COVID-19, Steroids and Hyperglycaemia

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13 August 2020

DM as risk factor for Covid-19

- SA prevalence – 12.8% (IDF; 2019)
- Immune dysregulation – more susceptible to infections
- Chronic inflammatory condition – NB inflammatory storm seen in DM pts with Covid-19
- Increased morbidity and mortality
- Metabolic phenotype – company it keeps
- Suboptimal DM care and follow up during pandemic
- Hyperglycaemia at time of infection - increase local viral replication

Effect of SARS-CoV-2

- DM first recognized in Covid-19

- Undiagnosed DM
- Sars-CoV-2 new onset DM

- Severe metabolic complications of DM

Acta Diabetol (2010) 47:193–199
DOI 10.1007/s00592-009-0109-4

ORIGINAL ARTICLE

Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes

Jin-Kui Yang · Shan-Shan Lin · Xiu-Juan Ji · Li-Min Guo

What contributes to the degree of hyperglycaemia?

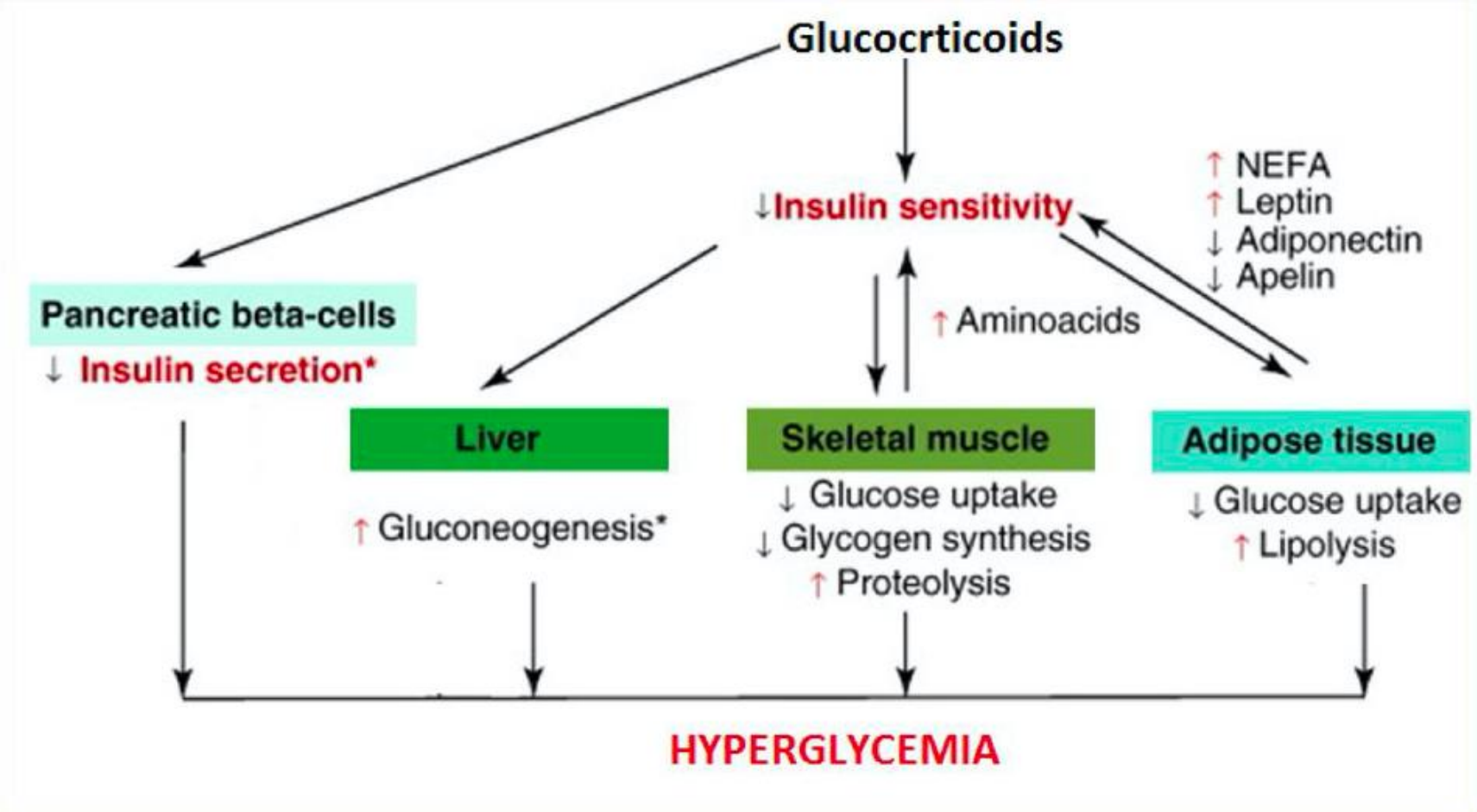
- Chronic underlying inflammation associated with DM and obesity
- Insulin resistance (multifactorial)
- Impaired insulin production (multifactorial)
- “Stress” hyperglycaemia
- Steroids

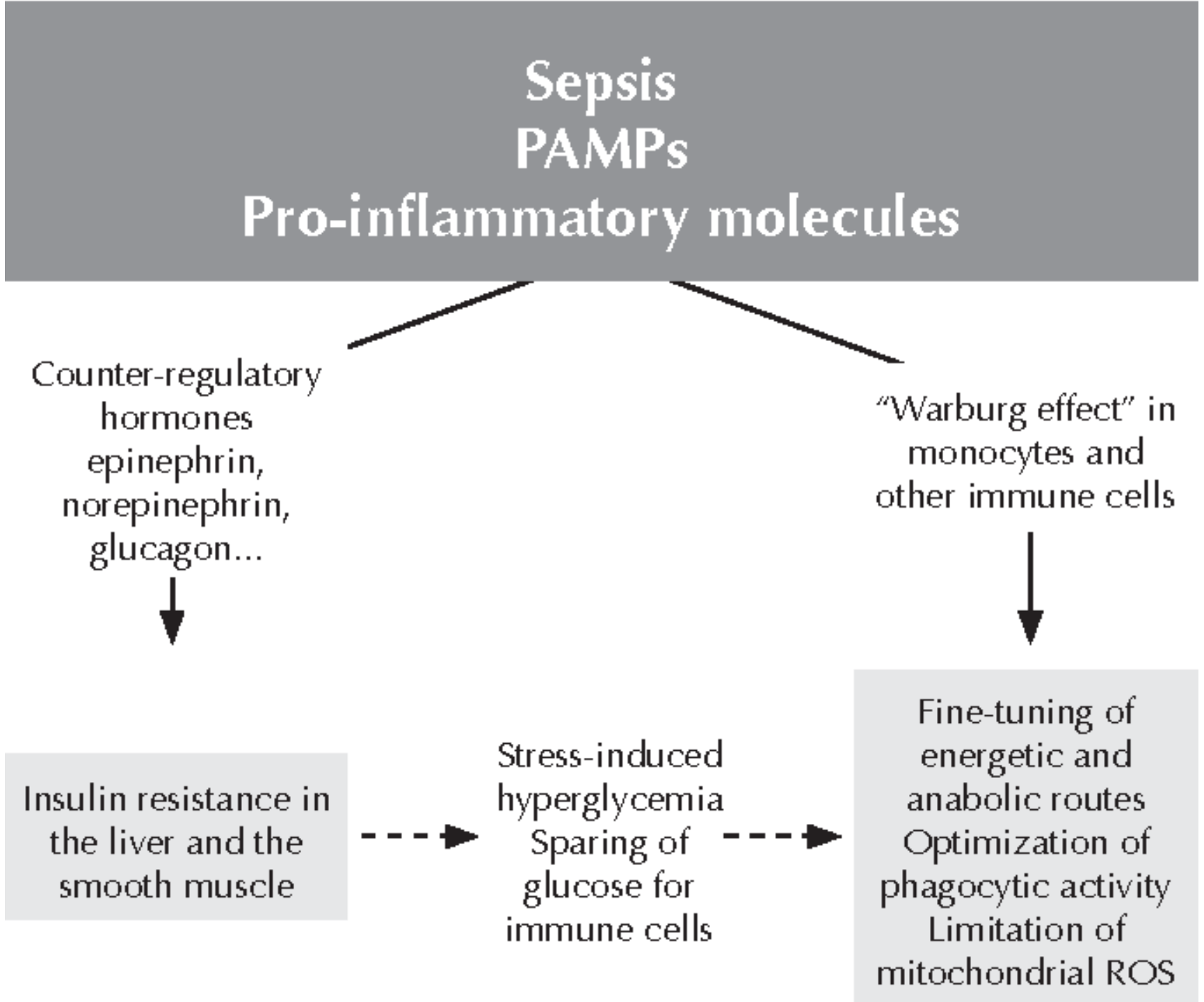
FIGHT

OR

FLIGHT

Effect of Glucocorticosteroids



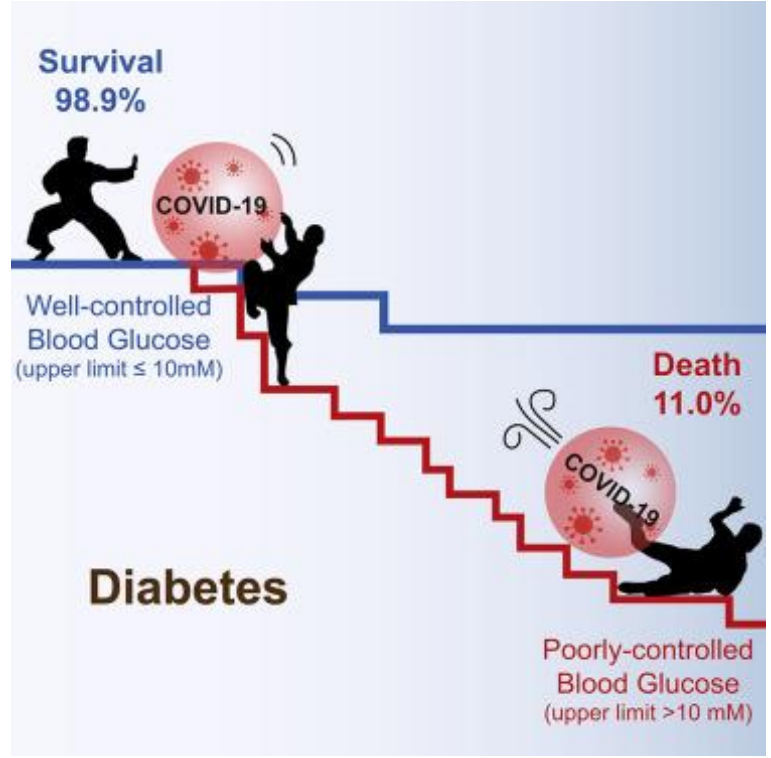

Sepsis
PAMPs
Pro-inflammatory molecules
Counter-regulatory hormones epinephrin, norepinephrin, glucagon...
"Warburg effect" in monocytes and other immune cells
Insulin resistance in the liver and the smooth muscle
Stress-induced hyperglycemia
Sparing of glucose for immune cells
Fine-tuning of energetic and anabolic routes
Optimization of phagocytic activity
Limitation of mitochondrial ROS

Effects of hyperglycaemia

- Poor glycaemic control in hospitalized patients linked to adverse outcomes

Covid-19

- Increased mortality
- Prolonged hospital stay and morbidity



Approach

1. Clinical picture
2. Mode of presentation
3. Resources and expertise

Clinical picture

- Pre-existing DM and control
- Newly diagnosed DM
- Phenotype

- Insulin Resistance
- Obesity
- Pre-DM
- Ketosis prone DM
- Likelihood of Covid-19, clinical severity and need for steroids

Mode of presentation

- DKA or HHS
- Incidental
- Related to dexamethazone use
- Longstanding poly symptoms
- Family history
- Presence of other endocrinopathies or autoimmune disorders
- Presence of TOD

Recourses and expertise

- High care facilities
- Trained nursing personnel
- Referral system

Diagnosing DM

TYPE 1, TYPE 2 ADA 2019 (OR OVERT DIABETES)

Diabetes is diagnosed at any age based on at least 2 of the following values:

- **FBG ≥7.0 mmol/l**
- **RBG / OGGT ≥11.1 mmol/l**

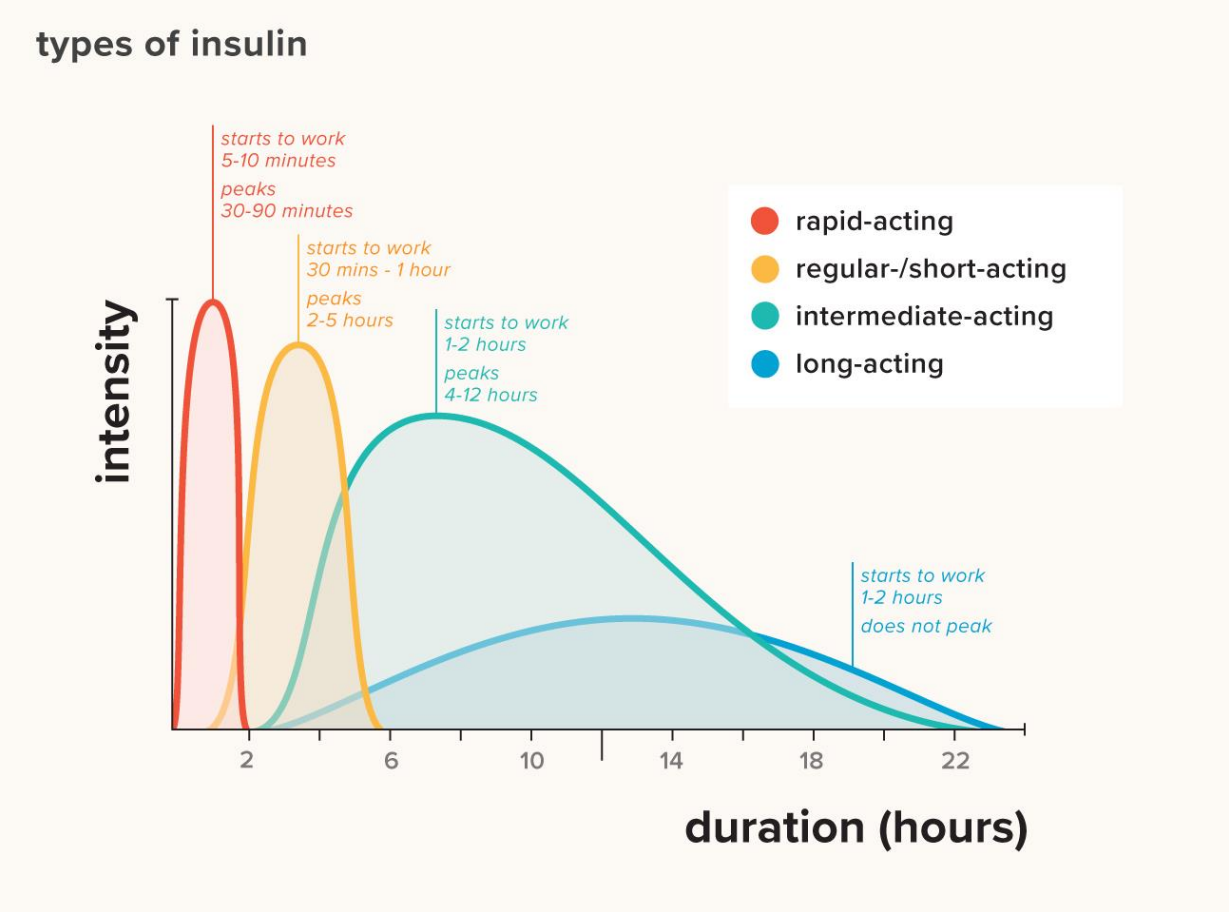
Diabetes is also diagnosed in the following circumstances without the need of other tests to confirm diabetes:

- **RBG ≥11.1 mmol/l** along with typical symptoms of hyperglycaemia
- **HbA1c ≥ 6.5 %**

Insulin

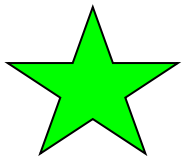
Type [*proprietary name*]	**Onset**	**Peak**	**Duration**
Short-acting regular human insulins [*Actrapid, Humulin-R, Insuman, Biosulin-R*]	30-60 minutes	2-3 hours	Up to 7-8 hours
Rapid-acting analogue insulins Aspart [*NovoRapid*] Glulisine [*Apidra*] Lispro [*Humalog*]	5-15 minutes	1.5-3.5 hours	5-8 hours
Intermediate-acting (basal) human insulins			
NPH - neutral protamine Hagedorn [*Humulin-N, Protaphane, Biosulin-N*]	120-240 minutes	4-10 hours	10-18 hours[§]
Lente – contains zinc [*Biosulin-L*]	90 minutes	4-8 hours	22-24 hours[§]
Long-acting (basal) analogue insulins Glargine [*Lantus, Optisulin, Basaglar*]	120-240 minutes	No peak	Up to 24 hours[§]
Pre-mixed human (biphasic) insulins 30% Regular + 70% NPH [*Actraphane, Humulin 30/70, Insuman, Biosulin 30/70*]	30-60 minutes	Dual peak	10-18 hours
Pre-mixed analogue insulins	5-15 minutes	Dual peak	10-16 hours
Rapid-acting plus basal Biphasic aspart [NovoMix] Biphasic lispro [Humalog Mix25, Humalog Mix50]			
Rapid-acting plus ultra-long-acting basal Pre-mixed aspart/degludec [Ryzodeg]	5-15 minutes	Dual peak	>24 hours

Insulin action



Subcutaneous human insulin injections

Actrapid / Humulin R / Insuman R



Protophane/ Humulin N/ Insuman

Actraphane / Humulin 30/70 (30% yellow & 70% green)

Vials with insulin syringes or pre-filled pensets

Targets in Covid-19

- **ISPAD 2018 and ADA 2019**

  7.8 – 10 mmol/L (ill and hospitalized)

- **COVID: DIABETES**

  6.0 – 10 mmol/L (up to 12 mmol/L)

Monitoring:

6 hourly – Preprandial and bed time

or 02:00 if taking bedtime insulin

Current evidence

Diabetes 1

Managing Hyperglycemia in the COVID-19 Inflammatory Storm

Roma Gianchandani, Nazanene H. Esfandiari, Lynn Ang, Jennifer Iyengar, Sharon Knotts, Palak Choksi, and Rodica Pop-Busui

https://doi.org/10.2337/dbi20-0022

- **Positives**

- Links inflammatory storm with DM

- **Negatives**

- Overall lack of data – mortality, ICU stay, etc

- Rational for certain cutoffs?

- Reduced insulin doses on bases of inflammatory markers

- Complex insulin regime – basal, regular 6hrly short acting insulin and sliding scale

- mg/dL

COncise adVice on Inpatient Diabetes (COVID:Diabetes):

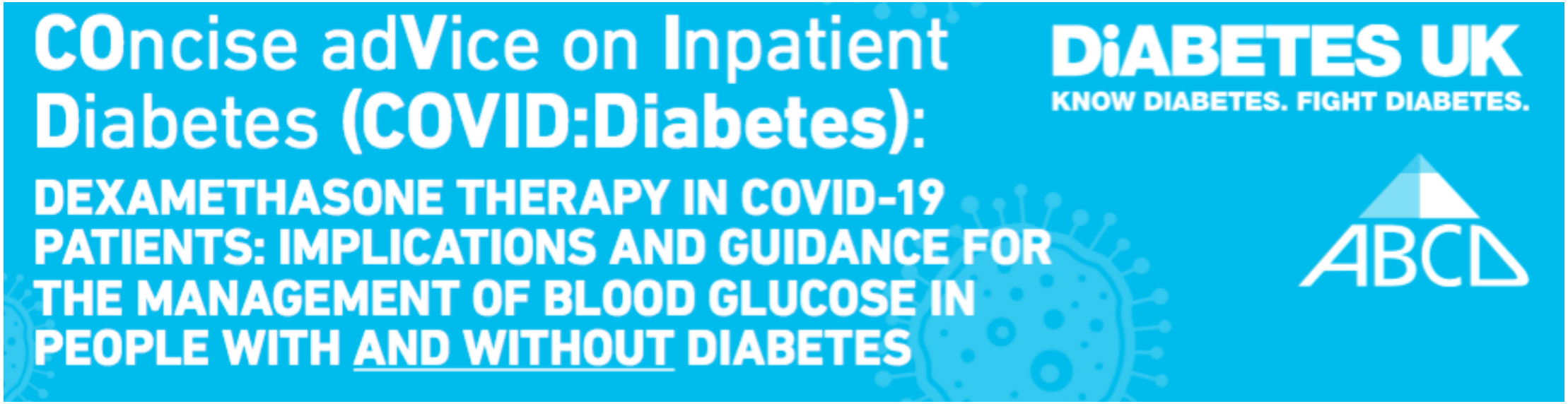
GUIDANCE FOR MANAGING INPATIENT HYPERGLYCAEMIA

DiABETES UK
KNOW DIABETES. FIGHT DIABETES.

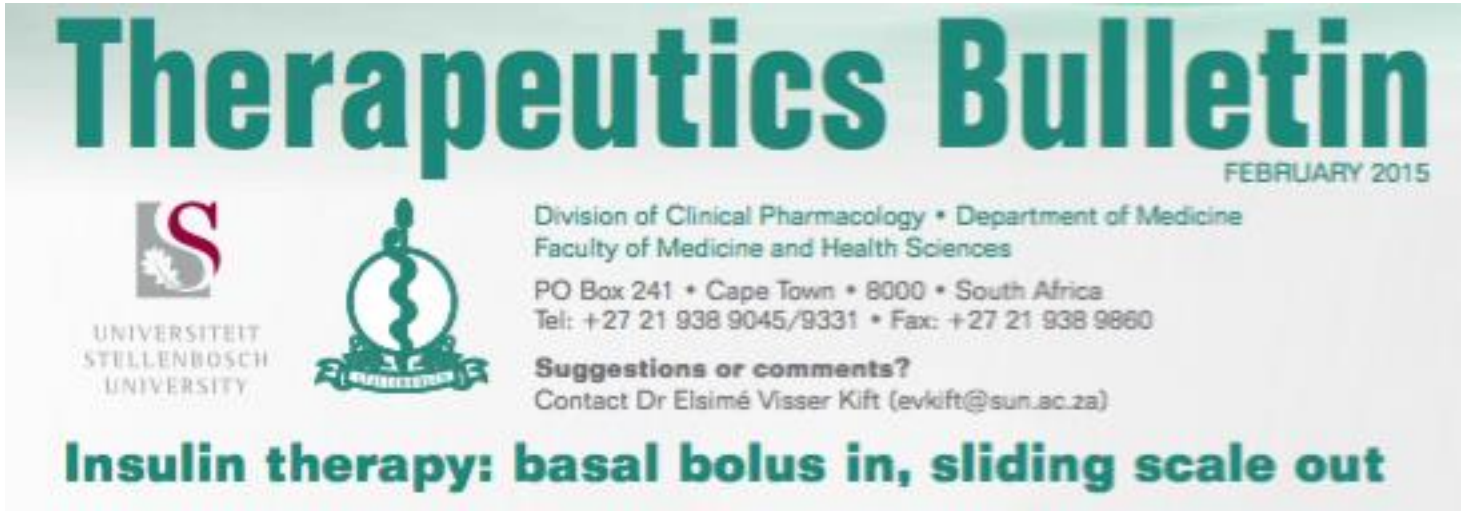
ABCD

Analogue based regime (not helpful in our setting)

Current evidence



Tygerberg



Therapeutics Bulletin

FEBRUARY 2015

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Suggestions or comments?
Contact Dr Elsimé Visser Kift (evkift@sun.ac.za)

Insulin therapy: basal bolus in, sliding scale out

Key points

Basal-bolus insulin regimens

- Basal + bolus + correctional insulin regimen is preferred to sliding scale (correctional) insulin alone.
- Correctional insulin alone is a reactive strategy to glucose control and if used, should only be used in conjunction with a basal-bolus regimen.
- Type 1 diabetics always require basal insulin, even if they are not eating.
- IV soluble insulin infusion may be preferred above SC insulin regimen in the critically ill.

Correctional insulin (also called short-acting insulin sliding scale)

- Avoid routine correctional insulin as the only insulin regimen in diabetics.
- The only place for correctional insulin is in conjunction with a basal-bolus insulin
- If patients are eating, inject bolus (prandial) insulin before meals as per plasma glucose level and predicted food intake and NOT every 4 (or 6) hours.
- Do not give correctional insulin at bedtime.

6 Step approach

1. TDD – depending on insulin sensitivity (0.3-0.7U/kg)
2. Basal (protophane) 30-40%

   60-70% (actrapid) divided doses before meals
3. Correction dose (add to pre-prandial dose depending on HGT)
5. Continues re-assessment and adjustment
6. Phone a friend

Sliding scale?

Correction dosing

Step 3

Estimate the correctional insulin dose for the **optional** short-acting insulin "sliding scale" to be given in conjunction with short-acting bolus insulin 30 min before meals.

A quick and easy estimation for the scale increment is to use 5% of the total daily dose of insulin (TDD insulin). For example, for TTD of 80 units insulin the scale should increase with 4 unit increments (5% of 80 = 4). No additional insulin should be given for blood glucose levels below 8.1 mmol/L (if hypoglycaemia is an concern use a higher blood glucose cut-off value).Thus, for a blood glucose of

8.1-11mmol/L give 4 extra units of short-acting insulin, for

11.1-14 mmol/L give 8 extra units of short-acting insulin, for

14.1-17 mmol/L give 12 extra units of short-acting insulin, for

> 17.1 mmol/L give 12 extra units of short acting insulin plus evaluate patient (measure serum ketones in DM1).

Review clinical status and steps 1 and 2 when correctional insulin is required.

Is this regime achievable in our current setting and is it appropriate?

- Individualize
- Severely glucose toxic post DKA patient or severe Covid
- Resources permit
- Most patients one can probably get away with adjustment chronic regime
- Patient driven testing and injection
- Realistic expectations – hospital/artificial setting
- Aim – safe profile rather than supra-normal control in acute setting
- Special considerations – Elderly, CKD, IHD

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

Respiratory Support at Randomization	Dexamethasone	Usual Care	Rate Ratio (95% CI)
	no. of events/total no. (%)		
Invasive mechanical ventilation	95/324 (29.3)	283/683 (41.4)	0.64 (0.51–0.81)
Oxygen only	298/1279 (23.3)	682/2604 (26.2)	0.82 (0.72–0.94)
No oxygen received	89/501 (17.8)	145/1034 (14.0)	1.19 (0.91–1.55)
All Patients	**482/2104 (22.9)**	**1110/4321 (25.7)**	**0.83 (0.75–0.93)**
			P<0.001

Chi-square trend across three categories: 11.5

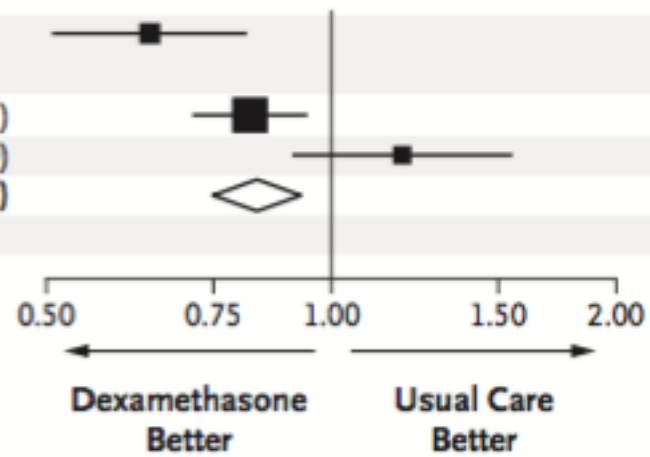


Figure 3. Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.

Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Steroids induced hyperglycaemia

- Montior for 48 hrs
- If < 10 mmol/L, continue once dly monitoring until dexa stopped
- Fasting > 10 mmol/L or > 12 mmol/L correct and continue monitoring
- Initial correction – DM or treatment naïve, BW and TDD of insulin
- Maintenance:

- Rx naïve:

    0.3U/kg Intermediate acting insulin (protophane/green)

    $^{2}/_{3}$ AM and $^{1}/_{3}$ between 5-8PM

Pre-existing DM

- Pre-Mix (Actraphane/brown)
- Start by increasing morning dose 20-40%
- Continue to adjust depending on HGT value targeting

- Basal regime (basaglar/lantus)
- Start by increasing basal by 20-40%
- Pre-prandial correction doses depending on intake

End of therapy

- Decline in insulin resistance and stabilization of glycaemic profile might take 2-3 days
- Continue monitoring 6 hrly and adjust treatment

- **New DM in Covid**

- Third can develop DM later in life

New onset DM in Covid-19

Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes

In our previous report, hyperglycemia was an independent predictor of death, and patients with even mild SARS (receiving no glucocorticoid medications during the course) had a higher level of FPG [1]. In our follow-up study, diabetes occurred during the hospitalization of 20 of 39 patients who received no corticosteroids during the course of SARS. But after 3 years of follow-up, only two of these patients had diabetes. Also after 3 years follow-up, FPG, PPG, and insulin levels were similar in the SARS group and their matched, healthy non-SARS siblings, which suggested that the damage of islets by SARS-CoV was transient

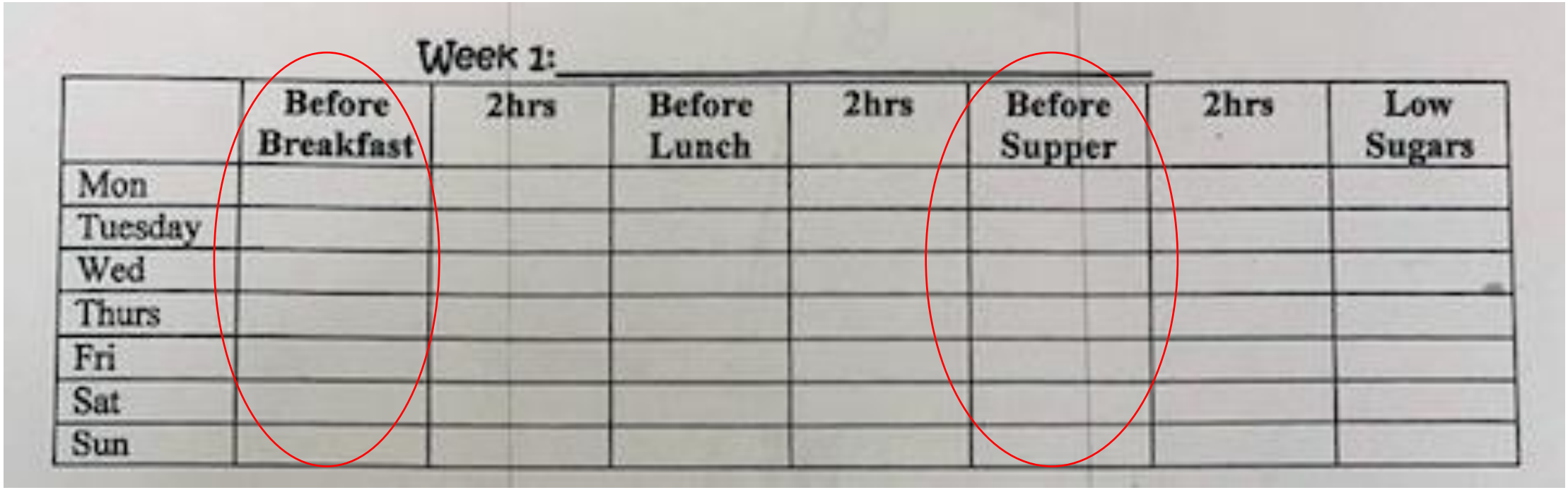
Discharge

- Aim: keep patient safe – most likely all will get insulin on discharge
- Once glucose toxicity has resolved, especially in the setting of newly diagnosed DM, patients will require prompt re-assessment and adjustment of treatment
- Metformin still cornerstone of treatment in T2DM

Discharge plan

- Every patient should have a planned follow up visit scheduled
- Preferably with a glucose profile
- Injection technique
- Glucometer
- Manage hypoglyceamia
- Danger signs of possible DKA
- All T1DM should have a hypo-kit and next of kin should be well practiced on how to use it

Glucose profile



Week 1: _____

	Before Breakfast	2hrs	Before Lunch	2hrs	Before Supper	2hrs	Low Sugars
Mon							
Tuesday							
Wed							
Thurs							
Fri							
Sat							
Sun							