Exercise and the Development of the Artificial Pancreas

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Until a cure is found…….

1. Insulin Therapy
2. Regular Exercise
3. A Healthy Diet


109
mg/dL
dexcomG4


120


10:00 AM
120
0.5 U
Act. Insulin


Animas vibe
1:29 PM
13.5
mmol/L
IOB 3.89U
OK


205
dexcomG5


clarityAGP
12AM
12PM
12AM


Accu-Chek
Aviva Combo

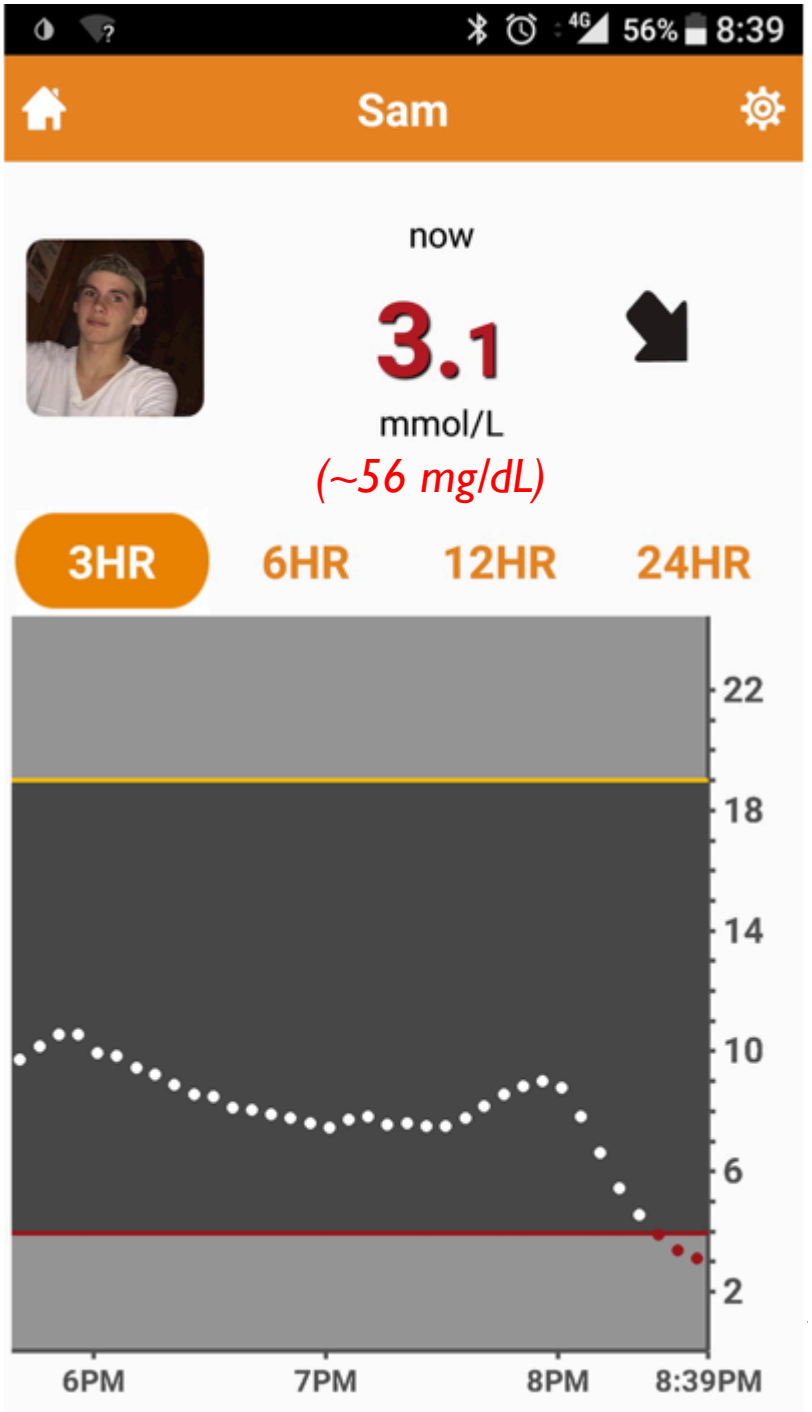

6.2
FreeStyle Libre


glooko


10:20 AM
July 22, 2015
190
mg/dL
3
HRS
OPTIONS
BOLUS

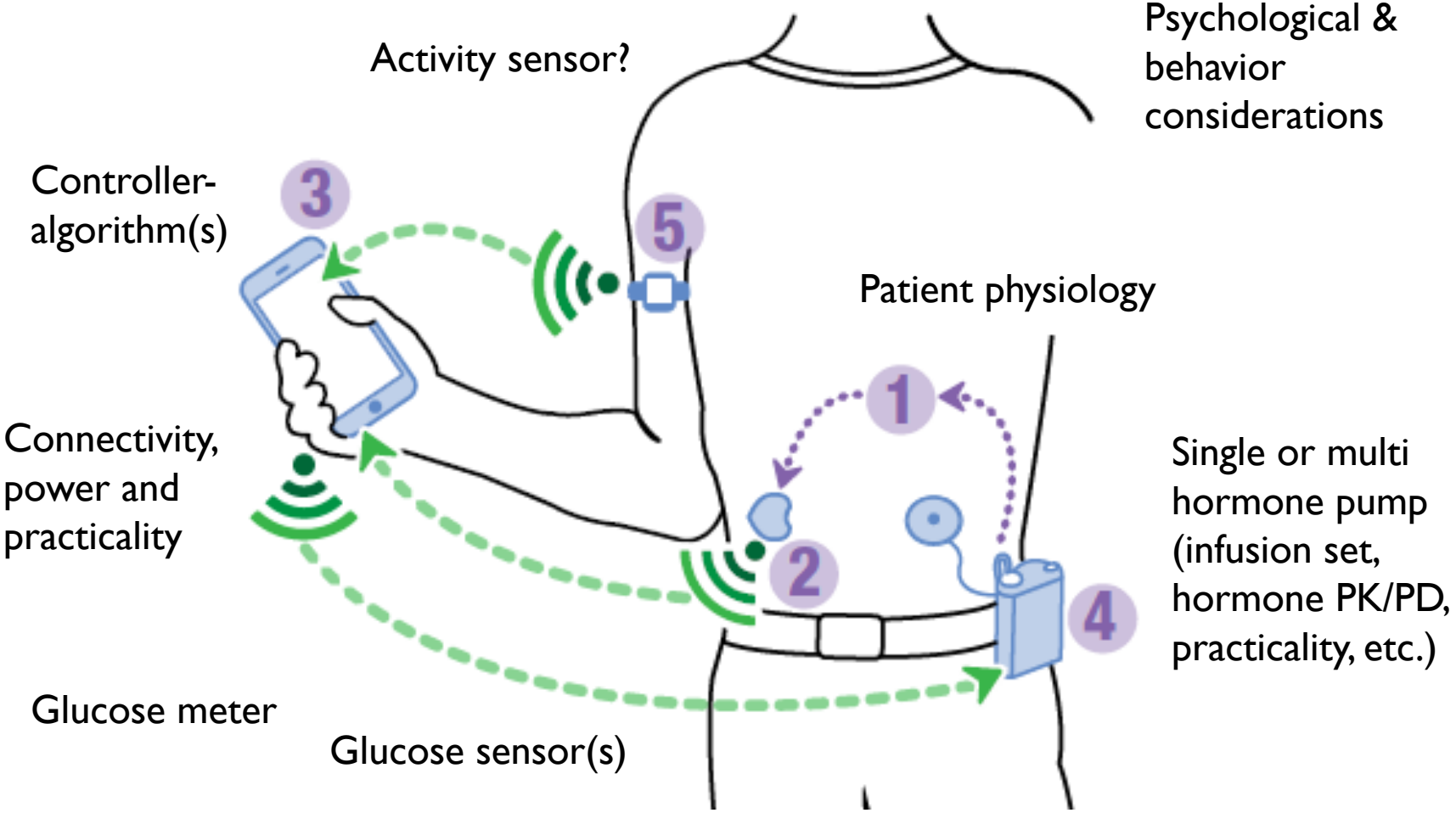

135
dexcomG5


BLOOD GLUCOSE mg/dL
BOLUS + & CARBOHYDRATES g
BASAL RATES u/hr
BASAL : BOLUS
37% : 63%
TIME IN TARGET RANGE
45%
AVERAGE BG
220 mg/dL


56% 8:39
Sam
now
3.1
mmol/L
(~56 mg/dL)
3HR
6HR
12HR
24HR
22
18
14
10
6
2
6PM
7PM
8PM
8:39PM

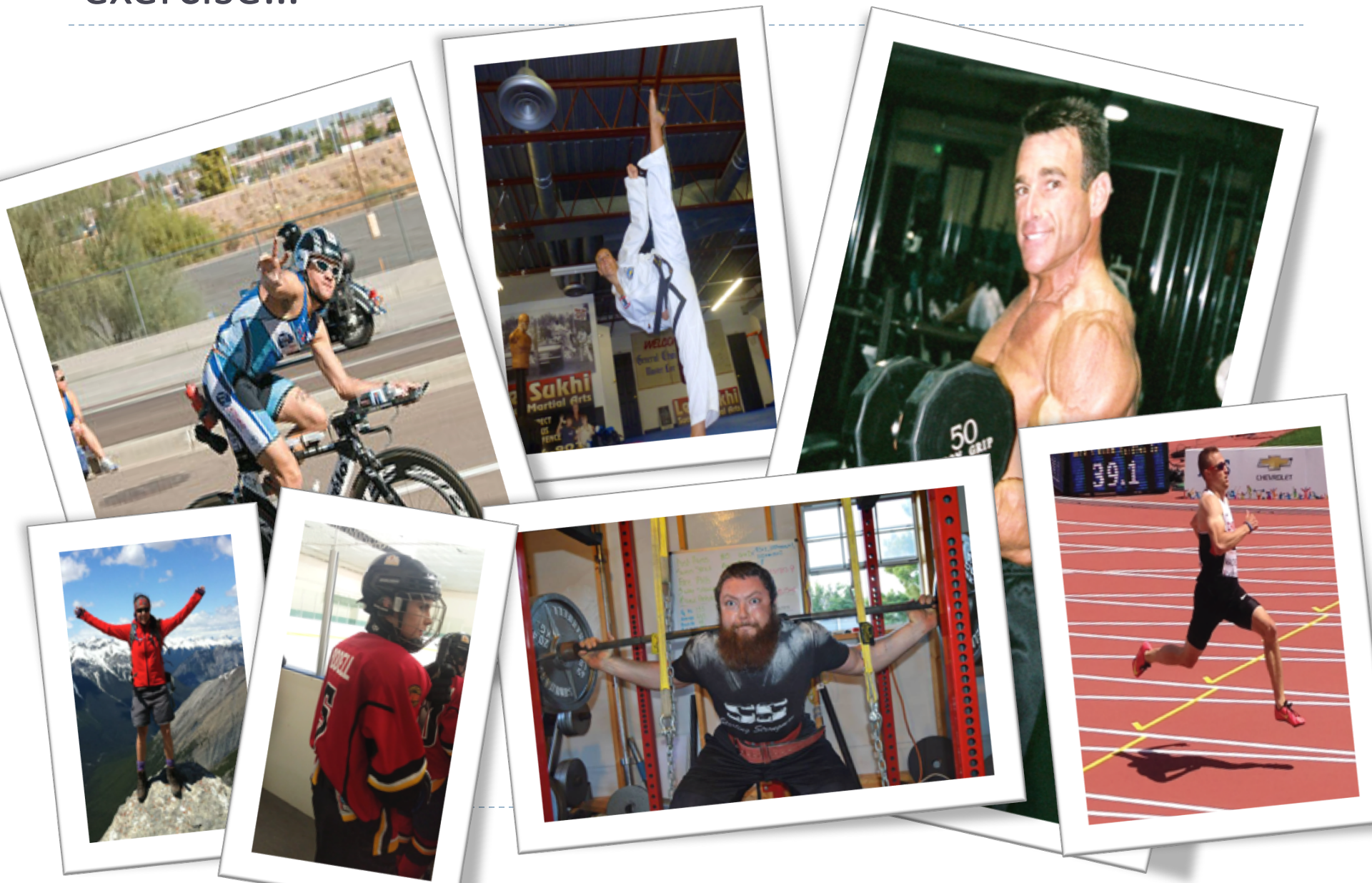
Exercise- A Series of Hurdles for the Artificial Pancreas

AP & Exercise-Several Components to Consider

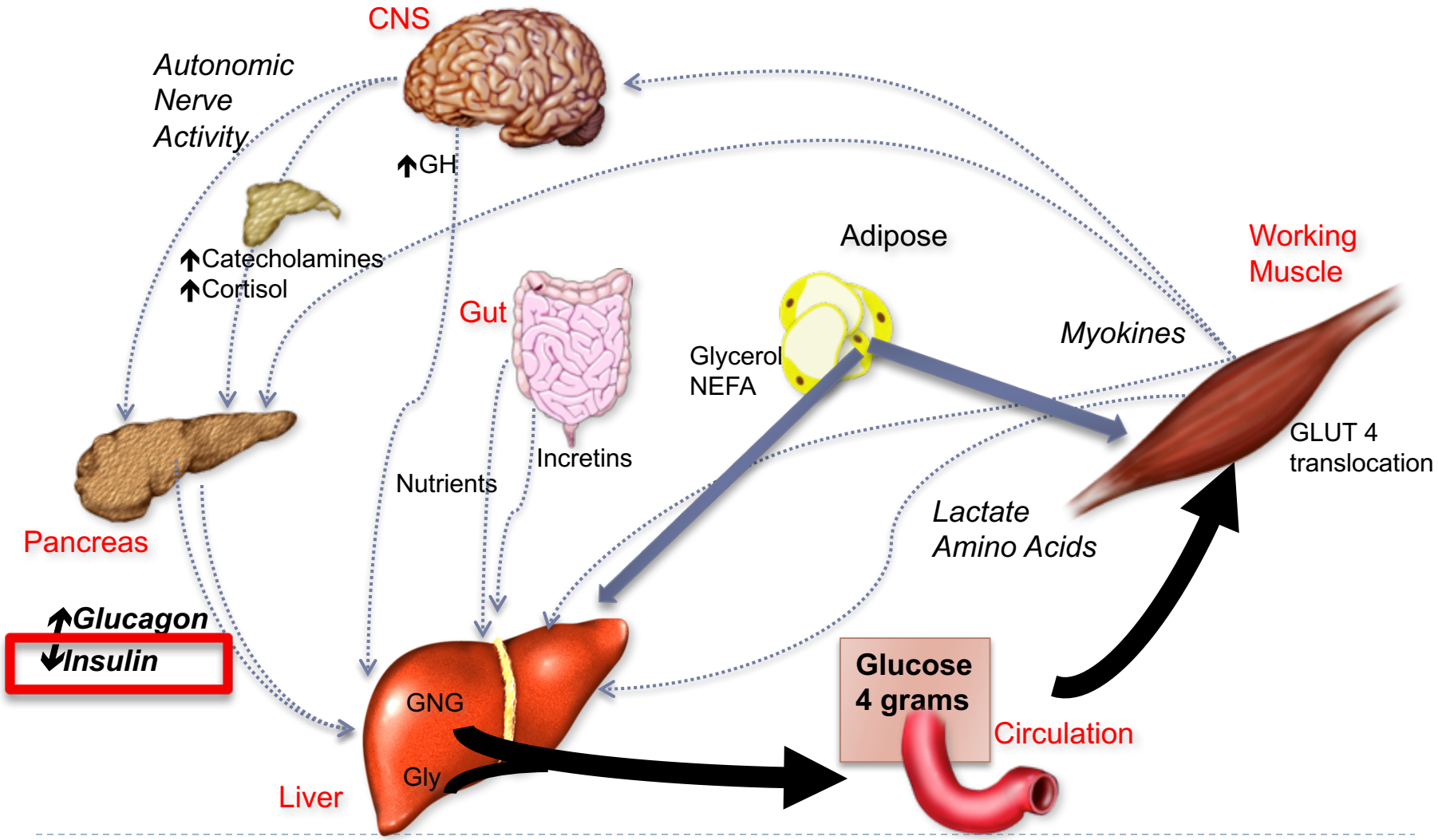


M.C. Riddell. Getting Pumped: A Insulin Pump Guide for Active Individuals with Type 1 Diabetes

Hurdle 1- Different patients, different types of exercise…

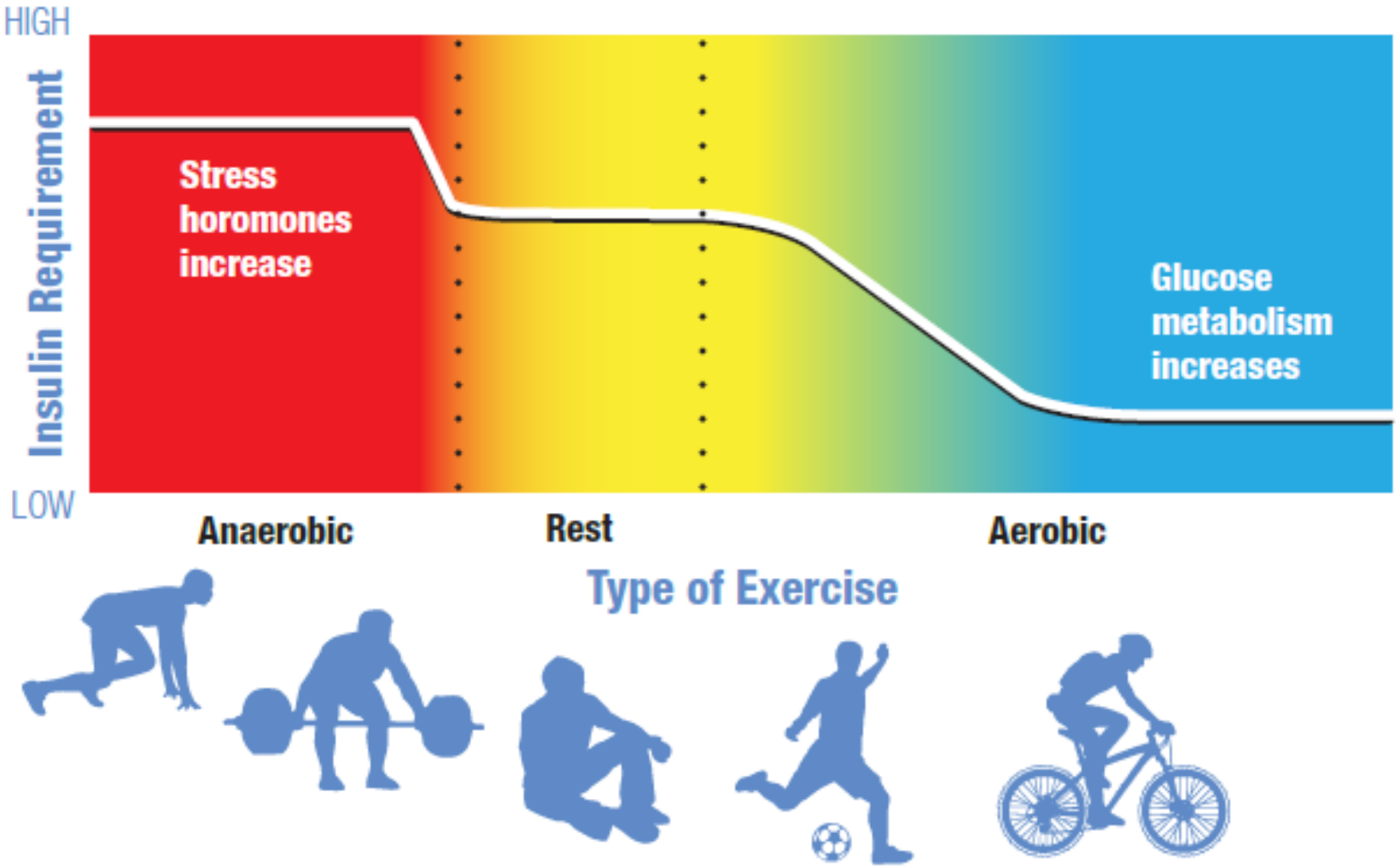


Hurdle 2- The regulation of glucose homeostasis during exercise is complex and difficult to mimic in T1D



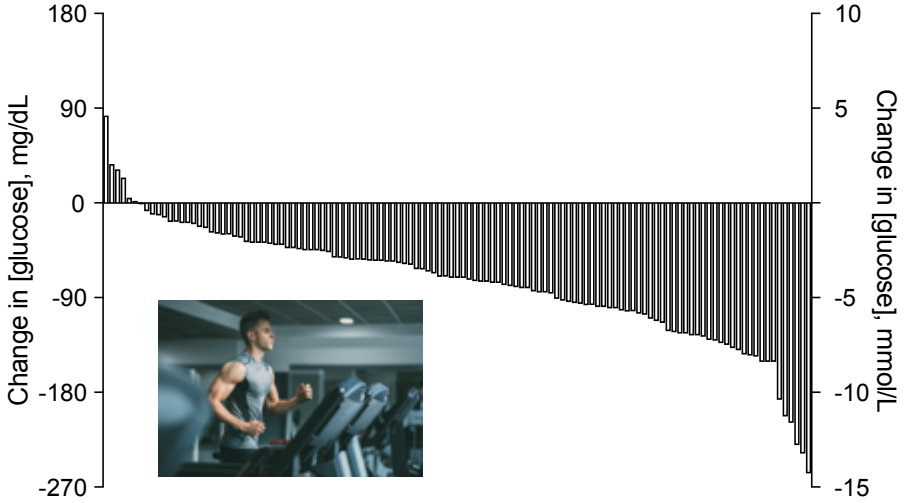
Slide inspired by Wasserman DH. Four grams of glucose. Am J Physiol Endocrinol Metab. 2009 Jan;296(1):E11-21.

Insulin needs in anaerobic vs. aerobic exercise

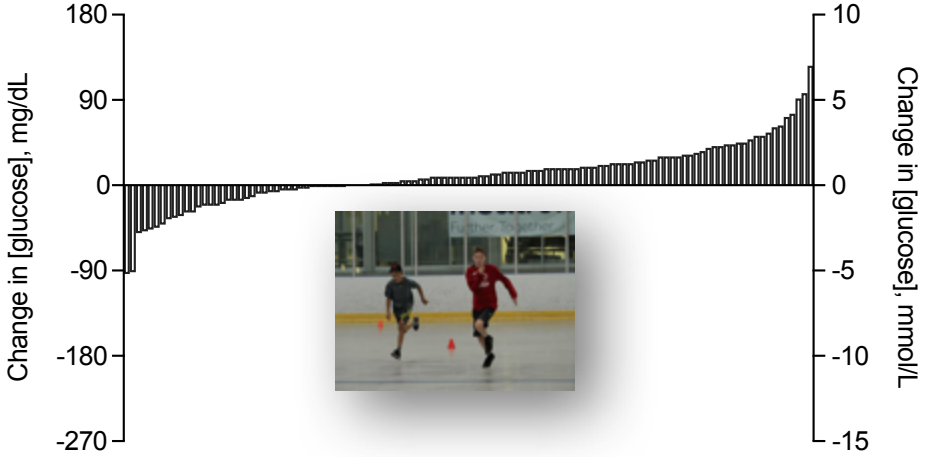


M.C. Riddell. Getting Pumped: A Insulin Pump Guide for Active Individuals with Type 1 Diabetes

Hurdle 2- **Patient variability** in response to standardized aerobic and anaerobic exercise in T1D



Aerobic exercise (45 minutes)
n= 121 youth with T1D*



Anaerobic exercise (20 seconds)
n= 121 youth with T1D

*Zaharieva et al., Blood glucose responses to aerobic exercise in youth with T1D- Poster 761-P (09 Exercise session on Monday)

Hurdle 3: How to trigger an exercise ‘event’?

- Glucose trigger only?
- **Manual trigger?**
- **Forecast trigger (calendar event?)**
- **Heart rate trigger (absolute or relative?)**
- **Movement trigger (accelerometer)**
- **Ventilation trigger**
- **Body temp or sweating rate trigger**
- **Lactate or other metabolites or hormone triggers**

Exercise/Activity Monitors

Research tools

Fitness trackers with apps

Sport Smart Watches with apps

Immerging Products

verily

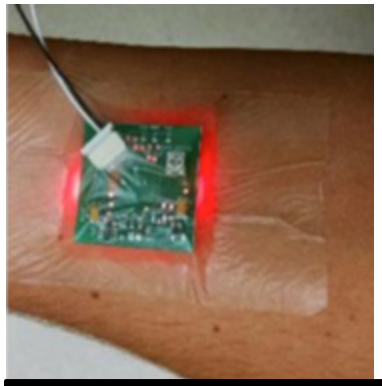
BIOSENSING WATCH FOR MEDICAL DATA

Verily, a subsidiary of Alphabet and owned by Google, has released a new device to capture health data for clinical research and monitoring medical care.

- **Biosensors:** Measure cardiopulminary rates for studies of heart, lung and movement disorders such as Parkinson's disease.
- **Data storage:** Can save data for weeks; less frequent need for uploading data.
- **Battery life:** Up to one week
- **Date and time** is the only information displayed.
- **Design:** Stylish looking to promote consistent wearing

Source: Verily

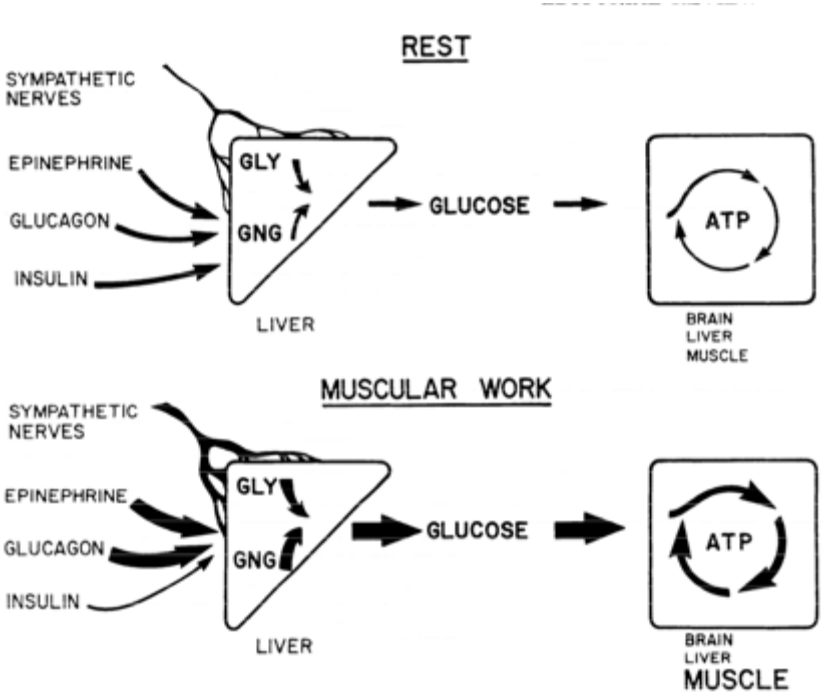
BAY AREA NEWS GROUP

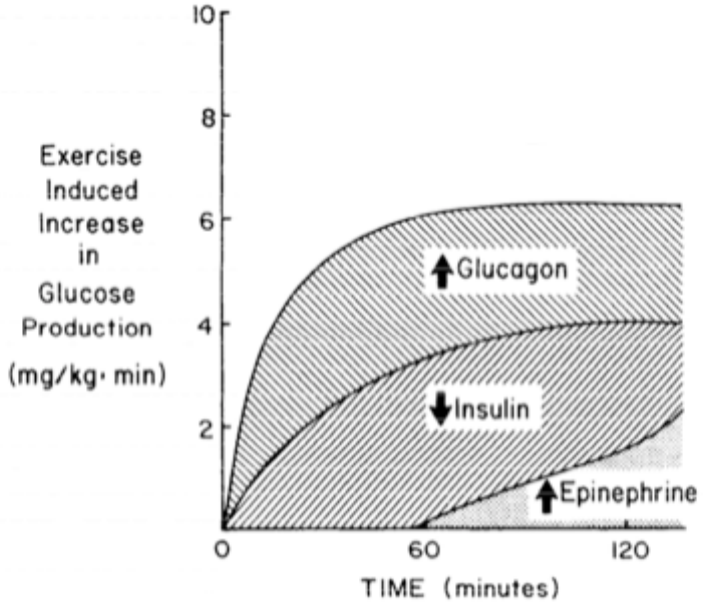


Dr. Elliot Botvinick, UC Irvine

Firefly Health Pty Ltd (Richmond, VIC)

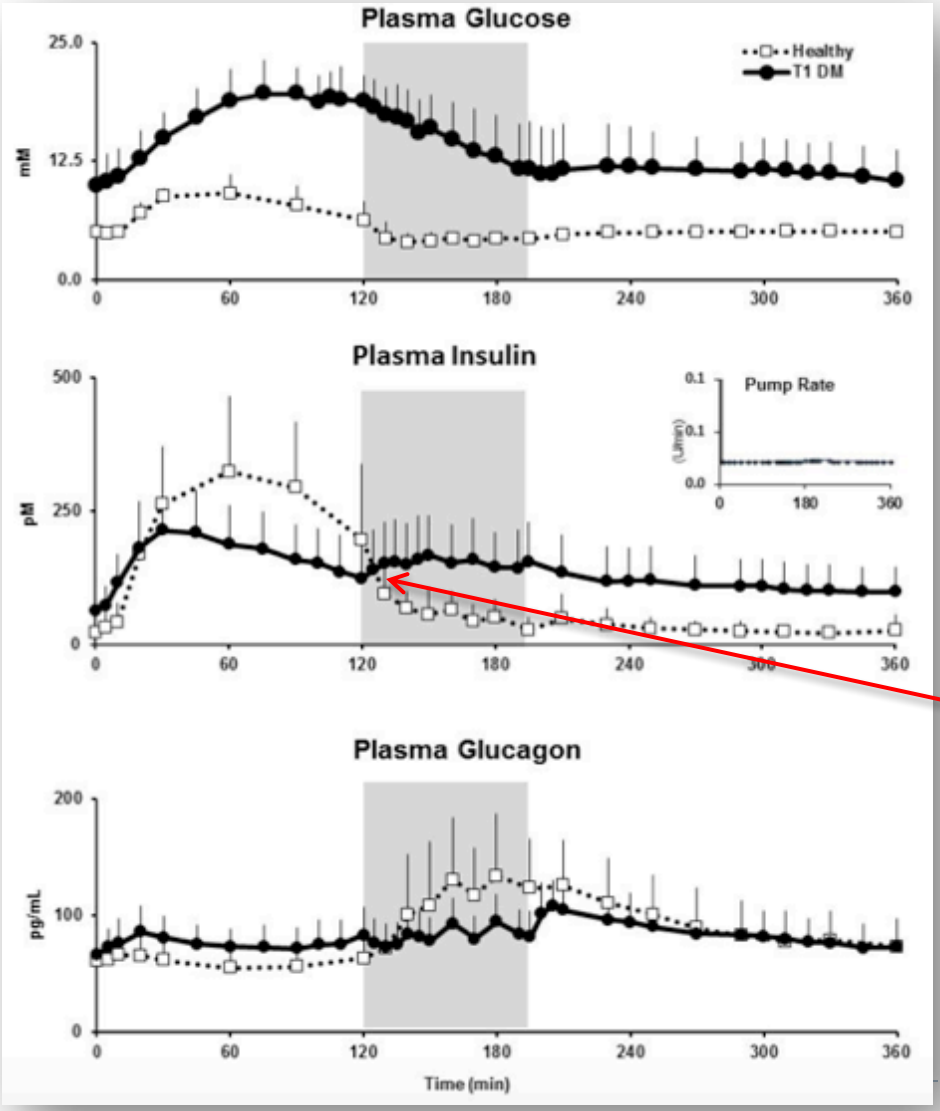
Hurdle 4: It's hard to get insulin down fast enough …And the rise in glucagon is sluggish in T1D





- Wasserman DH, Cherrington AD. Hepatic fuel metabolism during muscular work: role and regulation. Am J Physiol. 1991 Jun;260(6 Pt 1):E811-24.

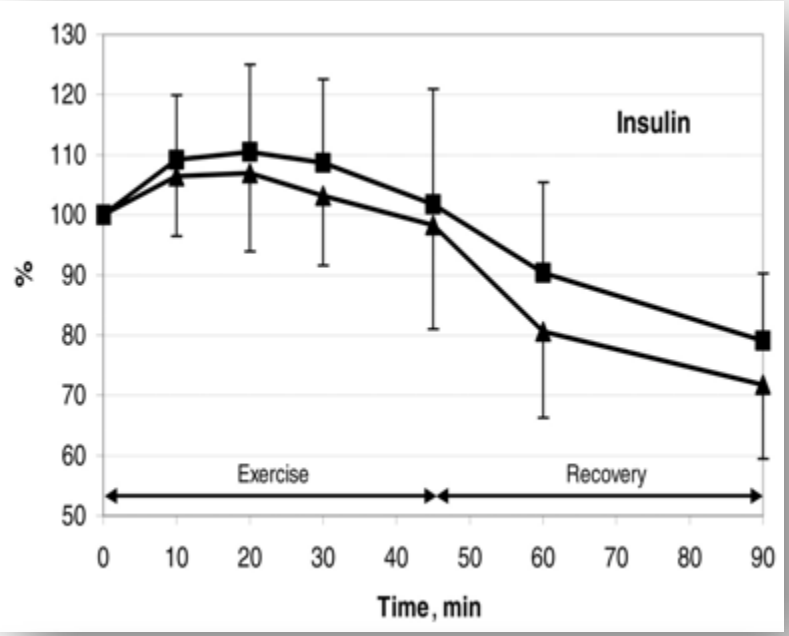
Aerobic exercise causes insulin to rise in T1D…. This causes glucose to drop…

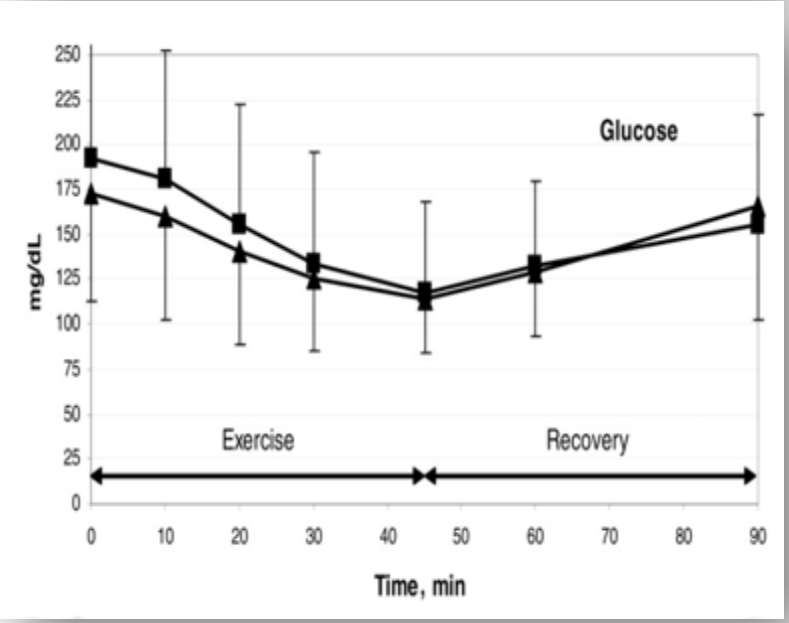


16 T1D "pumpers" exercising 120 minutes after a meal (75g CHO) with usual basal/bolus insulin

Insulin levels increased, even though basal rates were not changed

Mallad et al, Am J Physiol Endocrinol Metab (April 21, 2015)



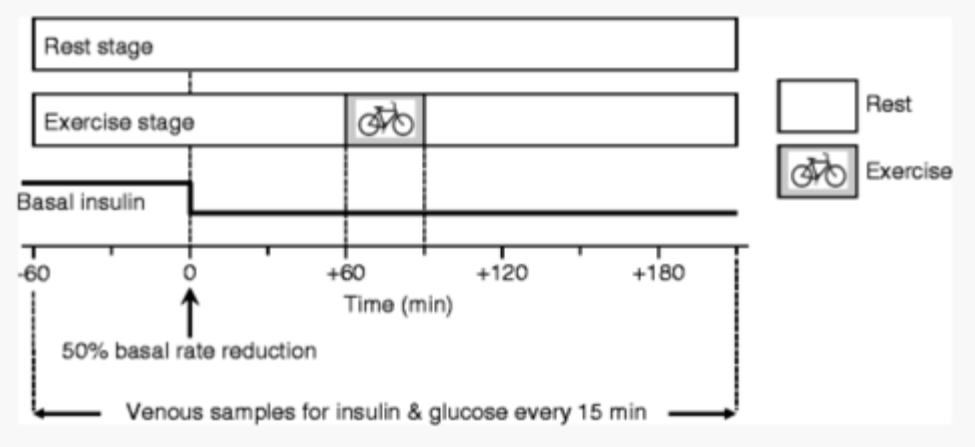


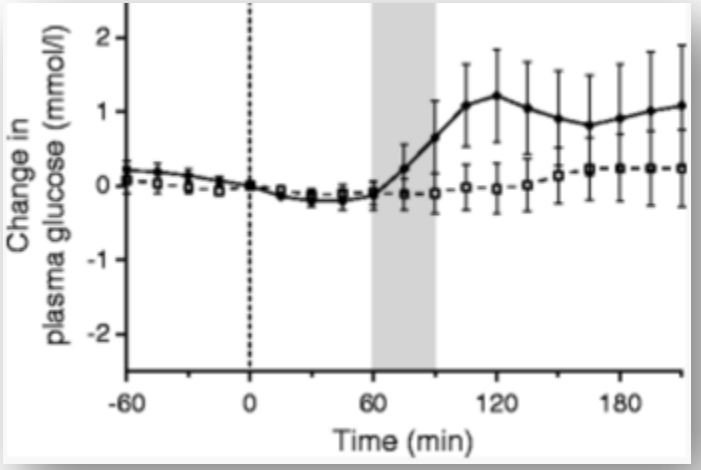
Insulin absorption rises at the onset of exercise

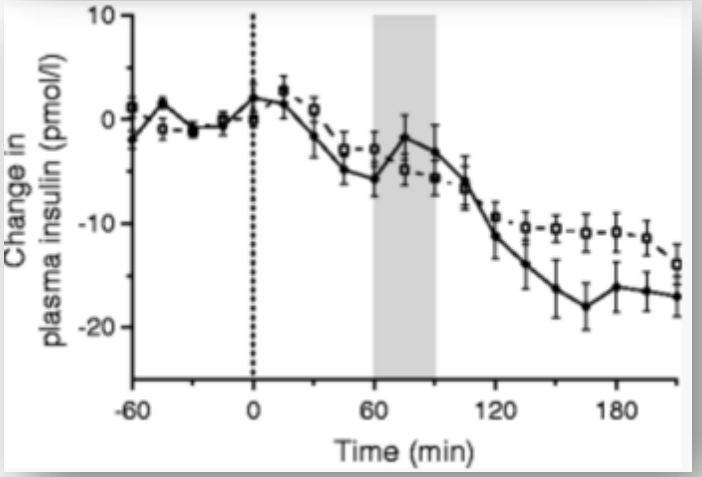
Shutting down insulin at the onset of exercise does not appear to lower insulin nor necessarily prevent hypoglycemia…..

Adom et al., Pediatrics 2005

For those on CSII, reducing basal insulin 60-90 minutes BEFORE exercise is required to get insulin levels down by exercise start time…







McAuley et al., Diabetologia 2016

An Exercise Solution- Add Glucagon

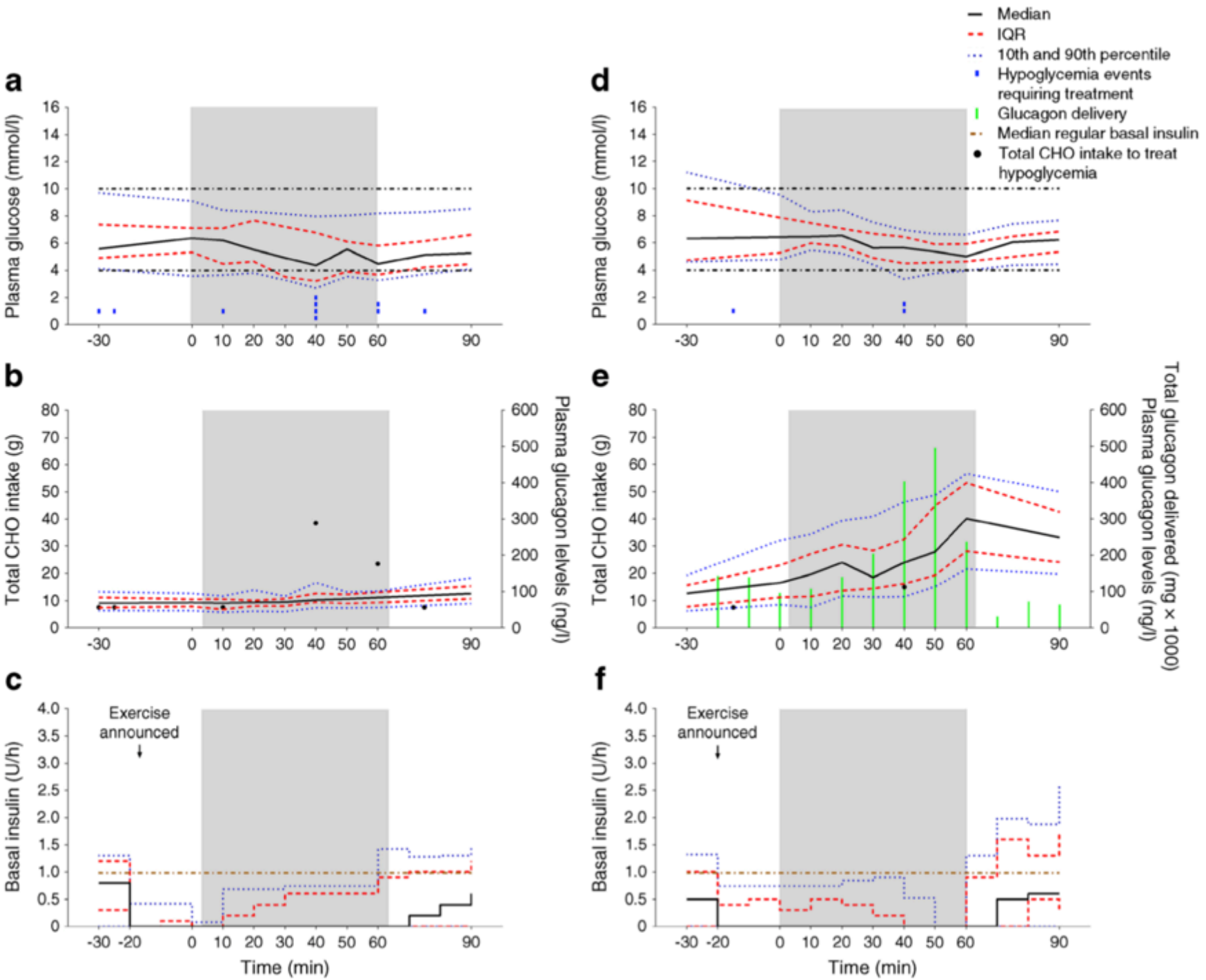
Diabetologia
DOI 10.1007/s00125-016-4107-0

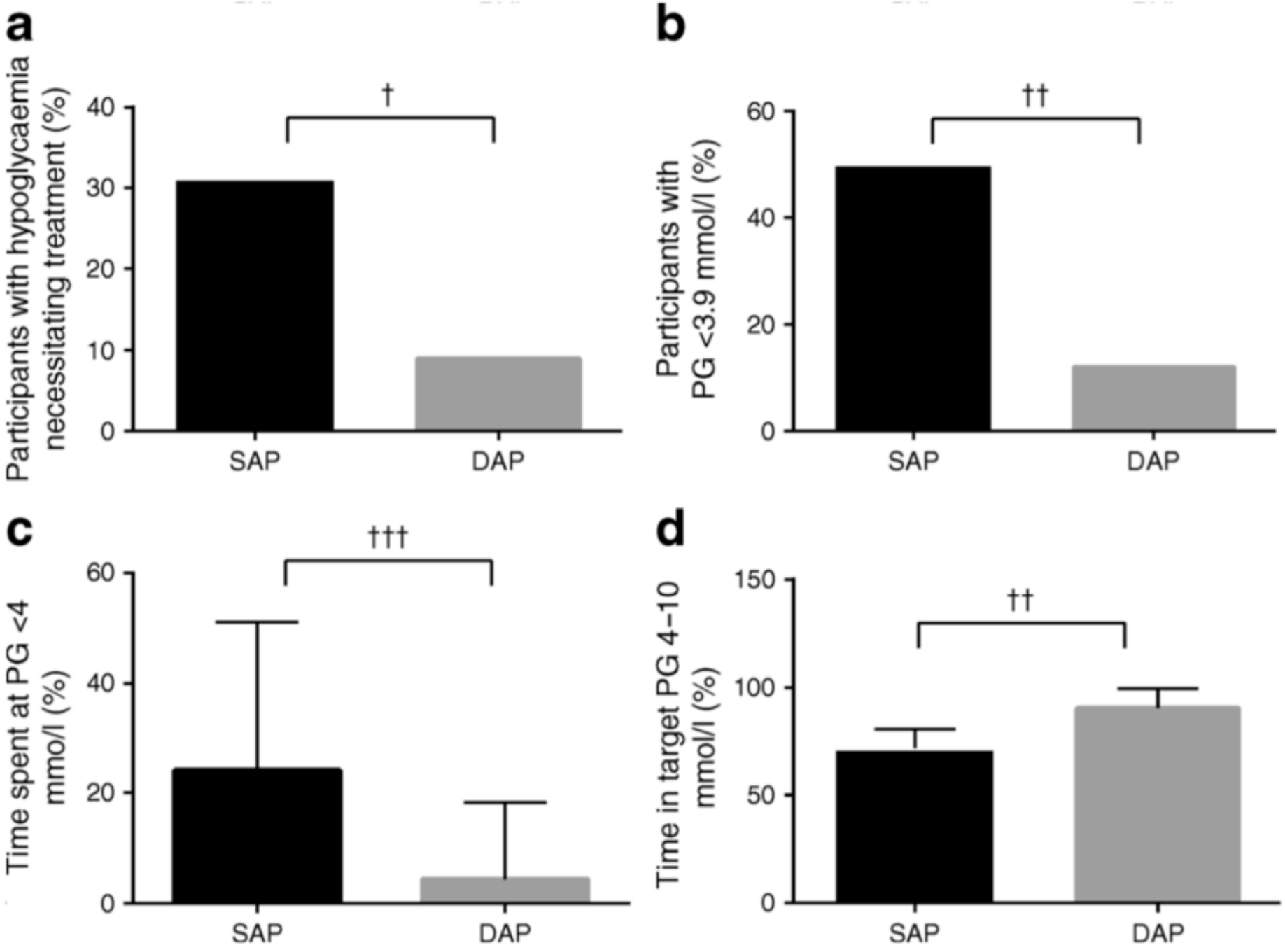
ARTICLE

Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial

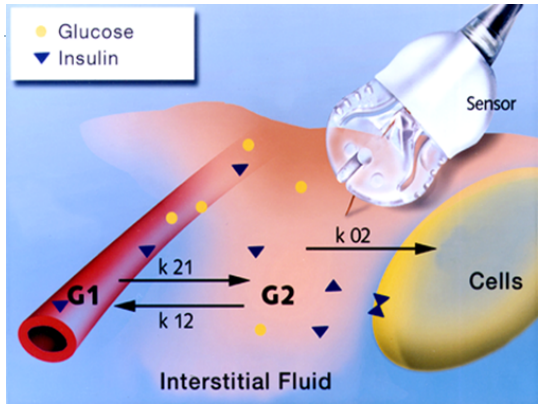
Nadine Taleb[1,2] · Ali Emami[1,3] · Corinne Suppere[1] · Virginie Messier[1] · Laurent Legault[4] · Martin Ladouceur[5] · Jean-Louis Chiasson[5,6] · Ahmad Haidar[7,8] · Rémi Rabasa-Lhoret[1,6,9]

Received: 25 May 2016 / Accepted: 16 August 2016


a
b
c
d
e
f
Median
IQR
10th and 90th percentile
Hypoglycemia events requiring treatment
Glucagon delivery
Median regular basal insulin
Total CHO intake to treat hypoglycemia
Plasma glucose (mmol/l)
Total CHO intake (g)
Plasma glucagon levels (ng/l)
Total glucagon delivered (mg × 1000)
Basal insulin (U/h)
Exercise announced
Time (min)


a
Participants with hypoglycaemia necessitating treatment (%)
40
30
20
10
0
†
SAP
DAP
b
Participants with PG <3.9 mmol/l (%)
60
40
20
0
††
SAP
DAP
c
Time spent at PG <4 mmol/l (%)
60
40
20
0
†††
SAP
DAP
d
Time in target PG 4–10 mmol/l (%)
150
100
50
0
††
SAP
DAP

Hurdle 5: Does exercise deteriorate CGM sensor accuracy?



- No or not meaningfully
  - Yardley et al. Diabetes Technol Ther. 2013 Jan;15(1):46-9
  - Bally et al., Diabetes Res Clin Pract. 2016 Feb;112:1-5
  - Moser et al., Nutrients. 2016 Aug 10;8(8)

- Yes, meaningfully
  - Davey et al., J Diabetes Sci Technol. 2010 Nov 1;4(6)1393-9
  - Herrington et al., Nutrients. 2012 Sep;4(9):1282-92
  - Kumareswaran et al., Diabetes Technol Ther. 2013 Mar;15(3):223-9
  - Taleb et al., Diabetes Technol Ther. 2016 Sep;18(9):561-7

DIABETES TECHNOLOGY & THERAPEUTICS
Volume 18, Number 9, 2016

DOI: 10.1089/dia.2015.0394

DTT

ORIGINAL ARTICLE

Comparison of Two Continuous Glucose Monitoring Systems, Dexcom G4 Platinum and Medtronic Paradigm Veo Enlite System, at Rest and During Exercise

Nadine Taleb, MD,[1,2,*] Ali Emami,[1,3,*] Corinne Suppere, MSc,[1]
Virginie Messier, MSc,[1] Laurent Legault, MD,[4] Jean-Louis Chiasson, MD,[5,6]
Rémi Rabasa-Lhoret, MD, PhD,[1,6,7] and Ahmad Haidar, PhD[8,9]

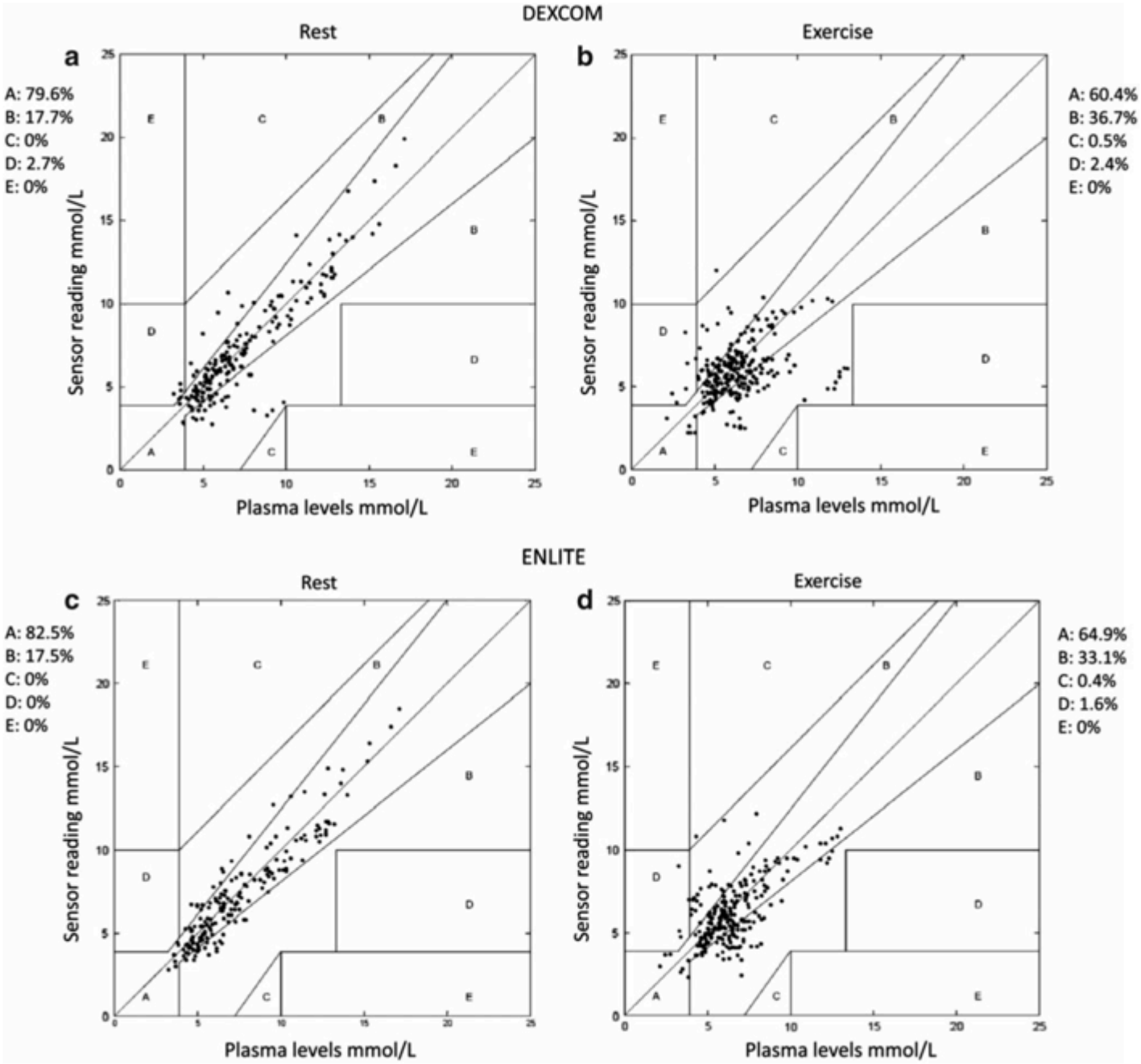


FIG. 1. Error grid analysis plot of glucose sensor readings against plasma levels at rest and exercise for Dexcom **(a, b)** and Enlite **(c, d)**, respectively. Dots represent all the collected data pairs.

Table 2. Comparison of the Performance of Dexcom and Enlite at Rest and During Exercise

	DEXCOM			*ENLITE*			*DEXCOM vs. ENLITE*	
Period	*Rest*	*Exercise*	P	*Rest*	*Exercise*	P	*Rest* P	*Exercise* P
Mean SB (SD), mmol/L	–0.12 (1.25)	–0.40 (1.80)	0.39	–0.18 (0.85)	–0.26 (1.41)	0.77	0.78	0.67
Median SB (IQR), mmol/L	–0.02 (–0.55 to 0.34)	–0.21 (–0.86 to 0.65)	0.46	–0.40 (–0.78 to 0.45)	–0.24 (–1.00 to 0.58)	0.91	0.66	0.62
Mean ARD (SD), %	13.77 (12.00)	22.53 (17.20)	0.005	12.38 (5.35)	20.44 (17.33)	0.007	0.53	0.58
Median ARD (IQR), %	13.34 (6.11 to 12.20)	15.13 (9.44 to 26.83)	0.02	11.95 (7.76 to 14.21)	14.11 (8.51 to 22.68)	0.02	0.70	0.68
ISO criteria, %	73.60	48.20		76.90	53.90			
Clarke EGA (zones A+B), %	97.30	97.10		100.00	98.00			

Data are collected during 31 interventions (17 participants); each intervention has 14 time points (six at rest and eight during the exercise period).
ARD, absolute relative difference; EGA, error grid analysis; IQR, interquartile range; ISO, International Organization for Standardization; PG, plasma glucose; SB, sensor bias.

Hurdle 6: Is AP practical for the various types of exercise people do?

No we are not there yet…

But a number of very smart people are looking into this at the moment…

- Huyett et al., Outpatient closed-loop control with unannounced moderate exercise in adolescents using zone model predictive control. *Diabetes Technol Ther.* 2017
- Turksoy et al., Use of wearable sensors and biometric variables in an artificial pancreas system. *Sensors.* 2017
- Patel et al., Mitigating reductions in glucose during exercise on closed-loop insulin delivery: the ex-snacks study. *Diabetes Technol Ther.* 2016
- DeBoer et al., Heart rate informed artificial pancreas system enhances glycemic control during exercise in adolescents with T1D. *Pediatr Diabetes.* 2016
- Taleb et al., Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. *Diabetologia.* 2016
- Jacobs et al., Randomized trial of a dual-hormone artificial pancreas with dosing adjustment during exercise compared with no adjustment and sensor-augmented pump therapy. *Diabetes Obes Metab.* 2016
- Resalat et al., Design of a dual-hormone model predictive control for artificial pancreas with exercise model. *Conf Proc IEEE Eng Med Biol Soc.* 2016
- Dadlani Vet al., Physical Activity Capture Technology With Potential for Incorporation Into Closed-Loop Control for Type 1 Diabetes. *J Diabetes Sci Technol.* 2015
- Turksoy et al., Classification of Physical Activity: Information to Artificial Pancreas Control Systems in Real Time. *J Diabetes Sci Technol.* 2015.
- Jacobs et al. Incorporating an Exercise Detection, Grading, and Hormone Dosing Algorithm Into the Artificial Pancreas Using Accelerometry and Heart Rate. *J Diabetes Sci Technol.* 2015

Current CL Strategies for Exercise Being Tested

A) Add CHOs (Ex Snack study- Yale)

B) Increase CL algorithm set-point (i.e. make the controller less aggressive during exercise; reduce the amount of 'on-board' active insulin at the start of exercise; increase the safety margin)

C) Add one, two or more input measures for exercise (HR, accelerometer, galvanic skin response, temp, etc.- Chicago/IIT, UVA, Harvard/Sansum/Barbara Davis/Stanford...)

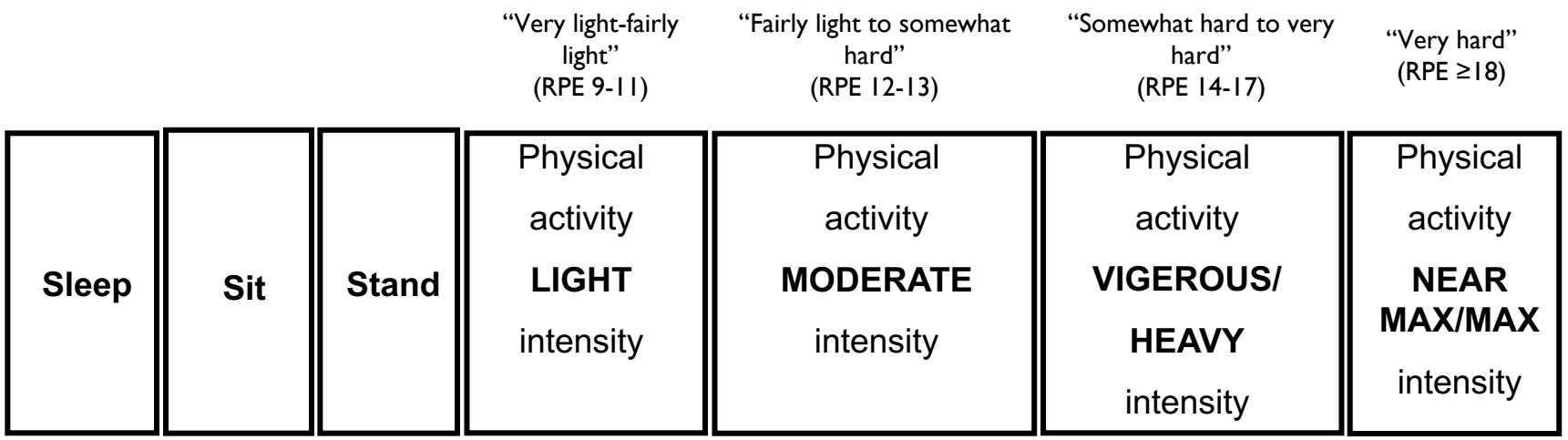
D) Add other hormones to CL to improve efficacy (glucagon, SGLT2?) (Boston, Yale, IRMC, OHSU, Toronto)

E) Measure novel biochemical sensor inputs (e.g. lactate, ketones, other hormones, etc.)- (Melbourne)

Summary

- Exercise is one of the last big challenges for closed loop AP (automated insulin delivery device systems)
- Patient variability, a potential stress response, and the non-linear needs of insulin for increasing exercise intensity makes CL challenging
- The nonphysiologic systemic rise, rather than a portal vein drop, in insulin and the dysregulation of glucagon is problematic for AP development
- Cost, additional patient burden and the patient factor may also limit uptake of the exercise smart AP

Human movement spectrum



METS	1	1.5	2	3	6	9
%HRR or % $VO2_{max}$			30	40	60	90
% HR_{max}			57	64	77	96
% VO_{2max}			37	46	64	91

Stress response threshold

- These numbers represent young healthy and fit adults… With age and with reduced fitness, the METS #'s will decrease but the other metrics expressed as percentages will remain the same……