

A clinical research informatics perspective on
glucose regulation and dysregulation
(plus some relevant emerging research
related to consequences of COVID-19)

JN Stroh

jn.stroh@cuanschutz.edu

Assistant Research Professor

University of Colorado Anschutz*

School of Medicine

Department of Biomedical Informatics

* located on the traditional territories and ancestral
homelands of the Cheyenne, Arapaho, and Ute nations



Anschutz

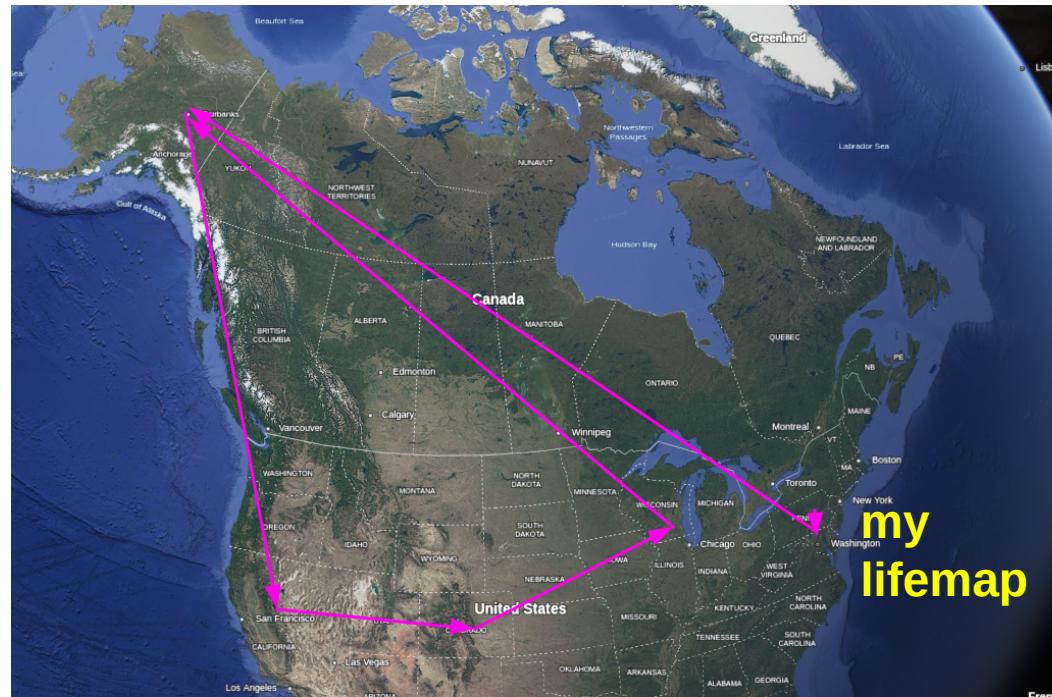


Outline:

- 1) Casual Introduction, some informatics
- 2) Some Rudiments of Glucose Regulation
- 3) Diabetes, exogenous insulin, etc
- 4) A perspective and some recent results

Disclosures:

- I have no financial, professional, or personal conflicts of interests to disclose.
- I'm an applied mathematician, not a medical doctor and a chemist.
 - And as an informatician, I mostly work in respiratory & brain injury modeling
 - I won't pretend to know details about e.g., "oxydative phosphorolation".
(So you know more about some of these details than I do.)
- This talk "light"/ informal rather than serious and hopes to communicate a big picture.
 - I neglect to appropriately attribute image sources for a bunch of internet diagrams... sorry!



ALSO: Opinions expressed in this presentation are mine and do not represent the position of the University of Colorado.

Informatics?...what is that?

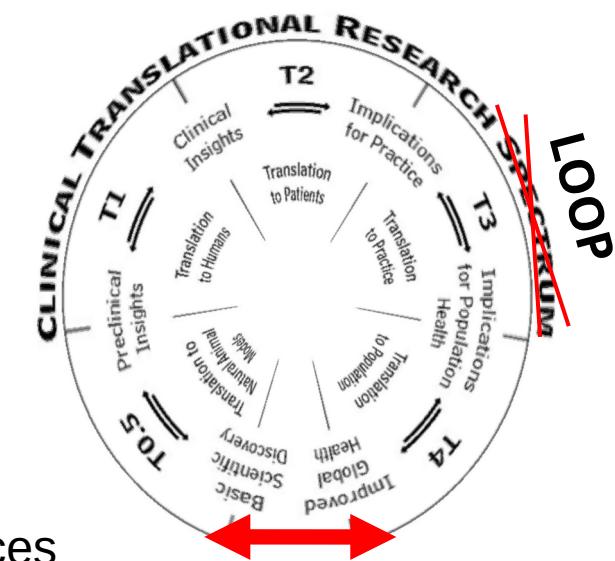
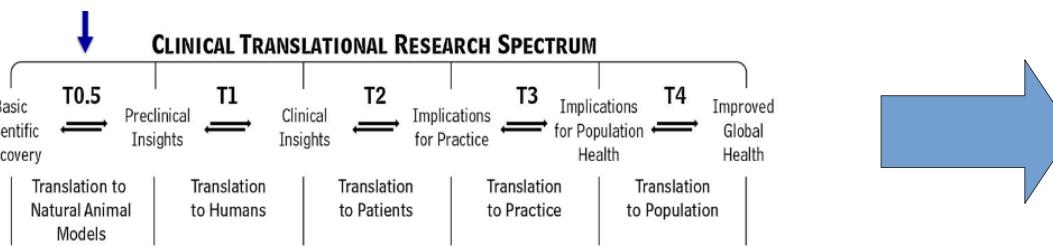
Informatics is the “theory of Scientific Information”

-- 1966, A. I. Mikhailov, A. I. Chernyi, R. S. Gilyarevskii

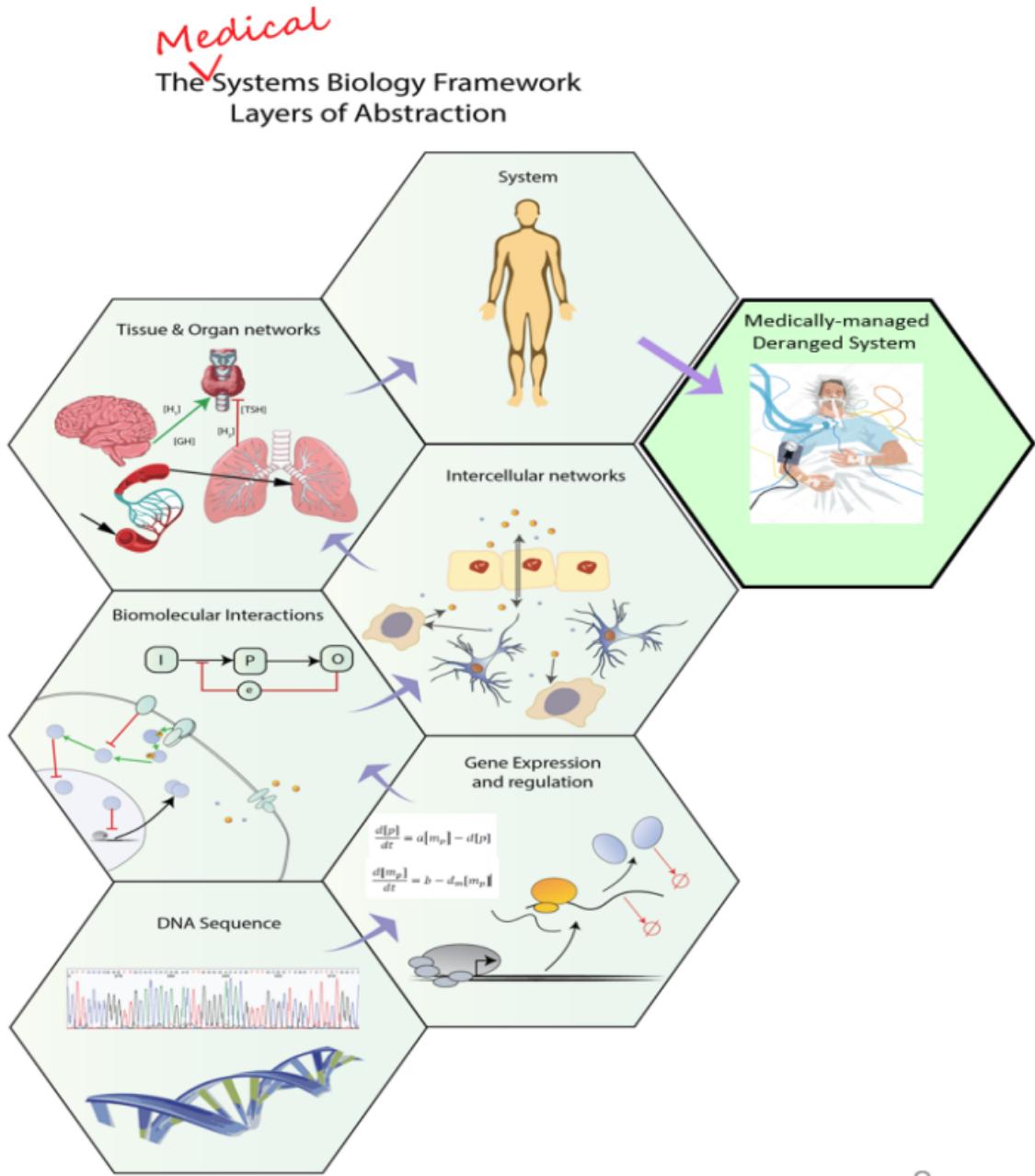
Biomedical informatics is, broadly, the study and use of medical data (clinical and otherwise) to improve medical practice and patient care...

including understanding interaction of their effects and medical pathologies

I work in *clinical research informatics* but, atypically,
work closer to basic science than “medicine”



Gist: Developing basic sciences
of medical care from clinical data
(red arrow)



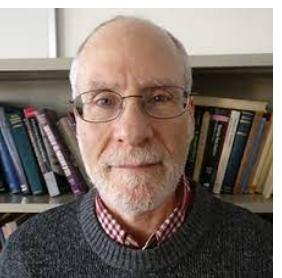
We study the observations at this level to work on building explanatory and predictive systems that includes:

- patient pathologies
- consequences of care decisions

A lot of what I'm sharing is informed by working on a few projects
with top-notch endocrinology and clinical informatics experts (it's NOT my area of expertise!)
(Warning: There are different groups of experts, and rarely consensus. It's active research.)



Jane Reusch, MD
former Board of Directors & former President of ADA
Center for Women's Health Research, Associate Director, CU Anschutz
Mitochondrial Oximetry Core at CU V/AMC, Co-director



Art Sherman, PhD
Endocrine and Neural Dynamics, Biological Modeling at NIDDK, Section Chief
(NIDDK = National Institute of Diabetes and Digestive and Kidney Diseases)



George Hripcsak, MD, PhD
Columbia University Informatics, Professor, former Chair



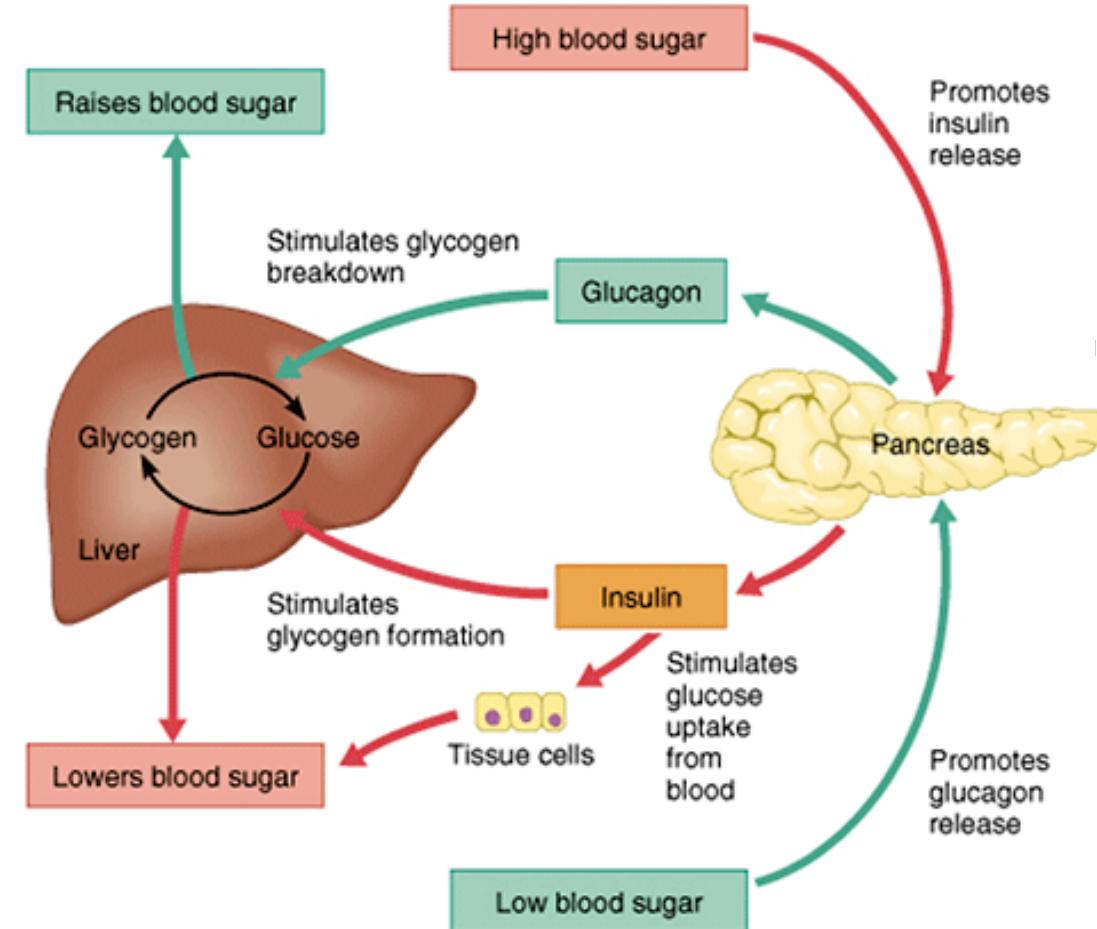
Dave Albers, PhD (my team leader/mentor)
CU Anschutz Biomedical Informatics
Columbia University Informatics

MAIN IDEA of Glycoregulation

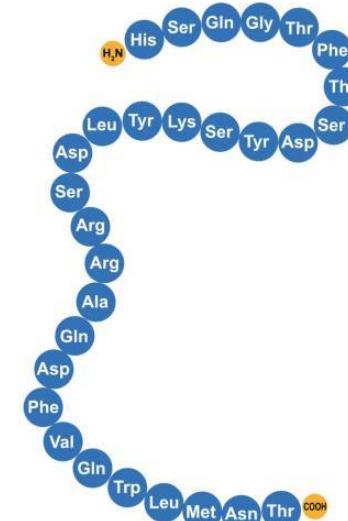
"The liver is a buffer for Blood Glucose"

Pancreas and Liver maintain BG homeostasis

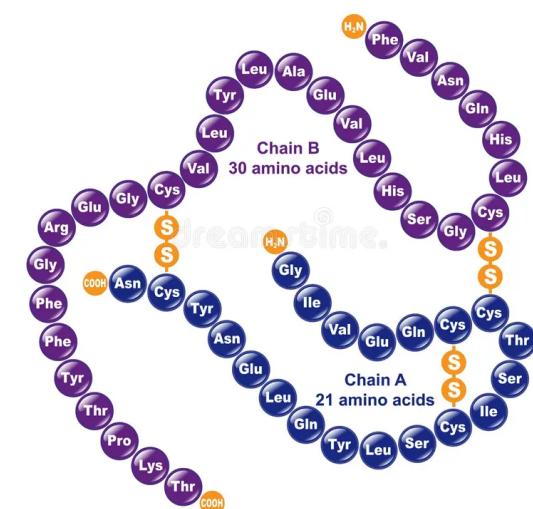
via feedback mechanisms involving two main hormones



Glucagon Structure



Human Insulin



Four main chemical processes involved in feedback mechanisms

Two primary regulatory pathways

Glycolysis: D-glucose → Pyruvate + energy in cell cytoplasm

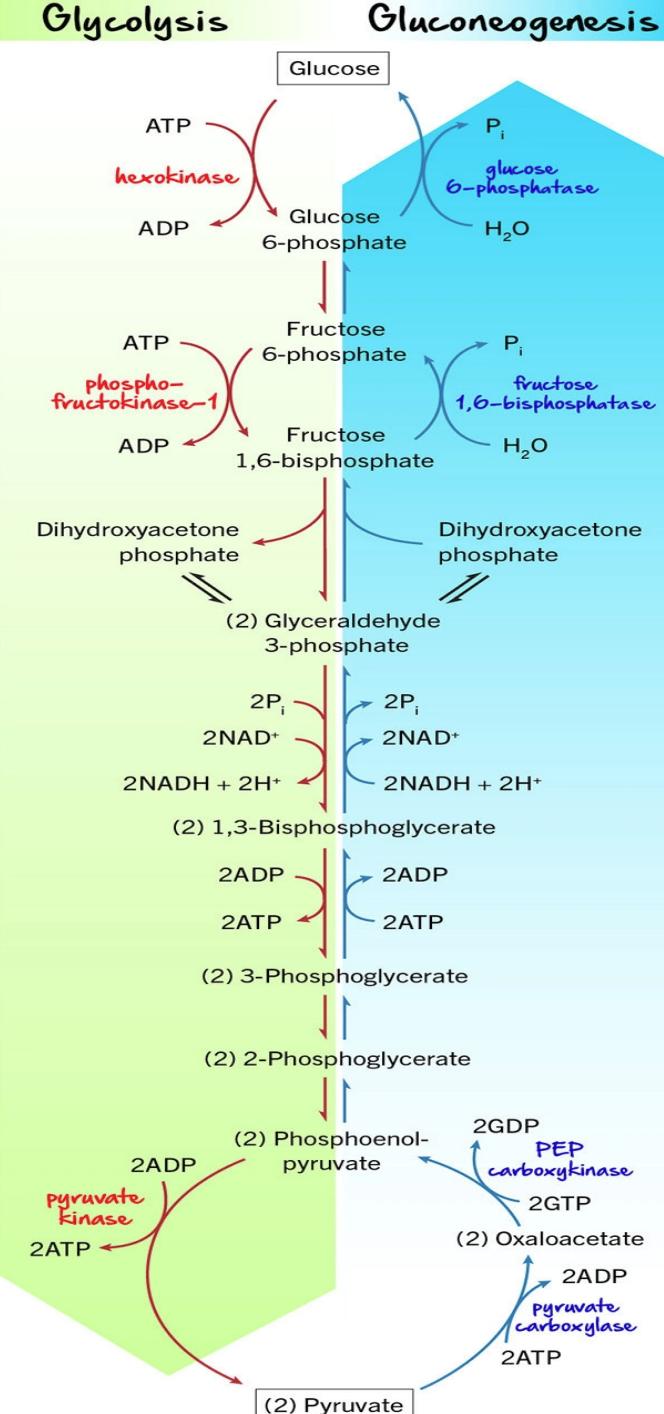
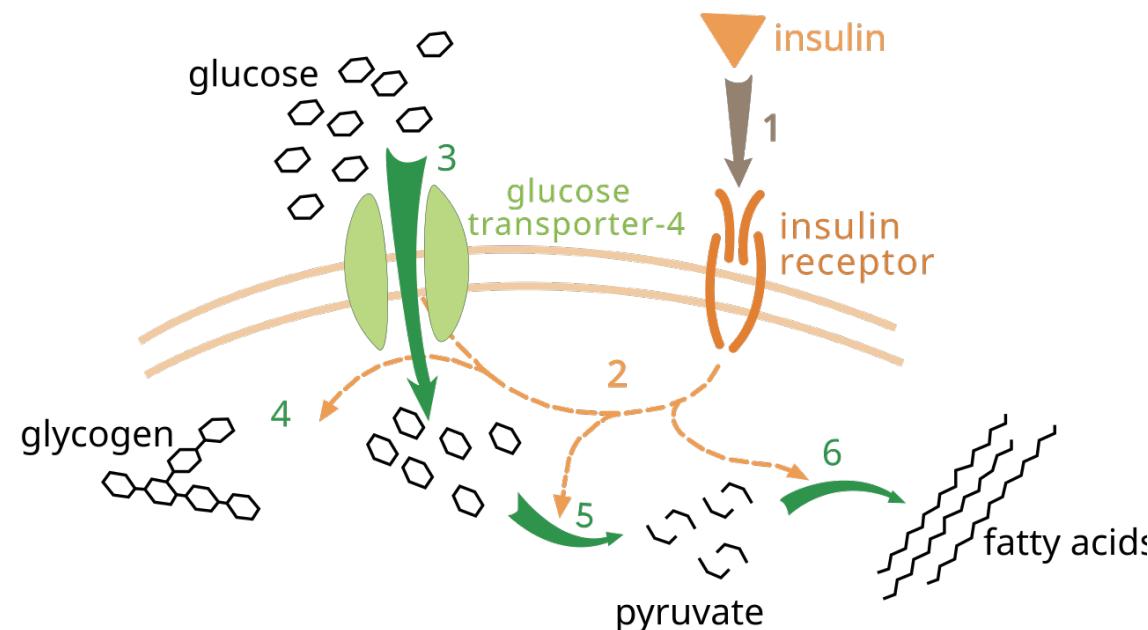
Insulin mediated:

mv GLUT-4 to membrane, transcribe rate-limiting **PFK-1**

Gluconeogenesis: *non-carbohydrate precursors* → glucose (90% in liver)

Glucagon mediated:

disinhibits and transcribes **FBPase-1**, transcribe **PEPCK**, etc



Four main chemical processes involved in feedback mechanisms

And two for the ‘buffering’ part

Glycogenolysis: Glycogen \rightarrow G1P \rightarrow G6P (\rightarrow Glucose in liver)

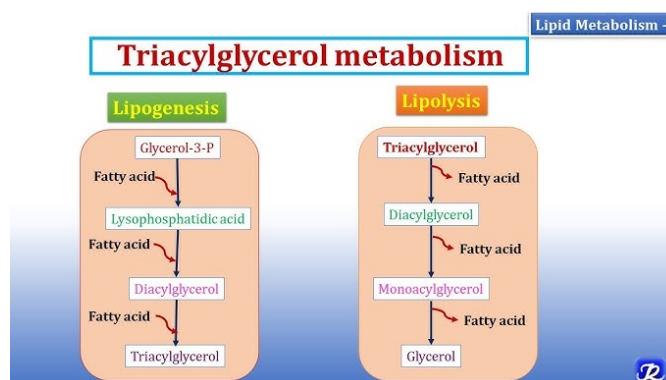
(FASTING) Glucagon stimulated, Insulin inhibited

Glycogenesis: G6P \rightarrow glycogen

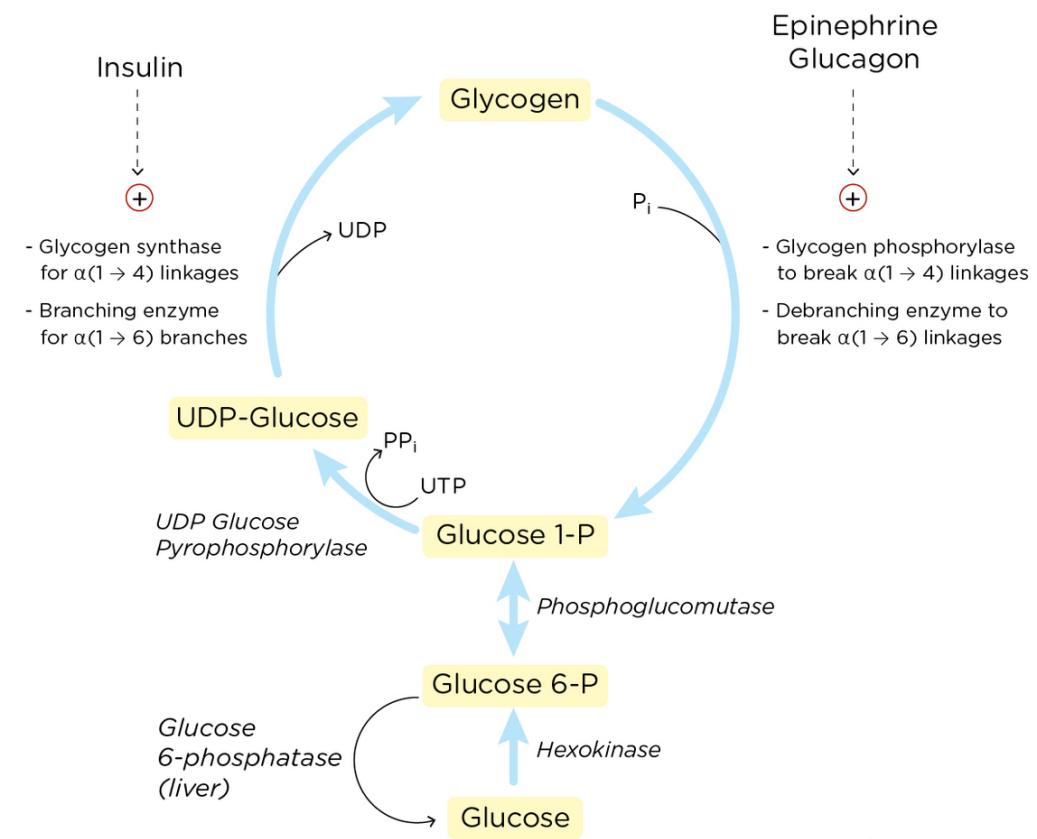
(FEEDING) Insulin stimulated, Glucagon/epinephrine inhibited

de novo Lipogenesis – a side effect of sorts

When glycogen stores are full,
excess glucose \rightarrow fatty acids
(e.g. triglycerides a.k.a. triacylglycerol,
can accumulate in liver)



Glycogenesis and Glycogenolysis
Occurs in Liver and Skeletal Muscle



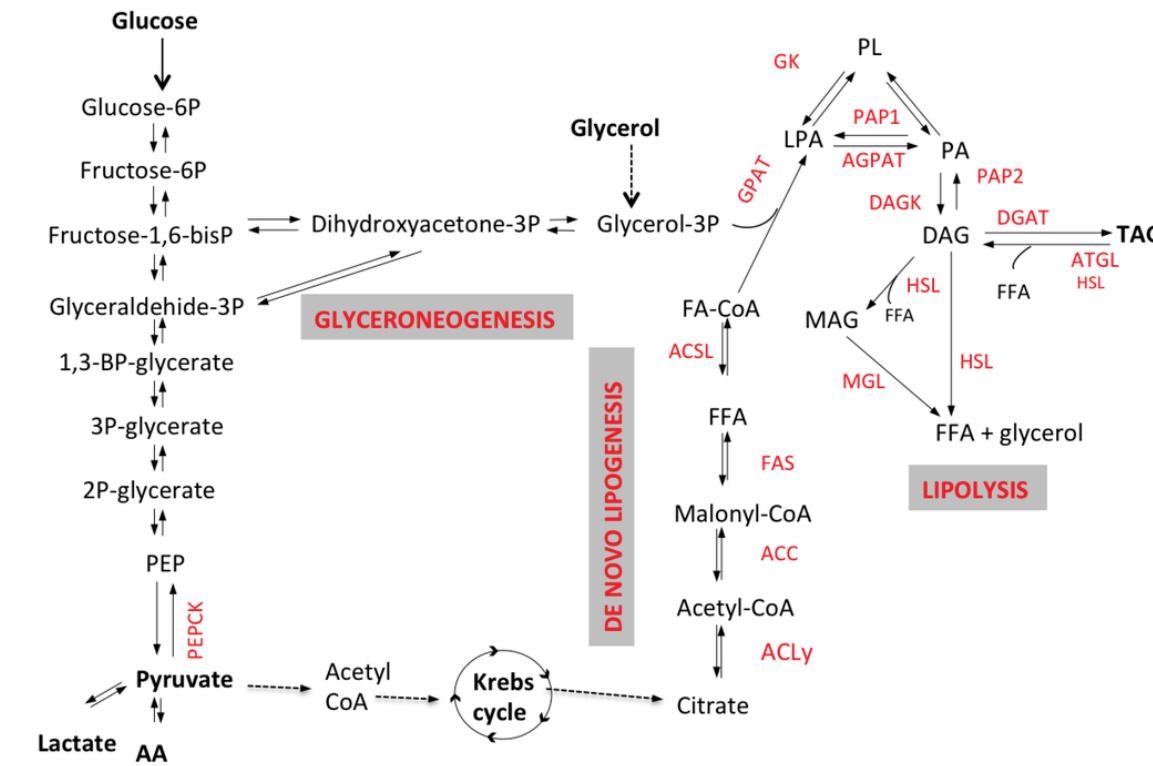
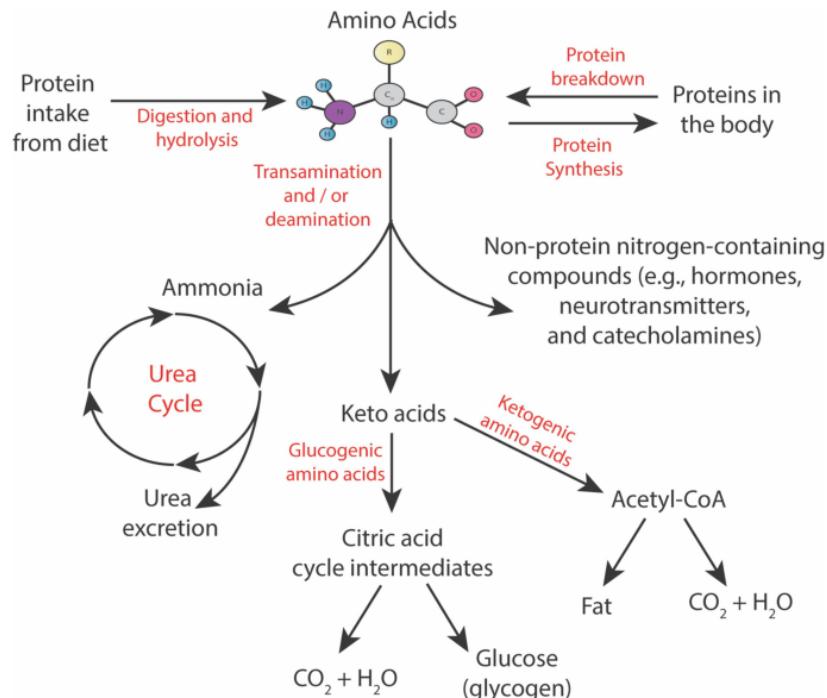
Fat and protein metabolism: part of the *non-carbohydrate precursors* in glycogenesis

e.g.

Lipolysis supplies Glycerol via



for Gluconeogenesis wing:

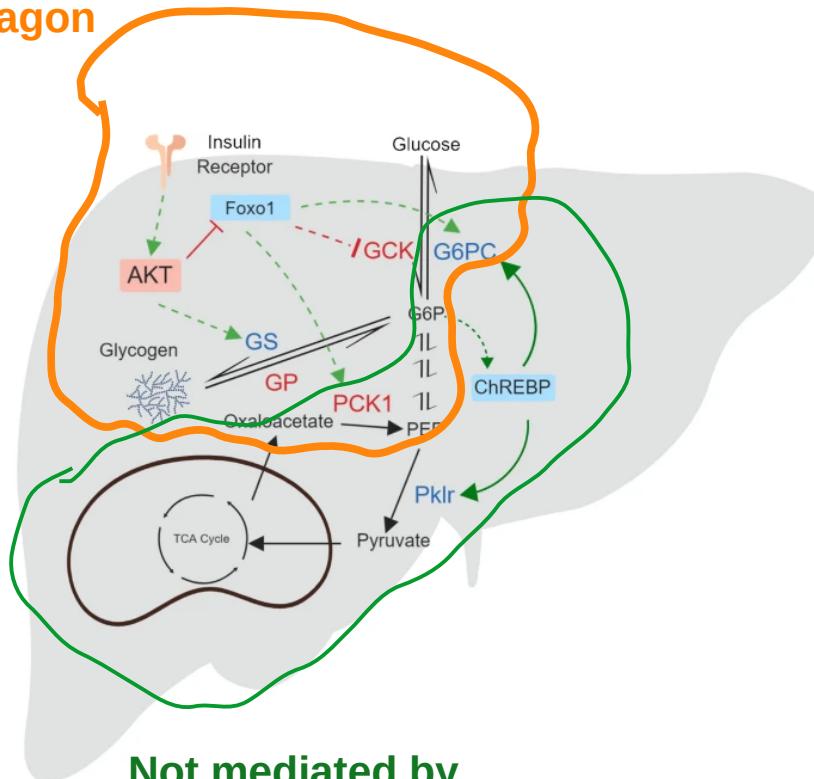


TG=Triglyceride
FFA=Free Fatty Acid

NOTE: This is all very simplistic

There are /sooo many/ coupled components (cycles, subsystems, etc)
so it's hard to draw a 'box' around any of it

**Insulin/Glucagon
Mediated**



**Not mediated by
Pancreas hormones directly
(e.g., thyroid controls hepatic mitochondria)**

Other Key players:

kidneys - filter insulin & glucagon from blood

gut - hormones, glucose production/removal

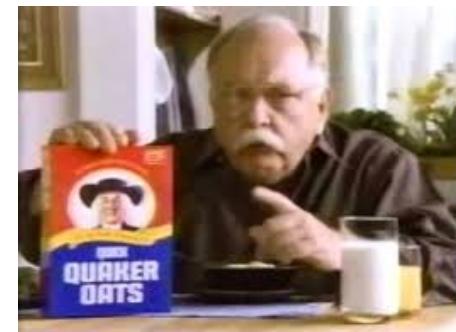
nervous system - controls pancreas

adipocytes - stores excesses, hormones

behavior, diet, SDOH, etc

Q: What is diabetes? (again, I'm not a doctor so bear with me)

A: "Chronic metabolic dysregulation of glucose homeostasis characterized by hyperglycemia", it's an *endocrine system* problem

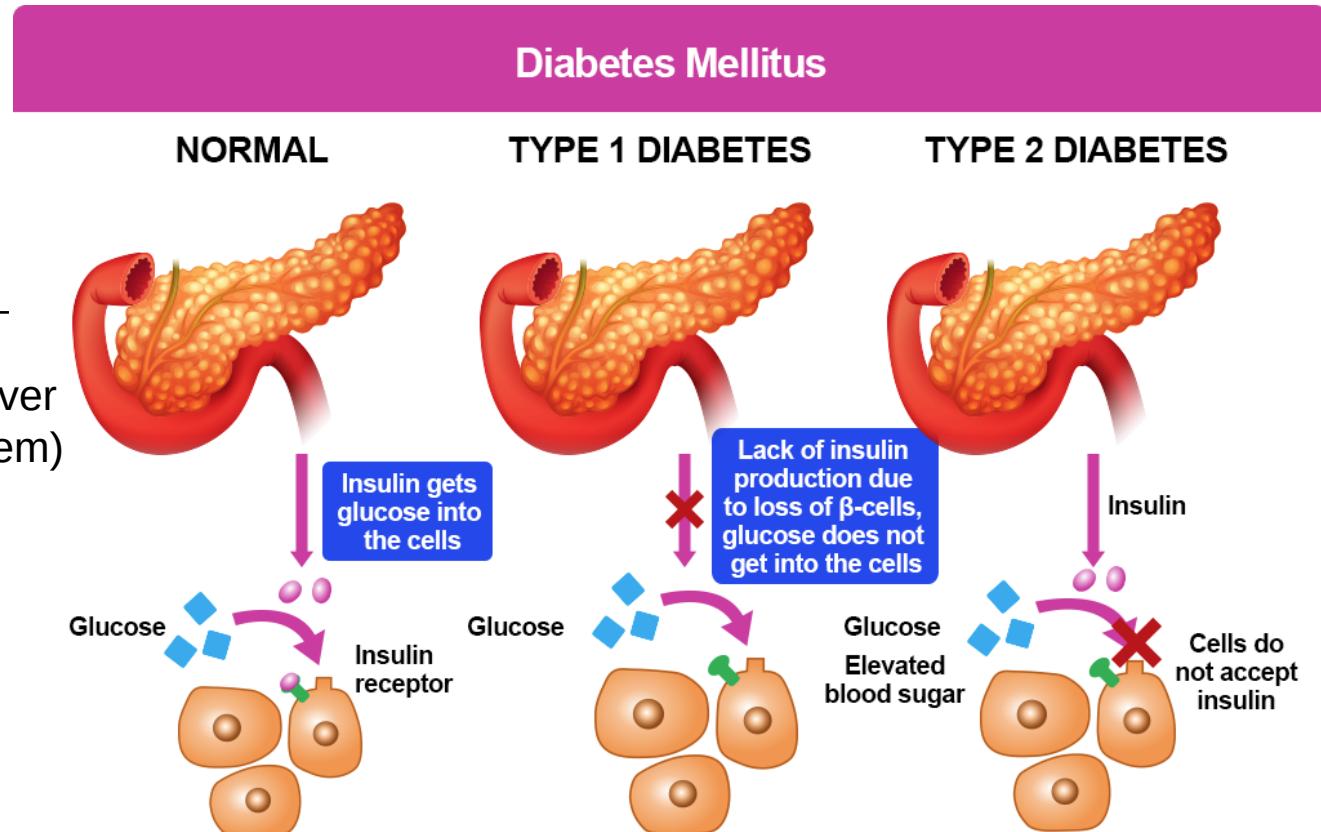


T1DM is autoimmune

- Attack of Beta cells in pancreas inhibits sufficient insulin production

T2DM is heterogeneous balancing problem

- Insufficient insulin production by pancreas to regulate glucose production by the liver (joint secretion and/or resistance problem)



+ "LADA"

Latent Autoimmune Diabetes in Adults

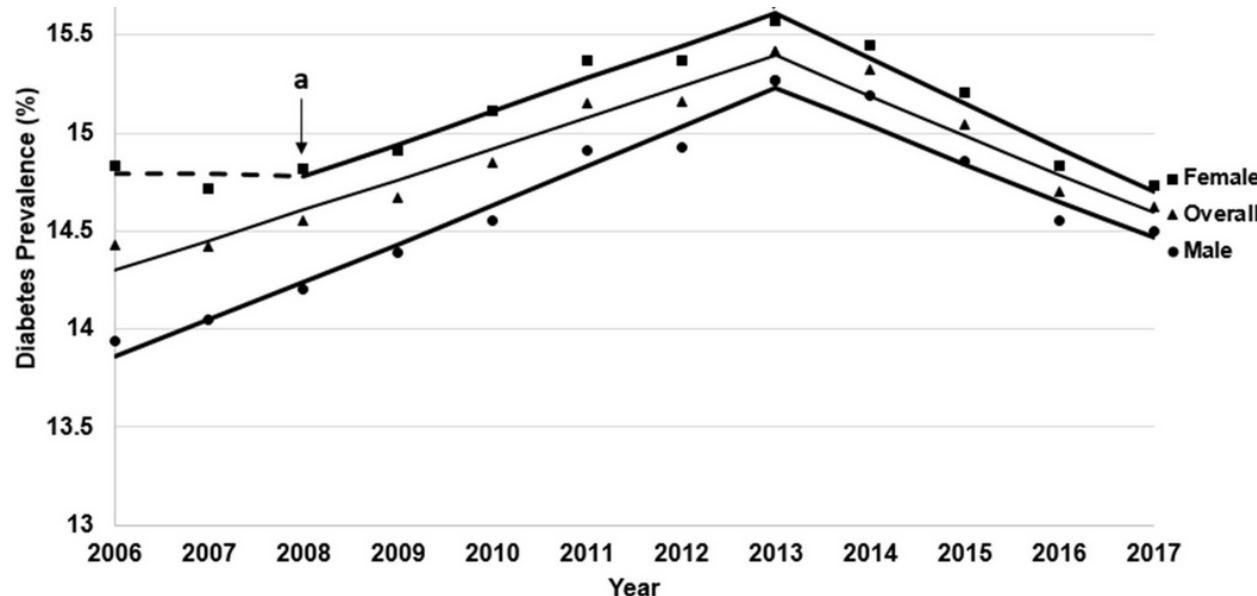
"Type 1.5

T2DM is a major, chronic, progressive health problem:
 Estimated prevalence 11%+ of US adults (~38M people) with large sex and race disparities in 2021
 + ~1.5M new diagnoses annually <https://www.cdc.gov/diabetes/php/data-research/index.html>

Table 2. Crude prevalence of diagnosed diabetes by detailed race and ethnicity among adults aged 18 years or older, United States, 2019–2021

Race and Ethnicity Subgroup	Total Percentage (95% CI)
American Indian or Alaska Native, non-Hispanic	16.0 (12.1–20.6)
Black, non-Hispanic	12.5 (11.6–13.4)
Native Hawaiian or Other Pacific Islander, non-Hispanic	11.7 (7.4–17.2)
Asian, non-Hispanic	9.2 (8.2–10.4)
Asian Indian, non-Hispanic	10.8 (8.3–13.7)
Chinese, non-Hispanic	7.1 (5.2–9.3)
Filipino, non-Hispanic	12.2 (9.4–15.6)
Japanese, non-Hispanic	6.8 (4.1–10.5)
Korean, non-Hispanic	6.1 (3.8–9.1)
Vietnamese, non-Hispanic	6.4 (3.7–10.0)
Other Asian, non-Hispanic	8.9 (5.9–12.8)
Hispanic	10.3 (9.4–11.1)
Mexican or Mexican American	11.1 (9.9–12.3)
Central American	7.3 (5.6–9.4)
South American	5.0 (3.3–7.1)
Puerto Rican	13.3 (11.0–15.9)
Cuban	9.0 (6.5–12.1)
Dominican	9.4 (5.9–14.2)
Other Hispanic, Latino, or Spanish	7.2 (5.5–9.2)
White, non-Hispanic	8.5 (8.2–8.8)

Note: CI = confidence interval. Data sources: National Center for Health Statistics; 2019–2021 National Health Interview Survey.



T2DM prevalence in AK across IHS hospital data

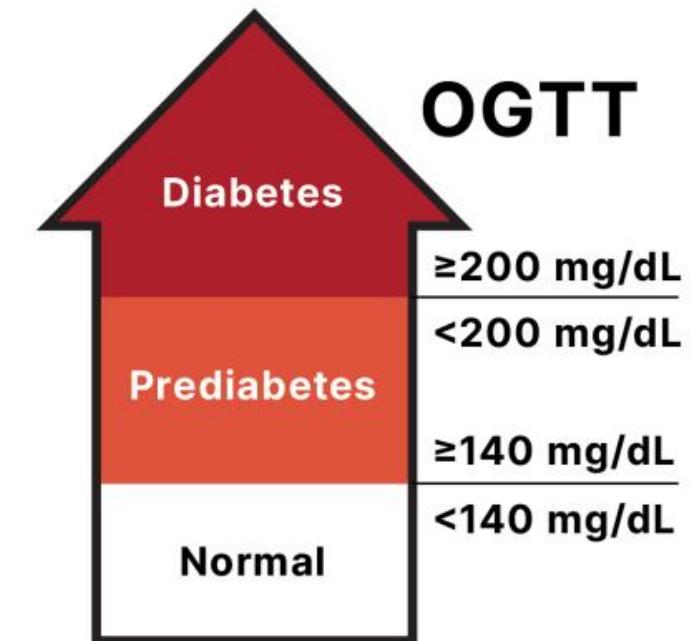
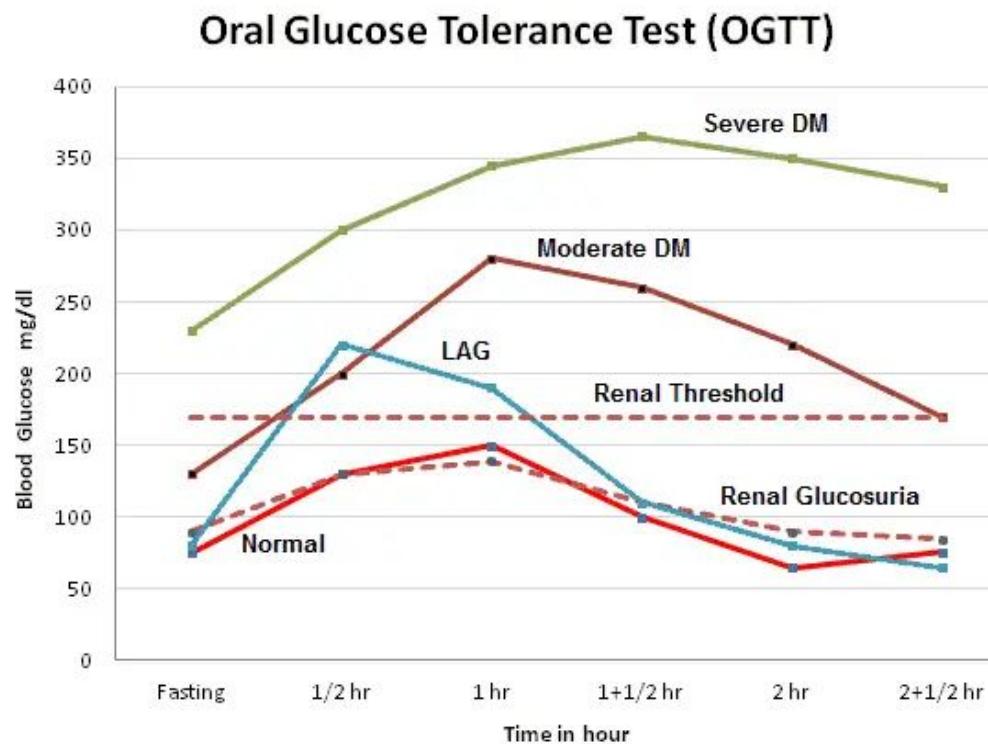
Bullock et al. BMJ Open Diabetes Research
 2020 doi: 10.1136/bmjdrc-2020-001218



Diabetes is diagnosed via Oral Glucose Tolerance Test (OGTT)

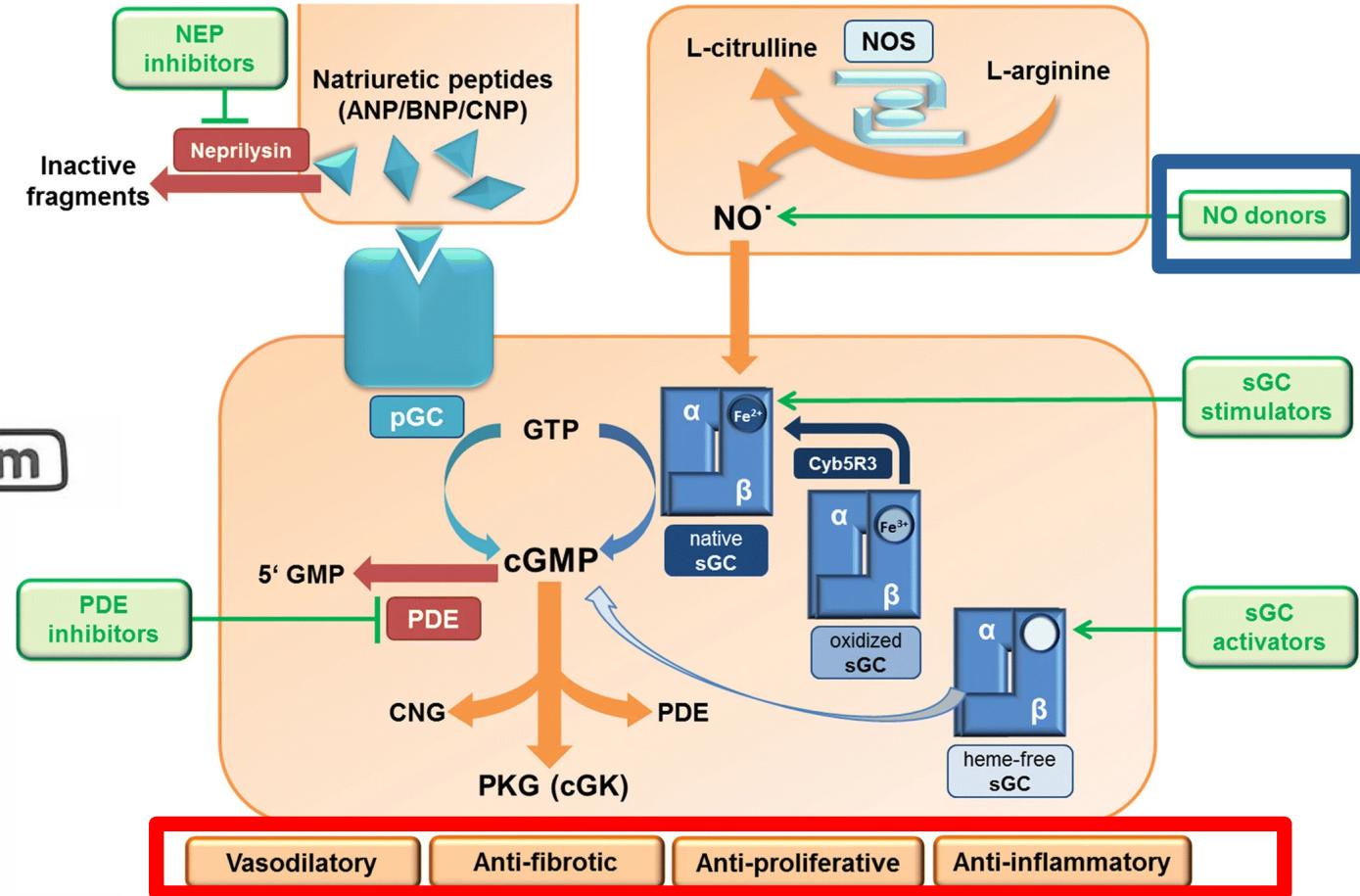
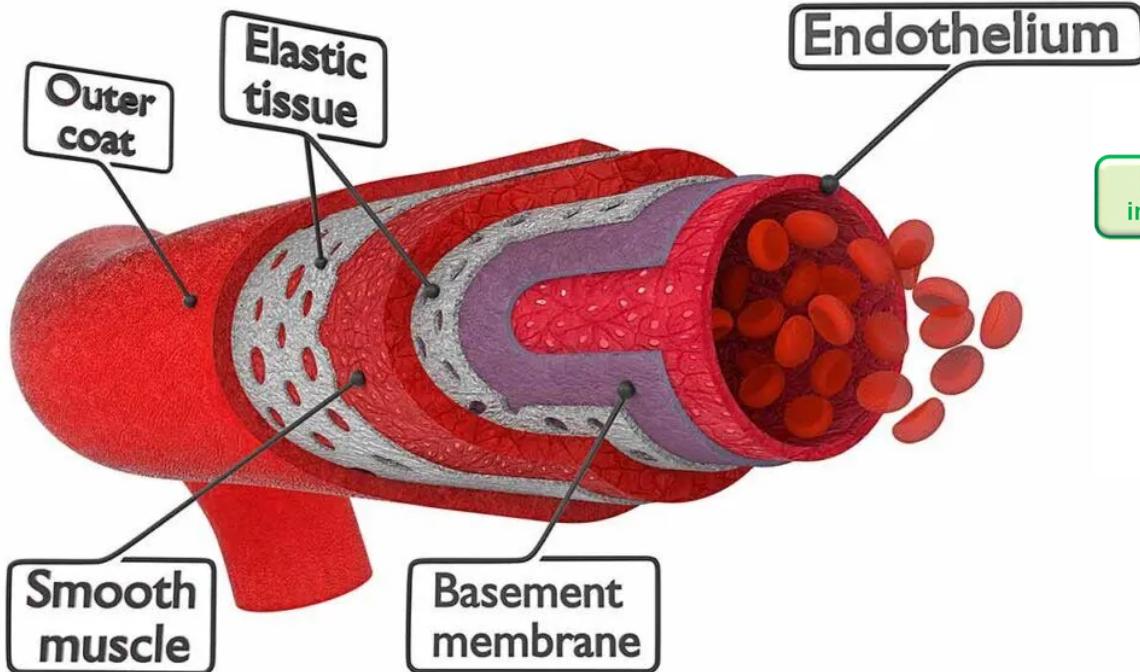
Fast 8 hours, then consume 75 g glucose, which is a sugar equivalent of:
a 4-serving 'share size' bag of skittles
Three standard size snickers bars
or about 50(!) pieces of candy corn

If BG spikes above 200 mg/dL, you get a diabetes diagnosis



BG on the Endothelium

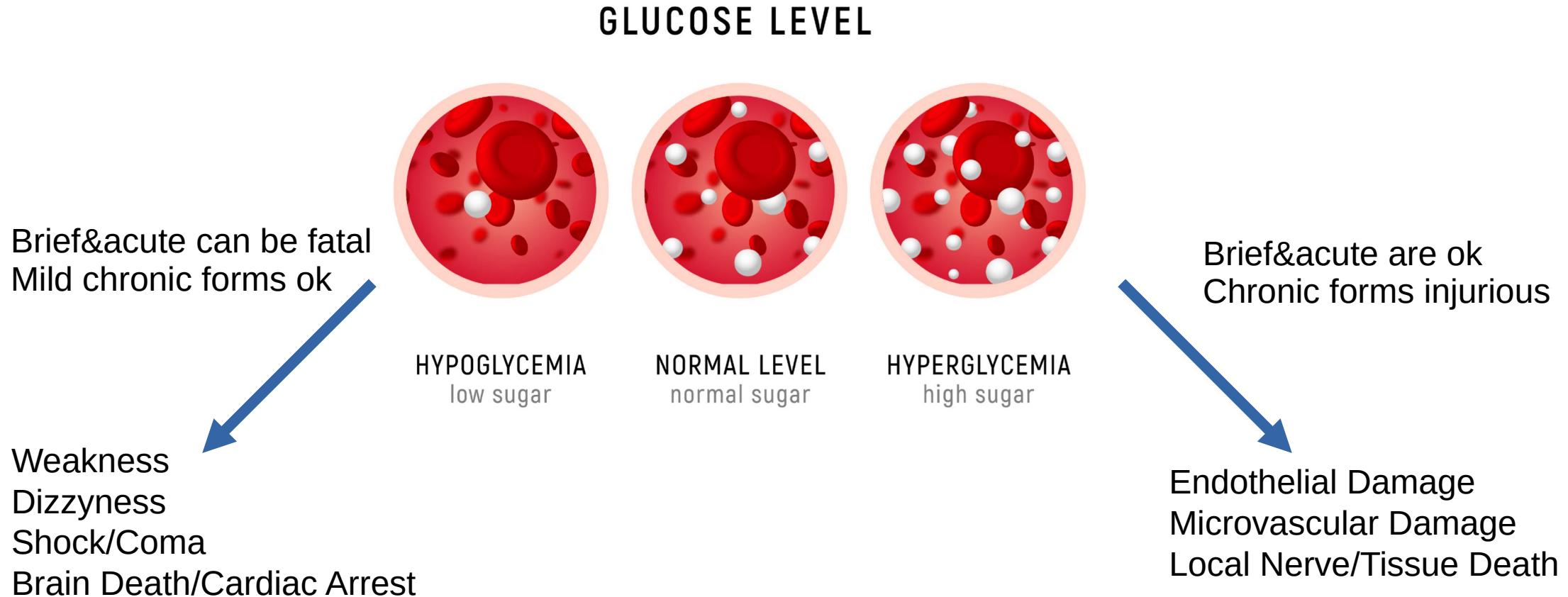
- The endothelium produces NO
 - NO diffuses to smooth muscle
 - cyclic GMP cycle contracts muscle
 - controls blood pressure/flow



Endothelial damage cycle:
 Less vasodilation → high blood pressure/low blood flow → Collapsed capillary beds → Inflammation → risk of clots and Infection → poor cellular repair → harder arteries → less vasodilation → ...

Consequences of glycodynamics/dysglycemia

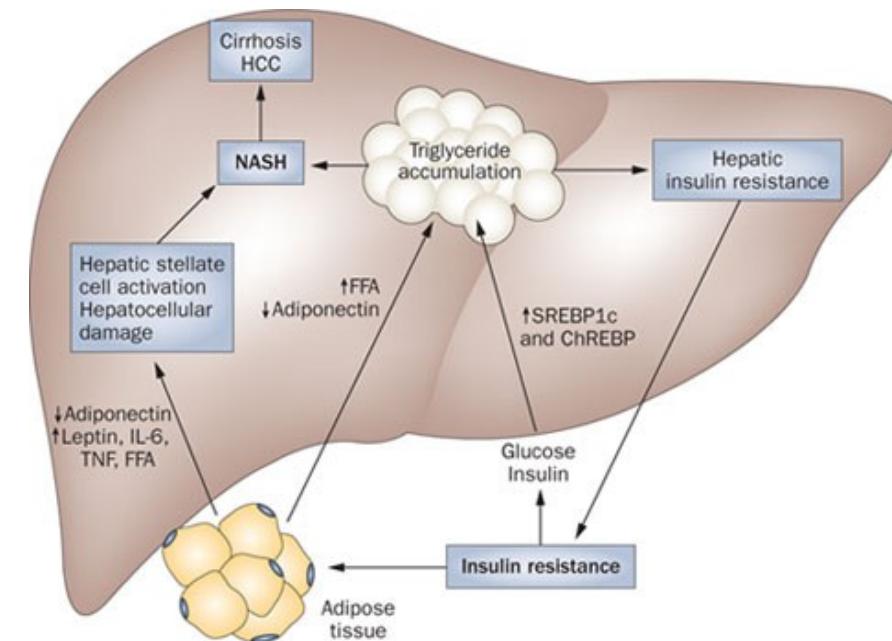
(not necessarily exclusive to diabetes!)



Example cascades attributed to chronic hyperglycemia

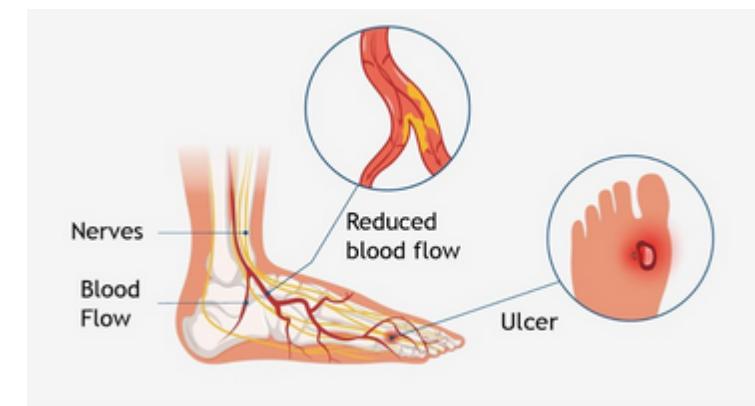
In the liver, insulin resistance progression

Chronic hyperglycemia →
Endothelial damage →
Hepatitis (liver inflammation) →
Scarring (fibrosis → cirrhosis) →
Impaired liver function/efficiency →
Insulin resistance →
Increased BG → (cycle continues)...
(+ non-endothelial storage of FFAs as triglycerides in the liver)



In vascular extremities, a metabolic-to-neuropathic progression:

Chronic hyperglycemia →
Endothelial dysfunction →
Poor blood flow/shunting/clotting →
impaired healing + local buildup of metabolic wastes →
infection →
necrosis & nerve damage → amputation



Treatments: usually Exogenous insulin (and/or analogues)

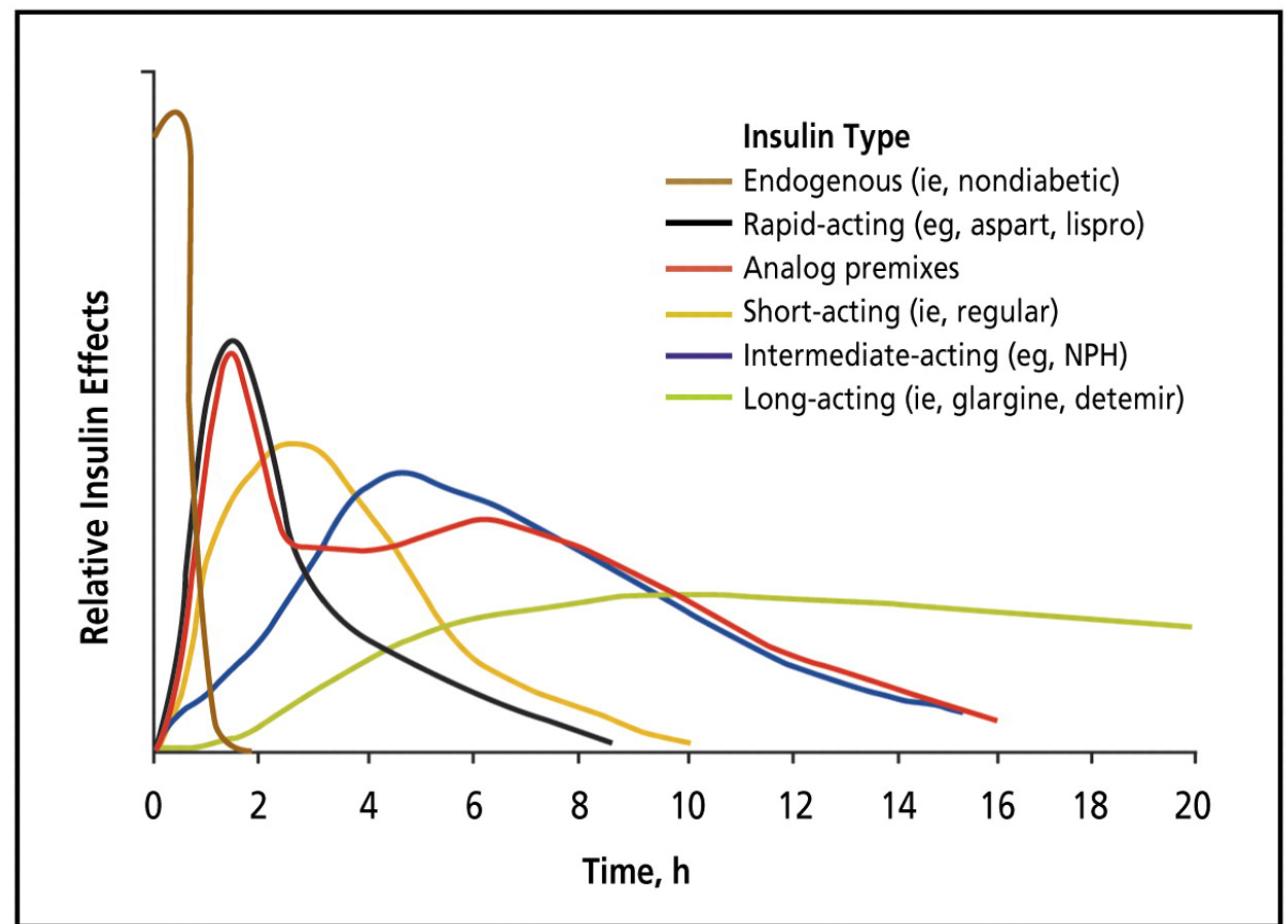
Quick notes:

- People *without diabetes* ALSO treated with insulin during intensive/critical care.
 - trauma → stress induced hyperglycemia
- Insulin is measured in units called “Units”
- Different PKs result from engineered stability via protein binding, dimer/hexamer tendencies, etc

How much insulin to give? (and which kind?)

Too much → weakness, shock, coma, etc

Too little → suboptimal endothelial processes
(reduced tissue healing, blood flow, etc)



Pharmacodynamics of different insulin formulations
(and they have different pharmacodynamics too...)

dosis sola facit venenum

Hypoglycemia is also bad, potentially lethal
They used to (1930s--60s) use insulin shock therapy (IST)
induce extreme hypoglycemia to treat mental disorders



MISSING STUDENT, Sylvia Plath, 20, found in cellar of her home and taken to hospital.

Frances Farmer describing IST: "a brutal physical attack... stunned the brain cells... shocked the body... and left the patient racked with nausea and pain"

Sylvia Plath was treated with IST; it's a key plot element of *The Bell Jar*

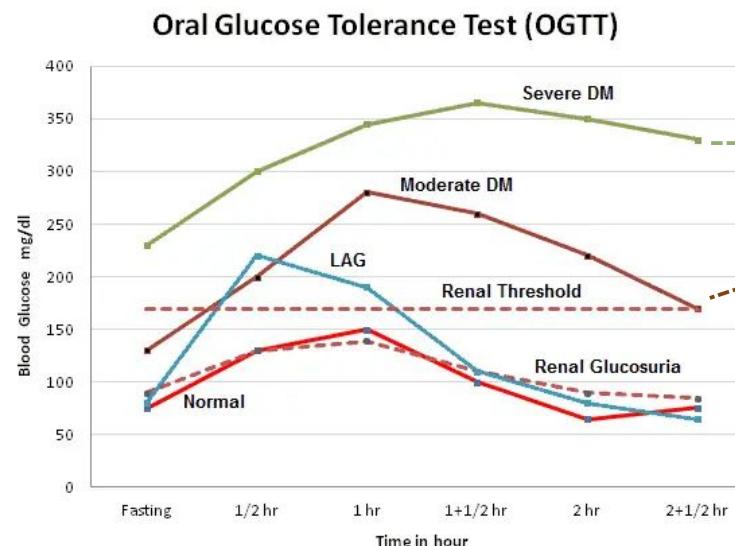


IST & insulin overdose are plot elements a bunch of movies

An Attempt to Define the Nature of Chemical Diabetes Using a Multidimensional Analysis

G. M. Reaven and R. G. Miller

Departments of Medicine and Statistics, Stanford University and Veterans Administration Hospital, Palo Alto, California, USA



Model Parameter Space:
one person's OGTT curve → one point

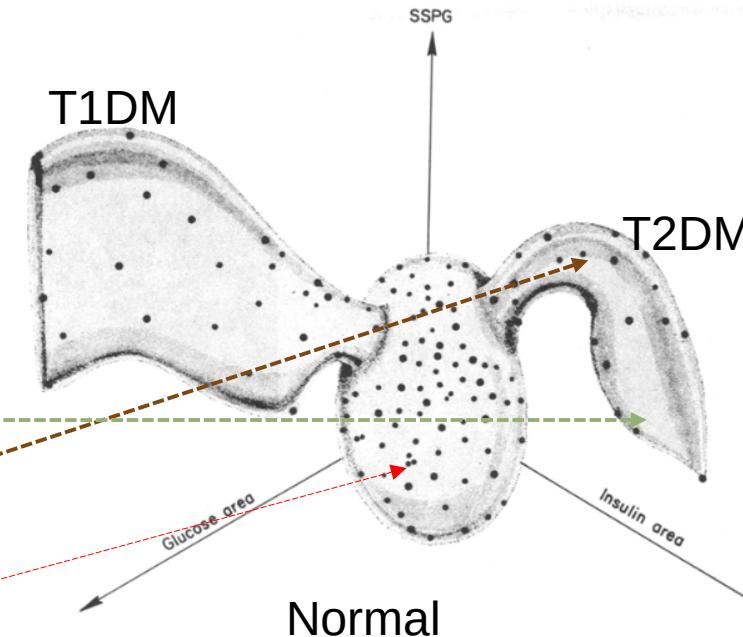


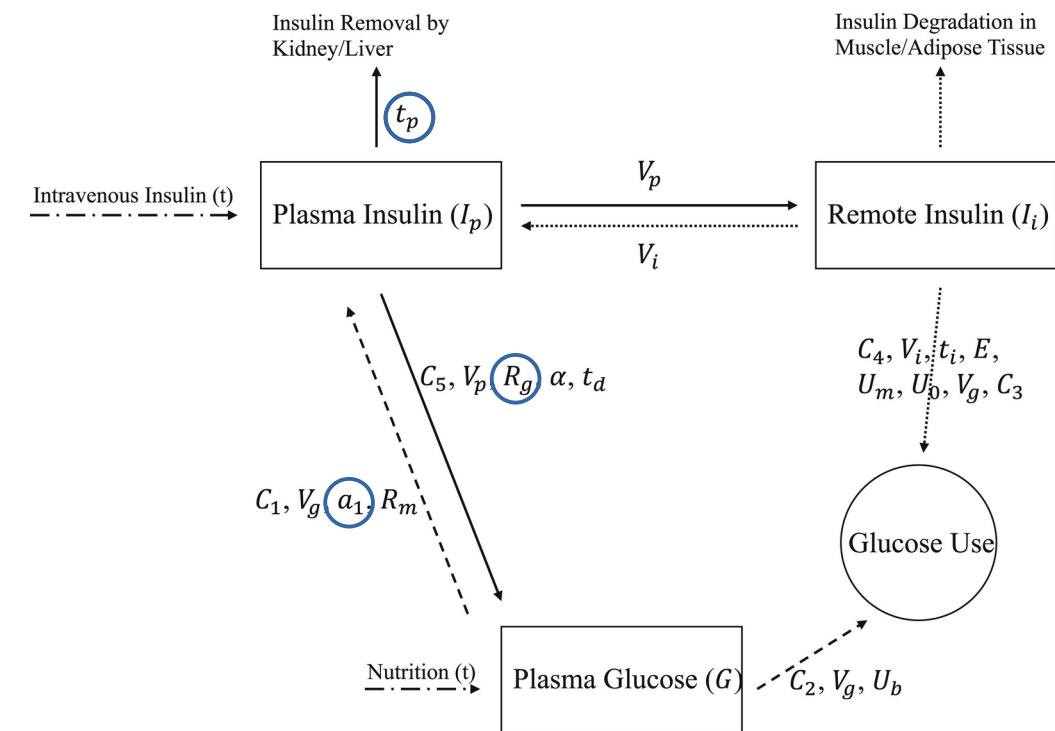
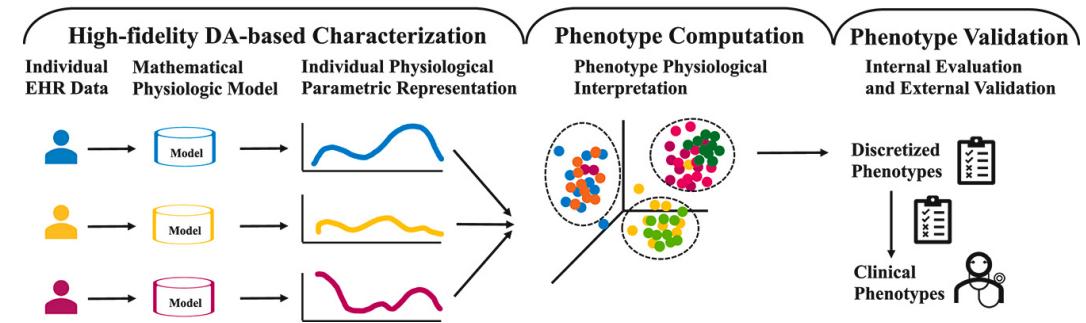
Fig. 1. Artist's rendition of data as seen in three dimensions. View is approximately along 45° line as seen through Prim 9 program on the computer; coordinate axes are in the background

Table 1. Classification of the 145 subjects into three groups on the basis of the oral glucose tolerance test

Group	Number	Metabolic characteristics (mean ± SD)			
		Rel.wt.	Glucose area (mg/100 ml · hr)	Insulin area (μU/ml · hr)	SSPG (mg/100 ml)
Normal	76	0.98 ± 0.11	350 ± 37	173 ± 69	114 ± 58
Chemical diabetes	36	1.02 ± 0.10	494 ± 55	288 ± 158	209 ± 60
Overt diabetes	33	0.98 ± 0.12	1044 ± 309	106 ± 93	319 ± 88

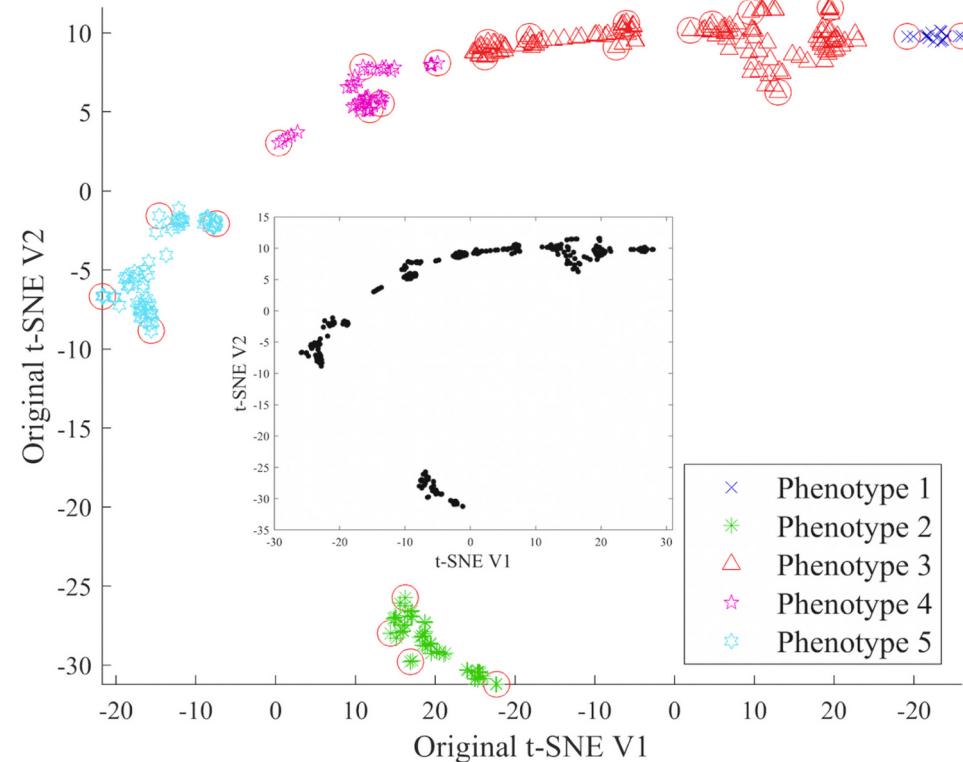
Characterizing glycoregulation in the general population via ICU data

- Features are *organ functions* instead of OGTT curve parameters



Original Research
A methodology of phenotyping ICU patients from EHR data: High-fidelity, personalized, and interpretable phenotypes estimation

Yanran Wang ^{a b} J.N. Stroh ^{b c}, George Hripcak ^d, Cecilia C. Low Wang ^e, Tellen D. Bennett ^b, Julia Wrobel ^f, Caroline Der Nigoghossian ^g, Scott W. Mueller ^h, Jan Claassen ⁱ, D.J. Albers ^{a b c d}



Clusters of “computational biomarkers”
= patients with similar **Kidney, liver, pancreas function**

Therefore, an effective model-based glycemic controller for ICU patients must: (a) *be safe, i.e., avoid hypoglycemia and hyperglycemia*; (b) *account for inter- and intra-patient variability*; and (c) *address challenges specific to the ICU setting*. In every step of the glycemic controller development process presented here, we aim to address all these challenges.

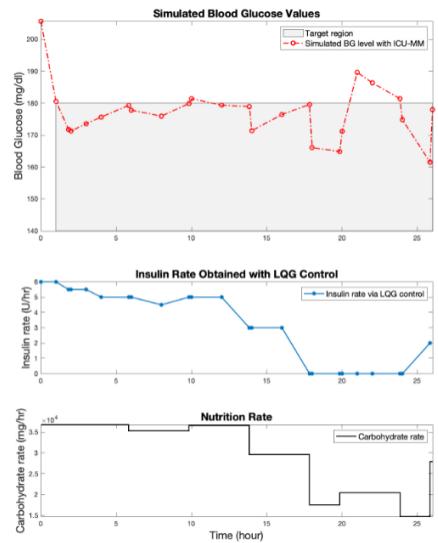


Figure 1a. LQG — ICUMM

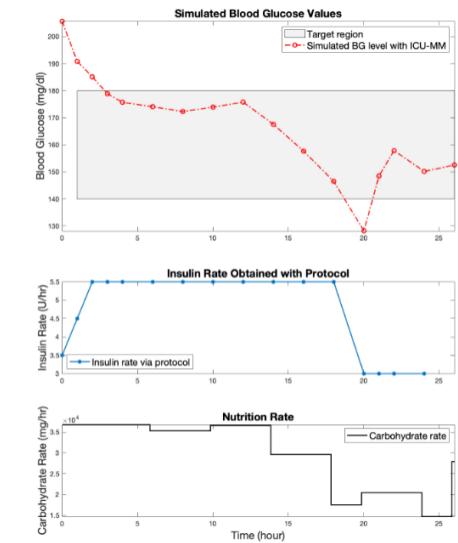
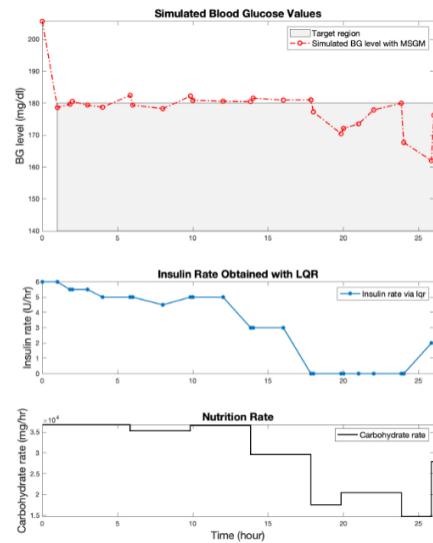


Figure 1b. Protocol — ICUMM **Figure 1c.** LQG - MSGM



A stochastic model-based control methodology for glycemic management in the intensive care unit

Melike Sirlancı^{1,2*}, George Hripcak³, Cecilia C. Low Wang⁴, J. N. Stroh¹, Yanran Wang⁵, Tellen D. Bennett^{1,6}, Andrew M. Stuart⁷ and David J. Albers^{1,3,5,8}

¹Department of Biomedical Informatics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, ²Department of Applied Mathematics, University of Colorado Boulder, Boulder, CO, United States, ³Department of Biomedical Informatics, Columbia University, New York, NY, United States, ⁴Division of Endocrinology, Metabolism and Diabetes, Department of Medicine, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, United States,

⁵Biostatistics and Informatics Department, Colorado School of Public Health, Aurora, CO, United States,

⁶Department of Pediatrics, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO, United States, ⁷Department of Computing and Mathematical Sciences, California Institute of Technology, Pasadena, CA, United States, ⁸Department of Bioengineering, University of Colorado Denver, Denver, CO, United States

Automated system measures nutrition and BG over time to provide the “right amount of insulin” so that patient BG stays in ideal region

Algorithm better than current ‘protocol’

Last Topic: T2DM, general glycodynamics regulation, and COVID-19

COVID19 appears to have persistent effects on Metabolism and glucose-insulin dynamics
(Also: COVID mortality rate was 2–3x higher for people with T2DM)

ARTICLES

<https://doi.org/10.1038/s42255-021-00407-6>

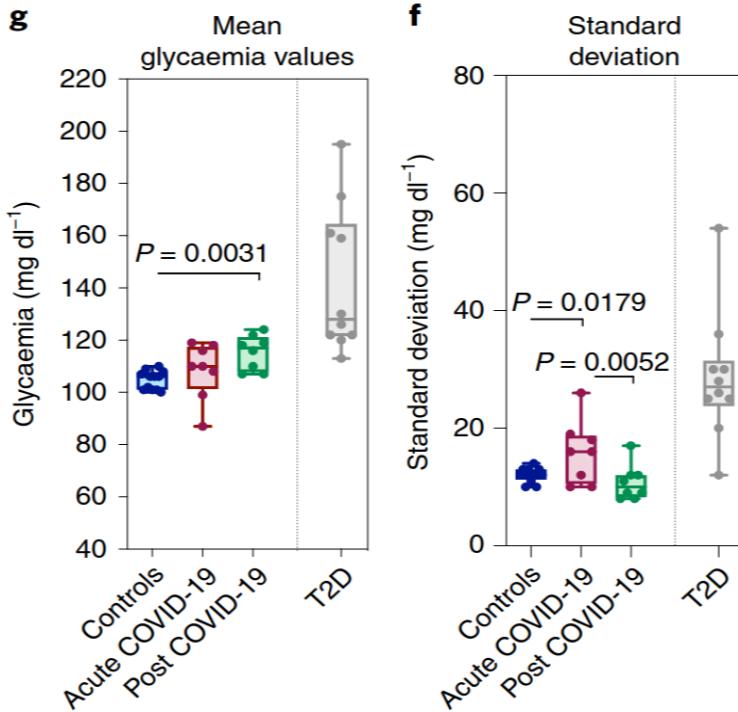
nature metabolism

Check for updates

Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection

Laura Montefusco^{1,6}, Moufida Ben Nasr^{2,3,16}, Francesca D'Addio^{2,16}, Cristian Loretelli², Antonio Rossi¹, Ida Pastore², Giuseppe Daniele⁴, Ahmed Abdelsalam², Anna Maestroni², Marco Dell'Acqua^{2,5}, Elio Ippolito², Emma Assi², Vera Usuelli², Andy Joe Seelam², Roberta Maria Fiorina², Enrica Chebat¹, Paola Morpurgo¹, Maria Elena Lunati¹, Andrea Mario Bolla¹, Giovanna Finzi⁶, Reza Abdi⁷, Joseph V. Bonventre², Stefano Rusconi², Agostino Riva², Domenico Corradi⁹, Pierachille Santus^{10,11}, Manuela Nebuloni^{2,12,13}, Franco Folli¹⁴, Gian Vincenzo Zucconi^{1,15}, Massimo Galli⁸ and Paolo Fiorina^{2,1,2,3}

290



Endocrine Reviews, 2024, 45, 281–308
<https://doi.org/10.1210/endrev/bnad032>
Advance access publication 2 November 2023
Review

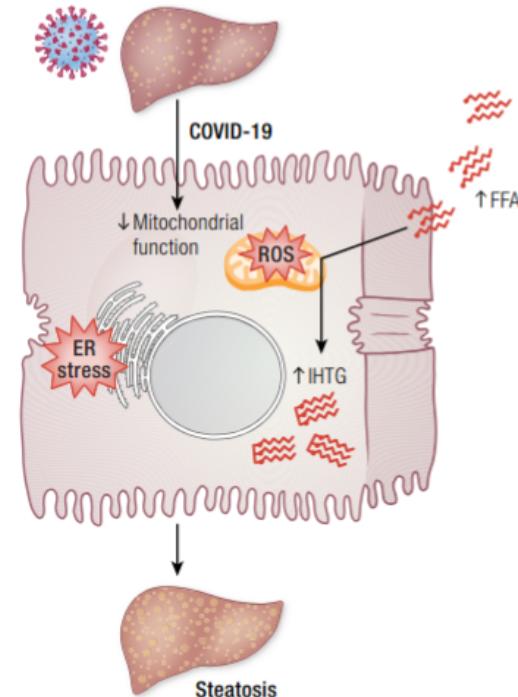


Diabetes Mellitus, Energy Metabolism, and COVID-19

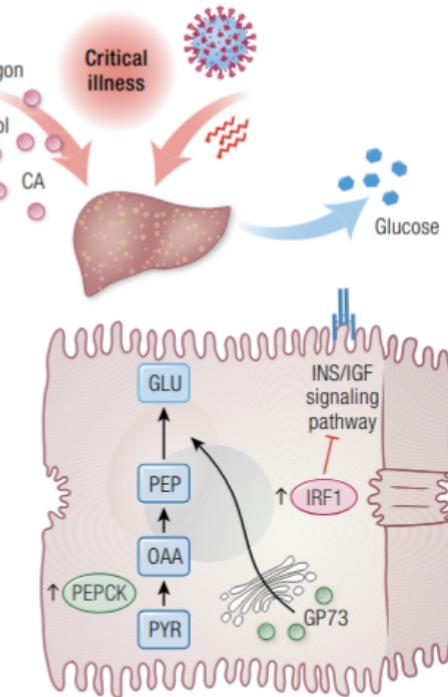
Caterina Conte,^{1,2} Elisa Cipponeri,² and Michael Roden^{3,4,5}

Endocrine Reviews, 2024, Vol. 45, No. 2

A Mechanisms by which COVID-19 might cause/worsen steatosis



B Mechanisms by which COVID-19 might increase glucose production



1519-P: Endothelial Injury Predicts Carbohydrate Metabolism Trajectories after COVID-19 FREE

JANE E.B. REUSCH; DAVID ALBERS; YANRAN WANG; JENNIFER BRIGGS; RICHARD MAICKI; J.N. STROH; AANCHAL GUPTA; ANN GARCIA; VATSALA SINGH; TERRA D. HILLER; ARTHUR SHERMAN; NEDA RASOULI; IVOR S. DOUGLAS

 Check for updates

Diabetes 2024;73(Supplement_1):1519-P

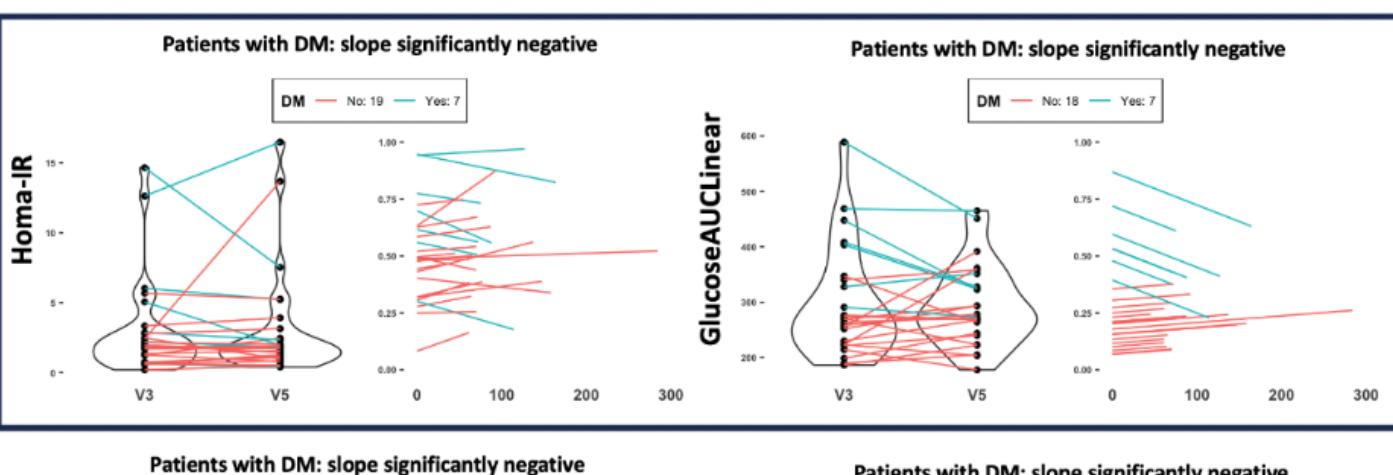
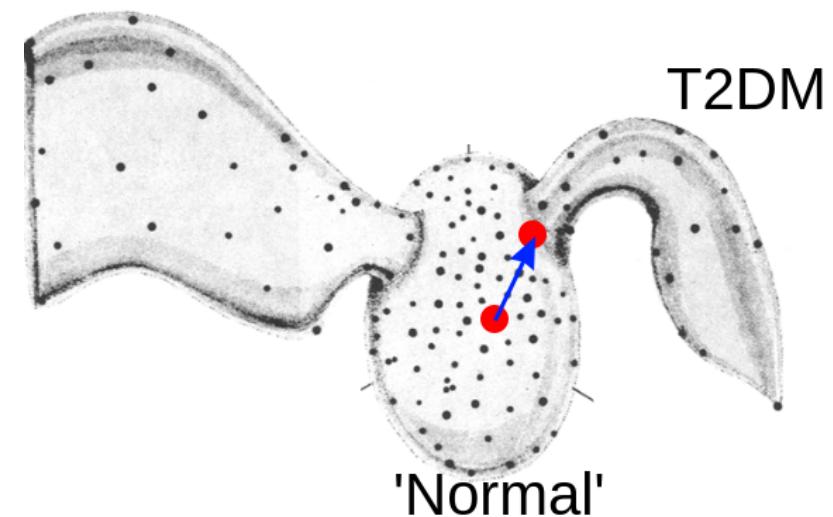
<https://doi.org/10.2337/db24-1519-P>

Conclusion: Changes in EI predict post-hospital recovery of carbohydrate metabolism.

Introduction & Objective: Diabetes and SARS-CoV-2 infection target the endothelium causing

(2025 update, in review @ Diabetes Management)

- EI significantly correlated with decreased insulin sensitivity and impaired insulin secretion.
- EI predicts worse carbometabolism trajectories.
- T2DM showed worse metabolic profiles but greater improvements in insulin action



Hinted (& un-nuanced) implication:
1) COVID-19 moves carbometabolism closer to T2DM" temporarily
2) Recovery rate depends on extent of endothelial damage

Thanks!

jn.stroh@cuanschutz.edu