

به نام خدا



# DM management in Covid 19 patients

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# Agenda :

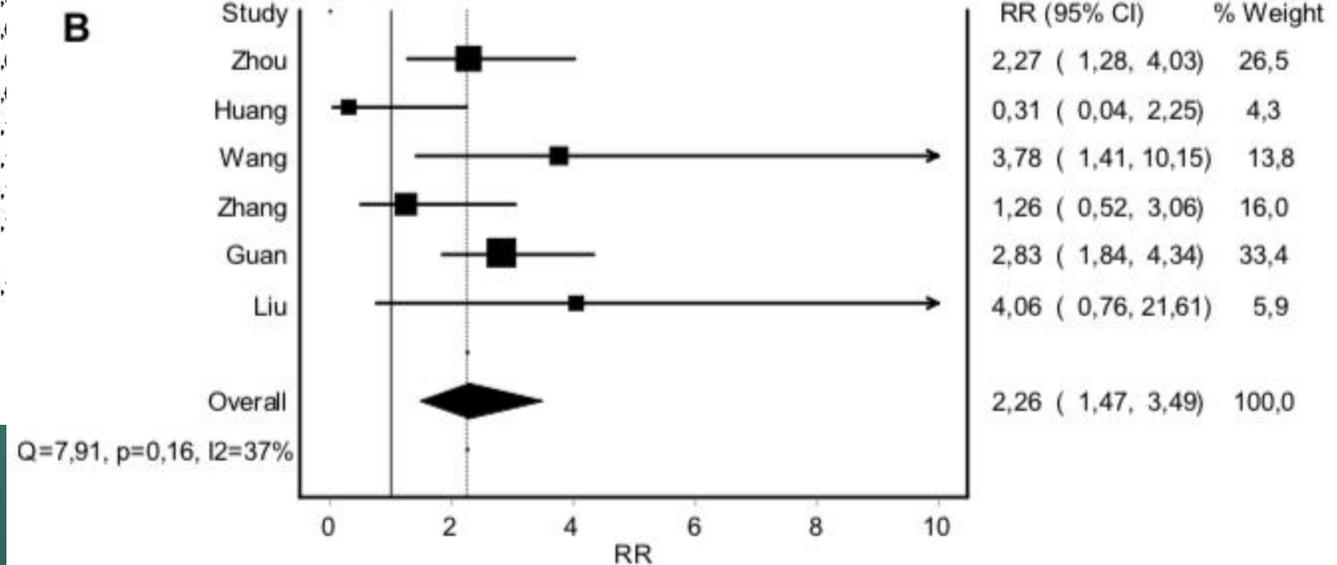
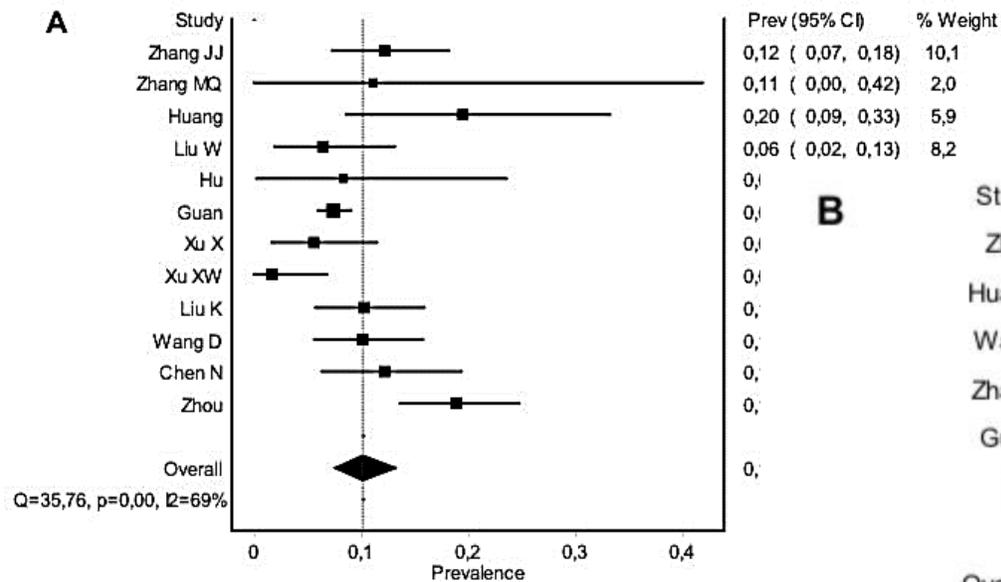
- ▶ Introduction
- ▶ Common questions about diabetes management in Covid 19
  - ▶ Out patient setting// Sick day rules
  - ▶ In patient setting
    - ▶ When Glucocorticoids are used
- ▶ Conclusion and take home message

# Corona viruses

- ❖ Covid patients developed symptoms at 5-6 days after infection
- ❖ Mild symptom in initial stage for 2 weeks
- ❖ Sever illness, ARDS , multi-organ involvement ,shock
- ❖ Mortality rate between 0.5 and 1%
- ❖ Most of the fatal cases occurred in patients with advanced age or underlying medical comorbidities
  - ❖ High risk covid patients:
    - advanced age
    - Male sex
    - CVD
    - Obesity
    - T1DM,T2DM

# Prevalence of DM among people more severe infected with covid-19

**Fig. 1** **a** Forest plot of diabetes prevalence among SARS-CoV-2 infected patients. **b** Forest plot of diabetes rate ratio (RR) among patients with more severe versus those with less severe infection





## Original Article

Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia – A systematic review, meta-analysis, and meta-regression<sup>☆</sup>Ian Huang, Michael Anthonius Lim, Raymond Pranata<sup>\*</sup>

Faculty of Medicine, Universitas Pelita Harapan, Tangerang, Indonesia

## ▶ Poor outcome

## ▶ Mortality

## ▶ Severe Covid 19

## ▶ ARDS

## ▶ ICU Care

## ▶ Disease progression

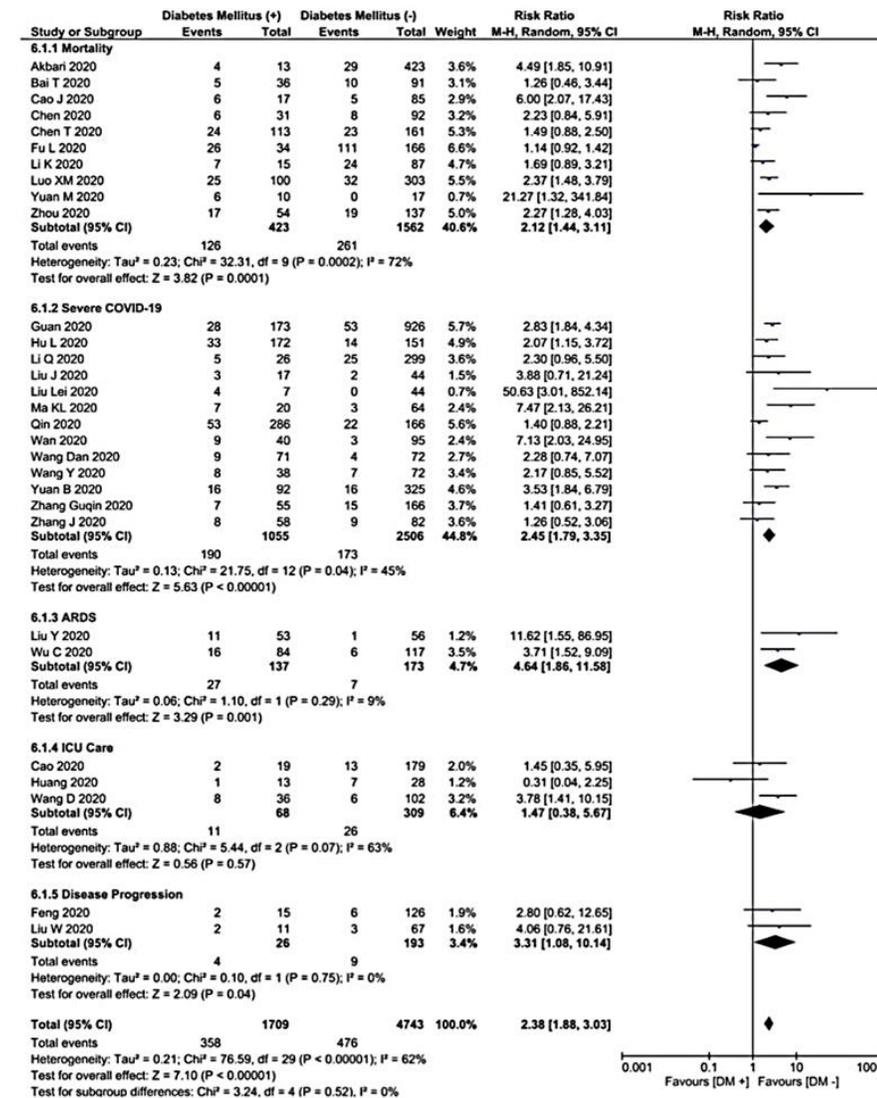
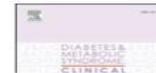
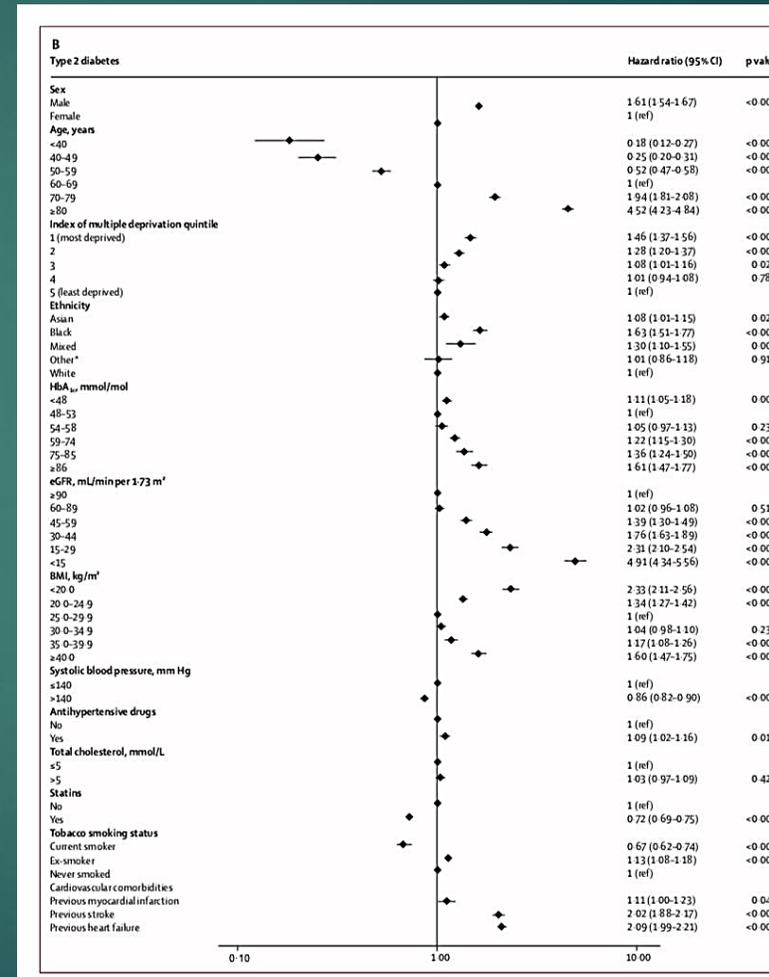
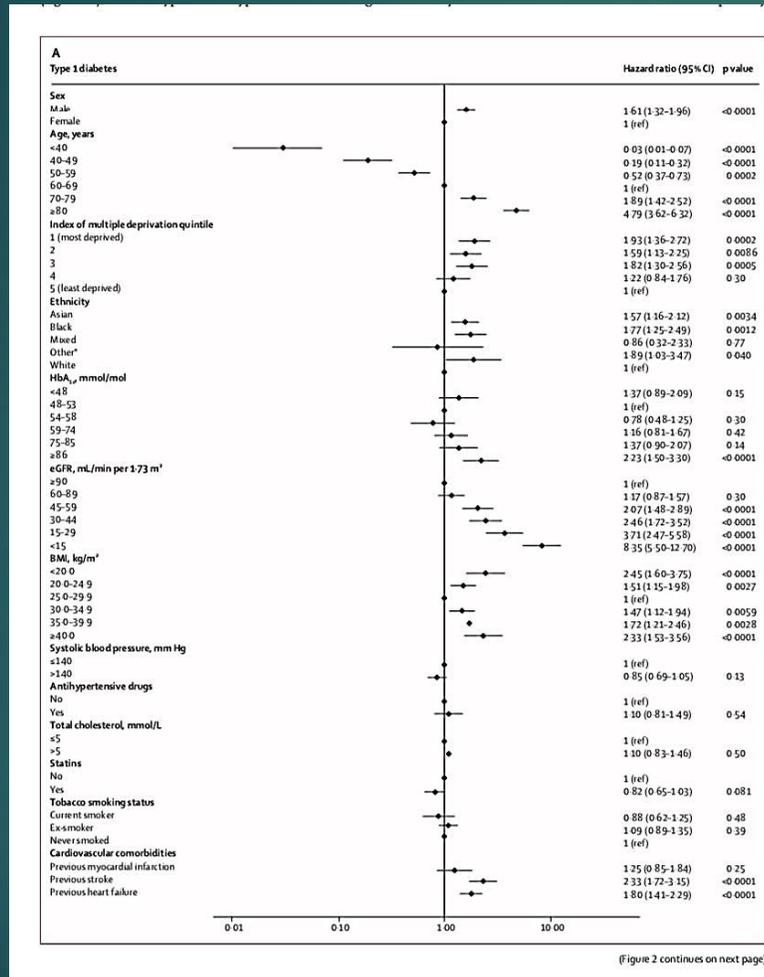


Fig. 2. Diabetes Mellitus and Poor Outcome. Forest-plot shows that diabetes mellitus was associated with increased composite poor outcome and its subgroup which comprises of mortality, severe COVID-19, ARDS, need for ICU care, and disease progression in patients with COVID-19. ARDS: Acute Respiratory Distress Syndrome, COVID-19: Coronavirus Disease 2019, ICU: Intensive Care Unit.

# Adjusted hazard ratios for COVID-19 death in people with T1 & T2 DM



# Covid mortality risk factor in people with diabetes

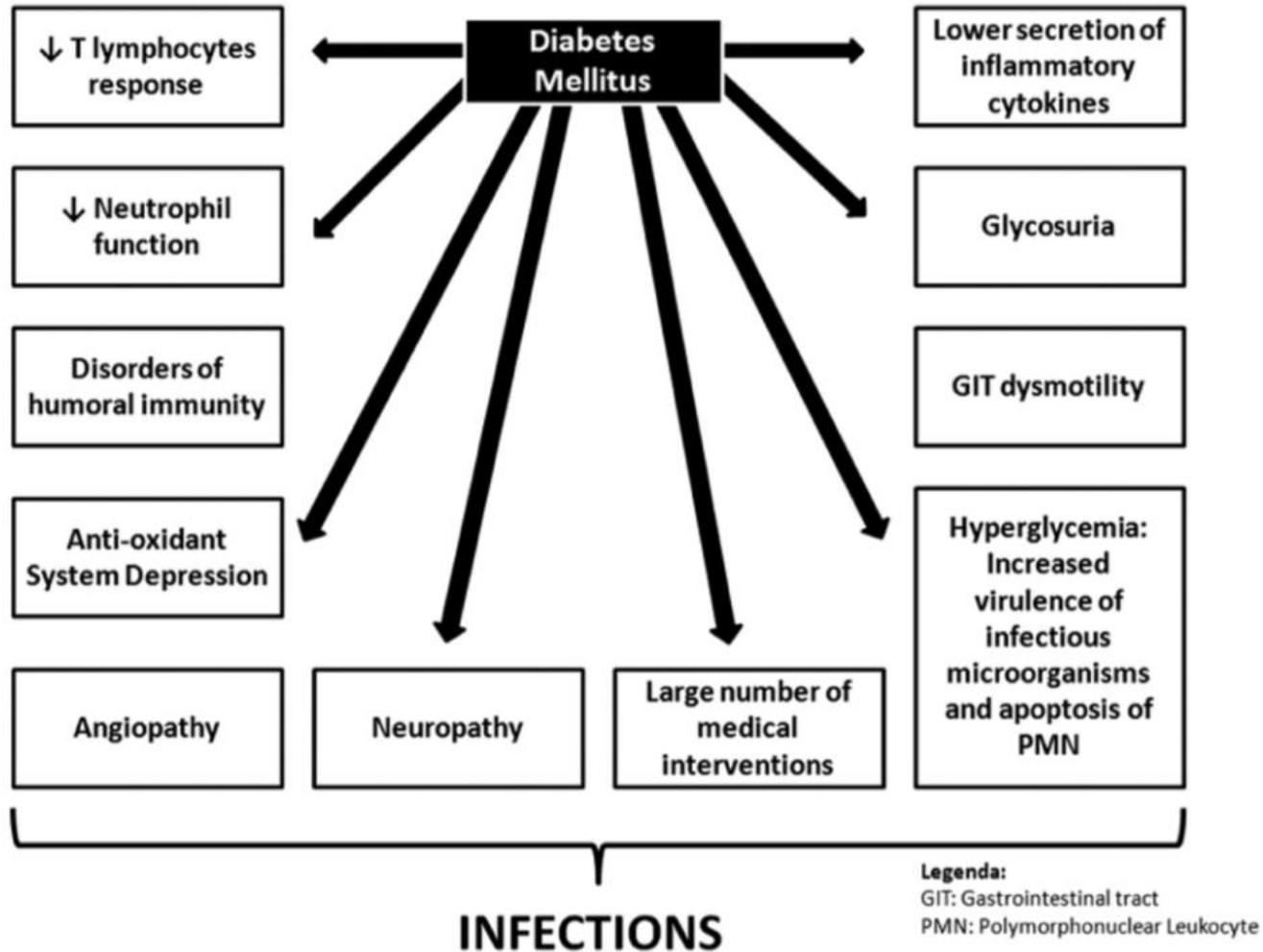
## Type 1

- ❖ Age > 70 y/o
- ❖ Male sex
- ❖ Socioeconomic deprivation
- ❖ Non-white ethnicity
- ❖ HBA1C > 10%
- ❖ GFR < 60
- ❖ BMI < 20 & > 30
- ❖ Previous stroke/HF
- ❖ No benefit for statin

## Type 2

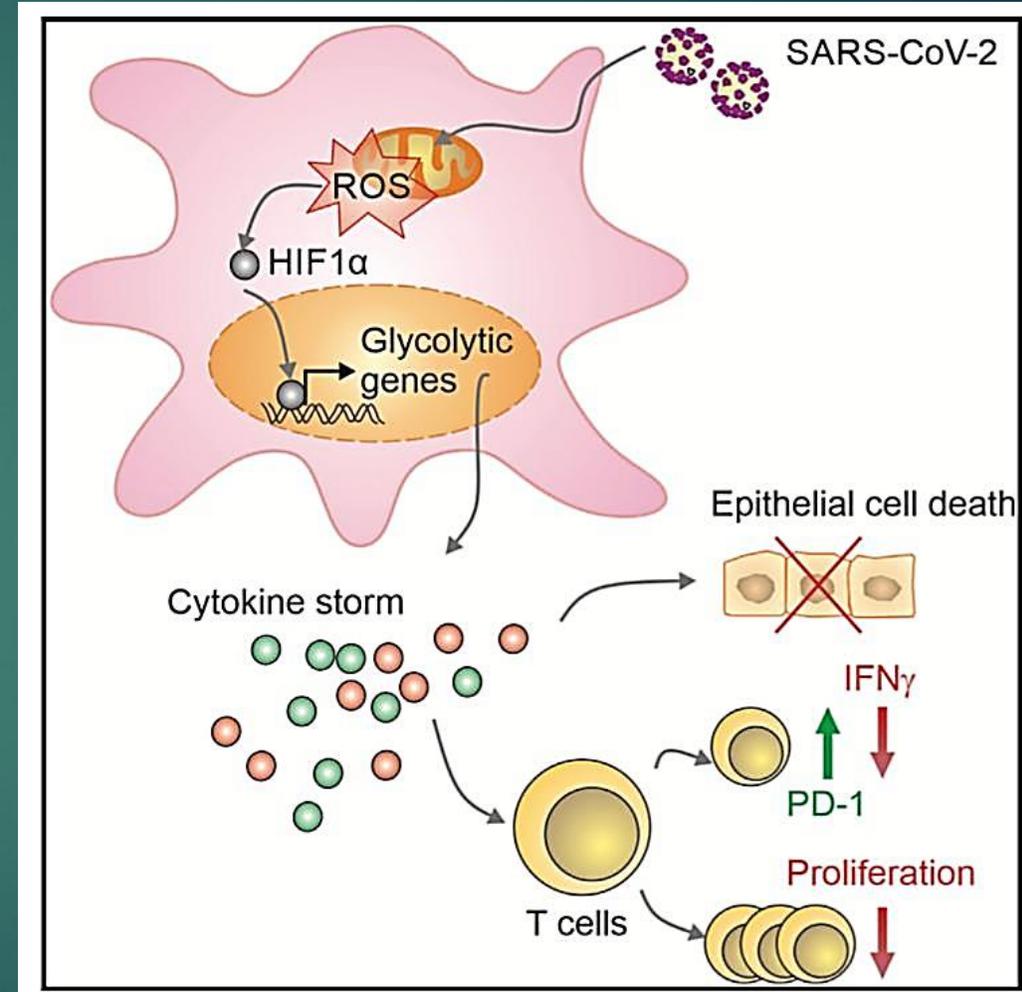
- ❖ Age > 70 y/o
- ❖ Male sex
- ❖ Socioeconomic deprivation
- ❖ Non-white ethnicity
- ❖ HBA1C > 7.6%
- ❖ GFR < 60
- ❖ BMI < 20 & > 35
- ❖ Previous stroke/HF
- ❖ Statin had benefit

# DM & defective immune system



# DM & Immune response

- ❖ Elevated glucose level & glycolysis promote **SARS-COV2 replication** & cytokine production in monocytes .
- ❖ Resulting in **T cell dysfunction** & **epithelial cell death**.



# Causes of hyperglycemia in covid 19 patients

- ❖ Stress hyperglycemia
- ❖ Inflammation
- ❖ Beta cell destruction
  - ❖ Autoimmune (molecular mimicry)
  - ❖ Pancreas direct damage by covid-19
- ❖ Drugs

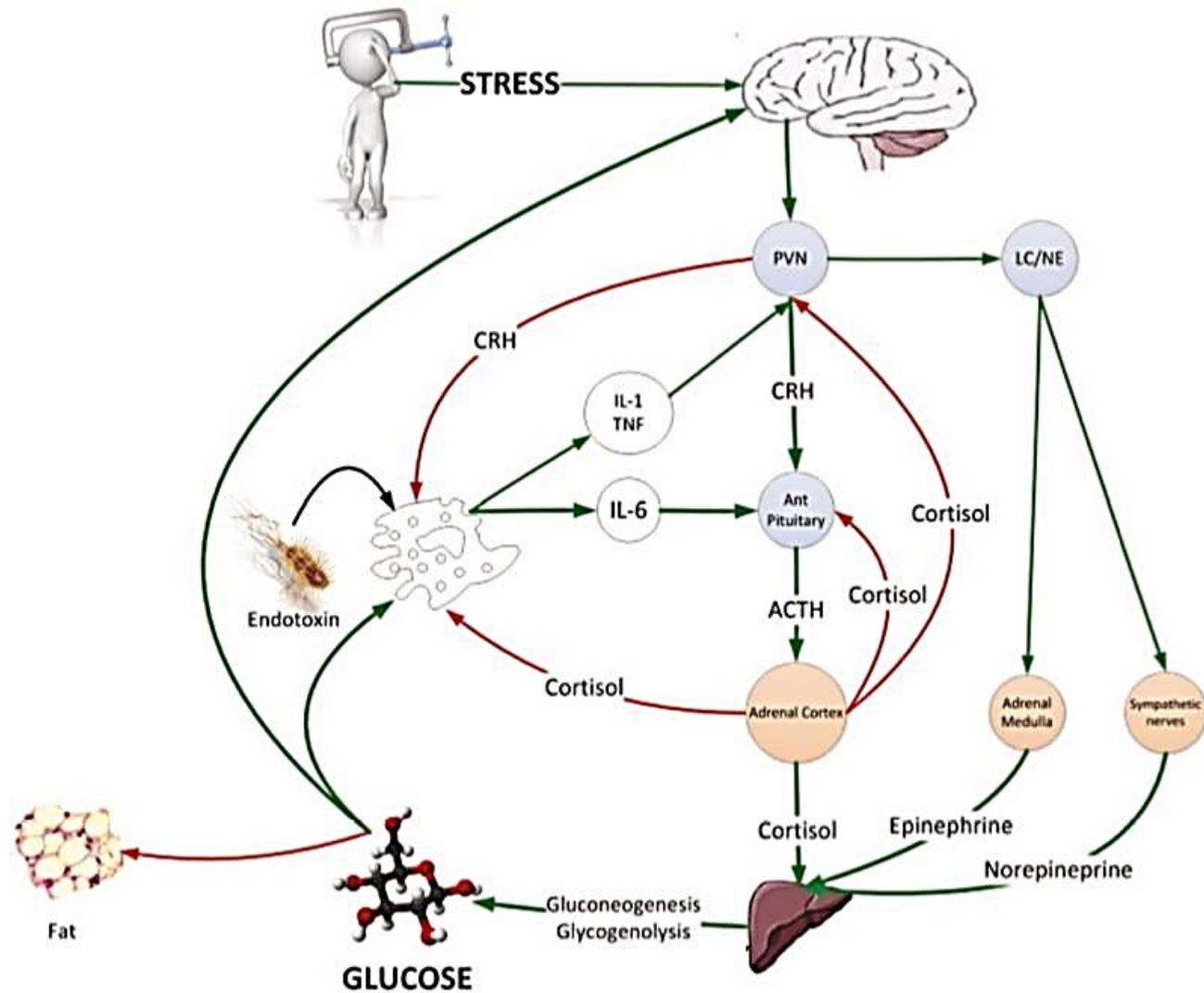


Figure 1. The neuroendocrine response to stress is characterized by gluconeogenesis and glycogenolysis resulting in stress hyperglycemia providing the immune system and brain with a ready source of fuel. ACTH, adrenocorticotrophic hormone; CRH, corticotrophin releasing hormone; LC/NE, locus ceruleus norepinephrine system; PVN, paraventricular nucleus.

# Stress hyperglycemia:

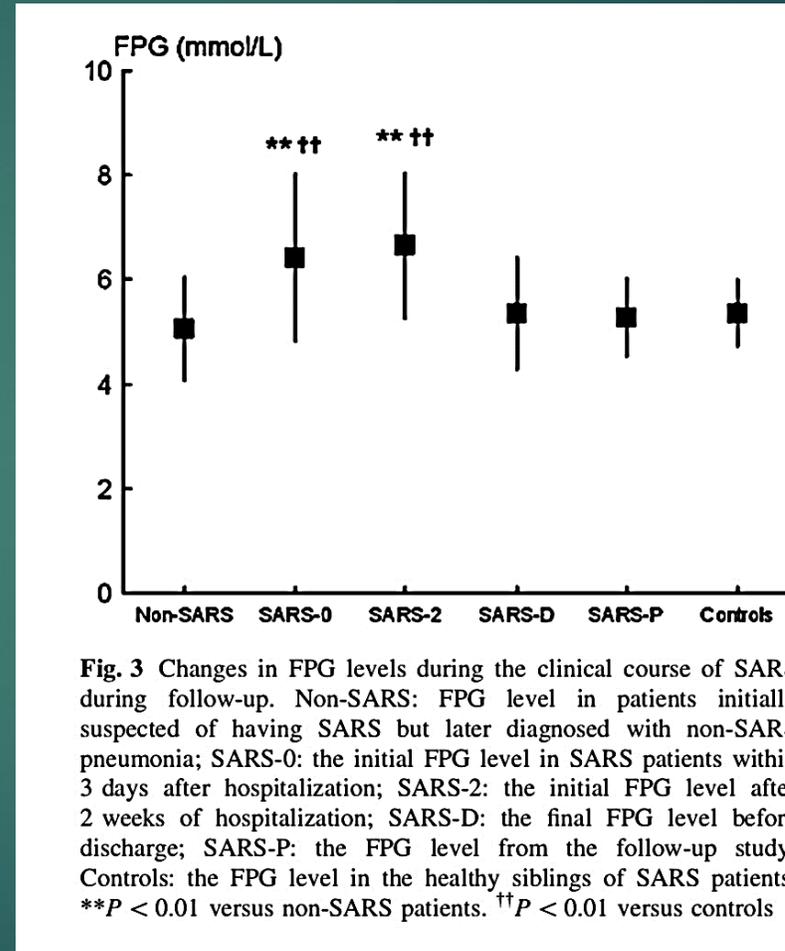
- ❖ Hyperglycemia, insulin resistance, glucose intolerance
- ❖ Stress hyperglycemia associated with:
  - ❖ Mortality
  - ❖ Morbidity
  - ❖ Length of stay
  - ❖ Infection
  - ❖ Overall complication
- ❖ Attempts at intensive glycemic control, don't improve health care outcome

# Stress hyperglycemia

- ❖ Hyperglycemia in acute illness setting is an adaptive response which increases host chance of survival.
- ❖ Degree of hyperglycemia associated with disease severity
- ❖ Patient with **BS > 220** mg/dl benefit from moderate glycemic control.

# SARS pancreatic damage & acute diabetes

- ❖ Infection with covid cause hyperglycemia in people without pre-existing DM
- ❖ Localization of ACE2 in endocrine pancreas
- ❖ ACE2 association of COVID & DM
- ❖ Hyperglycemia can persist after recovery , long term damage to pancreatic beta cell



## SARS pancreatic damage

- ❖ Although ketoacidosis is typically a problem associated with DM1, in patient with COVID 19 ketoacidosis also occur in T2DM.

**Table 2**

Showing demographic parameters of the COVID-19 patients with DKA (and combined DKA/HHS).

Parameter	Value
Age (years) [Median (IQR)]	45.5 (36.2–57.7) [7,8,10–16,18–21,23,24,28] <sup>a</sup> 57.0 (48.0–64.0) [22] <sup>b</sup> 59.0 (42.3–70.0) [9]
Sex (N = 102) <sup>c</sup>	Male (n = 64, 63%) Female (n = 38, 37%)
Ethnicity <sup>d</sup> (N = 84)	Black (n = 30, 36%) <sup>c</sup> Hispanic (n = 19, 23%) White (Caucasian) (n = 10, 12%) Asian (n = 6, 7%) Mixed (n = 4, 5%) Others (n = 8, 9%) Unknown (n = 7, 8%)
Type of diabetes <sup>f</sup> (N = 97)	Pre-existing T1DM (n = 12, 12%) Pre-existing T2DM (n = 74, 77%) Newly diagnosed (n = 10, 10%) Gestational DM (n = 1, 1%)
Use of SGLT2 inhibitors <sup>g</sup>	/
BMI (kg/m <sup>2</sup> ) [Median (IQR)]	26.6 (23.7–32.3) [7,11–13,16,28] <sup>h</sup> 24.7 (21.3–28.5) [22] <sup>b</sup> 27.1 (23.2–33.0) [9]

# Drugs for treating COVID & their glycemc effects:

Table 2 | Glycaemic effects of potential pharmacological agents for COVID-19

Drugs	Mechanisms of action	Source of data	Blood glucose	Insulin sensitivity or resistance	$\beta$ -Cell function
Camostat mesylate	Serine protease (TMPRSS2) inhibitor	Human studies	$\downarrow$ Patients with new-onset DM and chronic pancreatitis <sup>172</sup>	–	–
		Animal studies	$\downarrow$ BG <sup>175</sup> ; $\downarrow$ PPG <sup>215</sup>	$\downarrow$ Insulin level <sup>173</sup> ; $\downarrow$ insulin resistance <sup>175</sup>	$\downarrow$ Insulin secretion (reversed by GIP) <sup>216,217</sup>
		Cells/organs	$\downarrow$ BG <sup>176</sup>	$\downarrow$ Insulin level <sup>174</sup>	–
		Patients with DM and/or insulin resistance	$\downarrow$ BG <sup>175</sup> ; $\downarrow$ PPG <sup>215</sup>	$\downarrow$ Insulin level <sup>173</sup> ; $\downarrow$ insulin resistance <sup>175</sup>	–
Chloroquine or hydroxychloroquine	Blockade of virus entry and immunomodulation	Human studies	$\downarrow$ HbA <sub>1c</sub> (REFS <sup>178,180,218</sup> ); $\downarrow$ FPG <sup>178</sup> ; $\downarrow$ PPG or BG <sup>180</sup> ; $\downarrow$ hazard ratio for incident new-onset DM by 38% in patients with RA <sup>219</sup> ; hypoglycaemia <sup>180,181</sup>	$\uparrow$ Insulin sensitivity <sup>178</sup> ; $\uparrow$ hepatic insulin sensitivity <sup>220</sup>	$\uparrow$ $\beta$ -Cell function <sup>178</sup>
		Cells/organs	–	–	GLUT4 translocation and glucose uptake: $\downarrow$ in adipocytes <sup>221</sup> , $\uparrow$ in muscle cells <sup>222</sup>
		Patients with DM and/or insulin resistance	$\downarrow$ HbA <sub>1c</sub> (REFS <sup>178,180,218</sup> ); $\downarrow$ FPG <sup>178</sup> ; $\downarrow$ PPG or BG <sup>180</sup> ; $\downarrow$ hazard ratio for incident new-onset DM by 38% in patients with RA <sup>219</sup> ; hypoglycaemia <sup>180,181</sup>	–	–

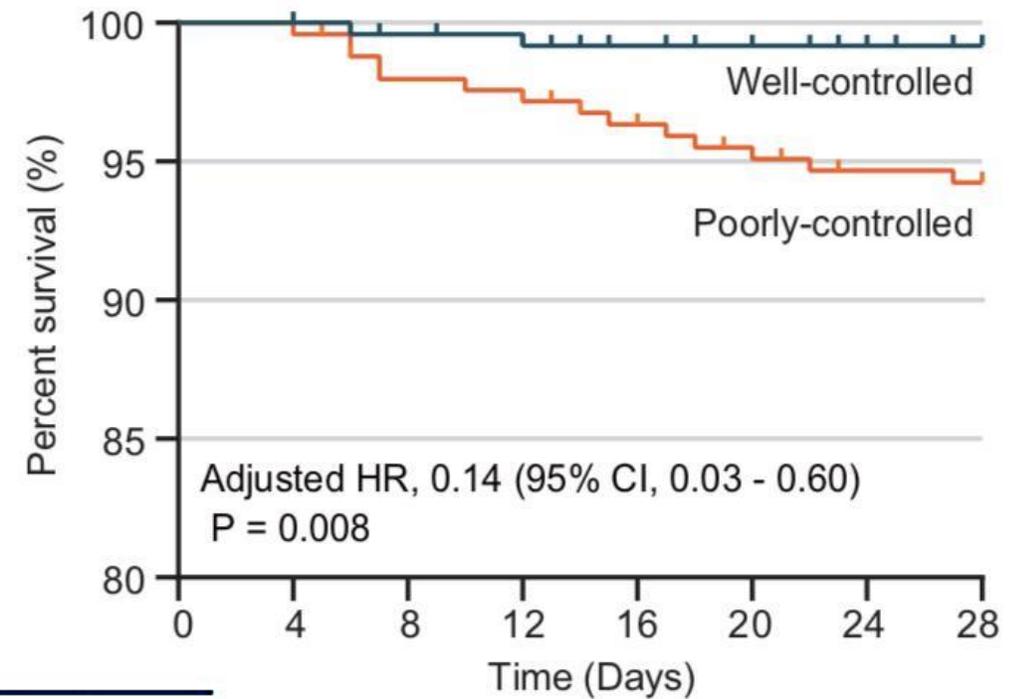
Protease inhibitors	Proteolytic processing of viral proteins	Human studies	↑ FPG <sup>185</sup> ; ↑ BG <sup>186,223</sup> ; ↑ in patients with new-onset DM <sup>187</sup>	↑ Insulin level <sup>188,223,224</sup> ; ↓ insulin sensitivity <sup>185,223,224</sup> ; ↓ glucose clearance <sup>185</sup> ; ↓ non-oxidative glucose disposal <sup>224,225</sup>	↓ β-Cell function <sup>185</sup> ; ↓ first-phase insulin release <sup>185</sup>
		Animal studies	–	–	↓ GLUT4 activity <sup>226,227</sup>
		Cells/organs	–	–	↓ GLUT4 activity <sup>228</sup> or mRNA <sup>229</sup>
RNA-dependent RNA polymerase inhibitors	Inhibition of RNA-dependent RNA polymerase	Animal studies	↓ FPG <sup>191</sup>	↓ Insulin level <sup>191</sup> ; ↓ insulin resistance <sup>193</sup>	–
		Patients with DM and/or insulin resistance	↓ FPG <sup>191</sup>	↓ Insulin level <sup>191</sup> ; ↓ insulin resistance <sup>193</sup>	–
IL-6 receptor inhibitors	IL-6 antagonism, suppressing the production of inflammatory molecules	Human studies	↓ HbA <sub>1c</sub> (REF. <sup>230</sup> )	↓ Insulin level <sup>194</sup> ; ↓ insulin-to-glucose ratio <sup>194</sup> ; ↑ insulin sensitivity <sup>194</sup> ; ↓ insulin resistance <sup>194</sup>	–
		Animal studies	↓ Glucose intolerance <sup>231</sup>	–	–
		Cells/organs	–	–	↓ Transplanted islet cell death <sup>231</sup>
		Patients with DM and/or insulin resistance	↓ HbA <sub>1c</sub> (REF. <sup>230</sup> ); ↓ glucose intolerance <sup>231</sup>	–	↓ Transplanted islet cell death <sup>231</sup>
IL-1 receptor inhibitors	IL-1 antagonism	Human studies	↓ HbA <sub>1c</sub> (REFS <sup>196,232</sup> ); ↓ FPG <sup>232</sup> ; no effect on HbA <sub>1c</sub> and BG in patients with recent-onset T1DM <sup>198</sup>	↑ C-peptide secretion <sup>196</sup> ; ↑ proinsulin-to-insulin ratio <sup>196</sup>	–
		Animal studies	↓ Glucose intolerance <sup>231</sup>	–	–
		Cells/organs	–	–	↑ Insulin secretion in transplanted islets <sup>231</sup> ; ↓ transplanted islet cell death <sup>231</sup>
		Patients with DM and/or insulin resistance	↓ HbA <sub>1c</sub> (REF. <sup>232</sup> ); ↓ FPG <sup>232</sup> ; no effect on HbA <sub>1c</sub> and BG in patients with recent-onset T1DM <sup>198</sup>	No effect on C-peptide secretion in patients with T1DM <sup>198</sup>	↑ Insulin secretion in transplanted islets <sup>231</sup> ; ↓ transplanted islet cell death <sup>231</sup>

Table 2 (cont.) | Glycaemic effects of potential pharmacological agents for COVID-19

Drugs	Mechanisms of action	Source of data	Blood glucose	Insulin sensitivity or resistance	$\beta$ -Cell function
IL-1 $\beta$ inhibitors	IL-1 $\beta$ antagonism	Human studies	No effect on HbA <sub>1c</sub> in patients with recent-onset T1DM <sup>198</sup>	No effect on C-peptide secretion in patients with recent-onset T1DM <sup>198</sup>	–
		Patients with DM and/or insulin resistance	No effect on HbA <sub>1c</sub> in patients with recent-onset T1DM <sup>198</sup>	No effect on C-peptide secretion in patients with recent-onset T1DM <sup>198</sup>	–
JAK1 and JAK2 inhibitors	Suppressing JAK–STAT signalling, inhibition of clathrin-mediated endocytosis, immunosuppression	Animal studies	↓ Reversal of new-onset DM in NOD mice <sup>200</sup>	↓ Insulin level <sup>233</sup>	–
		Patients with DM and/or insulin resistance	↓ DM development <sup>200</sup>	↓ Insulin level <sup>233</sup>	–
BTK inhibitor	Immunomodulatory effect on macrophages, reducing the production of cytokines	Animal studies	↓ BG <sup>201</sup>	–	–
TNF inhibitors	TNF antagonism	Human studies	↓ FBG <sup>206,234,235</sup> ; ↓ HbA <sub>1c</sub> (REFS <sup>230,235</sup> ); ↓ patients with new-onset DM and RA and psoriasis <sup>236</sup>	↓ Insulin resistance <sup>205,235,237</sup> ; ↑ insulin sensitivity <sup>205,237</sup>	↑ $\beta$ -Cell function <sup>205</sup>
		Patients with DM and/or insulin resistance	↓ FBG <sup>206,234,235</sup> ; ↓ HbA <sub>1c</sub> (REFS <sup>230,235</sup> )	↓ Insulin resistance <sup>205</sup> ; ↑ insulin sensitivity <sup>205</sup>	↑ $\beta$ -Cell function <sup>205</sup>
Corticosteroids <sup>206,238</sup>	Anti-inflammatory effects	Human studies	↑ HbA <sub>1c</sub> ; ↑ BG (mainly PPG)	↑ Insulin resistance; ↓ insulin sensitivity	↓ Insulin production and secretion

BG, blood glucose; BTK, Bruton's tyrosine kinase; COVID-19, coronavirus disease 19; DM, diabetes mellitus; FPG, fasting plasma glucose; GIP, glucose-dependent insulinotropic polypeptide; GLUT4, glucose transporter type 4; JAK, Janus kinase; NOD, non-obese diabetic; PPG, postprandial glucose; RA, rheumatoid arthritis; STAT, signal transducer and activator of transcription; T1DM, type 1 diabetes mellitus; TMPRSS2, transmembrane protease serine 2; TNF, tumour necrosis factor.

# DM control & covid



**Table 3. Hazard Ratios for Outcomes in Well-Controlled and Poorly Controlled BG Cohorts under Cox Adjusted Model and Propensity Score-Matching Model**

Well-Controlled versus Poorly Controlled	Unmatched		Adjusted <sup>a</sup>		Matched <sup>b</sup>	
	Crude HR (95% CI)	p Value <sup>d</sup>	HR (95% CI)	p Value <sup>d</sup>	Adjusted <sup>c</sup> HR (95% CI)	p Value <sup>d</sup>
All-cause mortality	0.09 (0.03,0.30)	<0.001	0.13 (0.04,0.44)	<0.001	0.14 (0.03,0.60)	0.008
Septic shock	-	-	-	-	-	-
ARDS	0.31 (0.19,0.50)	<0.001	0.41 (0.25,0.66)	<0.001	0.47 (0.27,0.83)	0.009
DIC	-	-	-	-	-	-
Acute kidney injury	0.19 (0.04,0.80)	0.024	0.22 (0.05,1.03)	0.055	0.12 (0.01,0.96)	0.046
Acute heart injury	0.14 (0.05,0.39)	<0.001	0.21 (0.07,0.59)	0.003	0.24 (0.08,0.71)	0.010

249	242	241	232	228	223	222
248	240	239	223	217	214	211

**Survival  
98.9%**



**Well-controlled  
Blood Glucose  
(upper limit  $\leq 10\text{mM}$ )**

**Diabetes**

**Death  
11.0%**



**Poorly-controlled  
Blood Glucose  
(upper limit  $> 10\text{ mM}$ )**

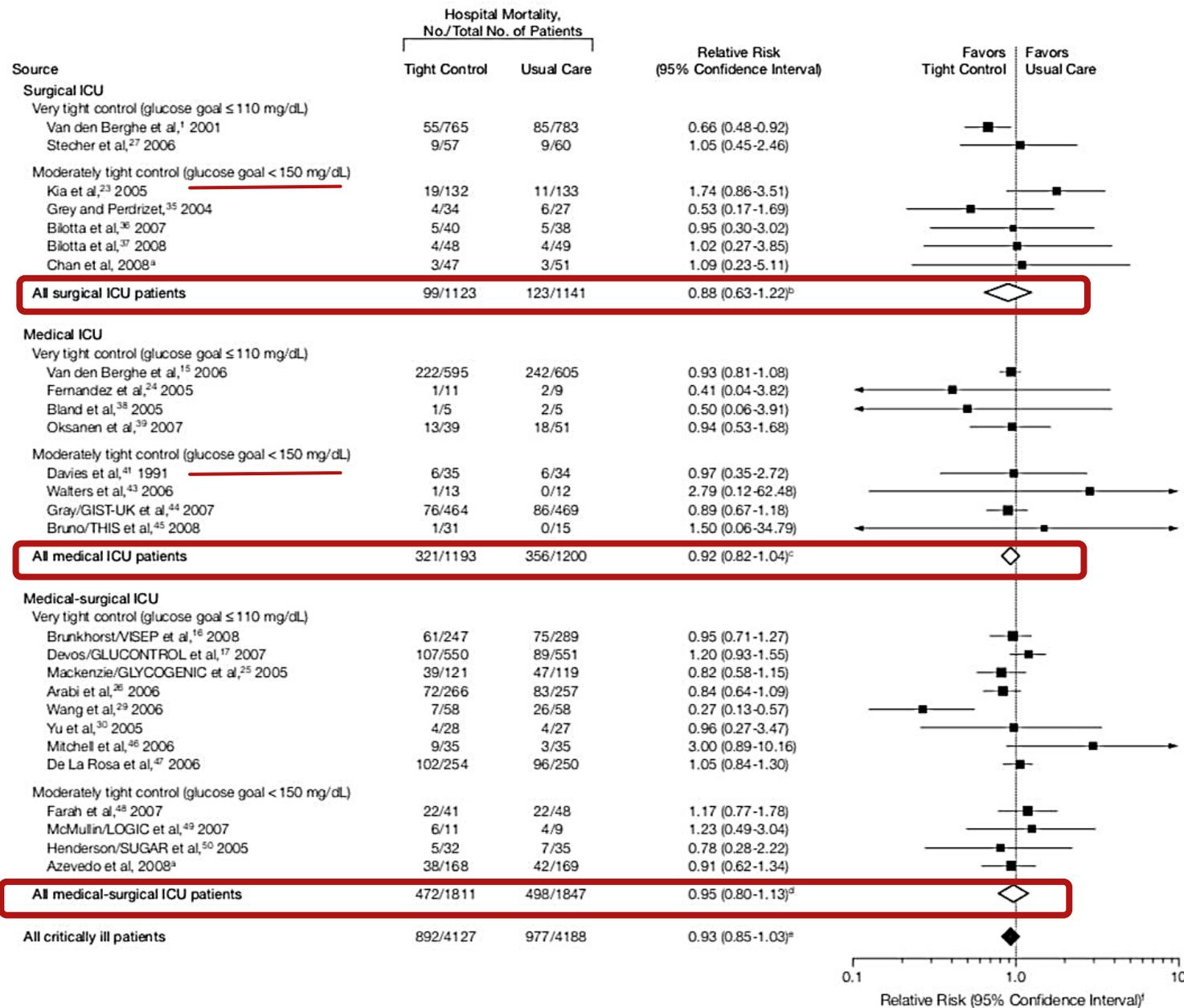
# Questions

1. What are the glycemic target in COVID patients?
2. What are the appropriate treatments in out patients?
3. What are the effective treatments in hospitalized patients?
4. How should GIH be managed?
5. What is the prognosis of DKA in covid-19
6. How should DKA be prevented/treated?

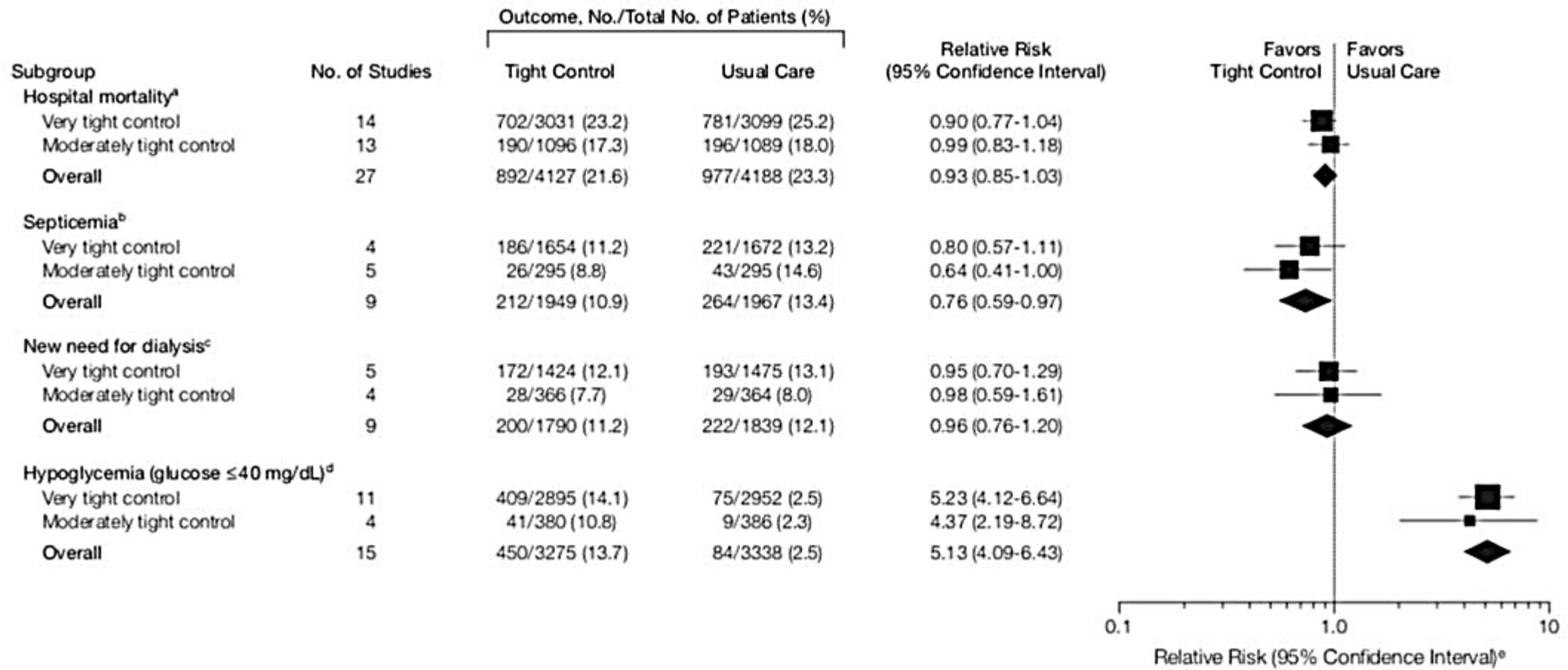
# Questions

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**Figure 2.** Association of Tight Glucose Control vs Usual Care With Hospital Mortality, Stratified by ICU Setting and Glucose Goal in Tight Control Group



**Figure 3.** Association of Tight Glucose Control vs Usual Care With Outcomes Among Critically Ill Adults, Stratified by Glucose Goal in Tight Control Group



# Questions

1. What are the glycemic target in COVID patients?
2. **What are the appropriate treatments in out patients?**
3. What are the effective treatments in hospitalized patients?
4. How should GIH be managed?
5. What is the prognosis of DKA in covid-19
6. How should DKA be prevented/treated?

# T2DM patients

- ▶ Diet
  - ▶ Metformine
  - ▶ Sulfonylurea
  - ▶ DPP4 Inhibitors
  - ▶ SGLT2 Inhibitors
  - ▶ Glitazones
  - ▶ Oral combination therapy
  - .....
  - ▶ **Injectable**
    - ▶ GLP1 Agonists
    - ▶ Insulin
      - ▶ Human
      - ▶ Analog
      - ▶ Premix
- ▶ Well controlled
  - ▶ Poor controlled
  - ▶ After admission
  - ▶ Before admissions
- 

# Treatment option in Out patients setting

	Uninfected but living in environment with prevalent COVID-19	Ambulatory mild disease	
Recommended to use	<ul style="list-style-type: none"><li>Insulin</li><li>Metformin</li><li>TZD</li><li>DPP4 inhibitors</li><li>GLP1 analogues</li><li><math>\alpha</math>-Glucosidase inhibitors</li></ul>	<ul style="list-style-type: none"><li>Insulin</li><li>DPP4 inhibitors</li><li>Metformin</li><li>GLP1 analogues</li></ul>	
Can be used with caution	<ul style="list-style-type: none"><li>Sulfonylurea</li><li>SGLT2 inhibitors</li></ul>	<ul style="list-style-type: none"><li>Sulfonylurea</li><li>SGLT2 inhibitors</li><li>TZD</li><li><math>\alpha</math>-Glucosidase inhibitors</li></ul>	
Not recommended			

# Managing COVID 19 in patients with diabetes (PWD):

- ▶ Management of PWD with COVID 19 generally follows standard **sick-day rules**.
- ▶ Decrease the need for hospitalization
- ▶ The plans need to be individualized taking into account factors such as:
  - ▶ Type of diabetes and treatment, Severity of Covid 19 ( $\pm$  Nausea)
  - ▶ Other medical conditions,
  - ▶ Life expectancy, remoteness from acute medical services, available support persons and services,
  - ▶ Previous experiences following acute illness, physical and cognitive capacity.

# What happen in sick day?

- ▶ Stress hormones are released by your body when you are sick. These hormones make your liver increase the amount of glucose in your bloodstream, and they can also make it difficult for insulin to do its job. This can cause your blood glucose levels to rise.
- ▶ While you are unwell it is VERY likely that your blood glucose will increase even if you are eating less than usual.
- ▶ If you are sick and have high blood glucose levels, you may be at risk of severe dehydration. This can result in you feeling drowsy and confused, and needing urgent medical attention.

# Maintain hydration

- ▶ **Stay hydrated:** drink at least ½ cup (100mls) of water/h  
(you can also drink any other sugar free drink)



Avoid strenuous exercise as this could affect your blood glucose levels



# Medications

## tablets or non-insulin injectable medications

- ▶ You may need to stop taking some medications during the period you are unwell
- ▶ You may find that because of reduced appetite or inability to eat your usual meals, these tablets may cause low sugars.
- ▶ Some of the tablets (oral hypoglycaemic agents) will need to be stopped during the period you are unwell and this may cause your blood sugar to go up.

## Insulin

- ▶ **Never stop insulin:** you may have to adjust the dose

**If you are taking any of the following diabetes medications you need to stop them when you are sick.**

Restart when you are well (normally after 24 to 48 hours of eating and drinking normally). When you restart your medicine, just take them as normal

**Metformin** – dehydration can make it more likely that you will develop a serious side effect called lactic acidosis

**Sulfonylureas** – if you are unable to eat or drink, it will be more likely that you develop low blood glucose (hypos)

- **Examples:** names ending with '*ide*' such as gliclazide, glibencamide, glipizide  
**If you are eating and drinking normally and blood sugars are high continue to take Sulfonylureas**

**GLP-1 analogues** –dehydration can make it more likely that you will develop a serious side effect.

- **Examples:** names ending with '*tide*' such as exenatide, dulaglutide, liraglutide, lixisenatide and semaglutide

**SGLT2 inhibitors** – dehydration can make it more likely that you will develop a serious side effect called ketoacidosis.

- **Examples:** names ending with '*flozin*' such as canagliflozin, dapagliflozin, empagliflozin and ertugliflozin

# Blood glucose measurement

If you already have access to blood glucose monitoring

- ▶ increase the frequency of checking your blood glucose every 4-6 h (q 2 to 4 hours if needed)

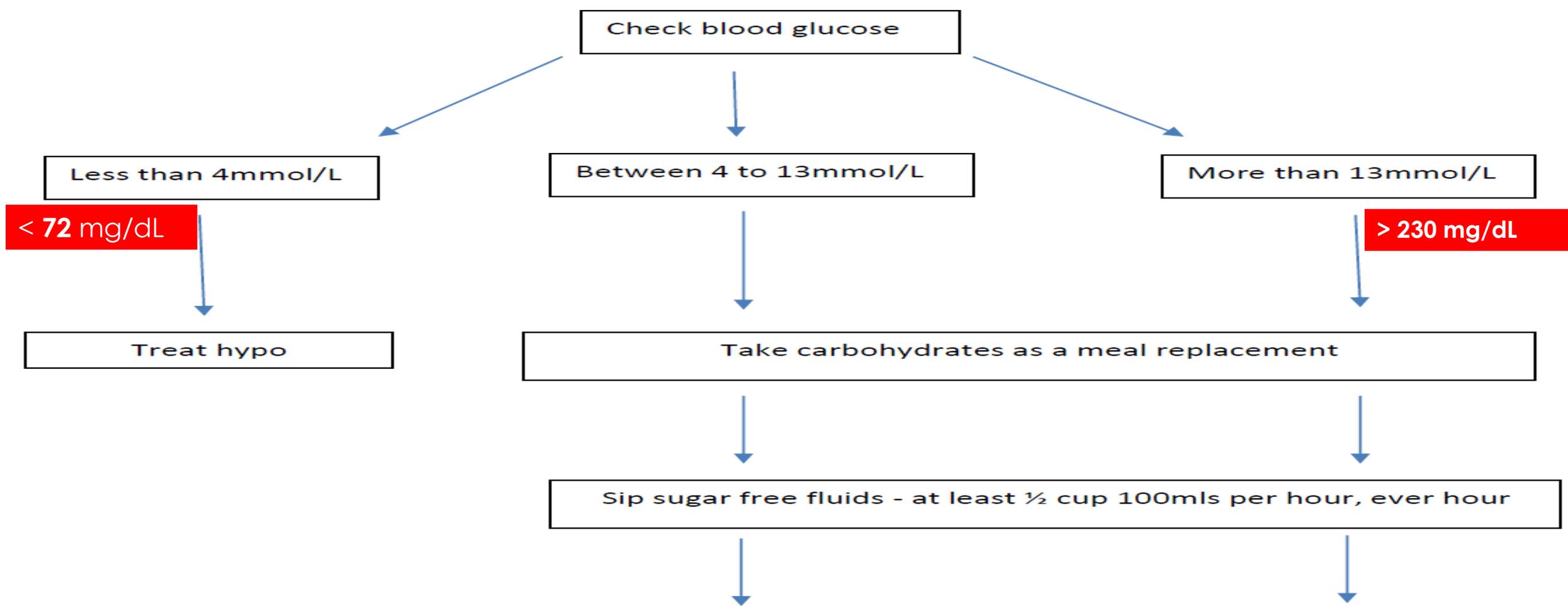
If you **DO NOT** have access to blood glucose monitoring

- ▶ look out for symptoms of high blood glucose. These include thirst, passing more urine than usual and tiredness. Seek medical advice if you have these symptoms.



## Striking the Right Balance

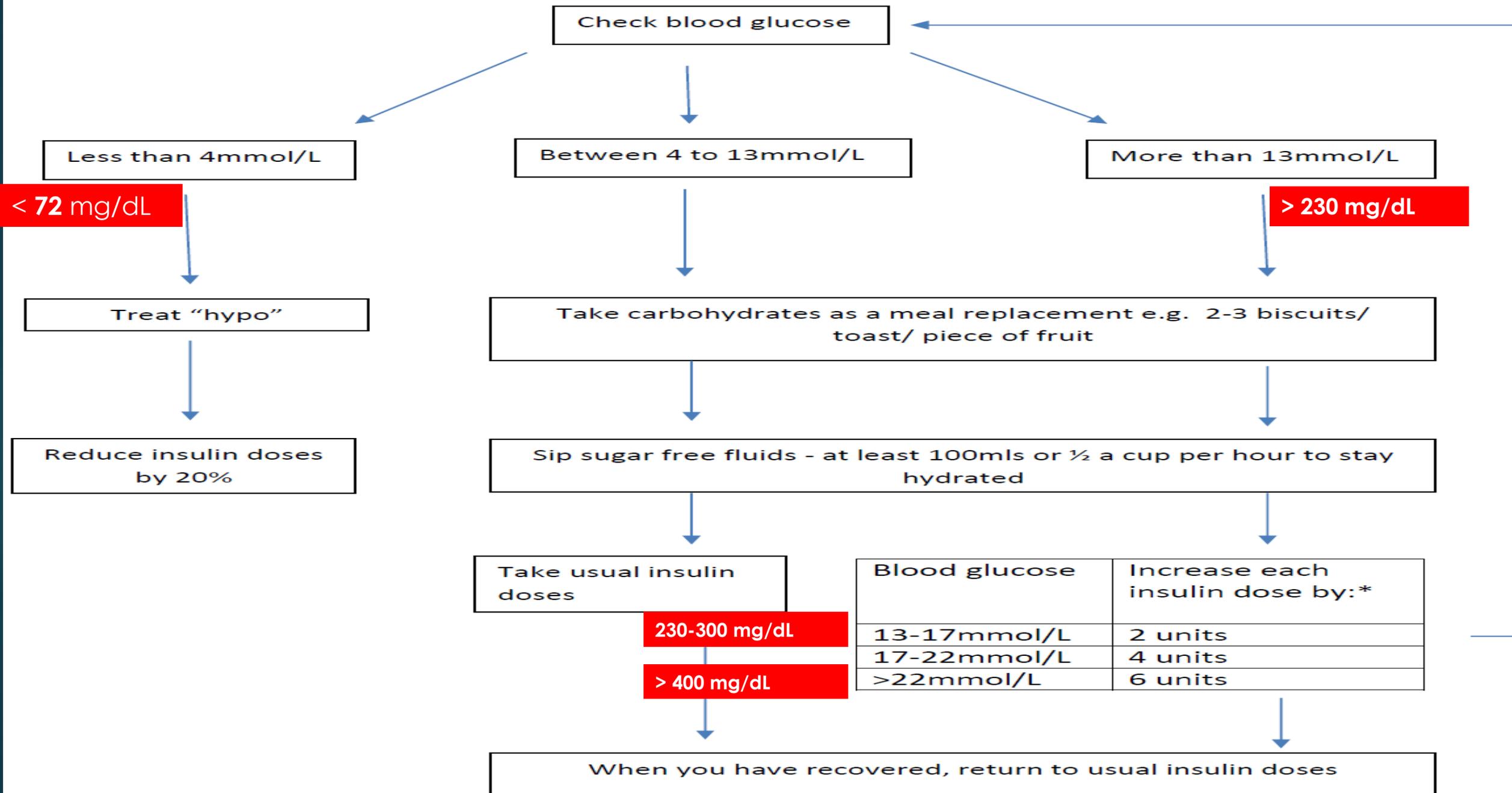




When stopping diabetes medication, it is likely your blood sugars will go up.

1. If you DO NOT have access to blood glucose monitoring, look out for symptoms of high blood glucose. These include thirst, passing more urine than usual and tiredness. Seek medical advice if you have these symptoms
2. If you do have access to blood glucose monitoring and are not on insulin and your blood sugars are consistently over 18 mmol/L, seek medical attention
3. If you do have access to blood glucose monitoring and are already on insulin, go to table 1 for instructions on how to adjust your

# What to do with your insulin, depending on your blood sugars



# DKA prevention in COVID

**TABLE 1.** How to calculate sick day's insulin adjustments, hydration, and monitoring [E]

A.		ADDITIONAL INSULIN HYPERGLYCEMIA		
KETONES		BLOOD GLUCOSE		
BLOOD	URINE	10 - 14 mmol/L 180 - 250 mg/dL	14 - 22 mmol/L 250 - 400 mg/dL	> 22 mmol/L > 400 mg/dL
< 0,6 mmol/L	Negative/trace	<ul style="list-style-type: none"> <li>• Give ordinary bolus</li> </ul>	<ul style="list-style-type: none"> <li>• Add +5% TDD or + 0,05 U/Kg to ordinary bolus</li> </ul>	
0,6 – 0,9 mmol/L	Trace/small	<ul style="list-style-type: none"> <li>• Add +5% TDD or +0,05 U/Kg to ordinary bolus or give 105% of calculated correction bolus</li> <li>• Oral sugar fluids</li> </ul>	<ul style="list-style-type: none"> <li>• Add + 5 - 10% TDD or + 0,05 - 0,1 U/Kg to ordinary bolus or give 105-110% of calculated correction bolus</li> <li>• Oral sugar-free fluids</li> </ul>	<ul style="list-style-type: none"> <li>• Add +10% TDD or +0,1 U/Kg to ordinary bolus</li> </ul>
1 – 1,4 mmol/L	small/moderate	<ul style="list-style-type: none"> <li>• Add + 5 - 10% TDD or 0,05 - 0,1 U/Kg to ordinary bolus or give 105-110% of calculated correction bolus</li> <li>• Oral sugar fluids</li> <li>• Extra CHO<sup>(*)</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Add +10% TDD or 0,1 U/Kg to ordinary bolus or give 110% of calculated correction bolus</li> <li>• Oral sugar-free fluids</li> </ul>	<ul style="list-style-type: none"> <li>• Oral sugar-free fluids</li> </ul>
1,5 – 2,9 mmol/L	Moderate/large		<ul style="list-style-type: none"> <li>• Add +20% TDD or 0,1-0,2 U/Kg to ordinary bolus or give 120% of calculated correction bolus</li> <li>• Oral sugar-free fluids</li> </ul>	<ul style="list-style-type: none"> <li>• Add +20% TDD or 0,1 U/Kg to ordinary bolus</li> </ul>
≥ 3 mmol/L	large	<ul style="list-style-type: none"> <li>• Add +10% TDD or 0,1 U/Kg to ordinary bolus or give 110% of calculated correction bolus</li> <li>• Oral sugar fluids</li> <li>• Extra CHO<sup>(*)</sup></li> </ul>	<ul style="list-style-type: none"> <li>• Add +20% TDD, or 0,1-0,2 U/Kg to ordinary bolus or give 120% of calculated correction bolus</li> <li>• Oral sugar-free fluids</li> </ul>	<ul style="list-style-type: none"> <li>• Oral sugar-free fluids</li> <li>• If vomiting, consider IV Saline +5% glucose solution</li> </ul>
Risk of Ketoacidosis! Consider DKA protocol and transfer to emergency department				
<b>CHECK BG AND KETONES EVERY 2 HOURS, REPEAT ADDITIONAL INSULIN IF NEEDED EVERY 2-4H</b>				

# DKA prevention in COVID

B. INSULIN REDUCTION NORMOGLYCEMIA/HYPOGLYCEMIA			
KETONES (starvation)		BLOOD GLUCOSE	
BLOOD	URINE	< 5,0 mmol/L < 90 mg/dL	5,0 - 10 mmol/L 90 - 180 mg/dL
< 0,6 mmol/L	Negative/trace	<ul style="list-style-type: none"> <li>• No extra insulin</li> <li>▪ Reduce TDD insulin 20%</li> <li>• Oral sugar fluids and extra CHO (*)</li> <li>▪ If BG &lt; 70mg/dl → Hypo correction (consider mini-dose of glucagon )</li> </ul>	<ul style="list-style-type: none"> <li>• No extra insulin</li> </ul>
0,6 – 0,9 mmol/L	Trace/small	<ul style="list-style-type: none"> <li>▪ Reduce TDD insulin 15%</li> <li>• Give ordinary bolus</li> <li>▪ Oral sugar fluids</li> <li>• Extra CHO (*)</li> </ul>	<ul style="list-style-type: none"> <li>• Oral sugar fluids</li> <li>• Extra CHO (*)</li> </ul>
1 – 1,4 mmol/L	small/moderate	<ul style="list-style-type: none"> <li>• Reduce TDD insulin 10%</li> <li>▪ Give ordinary bolus</li> <li>• Oral sugar fluids</li> <li>▪ Extra CHO (*)</li> </ul>	<ul style="list-style-type: none"> <li>• Give ordinary bolus</li> <li>• Oral sugar fluids</li> <li>• Extra CHO (*)</li> </ul>
1,5 – 2,9 mmol/L	Moderate/large	<ul style="list-style-type: none"> <li>▪ Do not reduce TDD insulin</li> <li>• Give ordinary bolus</li> <li>▪ Oral sugar fluids</li> <li>• Extra CHO (*)</li> </ul>	<ul style="list-style-type: none"> <li>• Add +5% TDD or 0,05 U/Kg to ordinary bolus</li> <li>• Oral sugar fluids</li> <li>• Extra CHO (*)</li> </ul>
≥ 3 mmol/L	large	<ul style="list-style-type: none"> <li>▪ If vomiting, cannot eat or drink, consider IV Saline +5% glucose solution</li> </ul>	<ul style="list-style-type: none"> <li>• Add +5% TDD or 0,05 U/Kg to ordinary bolus</li> </ul>
Risk of Ketoacidosis			
<b>CHECK FOR BG AND KETONES EVERY 2 HOURS</b>			

# Meal planning



- ▶ Do not fast: maintain carbohydrate intake
- ▶ If you are unable to eat or drink or are vomiting, replace meals with sugary fluids or ice cream



# Treating low blood glucose

First step: Treating the hypo, short acting carbohydrate

- ▶ 5 Dextrose tablets
- 5 jelly babies
- Half a can of sugary drink (non-diet)
- Fruit juice 200mls (non-diet)
- Ice cream 1 large scoop
- 5 spoonfuls sugar in warm water



After treating the hypo, try to eat 15-20g of slower acting carbohydrate

- ▶ Sandwich
- Piece of fruit
- Bowl of cereal
- Glass of milk 200ml



# Ask for help :



- ▶ If possible, have a friend or relative either stay with you or check on you frequently.
- ▶ Seek medical attention if:
  - ▶ High or low blood glucose levels persist despite changes
  - ▶ You are unable to maintain hydrated or take carbohydrates due to vomiting
- ▶ Seek urgent medical attention if you have symptoms such as shortness of breath, chest pain or a foot infection.

# Key Points :

- Drink at least ½ cup (100mls) of water/h
- Maintain carbohydrate intake
- Never stop insulin
- If you are unwell and have access to blood glucose monitoring, increase the frequency of checking to 4-6 hourly
- If you are unwell and do not have access to blood glucose monitoring, look for symptoms of high blood glucose and seek medical advice if you have these
- **Seek medical attention:**
  - if you are **unable to maintain hydrated or take carbohydrates** due to vomiting
  - if you have **persistently high or low blood glucose** readings despite altering your medications
- If you have altered your medication doses, remember to change them back to their usual doses gradually when you have recovered

# Please ensure you have access to the following at all times, not just when you become unwell:

- 1 month supply of all of your medicines
- If you normally check your blood sugar levels at home, ensure you have access to a blood glucose meter with 1 month supply of test strips and lancets
- If you have been advised to check ketones, please ensure you have access to a ketone testing system – either urine or blood.

If you are taking any of the following diabetes medications you need to **stop** them when you are sick.

**ACE inhibitors** – these medicines are used for heart conditions, high blood pressure and for kidney protection. If you are dehydrated, these medicines can stop your kidneys working properly.

- **Examples:** names ending in '*pril*' such as ramipril, lisinopril, perindopril, captopril

**ARBs** - these medicines are used for heart conditions, high blood pressure and for kidney protection. If you are dehydrated, these medicines can stop your kidneys working properly.

- **Examples:** names ending in '*sartan*' such as candesartan, irbesartan, losartan, valsartan

**Diuretics** – these medicines are used for excess fluid and high blood pressure and are sometimes called 'water pills'. These medicines can make dehydration more likely.

- **Examples** include bendroflumethiazide, furosemide, indapamide, bumetanide.
- If you are taking more than two tablets a day of either bumetanide or furosemide, please seek medical advice before stopping

**NSAIDs** – these are anti-inflammatory pain killers. If you are dehydrated, these medicines can stop your kidneys working properly.

- **Examples** include ibuprofen, naproxen

# Sick day in type 1 Diabetes

# SICK-DAY MANAGEMENT in T1DM

- ▶ Increased insulin requirements are due to an increase in counter-regulatory hormones released in response to stress.
- ▶ Decreased insulin requirements are due to reduced oral intake of carbohydrates because of decreased appetite, nausea, or vomiting.
- ▶ a patient with type 1 diabetes during an acute illness can develop:
  - ▶ ● Hypoglycemia
  - ▶ ● Significant hyperglycemia
  - ▶ ● Diabetic ketoacidosis due to inadequate insulin supplementation
  - ▶ ● Ketosis independent of hyperglycemia
- ▶ Sick-day management is directed towards prevention of the above complications

# SICK-DAY MANAGEMENT

- ▶ **Maintain hydration**
- ▶ **Maintain Carbohydrate intake**
- ▶ **Monitor blood glucose more frequently: q 2-3 h**
- ▶ **Monitor ketones frequently:** If home testing for **BOHB** is not available, the patient should monitor for **urinary ketones** with each void, regardless of blood glucose concentration.

# Insulin adjustment in SICK-DAY

- ▶ **Hyperglycemia without ketonuria or Ketonemia:**
  - ▶ 0.05-0.1 U/kg (5-10% TDD) q 2-4 h (Rapid acting 2-3 h- Short acting 4 h)
- ▶ **Hyperglycemia with ketonuria or ketonemia:**
  - ▶ 0.1-0.2 U/kg (10-20% TDD) q 2-4 h

## S (Sugar)

- Check your blood glucose level every 2 to 3 hours necessary (even more frequently for pregnant women and children)

## I (Insulin)

- Always continue to take your insulin even when you are sick to avoid DKA.

## C (Carbs)

- Make sure you take in enough carbs and drink enough fluids. If your glucose level is high, stick with sugar-free drinks. If your glucose level is low, drink carb-containing drinks.

## K (Ketones)

- Check your blood or urine ketone levels every 4 hours. Take rapid-acting insulin if ketones are present. Remember to drink plenty of water to flush out the ketones out of your system.

# Adjust the insulin dose

- ▶ **Patients with insufficient oral intake**
- ▶ To maintain glucose metabolism, **insulin should not be stopped** even if the child is not eating
- ▶ if blood glucose levels are **persistently low <80** mg/dL
  - ▶ Unable to ingest the required amount of carbohydrates
    - ▶ 10 to 20 percent decrease in basal or pump
    - ▶ Patients with fixed schedule with NPH (30-50% decrease in insulin dose)
  - ▶ Able to ingest the required amount of carbohydrates

# Indications for seeking urgent medical advice

- ▶ Age <5 years
- ▶ Vomiting >2 hours
- ▶ Child appears exhausted or confused
- ▶ Child is hyperventilating or has abdominal pain
- ▶ Blood glucose persistently low (<70 mg/dL) or continues to rise despite supplemental insulin doses
- ▶ Blood ketones remain elevated (>1.5 mmol/L) or urine ketones remain "large" despite extra insulin and hydration
- ▶ Child has a comorbid condition that complicates home care



## Sick day kit

The following items should be included in your kit:

- a copy of your sick day action plan
- a blood glucose meter (if you self-monitor)
- in-date blood glucose testing strips (if you self-monitor)
- your blood glucose diary
- a thermometer
- pain relief medication
- food and drinks for sick days
- hypo treatment
- in-date rapid-acting or short-acting insulin (if recommended by your health professional)
- insulin syringes or insulin pen (if you use insulin)
- telephone numbers for medical and support people.

Check your kit every six months to make sure it is still date and restock your kit if you have used it.

# In patients management:

- ▶ Move inpatient care for PWD to “Virtual” format if possible, to reduce the need for personal protective equipment.
  - ▶ use of electronic health records to interrogate data,
  - ▶ Telephone communication between diabetes care providers and inpatients and hospital
  - ▶ staff, expanded “diabetes self-management protocols”

# Glycemic control

- ❖ **Generally oral medication are not recommended in inpatient setting.**
  - ❖ **Sulfonylureas**, elevated hypoglycemia risk
  - ❖ **Metformin** CI in hypoxia/renal/hepatic dysfunction
  - ❖ **SGLT2 I** increase risk of DKA
  - ❖ **GLP1 A** risk of nausea/vomiting
- ❖ **DPP4 I**: sitagliptin, linagliptin in selected patients:
  - ❖ Hospitalized patients with type 2 DM & mild hyperglycemia (BS < 180 mg/dl) / in the recovery phase of covid
  - ❖ DPP4I + Insulin (correction/basal)

Table 1: Considerations for Non-Insulin 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 $\geq$ age 65, with eGFR $\leq$ 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 on board 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.

# Glycemic control

- ❖ Insulin is the preferred agent
- ❖ Insulin therapy should be initiated for those with BS >180 mg/dl
- ❖ **Target: 140-180 mg/dl,**
  - ❖ in selected cases: 110-140 mg/dl without hypoglycemia
- ❖ Intensive/moderate insulin therapy
- ❖ Insulin resistance, 50 unit/hr insulin requirement/close monitoring >20unit/hr

# Treatment option

	Uninfected but living in environment with prevalent COVID-19	Ambulatory mild disease	Hospitalized: moderate disease	Hospitalized: severe disease (admitted to ICU)
Recommended to use	<ul style="list-style-type: none"> <li>Insulin</li> <li>Metformin</li> <li>TZD</li> <li>DPP4 inhibitors</li> <li>GLP1 analogues</li> <li><math>\alpha</math>-Glucosidase inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Insulin</li> <li>DPP4 inhibitors</li> <li>Metformin</li> <li>GLP1 analogues</li> </ul>	<ul style="list-style-type: none"> <li>Insulin</li> <li>DPP4 inhibitors</li> <li>Metformin</li> <li>GLP1 analogues</li> </ul>	<ul style="list-style-type: none"> <li>Insulin</li> <li>DPP4 inhibitors</li> </ul>
Can be used with caution	<ul style="list-style-type: none"> <li>Sulfonylurea</li> <li>SGLT2 inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Sulfonylurea</li> <li>SGLT2 inhibitors</li> <li>TZD</li> <li><math>\alpha</math>-Glucosidase inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Sulfonylurea</li> <li><math>\alpha</math>-Glucosidase inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Metformin</li> <li>GLP1 analogues</li> <li><math>\alpha</math>-Glucosidase inhibitors</li> </ul>
Not recommended			<ul style="list-style-type: none"> <li>TZD</li> <li>SGLT2 inhibitors</li> </ul>	<ul style="list-style-type: none"> <li>Sulfonylurea</li> <li>TZD</li> <li>SGLT2 inhibitors</li> </ul>

**Table 2**

DETAILED TREATMENT GUIDANCE BG 200–250 mg/dL		
1.	<b>NO PRIOR KNOWN DIABETES or KNOWN DIABETES ON &lt;2 ORAL AGENTS</b>	<b>MONITORING</b>
	• Check HbA <sub>1c</sub> if none available in last 3 months	Check BG every 6 h
	<b>a Start sliding scale regular insulin: moderate to high dose and escalate scale if BG &gt;250 mg/dL</b>	
	<b>b Add scheduled regular insulin every 6 h if TF initiated (see above for regular insulin dosing based on eGFR and hourly TF rate) + scale</b>	
	<b>c Add scheduled regular insulin if BG remains &gt;250 mg/dL + scale even if no TF initiated</b>	
2.	<b>KNOWN DIABETES PRIOR TO ADMISSION</b>	Check BG every 6 h
	• Check HbA <sub>1c</sub> if none available in last 3 months	
	<b>a T1DM NPO: add basal insulin glargine ASAP (to avoid DKA): use 70% of home dose if eGFR &gt;50 and 50% if eGFR &lt;50 + scale</b>	
	<b>b T1DM on insulin pump and has supplies: if feasible, continue basal insulin via pump (use increased temporary basal rate if needed); rare use in ICU so calculate total basal as in a</b>	
	<b>c T1DM + TF: continue basal insulin (to prevent DKA) and add scheduled regular insulin for TF every 6 h (guidance above based on eGFR and TF rate) + scale</b>	
	<b>d T2DM NPO: on regimen that included insulin prior to admission: start 25–50% basal dose + scale</b>	
	<b>e T2DM on insulin PTA + TF: start 25–50% basal dose and regular insulin for TF coverage every 6 h; see above for dose calculations + scale</b>	

BG, blood glucose; DKA, diabetes ketoacidosis; eGFR, estimated glomerular filtration rate (mL/min/1.73m<sup>2</sup>); HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; NPO, nothing by mouth; PTA, prior to admission; T1DM, patients with type 1 diabetes; T2DM, patients with type 2 diabetes; TF, tube feeding.

## Sample insulin correction algorithm, using short-acting or rapid-acting insulin

Glucose values (mg/dL [mmol/L])	Insulin dose (units) every 4 to 6 hours
<150 (8.3)	0
151 to 200 (8.4 to 11.1)	0 to 2
201 to 250 (11.2 to 13.9)	4
251 to 300 (13.9 to 16.6)	6
301 to 350 (16.7 to 19.4)	8
351 to 400 (19.5 to 22.2)	10

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Older, lean, T1DM patients or individuals with renal or liver failure are usually considered to be "**insulin sensitive**," while obesity or treatment with glucocorticoids are usually associated with an insulin-resistant state

# Questions

1. Who are high risk patient for corona viruses?
2. Are all diabetics are similar in facing COVID 19?
3. How hyperglycemia affect immune system?
4. What are the cause of hyperglycemia in covid-19?
5. How glycemic control can influence COVID mortality?
6. What are the glycemic target in COVID patients?
7. What are the effective treatments in out patients & hospitalized patients?
8. **How should GIH be managed?**
9. What is the prognosis of DKA in covid-19
10. How should DKA be prevented/treated?

# Glucocorticoid induced hyperglycemia

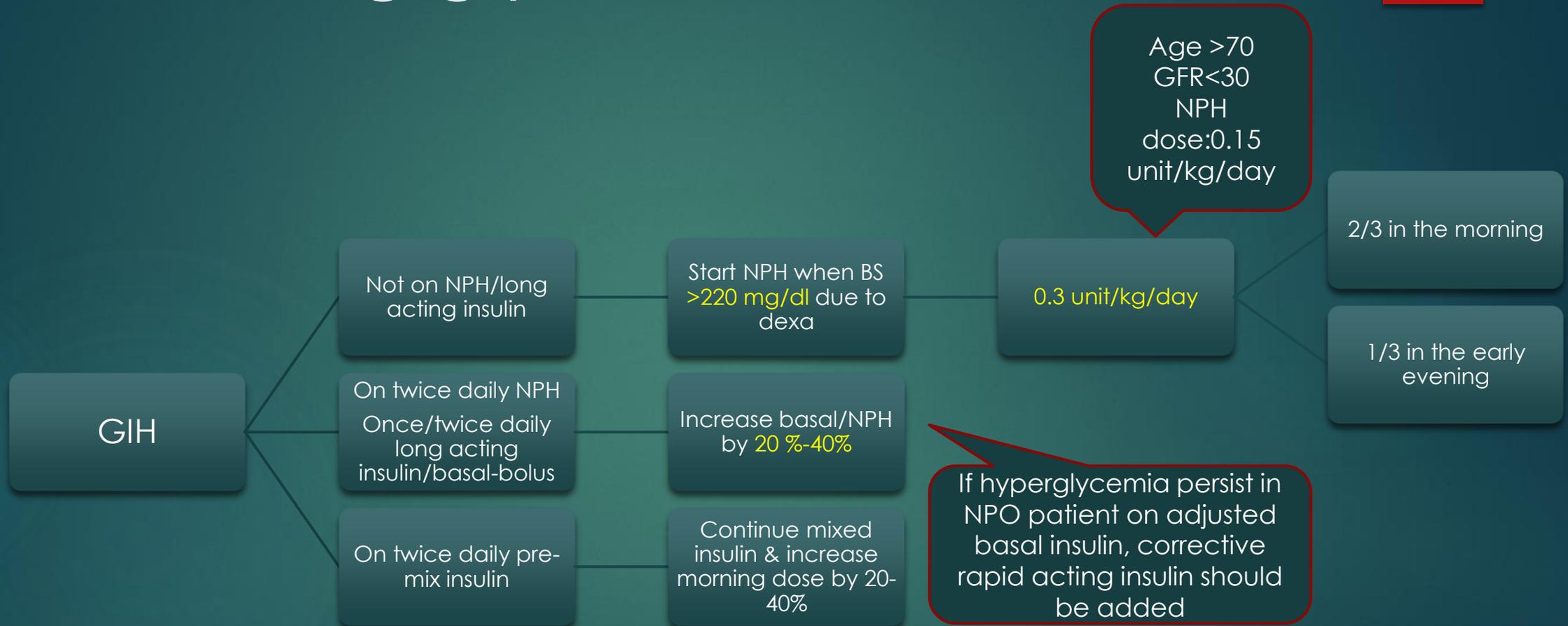
- ❖ Targeted glucose level:  
6-10/12 mmol/l  
**(110-180/220 mg/dl)**



# Correction dose of rapid acting insulin



# Maintaining glycemic control



# Questions

1. Who are high risk patient for corona viruses?
2. Are all diabetics are similar in facing COVID 19?
3. How hyperglycemia affect immune system?
4. What are the cause of hyperglycemia in covid-19?
5. How glycemetic control can influence COVID mortality?
6. What are the glycemetic target in COVID patients?
7. What are the effective treatments in out patients & hospitalized patients?
8. How should GIH be managed?
9. **What is the prognosis of DKA in covid-19**
10. How should DKA be prevented/treated?



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### Clinical profile and outcomes in COVID-19 patients with diabetic ketoacidosis: A systematic review of literature



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**Table 2**

Showing demographic parameters of the COVID-19 patients with DKA (and combined DKA/HHS).

Parameter	Value
Age (years) [Median (IQR)]	45.5 (36.2–57.7) [7,8,10–16,18–21,23,24,28] <sup>a</sup> 57.0 (48.0–64.0) [22] <sup>b</sup> 59.0 (42.3–70.0) [9]
Sex (N = 102) <sup>c</sup>	Male (n = 64, 63%) Female (n = 38, 37%)
Ethnicity <sup>d</sup> (N = 84)	Black (n = 30, 36%) <sup>e</sup> Hispanic (n = 19, 23%) White (Caucasian) (n = 10, 12%) Asian (n = 6, 7%) Mixed (n = 4, 5%) Others (n = 8, 9%) Unknown (n = 7, 8%)
Type of diabetes <sup>f</sup> (N = 97)	Pre-existing T1DM (n = 12, 12%) Pre-existing T2DM (n = 74, 77%) Newly diagnosed (n = 10, 10%) Gestational DM (n = 1, 1%)
Use of SGLT2 inhibitors <sup>g</sup>	7
BMI (kg/m <sup>2</sup> ) [Median (IQR)]	26.6 (23.7–32.3) [7,11–13,16,28] <sup>h</sup> 24.7 (21.3–28.5) [22] <sup>b</sup> 27.1 (23.2–33.0) [9]

**Table 3**

Showing biochemical parameters at presentation in COVID-19 patients with DKA (and combined DKA/HHS).

Biochemical parameter at presentation	Value <sup>a</sup>
Blood glucose (mg/dl)	568.5 (385.5–889.7) [7,8,10–16,18–21,23,24,28] <sup>b</sup> 486.0 (396.0–558.0) [22] <sup>g</sup> 506.5 (252.0–1485.0) [9]
HbA <sub>1c</sub> (%)	11.7 (9.5–13.2) [10–13,16,19,23,24,28] <sup>c</sup> 12.4 (10.7–14.2) [22] <sup>g</sup>
pH	7.17 (6.99–7.24) [7,8,10–16,18,21,23,24,28] <sup>d</sup> 7.20 (6.90–7.30) [22] <sup>g</sup>
Bicarbonate (mmol/l)	8.0 (6.0–12.5) [7,8,10–14,16,23,24,28] <sup>e</sup> 11.8 (7.8–15.4) [22] <sup>g</sup>
Anion gap (mEq/l)	29.0 (18.0–32.0) [7,8,12,13,15,20,24,28] <sup>f</sup> 14.8 (10.4–20.5) [22] <sup>g</sup> 28.1 (14.3–41.2) [9]

**Table 4**

Showing comparison of clinical outcomes of COVID-19 patients with DKA (and combined DKA/HHS) in whom individual patient data were available (N = 27).

Parameter	Discharged (n = 17)	Deceased (n = 10)	p value
Age (years)	46.0 (33.5–54.0)	42.5 (34.2–59.7)	1.000
Sex	Male = 11 Female = 6	Male = 10 Female = 0	–
DKA vs. Combined DKA/HHS	DKA = 15 (71%) DKA/HHS = 2 (33%)	DKA = 6 (29%) DKA/HHS = 4 (67%)	–
Blood glucose (mg/dl)	463.0 (347.0–641.0)	801.5 (376.5–1080.5)	0.120
pH	7.23 (7.09–7.26)	7.00 (6.91–7.11)	<b>0.017</b>
Bicarbonate (mmol/l)	10.4 (6.0–15.0)	7.0 (5.7–8.0)	0.098
Anion gap (mEq/l)	25.5 (16.8–34.0)	29.0 (28.0–30.5)	0.806

COVID-19: Novel coronavirus disease; DKA: Diabetic ketoacidosis; HHS: Hyperglycemic hyperosmolar syndrome.

# DKA treatment in COVID

**Table 1. Classification of hyperglycemic crisis severity (10) and insulin treatment options**

	<b>Mild DKA</b>	<b>Moderate DKA</b>	<b>Severe DKA</b>	<b>HHS</b>	<b>HK</b>
Blood glucose mg/dL (mmol/L)	> 250 (>13.8)	>250 (>13.8)	>250 (>13.8)	>600 (>33.3)	>600 (>33.3)
pH	7.25-7.30	7.00-7.24	<7.00	>7.30	
HCO <sub>2</sub> (mmol/L)	15-18	10-14	<10	>18	
Urine/serum ketones	+	+	±	±	+
Serum osmolality <sup>a</sup> (Osm <sub>eff</sub> )				320	320
Anion gap	Elevated	Elevated	Elevated	Elevated	Elevated
Mental status	Alert	Alert/drowsy	Stupor/coma	Stupor/coma	Stupor/coma
Insulin therapy	SC/IV	SC/IV	IV	IV	IV
Frequency of glucose monitoring	every 1-2 hours	every 1-2 hours	every 1 hour	every 1 hour	every 1 hour
Location of care	Intermediate care unit	Intermediate care unit/ICU	ICU	ICU	ICU

# Take home messages

- ▶ Potential pathogenetic links between COVID-19 and diabetes mellitus include effects on glucose homeostasis, inflammation, altered immune status and activation of the renin–angiotensin–aldosterone system (RAAS).
- ▶ During the COVID-19 pandemic, tight control of glucose levels and prevention of diabetes complications might be crucial in patients with diabetes mellitus to keep susceptibility low and to prevent severe courses of COVID-19.
  - ▶ Optimization of current therapy if appropriate
  - ▶ Caution with premature discontinuation of established therapy
  - ▶ Utilization of telehealth and remote consultation-patient empowerment
  - ▶ Cautious about Nonscientific message in media

# Take home messages

- ▶ Evidence suggests that insulin and DPP4 inhibitors can be used safely in patients with diabetes mellitus and COVID-19; metformin and sodium–glucose cotransporter 2 inhibitors might need to be withdrawn in patients at high risk of severe disease.
- ▶ Pharmacological agents under investigation for the treatment of COVID-19 can affect glucose metabolism, particularly in patients with diabetes mellitus; therefore, frequent blood glucose monitoring and personalized adjustment of medications are required.
- ▶ As COVID-19 lacks definitive treatment so far, patients with diabetes mellitus should follow general preventive rules strictly and monitor glucose levels more frequently, engage in physical activity, eat healthily and control other risk factors.



**Thanks for your attention**