	7.0%	34.0	17.0	8.0	7.0	1.0	NR
CCDCP, *China*	20,982	NR	12.8	5.3	4.2	2.4	NR	NR
COVID-19 in Italy								
Onder et al.	355	NR	NR	35.5	42.5	NR	NR	NR
Covid-19 surveillance group, Italy	481*	NR	73.8	33.9	30.1#	13.7	20.2	3.7
COVID-19 in USA								
Bhatraju et al.	24	22	NR	58.0	NR	4.0	21.0	NR
CDC COVID-19 Response Team, USA	7162	3.6	NR	10.9	9.0	9.2	3.0	0.6

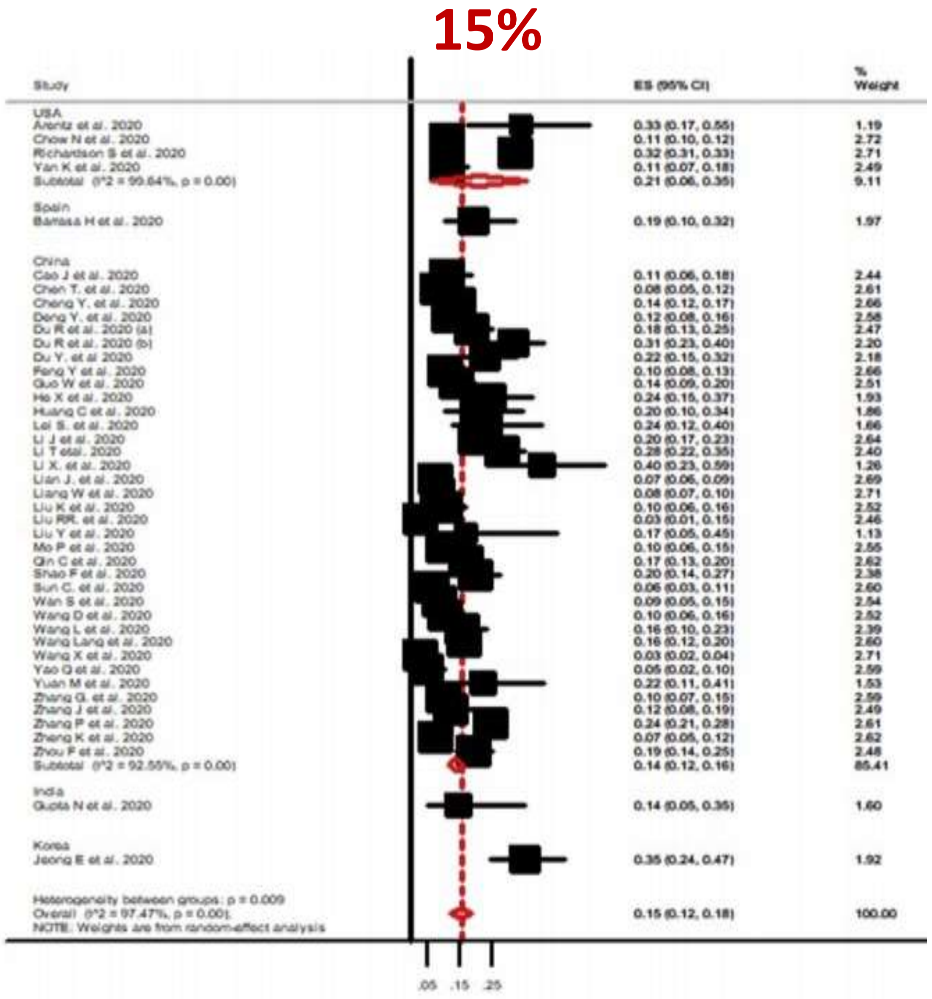
- High variability: 5.3%-58%
- Varied by country

reported coronary heart disease only, * COVID-19 patients who died, HTN- hypertension, CVD-cardiovascular disease, COPD-chronic obstructive pulmonary disease, CKD chronic kidney disease, CLD-chronic liver disease, NR-not reported, Ref.- references, CCDCP- Chinese Center for Disease Control and Prevention, CDC- Centers for Disease Control and Prevention.

Singh AK, et al. Diabetes Metab Syndr. 2020 Jul-Aug;14(4):303-310.

A Closer look: Diabetes Was Not Clearly Over-Represented Among *All* COVID-19 Infections

- 43 studies US, Spain, China, India, Korea
- 23,007 patients
- 15% Prevalence of Diabetes with COVID-19 (95% CI: 12%-18%), P≤0.0001
- May be similar to the prevalence of diabetes in these populations
- 1.61% Risk of Mortality (95% CI: 1.16-2.25%), P = 0.005
- 1.88% Risk of ICU Admission (1.20%–2.93%), P = 0.006



Hussain S, et al. Diabetes Metab Syndr. 2020 Nov-Dec;14(6):1595-1602.

Diabetes *is* Overrepresented Among Severe Infections and Death

State	Attribute	Condition Group	Condition	Month	Year
United States	COVID-19 Deaths	Diabetes	Diabetes	All	All

Month in which death occurred	Conditions contributing to deaths where COVID-19 was listed on the death certificate [1]	All Ages	0-24 years	25-34 years	35-44 years	45-54 years	55-64 years	65-74 years	75-84 years	85+ years
April 2021	Diabetes	149	0	1	0	8	25	41	48	26
March 2021	Diabetes	2,433	2	13	47	196	435	768	634	338
February 2021	Diabetes	6,894	4	21	146	441	1,221	2,075	1,882	1,104
January 2021	Diabetes	15,609	14	97	287	924	2,488	4,411	4,533	2,855
December 2020	Diabetes	15,173	13	66	258	842	2,270	4,091	4,490	3,142
November 2020	Diabetes	8,565	9	32	131	420	1,174	2,295	2,576	1,928
October 2020	Diabetes	3,983	3	24	72	208	594	1,046	1,184	852
September 2020	Diabetes	3,040	6	16	63	216	508	860	799	572
August 2020	Diabetes	5,552	7	38	133	382	954	1,522	1,524	992
July 2020	Diabetes	6,446	17	46	182	477	1,200	1,760	1,658	1,106
June 2020	Diabetes	3,118	3	31	76	257	535	858	749	609
May 2020	Diabetes	5,603	6	28	113	346	814	1,474	1,499	1,323
April 2020	Diabetes	9,402	13	58	181	606	1,494	2,533	2,581	1,936
March 2020	Diabetes	1,036	4	12	43	102	202	272	252	149
February 2020	Diabetes	5	0	0	1	0	1	2	0	1
January 2020	Diabetes	0	0	0	0	0	0	0	0	0

Diabetes contributed to **16% (87,008)** of U.S. COVID-19 **Deaths**

Jan 2020 - April 11, 2021

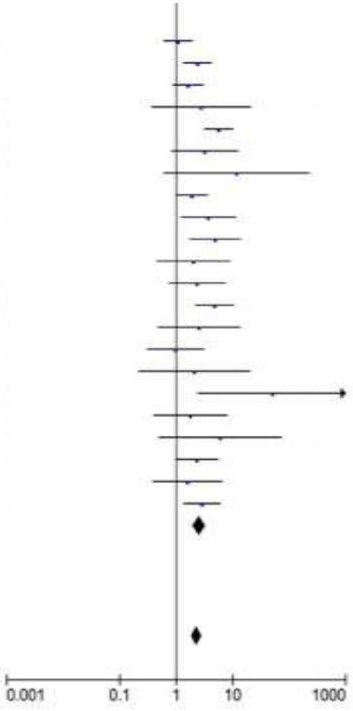
https://www.cdc.gov/nchs/nvss/vsrr/covid_weekly/index.htm#Comorbidities

Diabetes and COVID-19: Outcomes

Meta-analysis of 47 Studies

Increased Severity/Critical Illness

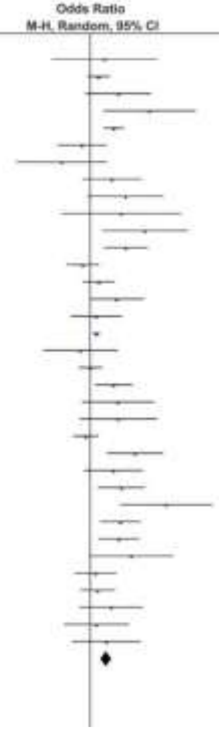
Study or Subgroup	Events	Total	Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.2 Diabetic events: Mortal/Non-Survival vs. Survival/Alive						
Auld Sara et al., 2020	29	62	66	147	3.2%	1.08 [0.59, 1.96]
Chen Ruchong et al., 2020	20	103	41	445	3.2%	2.37 [1.32, 4.26]
Chen Tao et al., 2020	24	113	23	161	3.1%	1.62 [0.86, 3.04]
Crespo Marta et al., 2020	5	8	3	8	0.8%	2.78 [0.37, 21.03]
Guan Wei-Jie et al., 2020	18	67	63	1032	3.2%	5.65 [3.11, 10.27]
Guo Weina et al., 2020	4	9	33	165	1.4%	3.20 [0.81, 12.58]
Guo Weina et al., 2020 (No Other Comorbidities)	4	4	20	46	0.4%	11.63 [0.59, 228.61]
Luo Xiaomin et al., 2020	18	84	27	214	3.0%	1.89 [0.98, 3.65]
Ma Simin et al., 2020	13	44	5	49	1.8%	3.69 [1.19, 11.41]
Wang Kun et al., 2020 (Training Cohort)	6	19	24	277	2.0%	4.87 [1.70, 13.96]
Wang Kun et al., 2020 (Validation Cohort)	4	14	5	30	1.3%	2.00 [0.44, 9.01]
Wu Chaomin et al., 2020	11	44	5	40	1.8%	2.33 [0.73, 7.44]
Yan Yongli et al., 2020	39	108	9	85	2.6%	4.77 [2.16, 10.57]
Yang Xiaobo et al., 2020	7	32	2	20	1.1%	2.52 [0.47, 13.58]
Yang Xiaobo et al., 2020 (Hyperglycemia)	11	32	7	20	1.8%	0.97 [0.30, 3.14]
Yao Qingchun et al., 2020	1	12	4	96	0.7%	2.09 [0.21, 20.42]
Yuan Mingli et al., 2020	6	10	0	17	0.4%	50.56 [2.38, 1075.32]
Zangrillo Alberto et al., 2020	3	17	6	56	1.3%	1.79 [0.40, 8.06]
Zhang Jinping et al., 2020	3	8	1	11	0.6%	6.00 [0.49, 73.45]
Zhang Yang et al., 2020	13	24	48	142	2.4%	2.31 [0.96, 5.55]
Zhang Yang et al., 2020 (Hyperglycemia)	3	11	18	94	1.4%	1.58 [0.38, 6.57]
Zhou Fei et al., 2020	17	54	19	137	2.7%	2.85 [1.35, 6.05]
Subtotal (95% CI)		**879**		**3292**	**40.1%**	**2.52 [1.93, 3.30]**
Total events	259		429			
Heterogeneity: Tau² = 0.11; Chi² = 30.60, df = 21 (P = 0.08); I² = 31%						
Test for overall effect: Z = 6.79 (P < 0.00001)						
Total (95% CI)		**3773**		**9495**	**100.0%**	**2.32 [1.90, 2.83]**
Total events	1009		1360			
Heterogeneity: Tau² = 0.23; Chi² = 123.66, df = 56 (P < 0.00001); I² = 55%						
Test for overall effect: Z = 8.30 (P < 0.00001)						
Test for subgroup differences: Chi² = 0.53, df = 1 (P = 0.47), I² = 0%						



HR 2.20

Decreased Survival

Study or Subgroup	Severe/Mortal Events	Severe/Mortal Total	Non-Severe/Alive Events	Non-Severe/Alive Total	Weight	Odds Ratio M-H, Random, 95% CI
1.1.1 Diabetic events: Severe/Critical vs. Non-Severe						
Chen Guang et al., 2020	2	11	1	10	0.5%	2.00 [0.15, 26.19]
Chen Ruchong et al., 2020	28	203	33	345	3.4%	1.51 [0.88, 2.59]
Duan Jun et al., 2020	2	20	9	328	1.1%	3.94 [0.79, 19.59]
Gao Yong et al., 2020	6	15	1	28	0.7%	18.00 [1.90, 170.34]
Guan Wei-Jie et al., 2020	28	173	53	926	3.5%	3.18 [1.95, 5.19]
Guo Ting et al., 2020	4	20	23	85	1.7%	0.67 [0.20, 2.23]
Huang Chaolin et al., 2020	1	13	7	28	0.7%	0.25 [0.03, 2.28]
Liu Fengjun et al., 2020	3	19	7	115	1.3%	2.89 [0.68, 12.34]
Liu Jiang et al., 2020	4	13	2	27	0.9%	5.56 [0.86, 35.71]
Liu Tao et al., 2020	11	69	0	11	0.4%	4.52 [0.25, 82.27]
Liu Yanli et al., 2020	11	53	1	56	0.8%	14.40 [1.79, 116.01]
Lu Hongzhou et al., 2020	6	22	15	243	2.0%	5.70 [1.95, 16.68]
Lv Zhihua et al., 2020	9	115	26	239	2.6%	0.70 [0.31, 1.54]
Mao Ling et al., 2020	15	88	15	126	2.7%	1.52 [0.70, 3.30]
Mo Pingzheng et al., 2020	12	85	3	70	1.5%	3.67 [0.99, 13.58]
Peng Youdong et al., 2020	4	16	19	96	1.6%	1.35 [0.39, 4.66]
Petrilli Christopher et al., 2020	389	990	561	1739	4.4%	1.36 [1.16, 1.60]
Rastrelli Giulia et al., 2020	2	10	6	21	0.9%	0.63 [0.10, 3.84]
Shang Weifeng et al., 2020	20	139	43	304	3.3%	1.02 [0.58, 1.81]
Shi Yu et al., 2020	7	49	22	438	2.3%	3.15 [1.27, 7.81]
Smadja David et al., 2020	6	20	2	20	1.0%	3.86 [0.67, 22.11]
Sun Ying et al., 2020	3	19	2	44	0.9%	3.94 [0.60, 25.79]
Tian Jianbo et al., 2020	33	148	22	84	3.1%	0.81 [0.43, 1.51]
Wan Suxin et al., 2020	9	40	3	95	1.4%	8.90 [2.27, 34.99]
Wang Chang-Zheng et al., 2020	7	39	3	46	1.4%	3.14 [0.75, 13.07]
Wang Dawei et al., 2020	8	36	6	102	1.8%	4.57 [1.46, 14.28]
Wang Zhongliang et al., 2020	6	14	1	55	0.7%	40.50 [4.30, 381.74]
Wu Chaomin et al., 2020	16	84	6	117	2.1%	4.35 [1.62, 11.66]
Yang Qiuxiang et al., 2020	10	33	10	103	2.1%	4.04 [1.51, 10.86]
Yao Qingchun et al., 2020	2	13	2	83	0.8%	7.36 [0.94, 57.70]
Zhang Jin-Jin et al., 2020	8	58	9	82	2.1%	1.30 [0.47, 3.59]
Zhang Yang et al., 2020	52	136	9	30	2.5%	1.44 [0.61, 3.39]
Zhang Yang et al., 2020 (Hyperglycemia)	19	84	2	21	1.2%	2.78 [0.59, 13.01]
Zheng Yi et al., 2020	4	15	4	19	1.2%	1.36 [0.28, 6.68]
Zheng Yongli et al., 2020	3	32	3	67	1.1%	2.21 [0.42, 11.60]
Subtotal (95% CI)		**2894**		**6203**	**58.9%**	**2.20 [1.69, 2.86]**
Total events	750		831			
Heterogeneity: Tau² = 0.26; Chi² = 80.72, df = 34 (P < 0.0001); I² = 58%						
Test for overall effect: Z = 5.82 (P < 0.00001)						



HR 2.32

Varikasuvu SR, et al. Prim Care Diabetes. 2021 Feb;15(1):24-27.

Predictors of Severe Disease in People with Diabetes Mellitus

- Older Age (>70 years)
- Male Sex
- Non-white ethnic groups
- Hypertension
- Cardiovascular Disease
- Chronic Kidney Disease
- Obesity

Chen Y, et al. *Diabetes Care.* 2020 Jul;43(7):1399-1407.

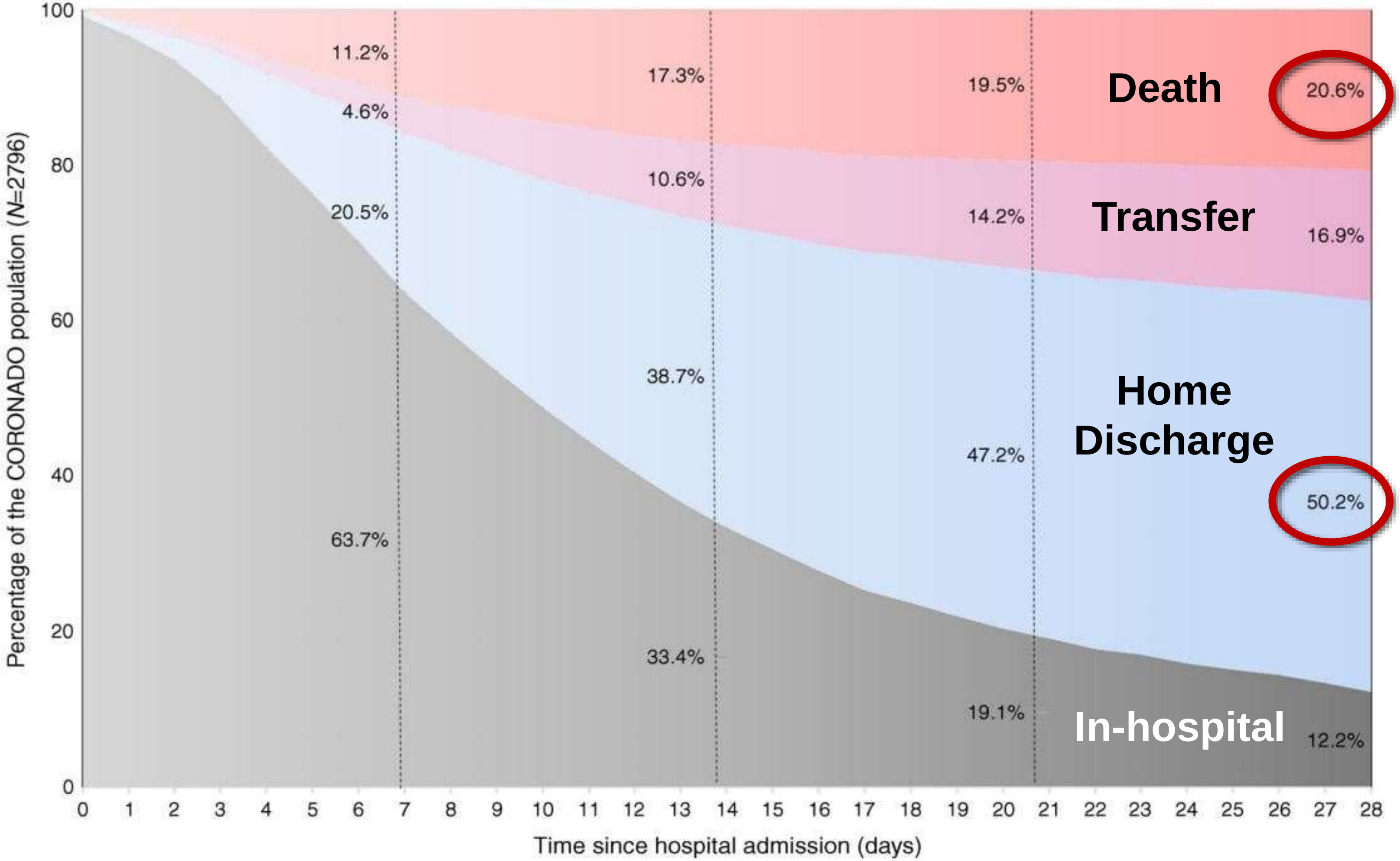
Apicella M, et al. *Lancet Diabetes Endocrinol.* 2020 Sep;8(9):782-792.

Characteristics of Hospitalized Patients with COVID-19 and Diabetes

- Coronavirus SARS-CoV-2 & Diabetes Outcomes (CORONADO) Study (interim analysis-phenotypic characteristics)
  - French multicenter observational study of hospitalized patients with Diabetes Mellitus (DM) and COVID-19 (n=1317)
  - Primary outcome: tracheal intubation for mechanical ventilation and/or death within 7 days of admission
    - Male sex: 64.9%
  - Mean age: 69.8 ± 13.0 yeas
  - Median body mass index (BMI): 28.4 (25-75%ile 25-32.7 kg/m2)
- Diabetes Type:
  - Type 2 diabetes (88.5%)
  - Type 1 diabetes (3.0%)
  - Other (5.4%)
  - Newly diagnosed (3.8%)
- Mean hemoglobin A1c (HbA1c): 8.1% ± 1.9%
- Microvascular complications (46.8%)
- Macrovascular complications (40.8%)

Cariou B, et al. Diabetologia. 2020 Aug;63(8):1500-1515.

Updated CORONADO



- N = 2796
  - 63.7% men
  - 69.7 years, mean age
  - 28.4 kg/m2 median BMI
- Median hospital length of stay:
  - 9 days (5-14 days)
- Death
  - 11.2% within 7 days
  - 20.6% within 28 days

Wargny M, et al. *Diabetologia.* 2021 Apr;64(4):778-794.

Updated CORONADO

CORONADO
CORONAVIRUS SARS-COV2 & DIABETES OUTCOMES

- Factors associated with HIGHER chance of discharge:
  - Metformin
  - Dipeptidyl peptidase 4 (DPP-4) inhibitors
  - Longer time between symptom onset and hospital admission
- Factors associated with LOWER chance of discharge:
  - Insulin
  - Diuretics
  - Beta blockers
  - Anticoagulation therapy

Wargny M, et al. *Diabetologia.* 2021 Apr;64(4):778-794.

Medications on Admission and Outcome

CORONADO
CORONAVIRUS SARS-COV2 & DIABETES OUTCOMES

Clinical features	Number of people with available data	All	Primary outcome ($n = 382$) OR (95% CI)	Death ($n = 140$) OR (95% CI)
Comorbidities				
Heart failure	1206	140/1206 (11.6)	0.78 (0.52, 1.17)	2.28 (1.42, 3.66)
NAFLD or liver cirrhosis	1107	119/1107 (10.7)	1.23 (0.81, 1.86)	0.70 (0.34, 1.41)
Active cancer	1282	194/1282 (15.1)	1.08 (0.77, 1.50)	1.55 (0.99, 2.42)
COPD	1278	133/1278 (10.4)	0.96 (0.64, 1.43)	1.36 (0.80, 2.32)
Treated OSA	1189	144/1189 (12.1)	1.44 (0.99, 2.08)	1.81 (1.12, 2.93)
Organ graft	1302	38/1302 (2.9)	1.14 (0.57, 2.28)	0.46 (0.11, 1.93)
End stage renal failure	831	60/831 (7.2)	0.66 (0.35, 1.27)	0.62 (0.24, 1.60)
Routine treatment before admission				
Metformin	1317	746/1317 (56.6)	0.95 (0.75, 1.21)	0.59 (0.42, 0.84)
Sulfonylurea/glinides	1317	367/1317 (27.9)	1.03 (0.79, 1.34)	0.74 (0.49, 1.13)
DPP-4 inhibitors	1317	285/1317 (21.6)	1.01 (0.75, 1.34)	0.85 (0.55, 1.32)
GLP1-RA	1317	123/1317 (9.3)	1.36 (0.92, 2.01)	0.64 (0.32, 1.29)
Insulin	1317	504/1317 (38.3)	1.01 (0.79, 1.29)	1.71 (1.20, 2.43)
Loop diuretics	1317	252/1317 (19.1)	1.10 (0.81, 1.48)	2.49 (1.70, 3.64)
Thiazide diuretics	1317	267/1317 (20.3)	1.08 (0.81, 1.45)	0.98 (0.63, 1.52)
Potassium-sparing diuretics	1317	59/1317 (4.5)	1.17 (0.67, 2.05)	1.77 (0.88, 3.58)
MRA	1317	53/1317 (4.0)	0.96 (0.52, 1.78)	2.03 (1.00, 4.13)
β-blockers	1317	442/1317 (33.6)	1.03 (0.80, 1.32)	1.84 (1.29, 2.62)
ACE inhibitors	1317	354/1317 (26.9)	1.17 (0.90, 1.52)	1.43 (0.99, 2.08)
ARBs	1317	389/1317 (29.5)	1.22 (0.94, 1.57)	1.15 (0.79, 1.67)
ARBs and/or ACE inhibitors	1317	737/1317 (56.0)	1.32 (1.03, 1.68)	1.58 (1.09, 2.28)
ARBs and/or ACE inhibitors and/or MRA	1317	752/1317 (57.1)	1.29 (1.01, 1.65)	1.67 (1.15, 2.43)

- No association with:
  - Angiotensin receptor blockers (ARBs)
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Magnetic Resonance Angiography (MRA)
- Insulin found to be associated with a higher risk of death - a common finding in all diabetes epidemiology studies

Cariou B, et al. Diabetologia. 2020 Aug;63(8):1500-1515.

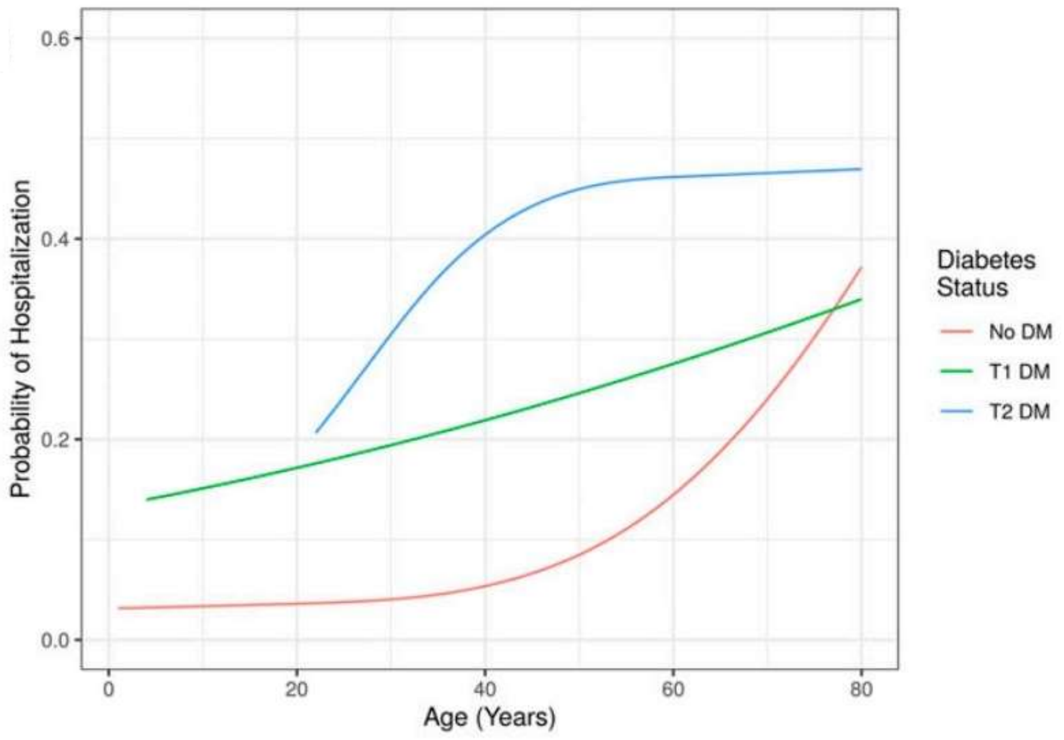
Metformin and Reduced Mortality in a *Diverse* Population With COVID-19 and Diabetes

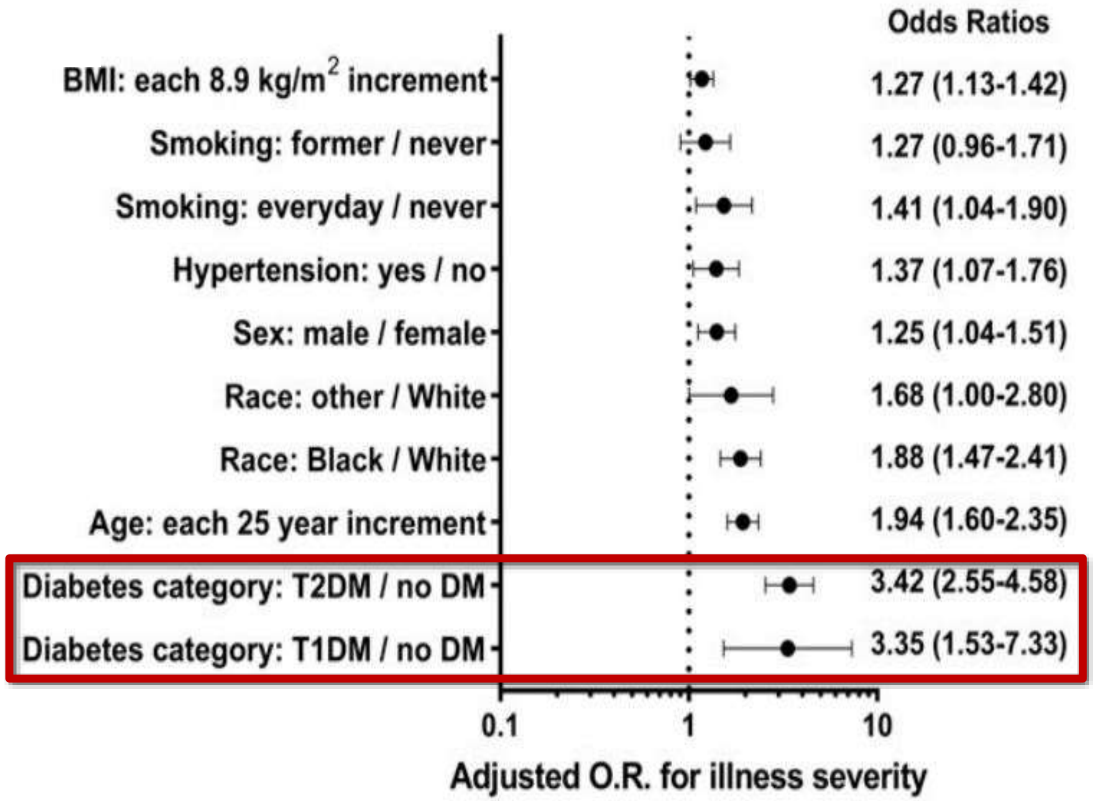
- N= 25,326 subjects tested for COVID-19 between 2/25/20 and 6/22/20 at the University of Alabama at Birmingham Hospital
- Risk of COVID-19 infection
  - Black/African American (OR 2.6; 95% CI 2.19–3.10; p<0.0001)
  - Obesity (OR 1.93; 95% CI 1.64–2.28; p<0.0001)
  - Hypertension (OR 2.46; 95% CI 2.07–2.93; p<0.0001)
- Diabetes (OR 2.11; 95% CI 1.78–2.48; p<0.0001).
- Mortality
  - Diabetes: OR 3.62; 95% CI 2.11–6.2; p<0.0001 *independent after adjustment*
  - Metformin treatment prior to diagnosis of COVID-19 was independently associated with a significant reduction in mortality in subjects with diabetes and COVID-19 (OR 0.33; 95% CI 0.13–0.84; p=0.0210).
- OR = Odds ratio

Crouse AB, et al. Front Endocrinol (Lausanne). 2021 Jan 13;11:600439.

Type 1 vs. Type 2 Diabetes and COVID-19

High risk of hospitalization and severe illness with T1D as T2D





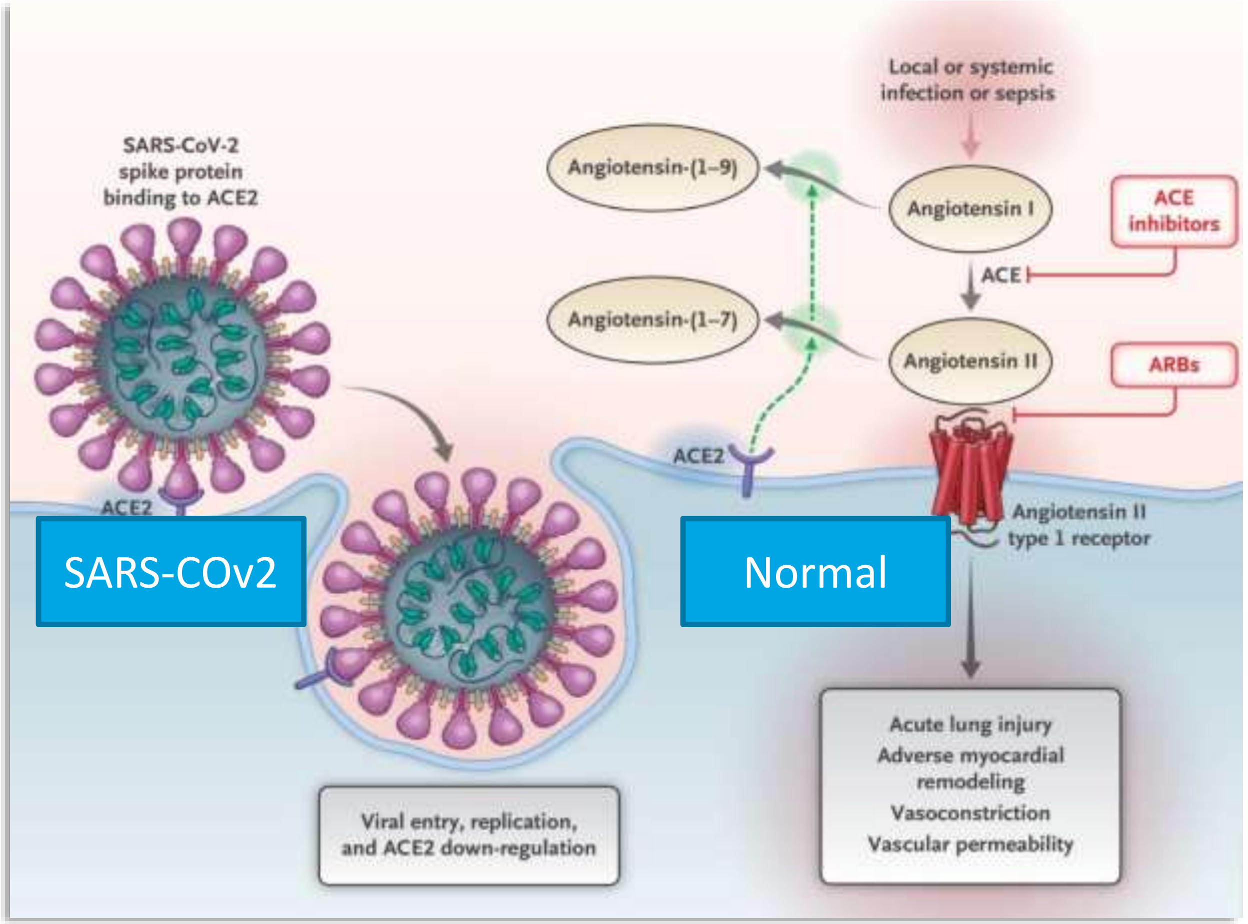
Gregory JM, et al. Diabetes Care. 2021 Feb;44(2):526-532.

Pathophysiology of COVID-19 in Diabetes

Angiotensin-Converting Enzyme 2 (ACE2) Receptor Common Pathway

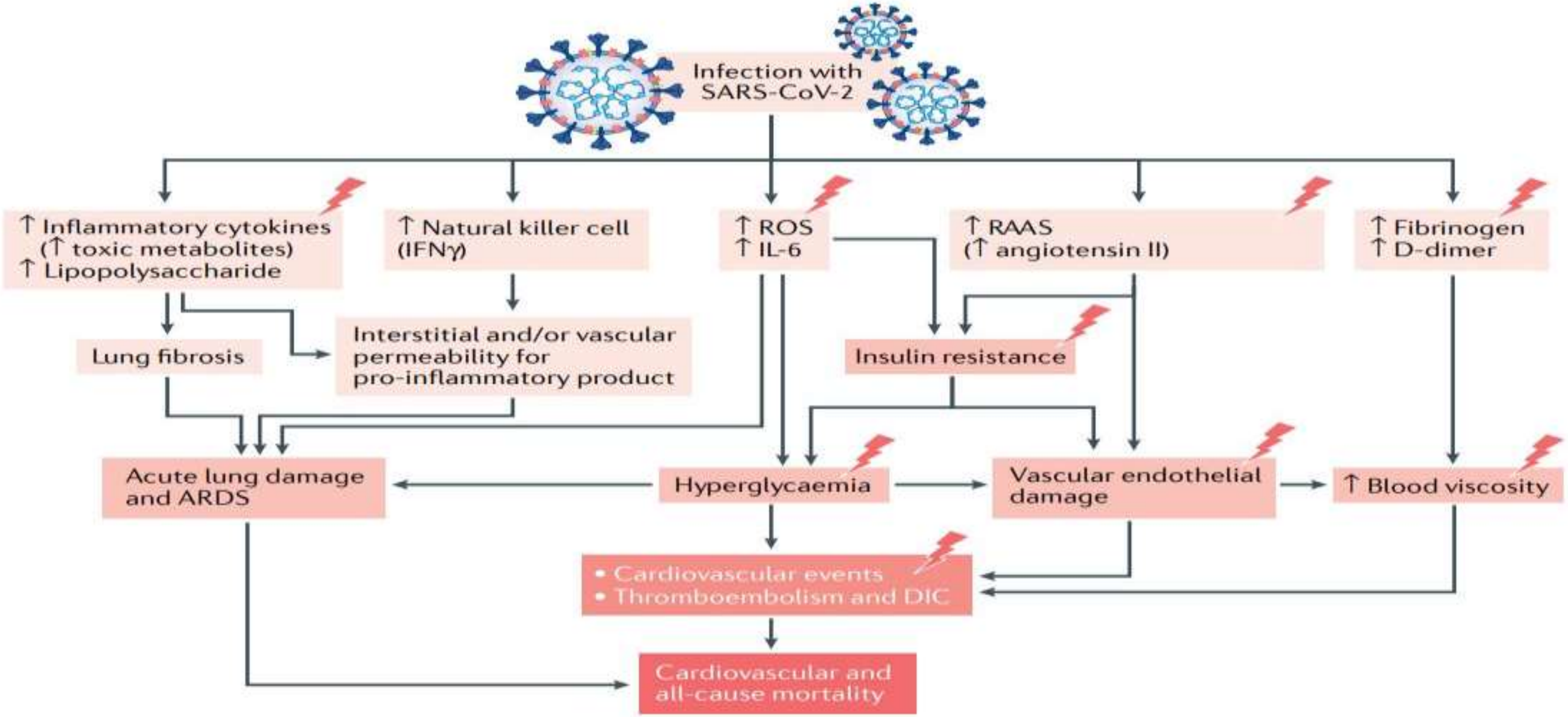
ACE2 receptors:

- Lungs
- Heart
- Blood vessels
- Kidneys
- Liver
- Gastrointestinal tract
- Beta cell



Vaduganathan M, et al. *N Engl J Med*. 2020 Apr 23;382(17):1653-1659.

Cascade in COVID-19

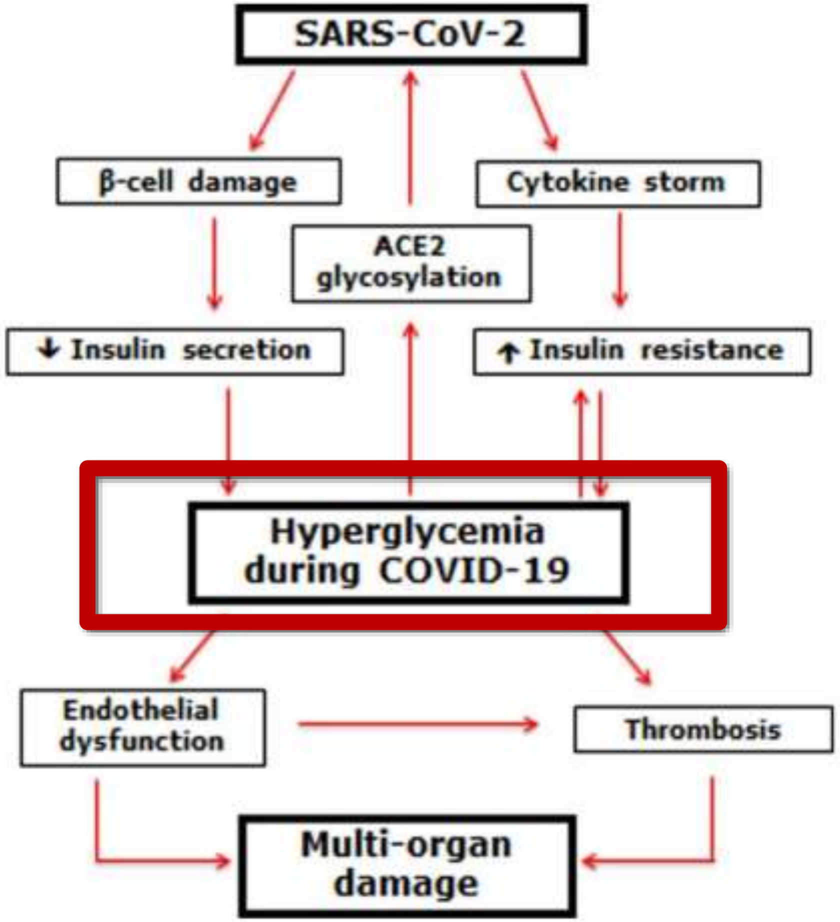


Lightening bolts = accentuated mechanisms

Lim S, Bae JH, Kwon HS, Nauck MA. Nat Rev Endocrinol. 2021 Jan;17(1):11-30.

Focus on Diabetes: Proposed Mechanisms of Harm

New onset diabetes?



Caballero AE, McDonnell ME, et al. J Diabetes Complications. 2020 Sep;34(9):107671.

Does SARS CoV-2 Impair/Destroy Pancreatic Beta Cells?

- Overall, this is *unclear*
- There is no virus known to directly cause permanent β cell damage
- SARS-***CoV-1*** was reported to bind to ACE2 receptor in the islets causes damage, insulinopenia and diabetes[2] and the ACE2 Receptor appears to be common to SARS-CoV-1 and SARS-CoV-2
- While ACE2 has not been consistently identified on β cells, other receptors for SARS-CoV-2 have been identified as well, transmembrane protease serine subfamily (TMPRSS) and Neuropilin 1 (NRP1) co-receptor
- Could the receptors be induced in beta (β) cells in COVID-19? *Possibly*

1. Yang JK, et al. *Diabet Med*. 2006 Jun;23(6):623-8.
2. Yang JK, et al. *Acta Diabetol*. 2010 Sep;47(3):193-9.

Can COVID-19 Cause Diabetes?

- Not the result of a single event but a combination of disease susceptibility due to chronic disease, plus a COVID-19 specific mechanism(s).
- ANY inflammatory state can cause insulin resistance, increased hepatic glucose production through counter-regulatory hormones, release of cytokines and lipids, and impair glucose uptake in the periphery.
- High prevalence of diabetic ketoacidosis (DKA) is concerning for actual β cell impairment but requires CAREFUL scrutiny
  - Likely multifactorial
  - β cell function is impaired by cytokine storm, possible prothrombotic state (vasculature), and hyperglycemia itself

Accili, D. Can COVID-19 cause diabetes?. Nat Metab 3, 123–125 (2021).

COVID-19 Related Diabetes Registry

This Project

is a joint initiative of

KING'S College LONDON

MONASH University

FUNDERS

Organisations that provided funds to support the CoviDiab Registry

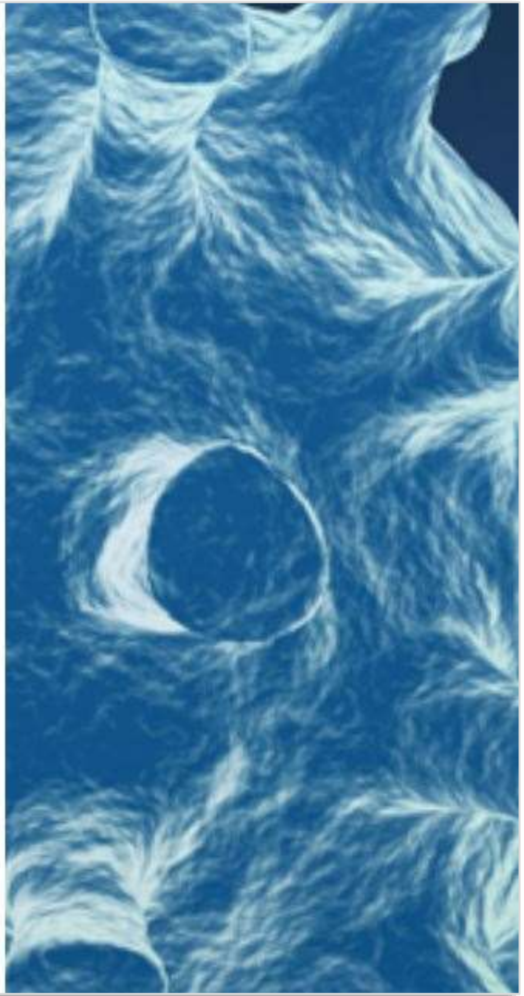
Funders →

PRIVACY NOTICE

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).

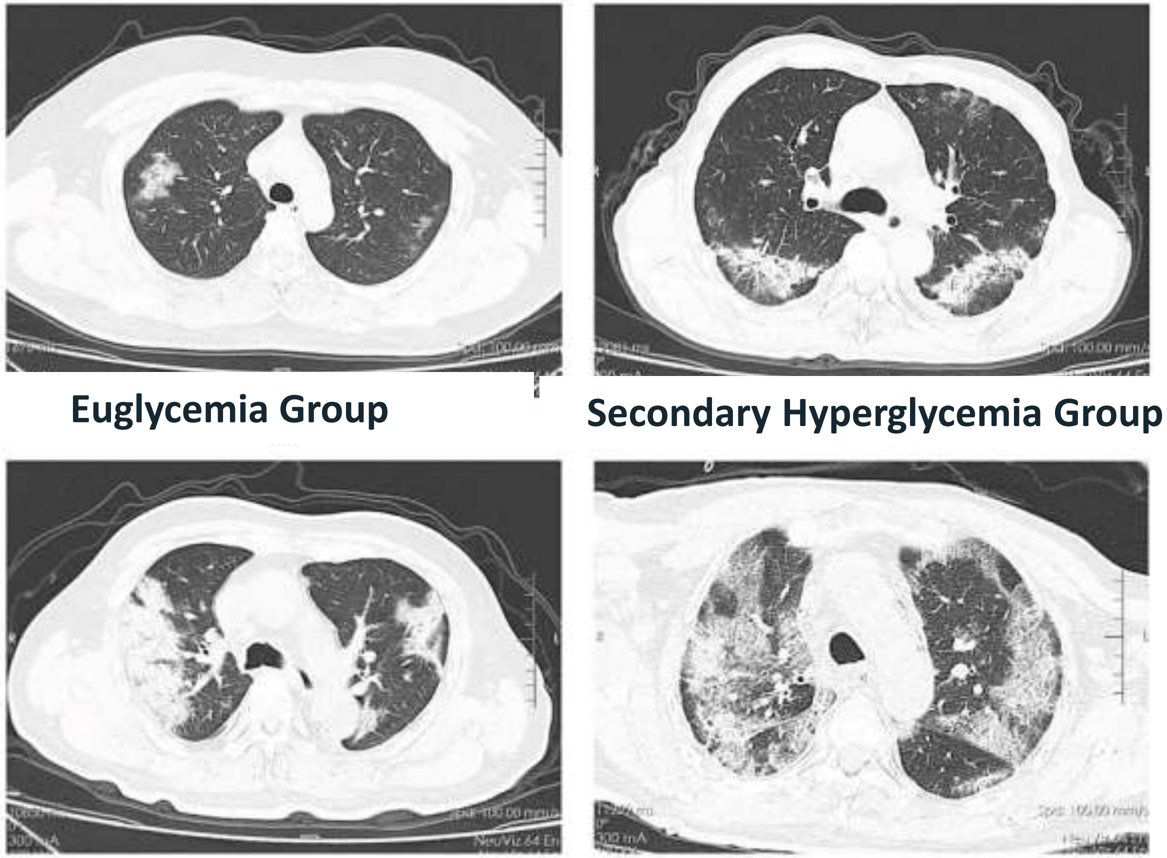
Given the very short history of human contact with COVID-19, this registry will rapidly help us understand how COVID-19 related diabetes develops, its natural history and its best management. Studying COVID-19-related diabetes may also uncover novel mechanisms of disease.



http://covidiab.e-dendrite.com

Pulmonary Disease: More Severe in Diabetes

Typical CT Images of the Patients in Three Groups

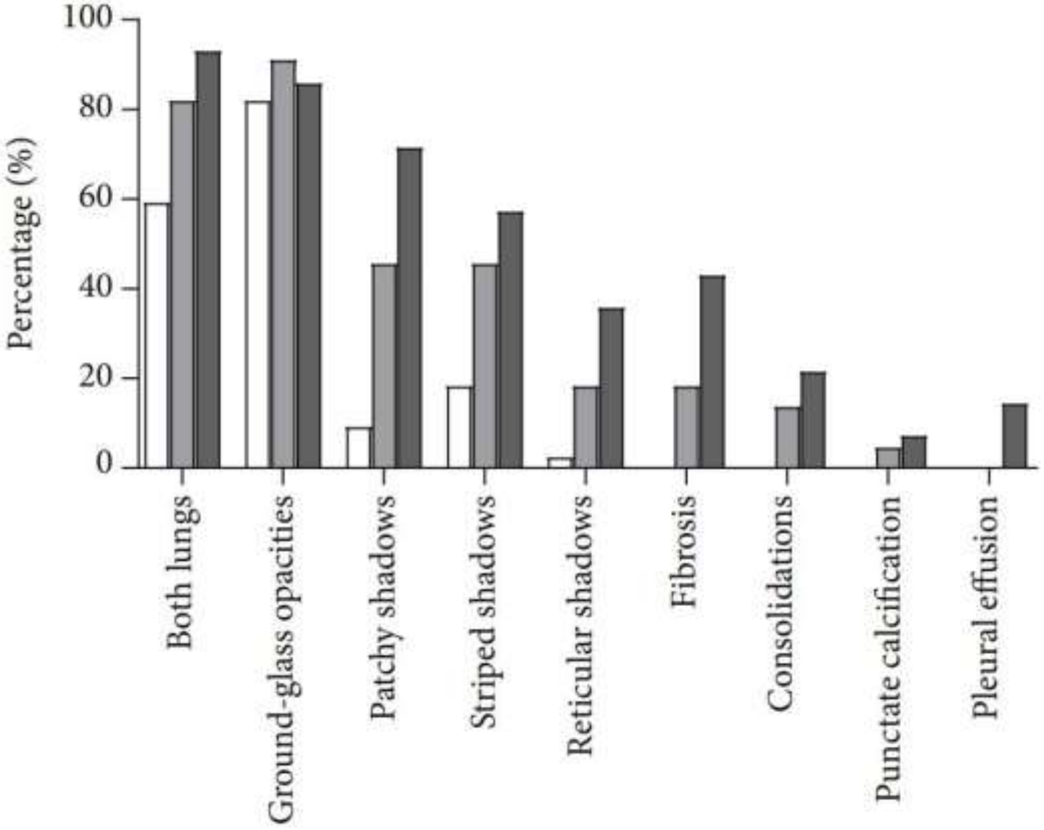


Euglycemia Group

Secondary Hyperglycemia Group

Diabetes Group

Frequency of Evaluated CT Imaging Features in Three Groups



Zhou W, et al. J Diabetes Res. 2020 Aug 24; Article ID 3918723.

Lab Findings in Diabetes: (vs. Euglycemia or Secondary Hyperglycemia)

- Higher inflammatory markers
  - High-sensitivity C-reactive protein (hs-CRP)
  - Lactate dehydrogenase (LDH)
  - Interleukin-6 (IL-6)
- Lower CD4, CD8, CD4/CD8 and CD3 cell counts
- No difference in:
  - Lymphocyte/neutrophil counts, Procalcitonin (PCT), Creatinine, blood urea nitrogen (BUN), Liver function tests (LFTs or LFs), erythrocyte sedimentation rate (ESR), D-Dimer, Creatine kinase (CK/CK-MB), high-sensitivity troponin I (hsTnI), Prothrombin Time (PT) and Partial Thromboplastin Time (PTT)

No Surprise: Admission Glucose Does Predict Disease Severity

Meta-analysis of 35 Studies[1] 14,502 patients

- Non-linear relationship between admission FBG and severity (Pnon-linearity < 0.001), where each 1 mmol/L (18 mg/dL) increase augmented the risk of severity by 33% (risk ratio 1.33 [95% CI: 1.26-1.40])

605 Patients WITHOUT Previous Diagnosis of Diabetes

- FBG ≥126 mg/dL (HR 2.30 [95% CI 1.49, 3.55]) independent predictors for 28-day mortality
- OR for 28-day in-hospital complications:
  - FBG ≥126 mg/dL vs <100 mg/dL: OR 3.99 (95% CI 2.71, 5.88)
  - FBG 110 mg/dL-125 mg/dL vs 100 mg/dL: OR 2.61 (95% CI 1.64, 4.41)

Lazarus G, et al. *Diabetes Res Clin Pract*. 2021 Jan;171:108561.
Wang S, et al. *Diabetologia.* 2020 Oct;63(10):2102-2111.

Surprise? Long-term Glycemic Control May Not Predict COVID-19 Severity

Retrospective cohort study, New York City
2020: March 11- May 7 (n=1126)

Mortality odds ratios of preadmission clinical characteristics in hospitalized patients with DM and COVID-19

	Unadjusted OR	Unadjusted 95% CI	Adjusted OR*	Adjusted 95% CI*
Glycemic control: HbA_{1c}‡	1.02	0.96, 1.08	1.01	0.94, 1.09
Treatment regimen (Ref: no treatment)				
Noninsulin only	1.45	1.00, 2.10	1.30	0.89, 1.91
Insulin + noninsulin	1.68	1.15, 2.45	1.74	1.13, 2.68
Insulin only	1.98	1.20, 3.26	2.30	1.32, 4.01
Comorbidity or long-term diabetes complication				
Hypertension	0.84	0.44, 1.58	0.54	0.28, 1.05
Cardiovascular disease	1.57	1.21, 2.04	1.18	0.88, 1.57
Chronic kidney disease	1.34	1.05, 1.72	1.11	0.84, 1.45
Chronic obstructive pulmonary disease	1.63	1.16, 2.29	1.46	1.02, 2.08

HbA1c did not predict in-hospital mortality in *NYC*

Agarwal S, et al. Diabetes Care. 2020 Oct;43(10):2339-2344.

Prognostic Factors of Inpatients with COVID-19 and Diabetes

CORONADO
CORONAVIRUS SARS-COV2 & DIABETES OUTCOMES

France

- Primary Outcome: 382 patients (29%; 95% CI 26.6,31.5)
- ICU admission within 7 days: 410 patients (31.1%; 95% CI 28.6, 33.7)
- Intubation: 267 patients (20.3%; 95% CI 19.1, 22.5)

Cariou B, et al. Diabetologia. 2020 Aug;63(8):1500-1515.

Prognostic Factors of Inpatients with COVID-19 and Diabetes

CORONADO
CORONAVIRUS SARS-COV2 & DIABETES OUTCOMES

- On multivariate analyses, independent predictors for mortality were:
  - Age
  - BMI (OR 1.28 [1.10, 1.47])
  - Microvascular and macrovascular complications (OR 1.28 [1.10, 1.47])
  - OSA (OR 1.28 [1.10, 1.47])
  - Dyspnea on admission (OR 1.28 [1.10, 1.47])
  - Elevated AST (OR 1.28 [1.10, 1.47])
  - Elevated CRP (OR 1.28 [1.10, 1.47])
  - Reduced eGFR (OR 1.28 [1.10, 1.47])
  - Lymphocyte count (OR0.67 [0.50, 0.88])
  - Platelet count (OR 1.28 [1.10, 1.47])
- HbA1c did not predict in-hospital mortality in France

Cariou B, et al. *Diabetologia*. **2020 Aug**;63(8):1500-1515.

The Relationship Between Dysglycemia and Outcomes is Likely Complex

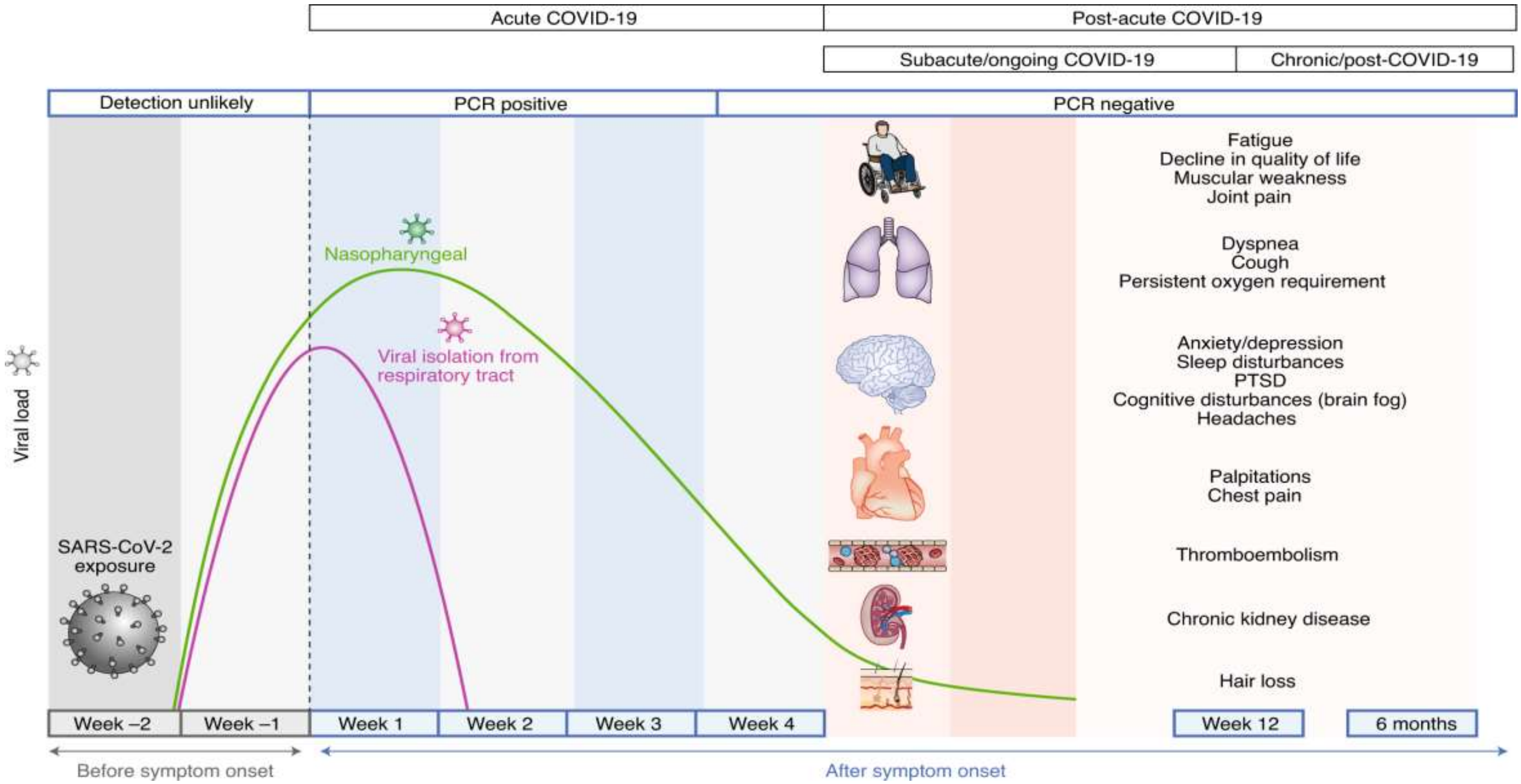
- N=5401 hospitalized people with COVID-19
- Those with discordant HbA1c and glucose (HbA1c < 6.5% and admission glucose > 180 mg/dl], were twice as likely to required mechanical ventilation than those with chronic hyperglycemia [HbA1c ≥ 6.5%, admission glucose > 180 mg/dl]
- OR** = 1.93 [95% CI 1.01 3.68]
- **adjusted for age, sex, race, ethnicity, and hemoglobin

McDonnell M for COVIDEast Consortium, Diabetes Jun 2021, 70 (Supplement 1) 175-LB; DOI: 10.2337/db21-175-LB

What About "Long COVID"?

A New Medical Condition is Born – *What's the Name?*

- Long COVID…
- Post-acute COVID-19…
- Long-term effects of COVID….
- Post-acute COVID syndrome…
- Chronic COVID…
- Long-haul COVID…
- CDC: "post-COVID conditions" consist of a lack of return to a usual state of health following acute COVID-19 illness (generally defined as 4or more weeks), and may include new or recurrent symptoms after the acute syndrome has resolved



Nalbandian A. et al. Post-acute COVID-19 syndrome. Nat Med 27, 601–615 (2021).

Prevalence and Risk of Post-COVID Conditions

- Prevalence: highly variable 5% to 80%
- Most survey data 60-90 days post acute infection:
  - 30% have specific persistent symptoms that are observable or measurable (e.g., dyspnea on exertion)
  - 70-90% report have either specific or nonspecific symptoms such as fatigue and depression
- Risk factors remain unclear
  - Persistent Immunoglobulin G (IgG) antibody seropositivity after infection
  - Severe illness during acute COVID-19 and/or requirement for care in an ICU, advanced age and the presence of organ comorbidities
  - Pre-existing respiratory disease
- Unclear if COVID-19 comorbidities increase risk (including Diabetes)

Some Good News?

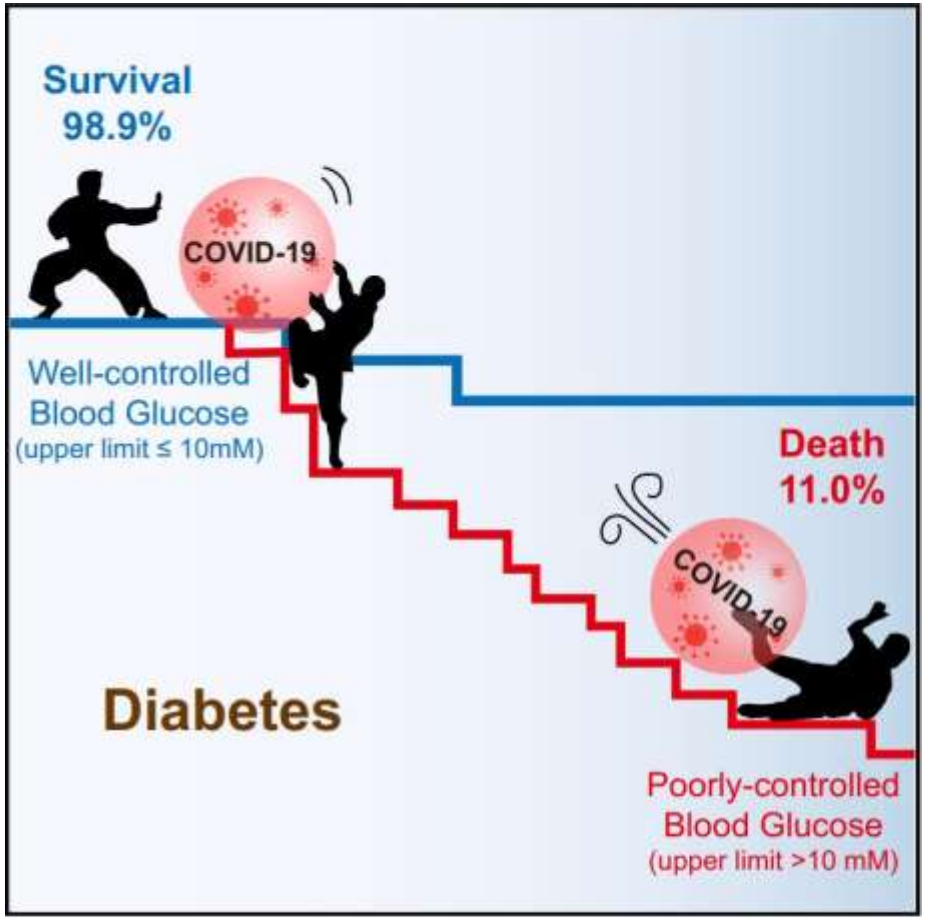
- Some diabetes patients improved due to more regular daily life activities and reduced work-related distress
  - 63 Type 1 diabetes patients, >90% using continuous glucose monitoring
  - Time in Range and Average glucose improved (165 vs. 158 mg/dl, p = 0.040)
  - Bi-hourly analysis of glucose profile showed an improvement particularly in the early morning hours.
- Weight loss following bariatric surgery protective against severe COVID
  - N=11809 people with obesity who had COVID-19
  - Prior weight loss surgery vs no surgery: 15.5% vs 28.2% for hospitalization, 9.2% vs 22.3% for need for supplemental oxygen, 3.9% vs 9.3% for severe COVID-19 infection, and 1.0% vs 3.6% for death

Aragona M, et alDiabetes Res Clin Pract. 2020 Dec;170:108468.; Aminian A, at al. JAMA Surg. 2022

Management of Patients with Diabetes and COVID-19

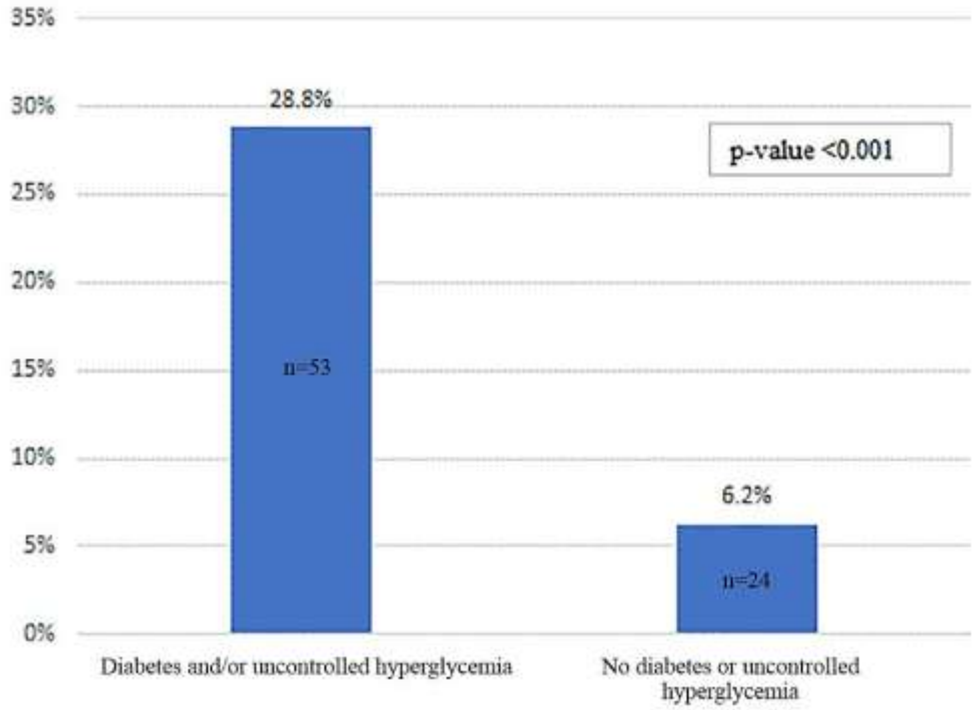
Does Glycemic Control Matter?

- Retrospective 7,337 COVD-19 with diabetes (n=952) vs. without diabetes
- Diabetes increased the need for medical interventions
- Diabetes increased the mortality risk of patients
  - 7.8% vs 2.7%; adjusted hazard ratio (HR) 1.49
- Well-controlled blood glucose (70-180 mg/dL) correlated with improved outcomes compared to uncontrolled (>180 mg/dL) adjusted HR 0.14



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

Benefits of Glycemic Control in Hospitalized Patients with COVID-19



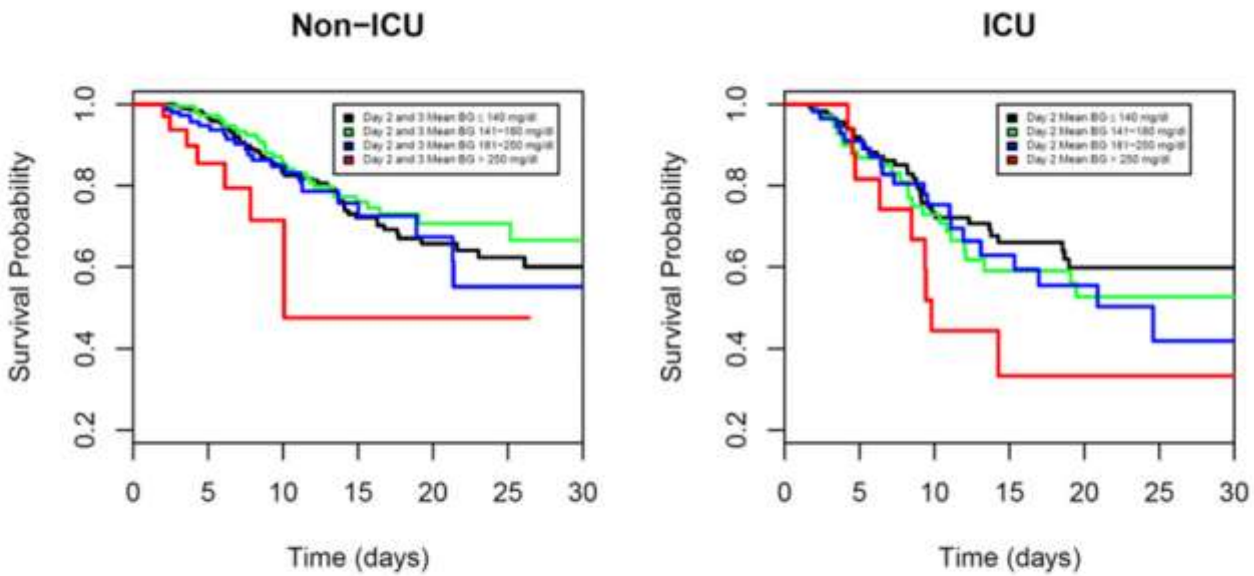
Mortality rates among patients who were discharged or died comparing diabetes and/or uncontrolled hyperglycemia (*n* = 184) with patients without diabetes or hyperglycemia (*n* = 386)

- Retrospective observational study in patients with COVID-19 with and without DM (n=1122, 88 US hospitals)
  - 451 patients with DM and/or uncontrolled hyperglycemia vs. 671 patients without DM or hyperglycemia:
    - DM HbA1c ≥ 6.5%
    - Uncontrolled hyperglycemia ≥ 2 BG > 180 mg/dL within 24h
- 28.8% vs. 6.2% Mortality Rate DM or uncontrolled hyperglycemia pts vs. without (p< 0.01)
- 5.7 vs. 4.3 Days/LOS DM or uncontrolled hyperglycemia pts vs. without (p<0.01)

Bode B, et al. J Diabetes Sci Technol. 2020 Jul;14(4):813-821.

Glycemic Control Matters: Window of Opportunity

Patients hospitalized for COVID-19 in critical care and non-critical care units
Glytec Database: 91 hospitals, 12 US states (N=1544)



BG >13.88 mmol/L (250 mg/dL) on days 2-3 was independently associated with mortality [HR] 7.17;95%CI 2.62–19.62) compared with patients with BG<7.77 mmol/L (140 mg/dL).

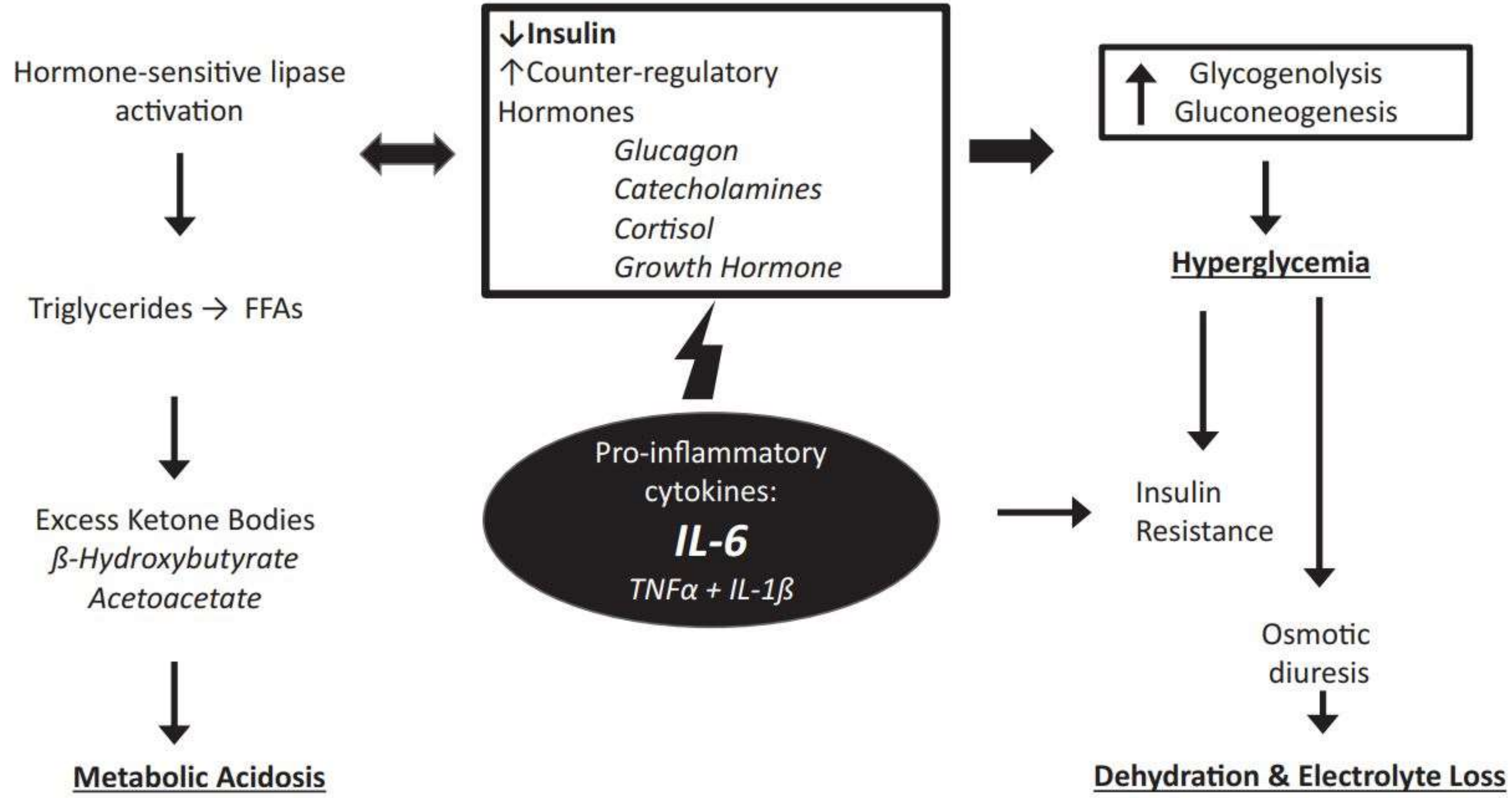
Klonoff DC et al. Diabetes Care. 2021 Feb;44(2):578-585.

Challenges in Achieving Glycemic Control with COVID-19

- Variability in insulin sensitivity over course of illness (daily and in some patients hourly)
- Patients with pre-existing chronic kidney disease (CKD) or acute kidney injury (AKI) in the setting of SARS-CoV-2 are at increased risk of hypoglycemia
- Significant variability in both subcutaneous (SC) and intravenous (IV) insulin requirements, independent of therapy with glucocorticoids and vasopressors

Korytkowski M, McDonnell ME, et al. J Clin Endocrinol Metab. 2020 Jun 4

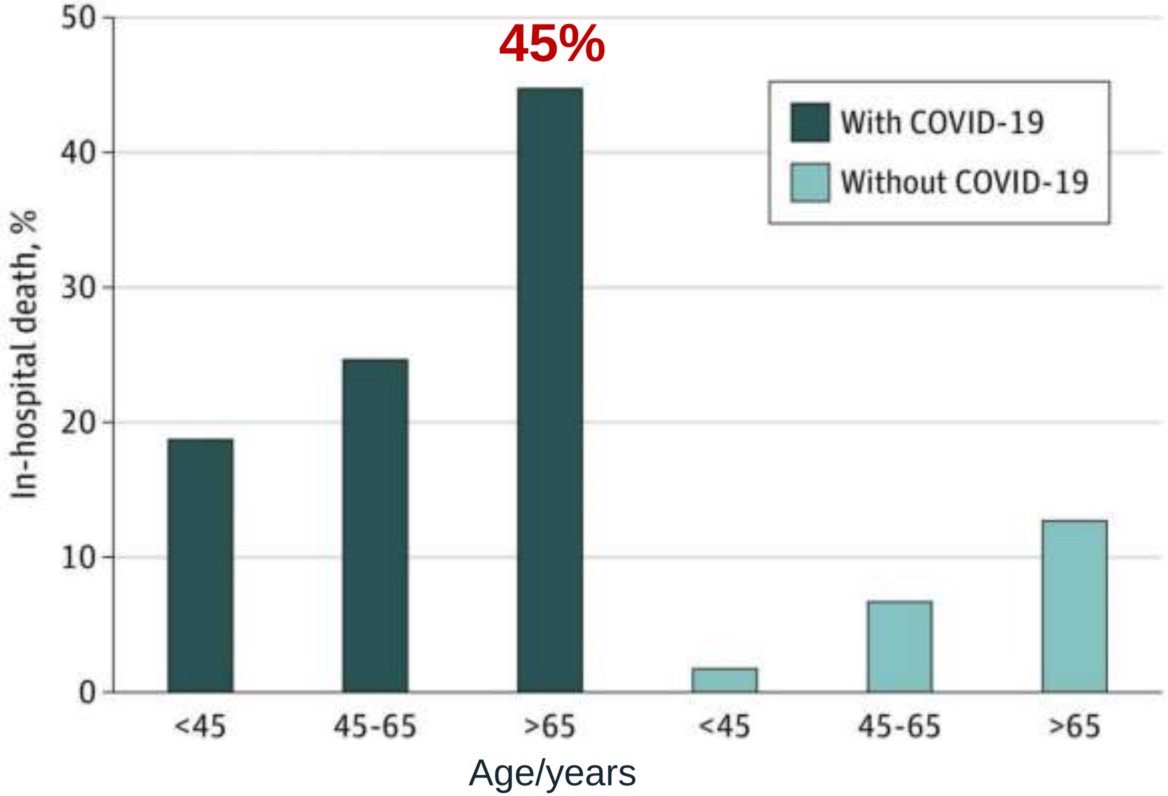
The Other Side of Cytokine Storm: Ketosis in Diabetes and COVID



Palermo NE, Sadhu AR, McDonnell ME. J Clin Endocrinol Metab. 2020 Aug 1;105(8):dgaa360.

Diabetic Ketoacidosis (DKA) and COVID-19

DKA-related mortality among patients with and without COVID-19 Across 175 US Hospitals



- 5029 patients in 175 hospitals with DKA 2/20-9/20
- 210 (4%) with COVID-19 + DKA
  - Older age
  - Higher BMI
  - Older patients with higher CVD, diabetes complications
  - Similar HbA1C, electrolytes and anion gap
  - Higher insulin requirements
  - Longer time on CII
  - Longer time to resolution of DKA

Pasquel FJ, et al. JAMA Netw Open. 2021 Mar 1;4(3):e211091.

Euglycemic DKA in the Setting of SGLT-2 Inhibitors and COVID-19

5 cases of euDKA at BWH, Boston between March 2020–May 2020

Case Details

Case	1	2	3	4	5
Age (y)	79	52	69	53	70
Sex	Male	Male	Male	Female	Female
T2DM duration (y)	17	14	Unknown	15	Unknown
BMI (kg/m^2)	28.9	28.3	30.7	24.0	32.4
Admission month	March 2020	April 2020	April 2020	April 2020	May 2020
Prior HbA1C (%, mmol/mol), (mo/y)	7.8, 62 (February 2020)	7.9, 63 (October 2018)	7.3, 56 (April 2020)	6.7, 50 (January 2020)	7.9, 63 (May 2020)
SGLT2i dose	Empagliflozin 10 mg	Empagliflozin 25 mg	Empagliflozin 10 mg	Empagliflozin 10 mg	Canagliflozin 300 mg
Insulin dose prior to DKA	none	none	none	glargine 22 units nightly	None
Potential contributors	COVID-19, cholecystitis, vomiting	COVID-19, anorexia	COVID-19, anorexia	COVID-19, anorexia	COVID-19, ischemic foot, anorexia
Plasma glucose when DKA diagnosed (mg/dL)	286	146	166	151	190
pH	7.16 (venous)	7.30 (venous)	7.31 (venous)	7.27 (arterial)	7.09 (arterial)
pco_2	22	39	43	19	40
Bicarbonate (mmol/L)	5	15	20	5	10
Lactate (mmol/L)	2.4	2.1	1.1	1.5	1.5
Anion gap	40	23	20	30	20
β-Hydroxybutyrate (mmol/L)	11.2	4.9	3.0	5.9	5.3
Creatinine (mg/dL)	1.20	0.86	0.80	0.85	0.73
eGFR (mL/min/1.73 m^2)	57	100	91	78	83
Clinical outcome	Discharged to rehabilitation facility	Died	Discharged to rehabilitation facility	Discharged home	Discharged to rehabilitation facility

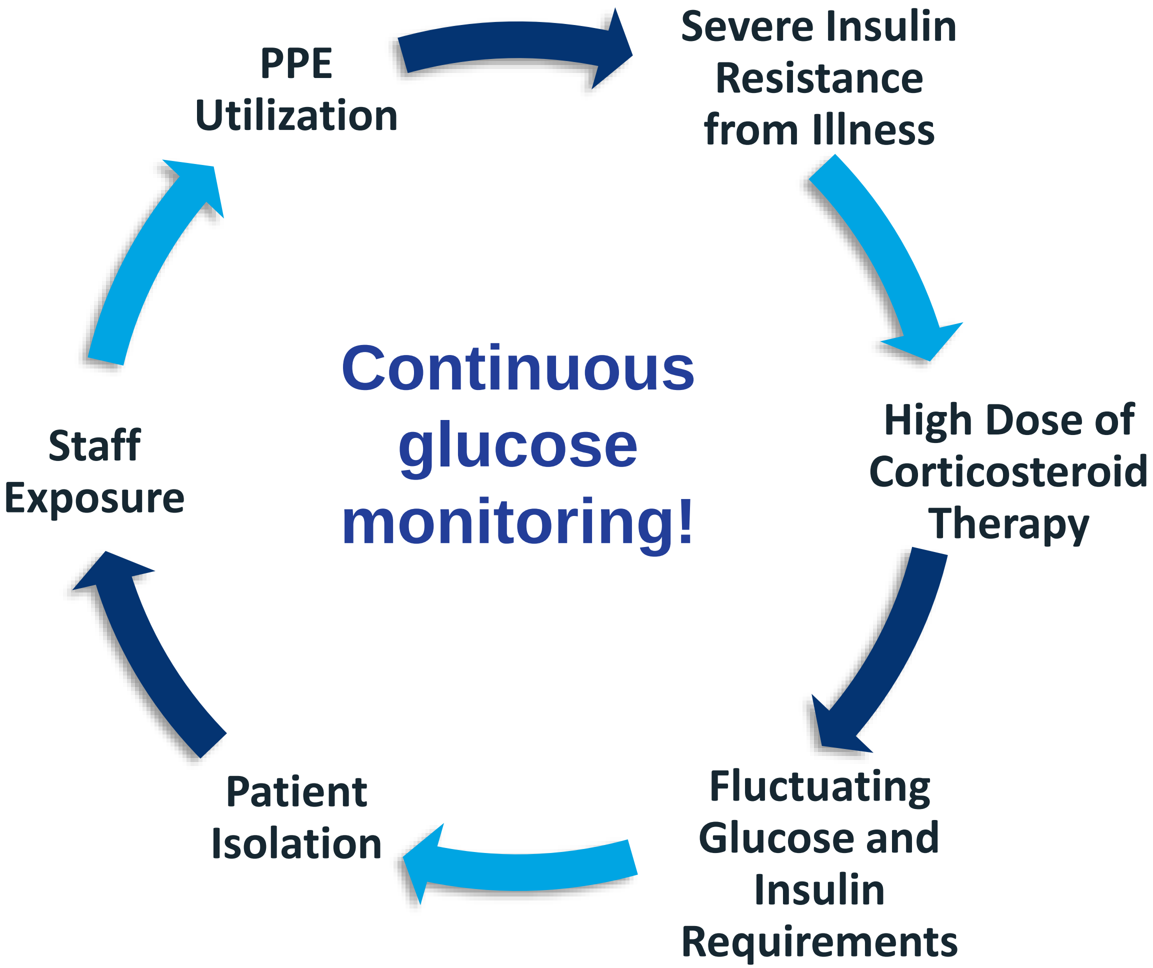
- DKA = Diabetic Ketoacidosis
- Egfr = Estimated Glomerular Filtration Rate
- Hba1c = Glycated Hemoglobin
- Sglt2i = Sodium-glucose Cotransporter-2 Inhibitors T2DM = Type 2 Diabetes Mellitus.

Vitale RJ, McDonnell ME, Palermo NE et al. AACE Clin Case Rep. 2021 Jan-Feb;7(1):10-13.

Adopting the New and Re-installing the Old

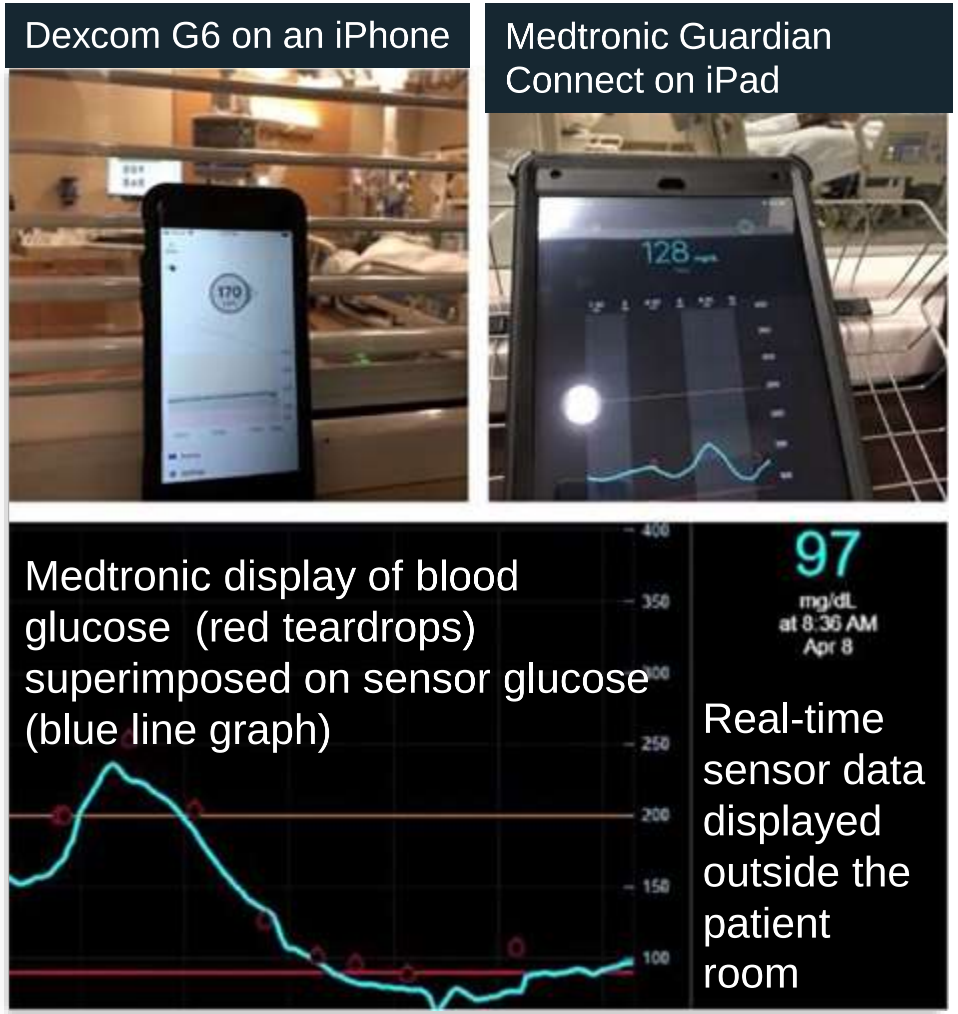
- New goals of care: Optimize glycemic control, preserve PPE, minimize time at bedside
- New guidelines on management were rapidly developed and shared
  - BWH COVID-19 Protocol 2020 https://covidprotocols.org/protocols/endocrine/
- Reminders of evidence-based practice: Subcutaneous insulin for DKA
  - Palermo NE, Sadhu AR, McDonnell ME. Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. J Clin Endocrinol Metab. 2020 Aug 1;105(8)

New Challenges with COVID-19 and Diabetes



Continuous Glucose Monitoring (CGM) in Critically Ill COVID-19 Patients

- 11 ICU patients
- Dexcom G6 and Medtronic Guardian Connect
- Feasibility in the ICU
- Accuracy/Agreement with POC Glucose
- Frequency of POC - glucose monitoring
- Nursing Acceptance



Sadhu AR, et al. J Diabetes Sci Technol. 2020 Nov;14(6):1065-1073.

Trending of Paired Glucose

Point-of-Care (POC) and Continuous Glucose Monitoring (CGM) Glucose Values

Example of Patient on Medtronic Guardian Connect

Example of Patient on Dexcom G6

Examples of a patient on each of the CGM systems with paired sensor glucose and blood glucose measurements graphed over time to demonstrate superimposed trending

Sadhu AR, et al. J Diabetes Sci Technol. 2020 Nov;14(6):1065-1073.

Reduction in POC Glucose monitoring

Number of POC-BG Glucose Measurements for Each Day After Sensor Insertion

	Day 0	Day 1	Day 2	% reduction from day 0 to day 1		% reduction from day 0 to day 2
Overall	14.18 ± 5.60	12.36 ± 4.82	8.75 ± 3.92[a,b]	6.7 ± 29.7	OVERALL	33.11 ± 29.03[a] ←
Dexcom	13.4 ± 5.41	10.8 ± 3.96	6.67 ± 0.58	9.62 ± 38.83	DEXCOM	52.2 ± 11.09 ←
Medtronic	14.83 ± 6.18	13.76 ± 5.43	10 ± 4.64	4.33 ± 23.30	MEDTRONIC	21.65 ± 31.24

Day 2:

33% reduction Overall

52% reduction with Dexcom System

POC glucose readings

Data were presented as mean ± SD.

Day 0, first 24 hours after sensor insertion, with usual care frequency of POC-BG

Days 1 and 2, guidance to decrease

POC-BG if SG in target glucose range

a*p*=.023 compared with day 0

b*p*=.031 compared with day 1

POC-BG, point-of-care blood glucose

Sadhu AR, et al. J Diabetes Sci Technol. 2020 Nov;14(6):1065-1073.

Antidiabetic Agents: Prospective Trials

- SGLT2i
  - DARE-19, published
    - RCT dapagliflozin in severe COVID, diabetes and nondiabetes
    - No observed statistically significant benefit
    - No significant harm overall
    - eDKA seen in diabetes subjects only
- DPP4is
  - sitagliptin and others (U Miami)
- TZD
  - pioglitazone (Kuwait)
  - ongoing
- GLP-1RA
  - Semaglutide (U Health Network, Toronto)
  - Ongoing

Ambulatory Care During COVID-19

Diabetes care during COVID-19

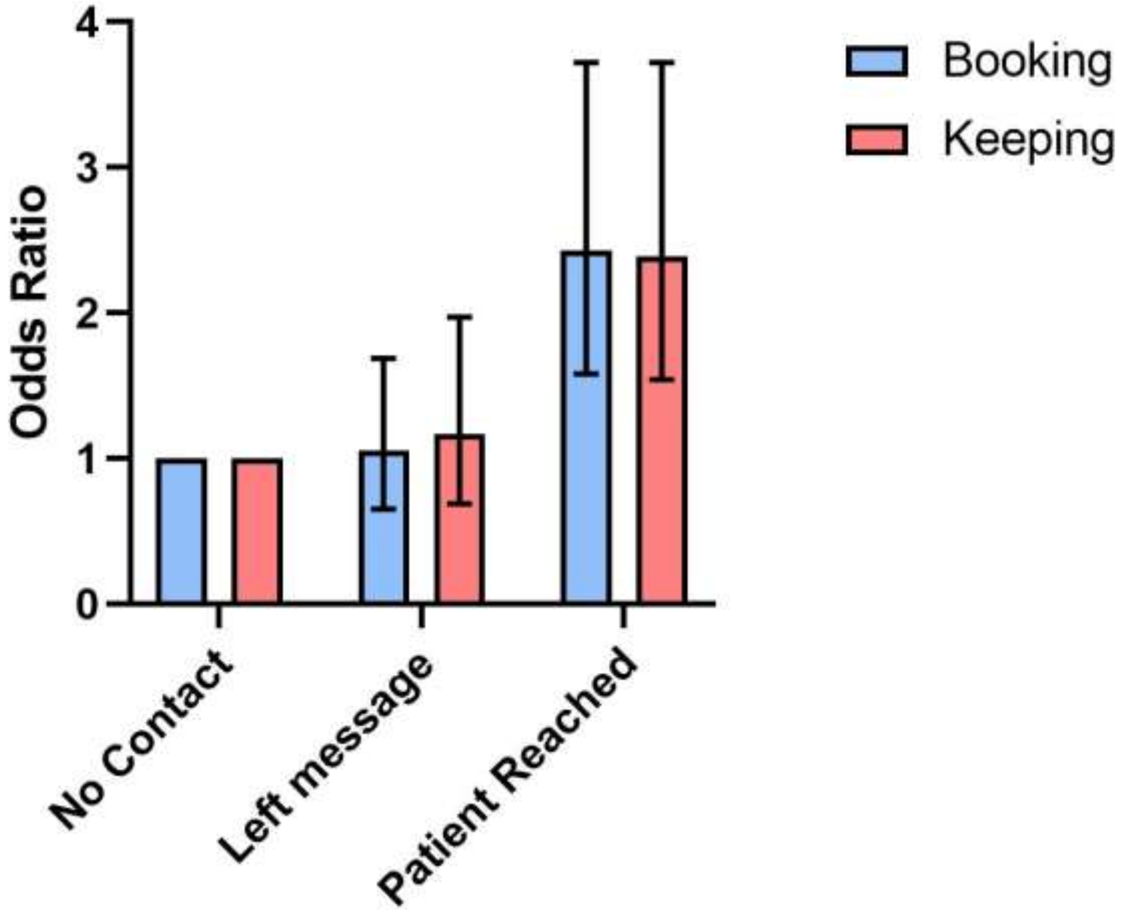
- "Health systems turned the focus solely on hospital care which overlooked the necessity of primary / chronic care which was a mistake"
  - Beran D, et al Beyond the virus: Ensuring continuity of care for people with diabetes during COVID-19. Prim Care Diabetes. 2020 May 30

- During the national lockdown in Italy, pediatric emergency department visits decreased 73%-88%. Delayed care for new onset T1D was documented.
  - Lazzerini M., et al. Delayed access or provision of care in Italy resulting from fear of COVID-19. Lancet Child Adolesc Health. 2020

Diabetes care during COVID-19

- Delayed cancer screenings estimated to result in a 7.9 – 9.6% increase of deaths due to breast cancer, 15.3-16.6% increase for colorectal cancer, 4.8-5.3% for lung cancer, 5.8-6.0% for esophageal cancer within 5 years of diagnosis
  - Chen-See S. Disruption of cancer care in Canada during COVID-19. Lancet Oncol. 2020 Aug
- Increased amputations and severe presentations of foot ulcers
  - Musajee M, Zayed H, Thulasidasan N, Sayed M, Francia F, Green M, Arissol M, Lakhani A, Biasi L, Patel S. Impact of COVID-19 Pandemic on the outcomes in patients with Critical Limb Threatening Ischaemia and Diabetic Foot Infection. Ann Surg. 2020, =Dec.
  - Casciato DJ, Yancovitz S, Thompson J, Anderson S, Bischoff A, Ayres S, Barron I. Diabetes-related major and minor amputation risk increased during the COVID-19 pandemic. J Am Podiatr Med Assoc. 2020 Nov

New Insights: How to Reengage the Disengaged?



- 1,079 Diabetes visits were cancelled in the first 3 months of the pandemic.
- Bidirectional communication (Patient Reached) to reestablish care increased likelihood of a booked and kept appointment by 2.4x

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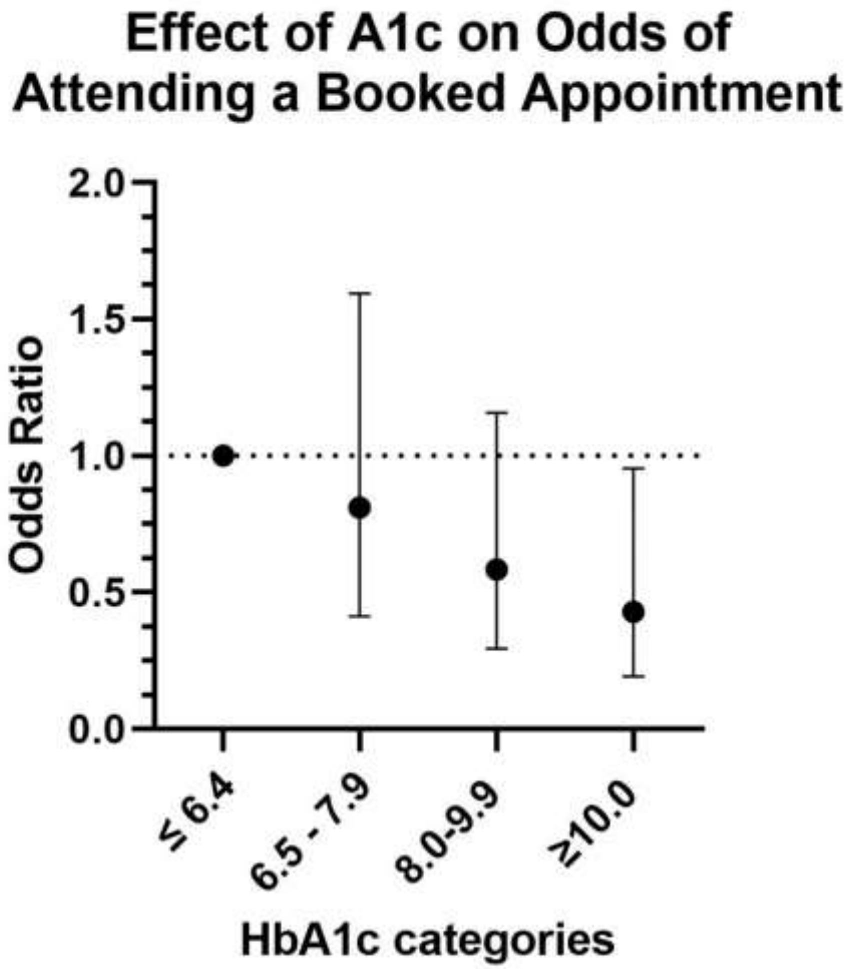
Cromwell GE, Hudson MS, Simonson DC, McDonnell ME.. Endocr Pract. 2021 Sep 14:



- Patients with higher HbA1c were less likely to keep their appointment.
- (OR = 0.87 for each 1.0% increase in HbA1c, p for trend =0.01).

Cromwell GE, Hudson MS, Simonson DC, McDonnell ME.. Endocr Pract. 2021 Sep 14:

“The Lockdown Effect” and Impact to Patients

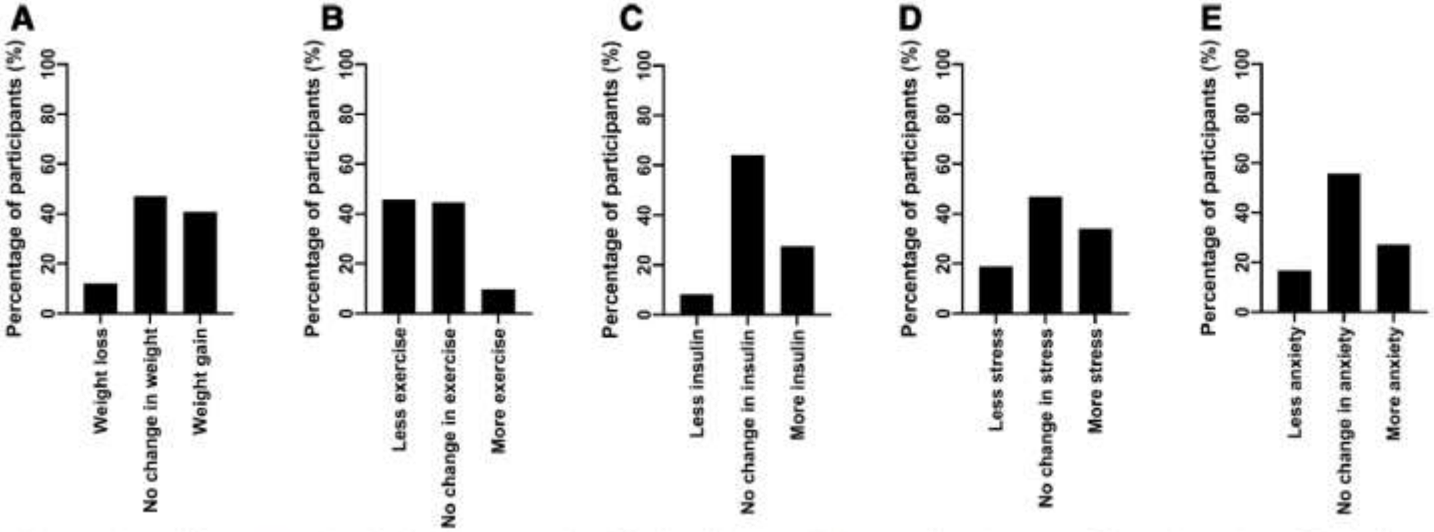


Figure 1 Change in self-reported weight (A), exercise (B), insulin use (C), perceived stress (D) and anxiety (E) during the lockdown period. (A) Weight loss: sum of percentage of participants in different categories of weight loss (online supplemental table 1). Weight gain: sum of percentage of participants in different categories of weight gain (online supplemental table 1). (C) Less insulin: sum of percentage of participants in different categories of less insulin use. More insulin: sum of percentage of participants in different categories of more insulin use. (D) Less stress: sum of percentage of participants in categories of less stress. More stress: sum of percentage of participants in different categories of more stress. (E) Less anxiety: sum of percentage of participants in different categories of less anxiety. More anxiety: sum of percentage of participants in different categories of more anxiety.

Patient self-reported changed in weight, stress, insulin use and anxiety

Ruissen M et al BMJ Open Diabetes Res Care. 2021 Jan;9(1):e002035

A Perfect Storm for New-Onset Diabetes

- Beta cell dysfunction from COVID-19?
- Insulin resistance
- Sarcopenia
- Weight gain
- Reduced movement
- Disparate impact on ethnic groups already with higher risk of developing diabetes

Figure 1—Potential mechanisms for development of new-onset diabetes in people with COVID-19.

Yang JK, Feng Y et al. Diabet Med. 2006 Jun;23(6):623-8
Kamlesh Khunti, et al Diabetes Care Oct 2021
Yang JK et al Acta Diabetol. 2010 Sep;47(3):193-9
Bornstein SR et al.Nat Rev Endocrinol. 2020 Apr 2.

At the Storm Front: The Youth

- At the Children's National Hospital in DC, the number of cases of type 2 diabetes increased by 182%, from 50 in 2019 to 141 in 2020.
- The average age at diagnosis was about 14 years in both time periods.
- The proportions of youth with new-onset type 2 diabetes who presented in diabetic ketoacidosis (DKA) rose from 2 (4%) pre-pandemic to 33 (23.4%) during the pandemic.
- Presentation with hyperosmolar DKA rose from 0 to 13 (9.2%)

Impact on the Health Care System

- Ambulatory care shifted to telemedicine:
  - Patients learning new technology
  - Remote glucose monitoring
  - Focus on inpatient care:
  - Inpatient endocrine consultation 50% diabetes to 95-100% hyperglycemia in the setting of SARS-CoV-2 infection
  - New strategies to care for patients (SC protocols), new programs

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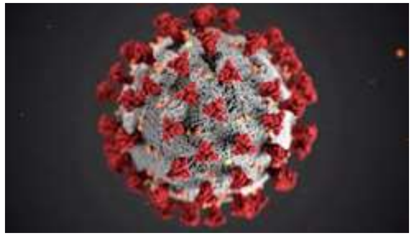
Two Years Later: What Have We Learned? What More do We Need to Know?



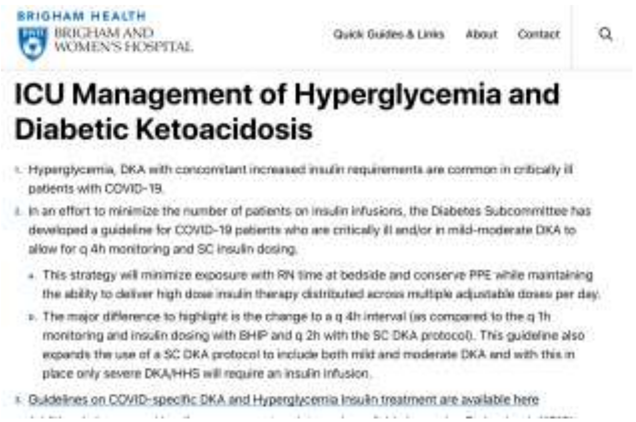
- Pathophysiology and Impact of SARS-CoV-2 on patients:
  - Worsening of Diabetes Following COVID-19
  - New Diabetes
- Guidance to prevent adverse events among patients with diabetes at risk for COVID-19
- Role of glycemic control during COVID hospitalization
- Strategies for improved health care delivery to all of our patients
  - Connected Health and Telemedicine
  - Special programs to meet patients where there are (ie virtual, EDRP)

Summary: Diabetes and COVID-19

- People with diabetes are more likely to become ill enough to seek help for COVID-19 infection
  - 2-4 more people with diabetes in reported COVID-19 patients under care
- People with diabetes are more likely to require mechanical ventilation, and more likely to die
  - About 2-3 times
  - Stress hyperglycemia may be a more
- In the setting of care disruption, our most vulnerable patients are at highest risk of disengagement
- We will continue to see high rates of new-onset diabetes – type 1 and type 2
- The COVID-19 pandemic has pushed the timeline toward quality-based, integrated connected health and we should embrace it

Resources for COVID-19 and Diabetes

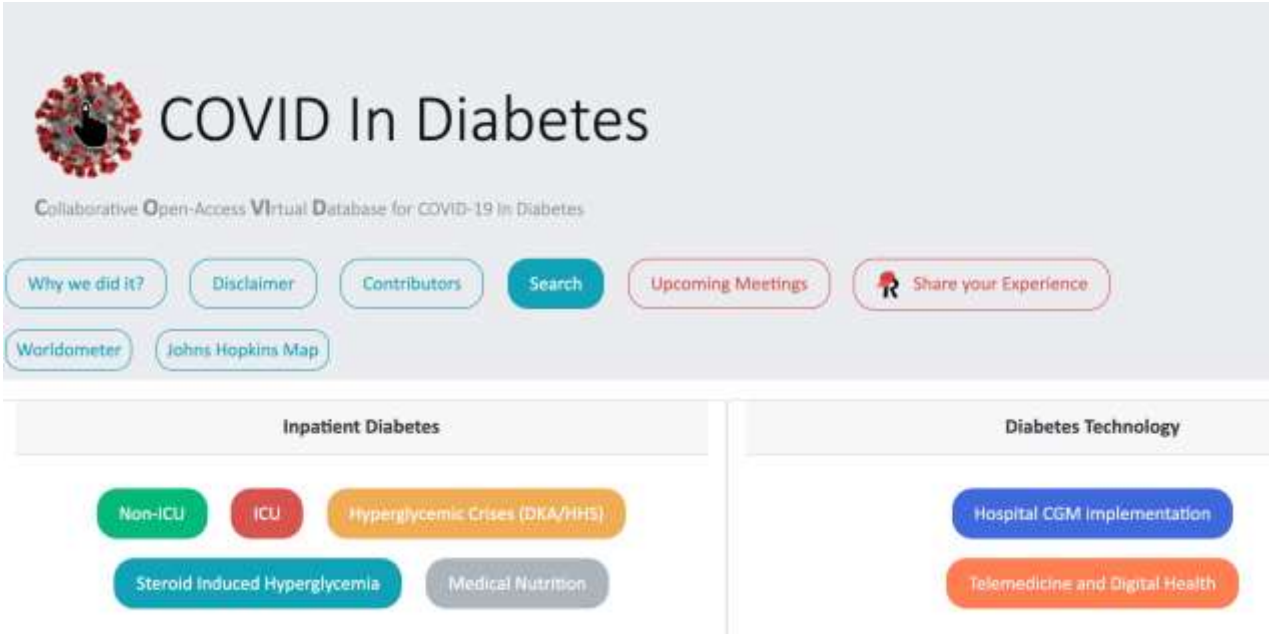
https://covidprotocols.org/


BRIGHAM HEALTH
BRIGHAM AND WOMEN'S HOSPITAL
Quick Guides & Links About Contact

ICU Management of Hyperglycemia and Diabetic Ketoacidosis

1. Hyperglycemia, DKA with concomitant increased insulin requirements are common in critically ill patients with COVID-19.
2. In an effort to minimize the number of patients on insulin infusions, the Diabetes Subcommittee has developed a guideline for COVID-19 patients who are critically ill and/or in mild-moderate DKA to allow for q 4h monitoring and SC insulin dosing.
   - This strategy will minimize exposure with RN time at bedside and conserve PPE while maintaining the ability to deliver high dose insulin therapy distributed across multiple adjustable doses per day.
   - The major difference to highlight is the change to a q 4h interval (as compared to the q 1h monitoring and insulin dosing with BHIP and q 2h with the SC DKA protocol). This guideline also expands the use of a SC DKA protocol to include both mild and moderate DKA and with this in place only severe DKA/HHS will require an insulin infusion.
3. Guidelines on COVID-specific DKA and Hyperglycemia Insulin treatment are available here

https://covidindiabetes.org



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NATIONAL LGBTQIA+ HEALTH EDUCATION CENTER

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Questions?