LOW CARBOHYDRATE DIETS WITHIN CONTEXT OF TYPE 2 DIABETES CARE

BE LIKE ZOG

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Department of Internal Medicine

DISCLOSURES

Position & Organization	Details
Member of Expert Advisory Committee Institute for Personalized Therapeutic Nutrition (not-for-profit)	https://www.therapeuticnutrition.org/
Novo Nordisk	Receives consulting fees.
Diet Doctor	Receives consulting fees.

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OBJECTIVES

- Broadly understand the evidence for LCHF and type 2 diabetes.
- Consider type 2 diabetes as a disease of "adiposopathy".
- Understand physiologic principles of diabetes remission.
- Learn a wee bit about metabolism
- Consider medication adjustments needed when taking a low carb approach for type 2 DM.

Paul is a 56 years old who was diagnosed with type 2 diabetes 5 years ago. He has no complications of T2D.

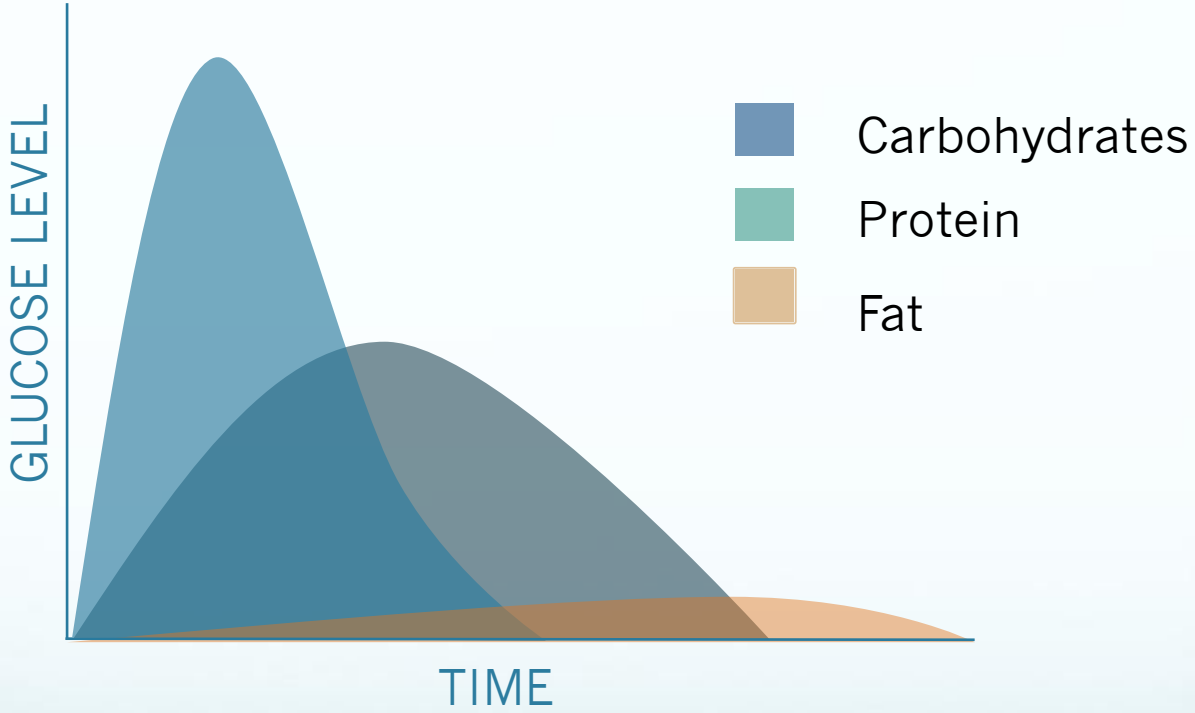
He was intolerant to metformin and sulfonylureas. He is hesitant to try any other medications. He takes a statin and ACE inhibitor. He has no private drug plan.

His BMI is 36, BP 130/80 and A1c is 8.4%,

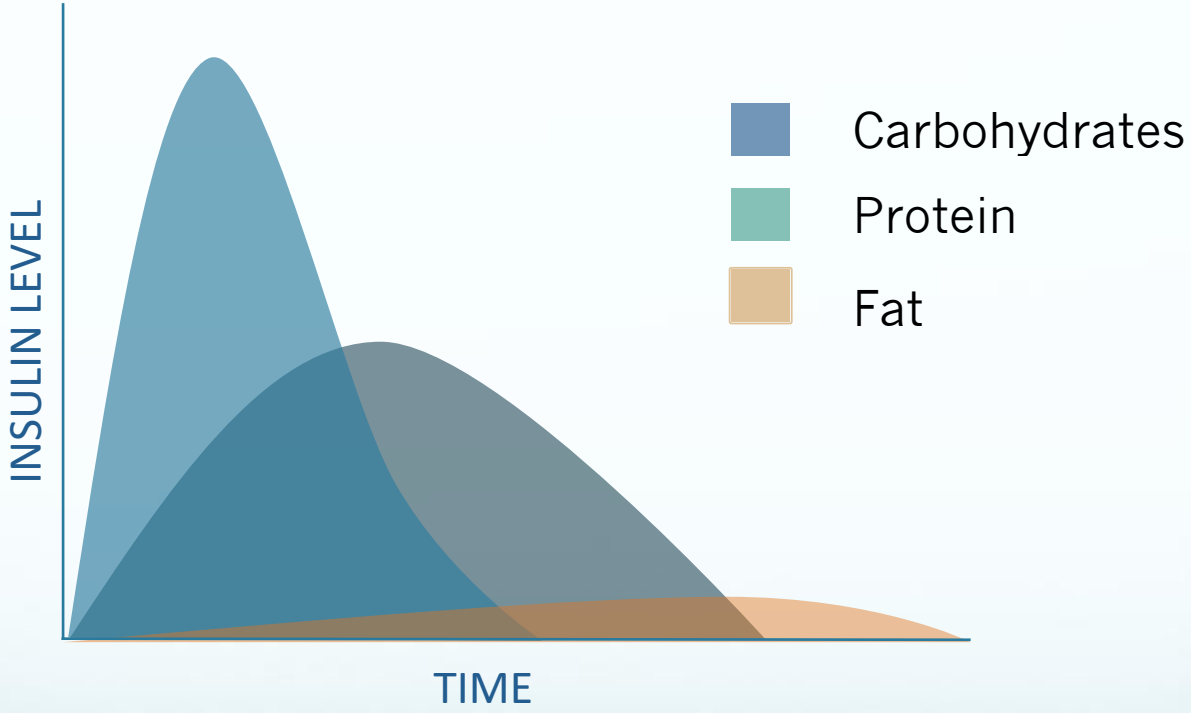
A friend placed his T2D in remission with LCHF and wants to know if you would support him.

He is very excited and asks you that if carbs turn into glucose that shouldn't we just reduce the carbs?

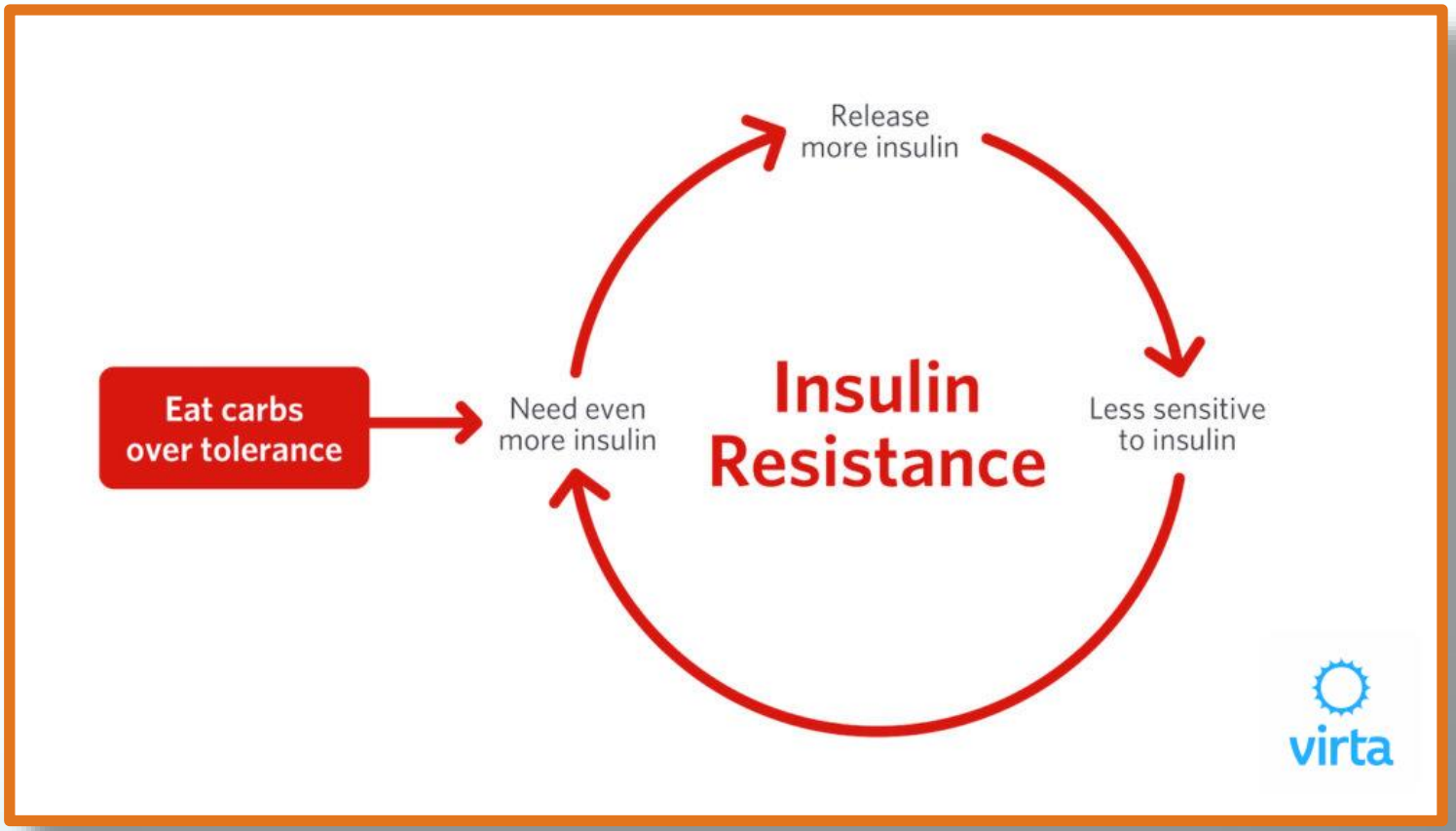
Macronutrients and Glucose

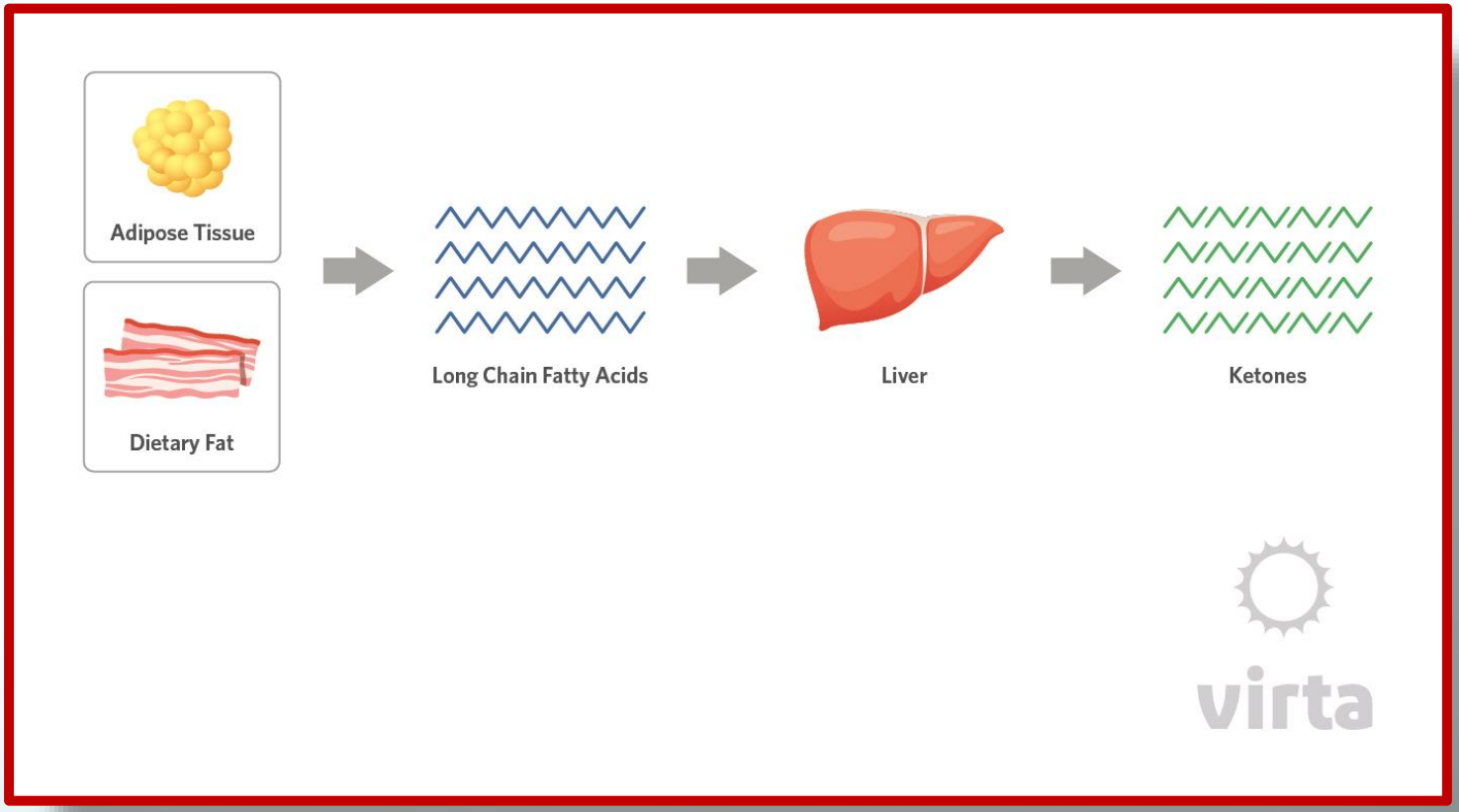


Macronutrients and INSULIN



Type 2 Diabetes = Carb Intolerance?




Adipose Tissue
Dietary Fat
Long Chain Fatty Acids
Liver
Ketones
virta

In considering Paul's case, which of the following is true:

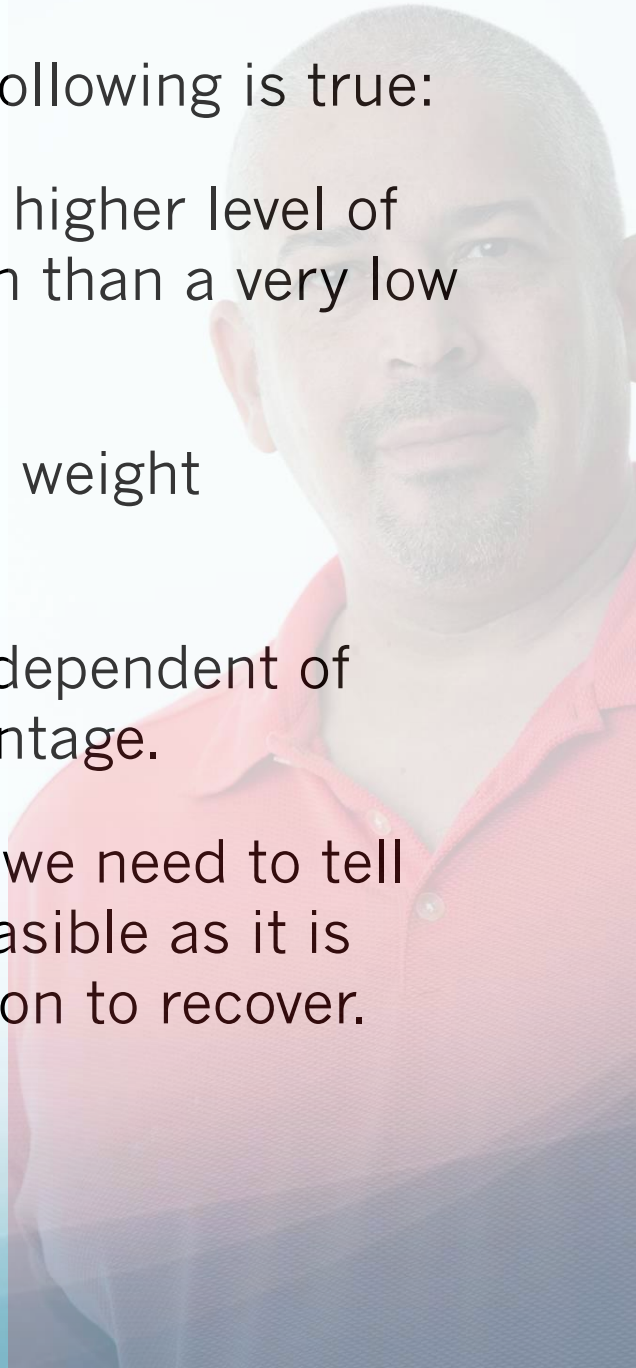
A. Studies demonstrate that LCHF has a higher level of evidence for type 2 diabetes remission than a very low energy diet.

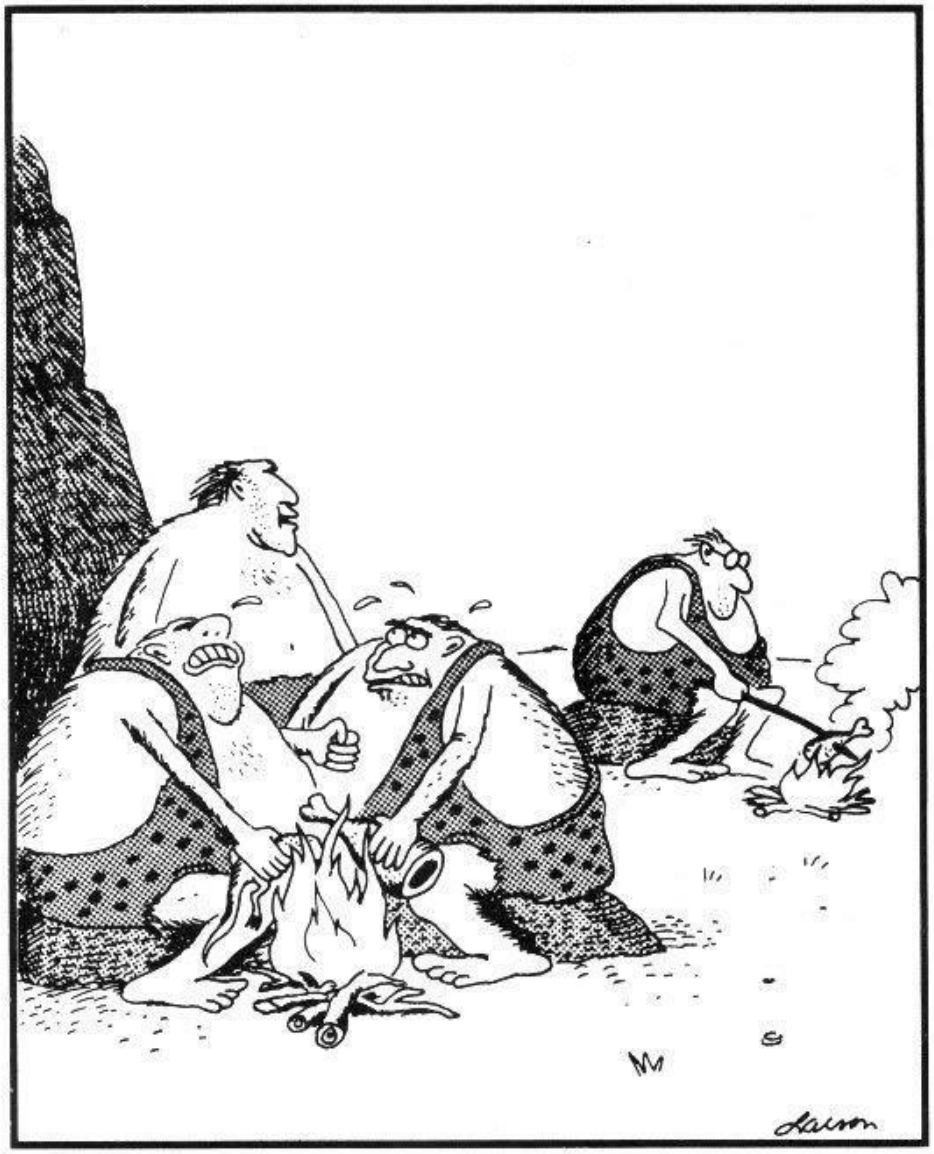
B. LCHF is the most effective way to lose weight compared to other diets.

C. LCHF works for diabetes remission independent of weight loss which is a particular advantage.

D. Since he is 5 years into his diagnosis we need to tell Paul that diabetes remission is not feasible as it is unlikely for pancreatic beta-cell function to recover.

E. None of the above are true.





"Hey! Look what Zog do!"

Obesity Prevalence

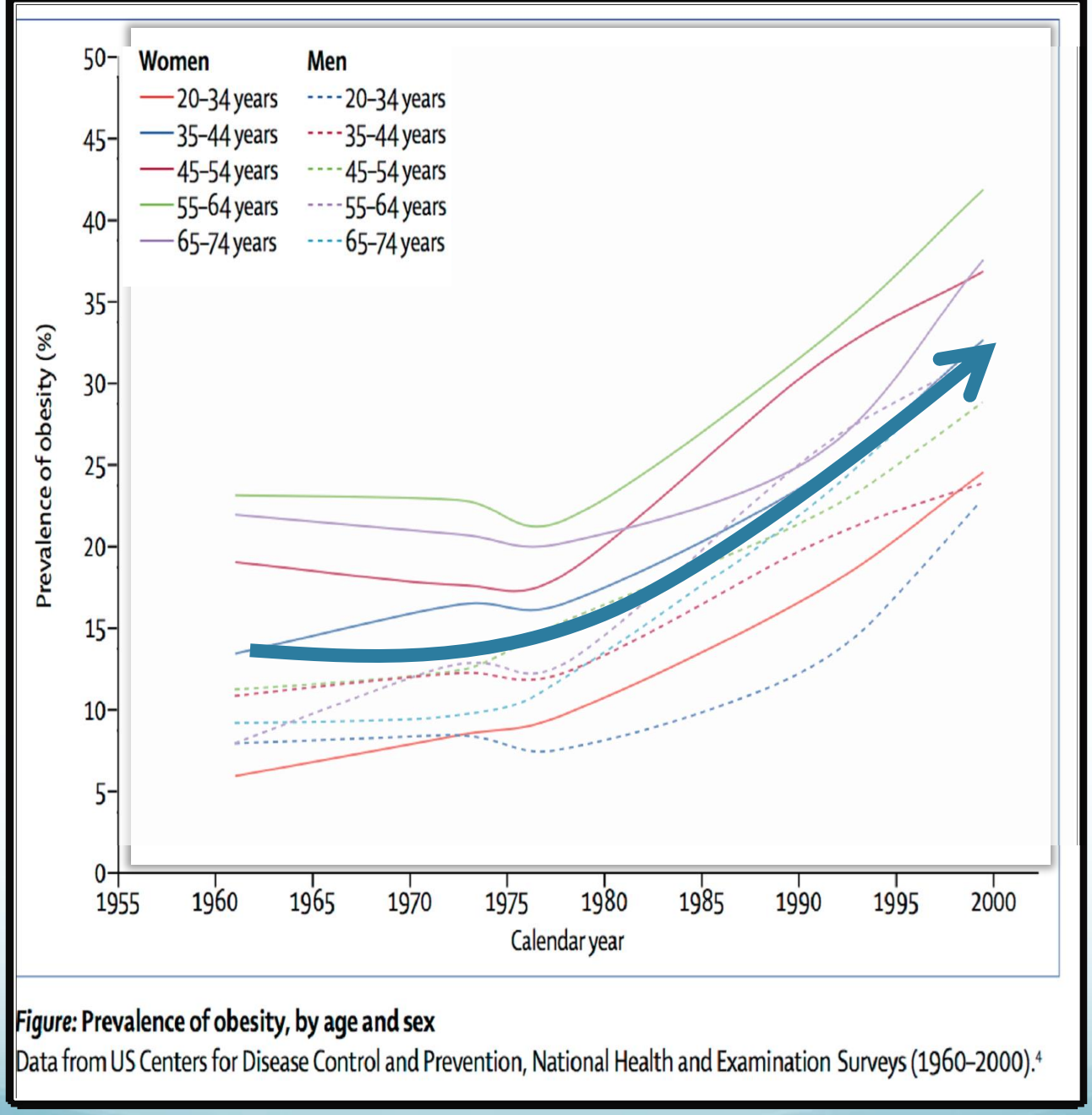


Figure: **Prevalence of obesity, by age and sex**

Data from US Centers for Disease Control and Prevention, National Health and Examination Surveys (1960–2000).[4]

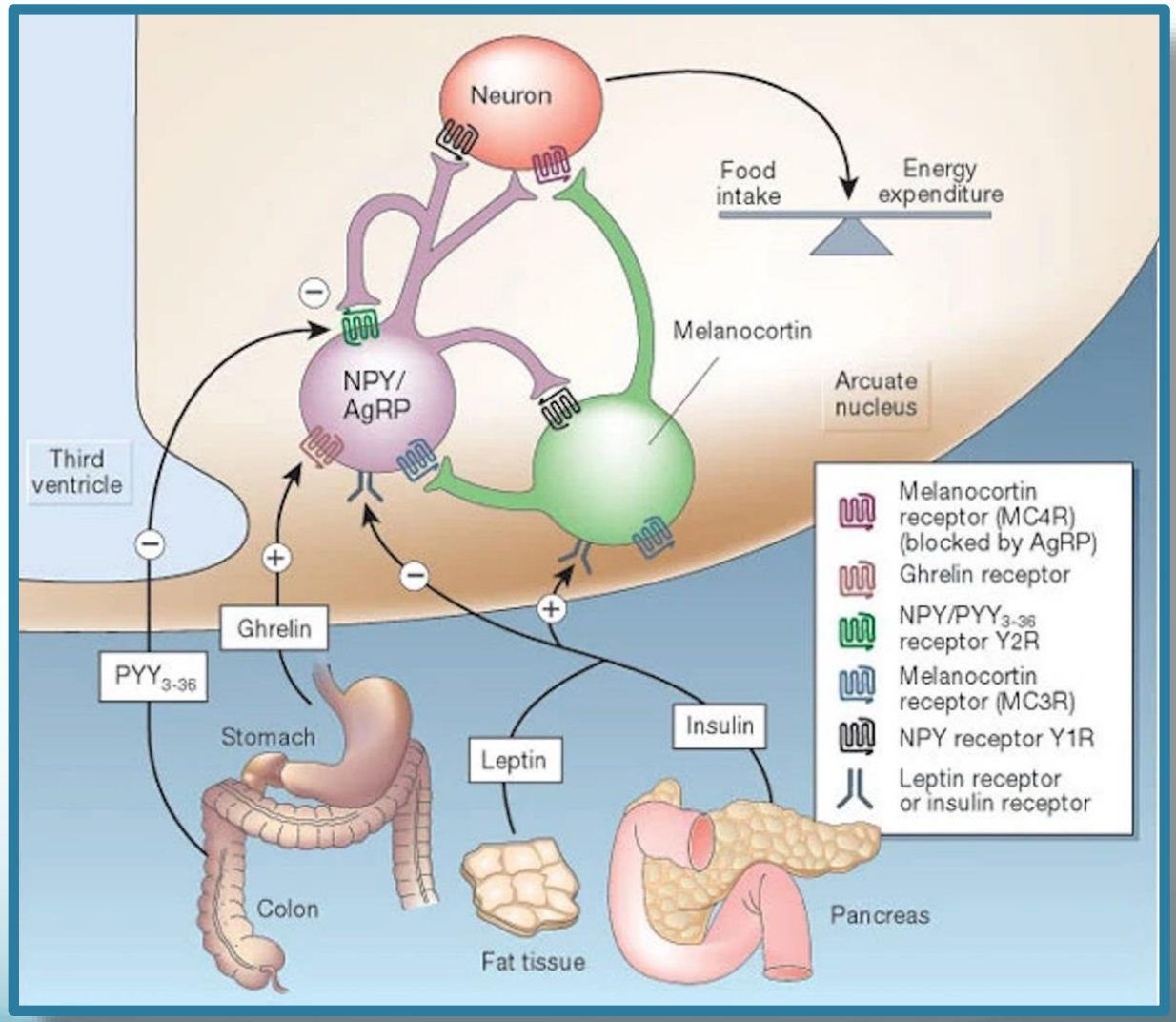
Rodgers, A., Woodward, A., Swinburn, B., & Dietz, W. H. (2018). Comment Prevalence trends tell us what did not precipitate the US obesity epidemic. *The Lancet Public Health*, *3*(4), e162–e163. http://doi.org/10.1016/S2468-2667(18)30021-5

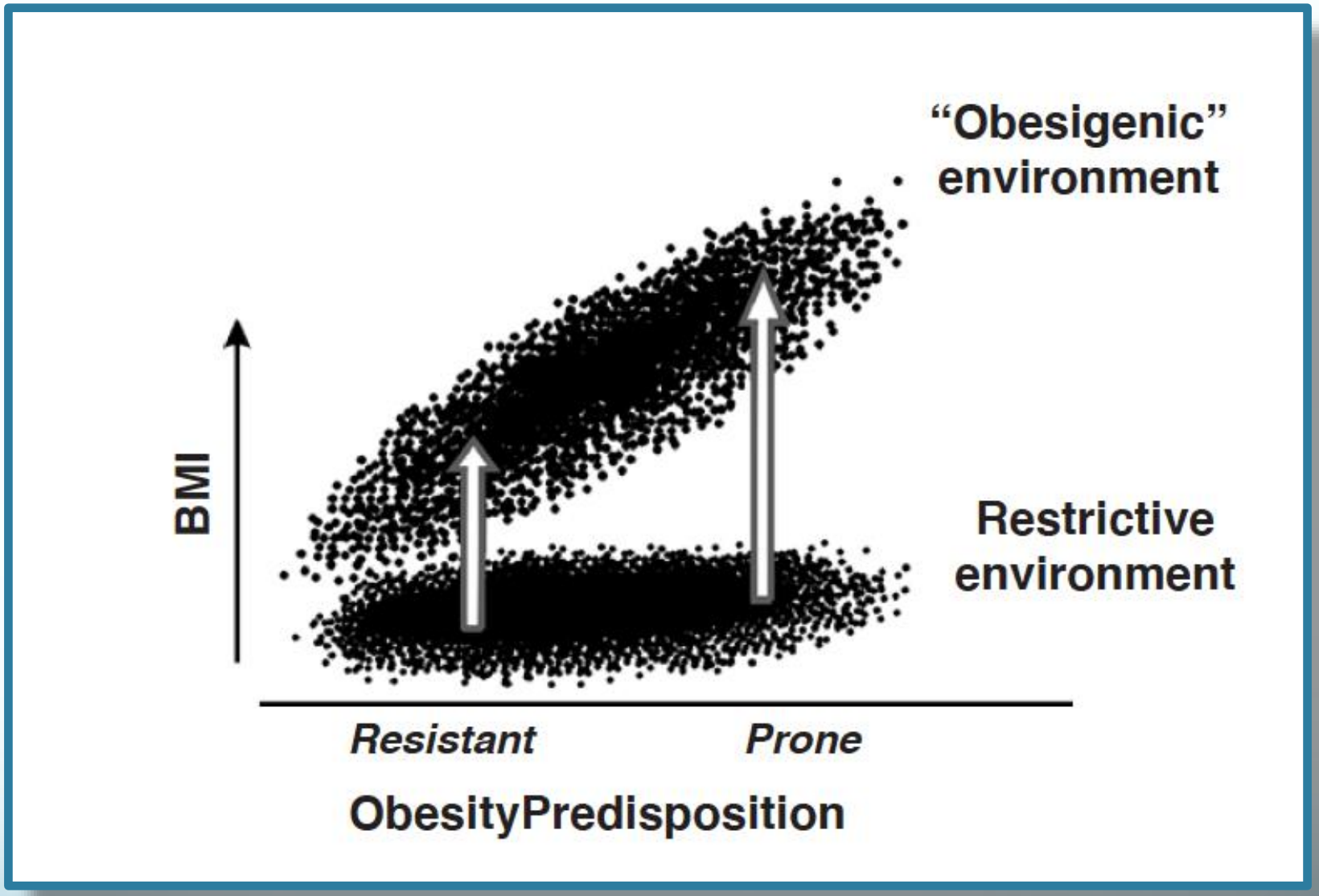
THE SEAT OF OBESITY

MODERN OBESOGENIC ENVIRONMENT

A GENETICALLY INHERITED APPETITE SYSTEM

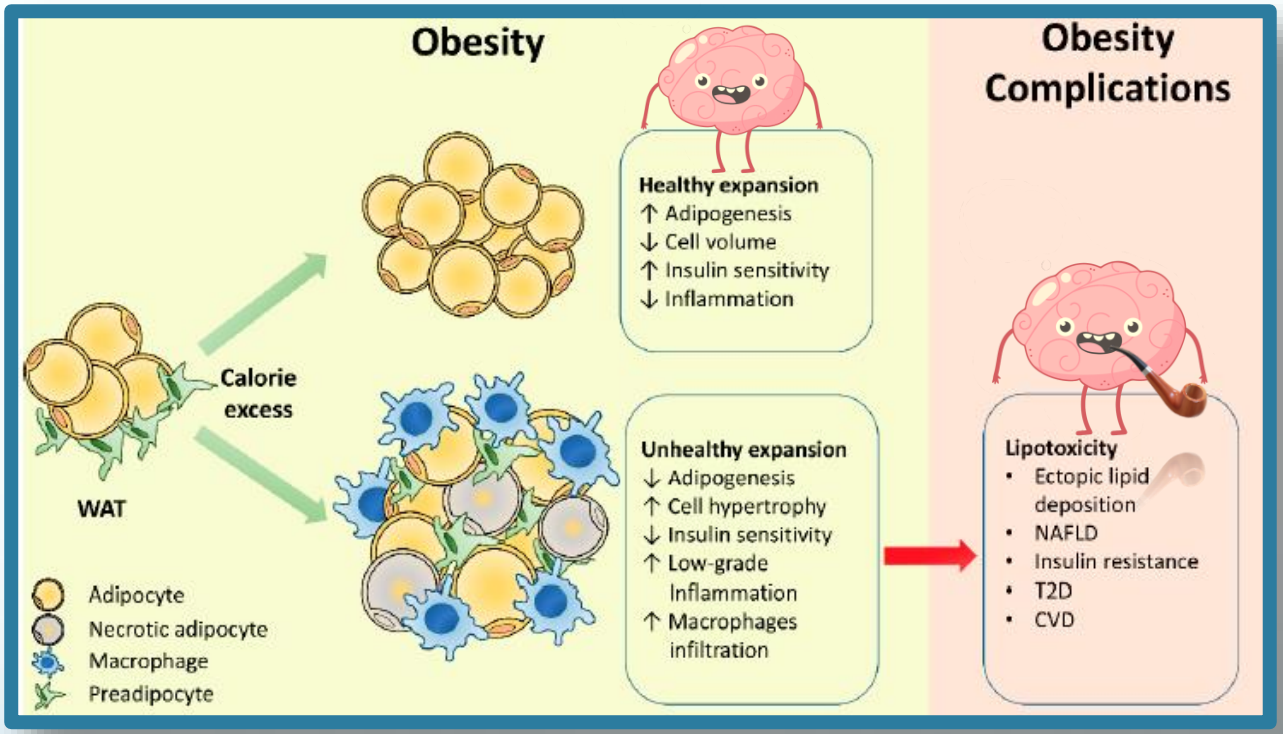
ENERGY BALANCE OCCURS IN THE SUB-CORTICAL BRAIN



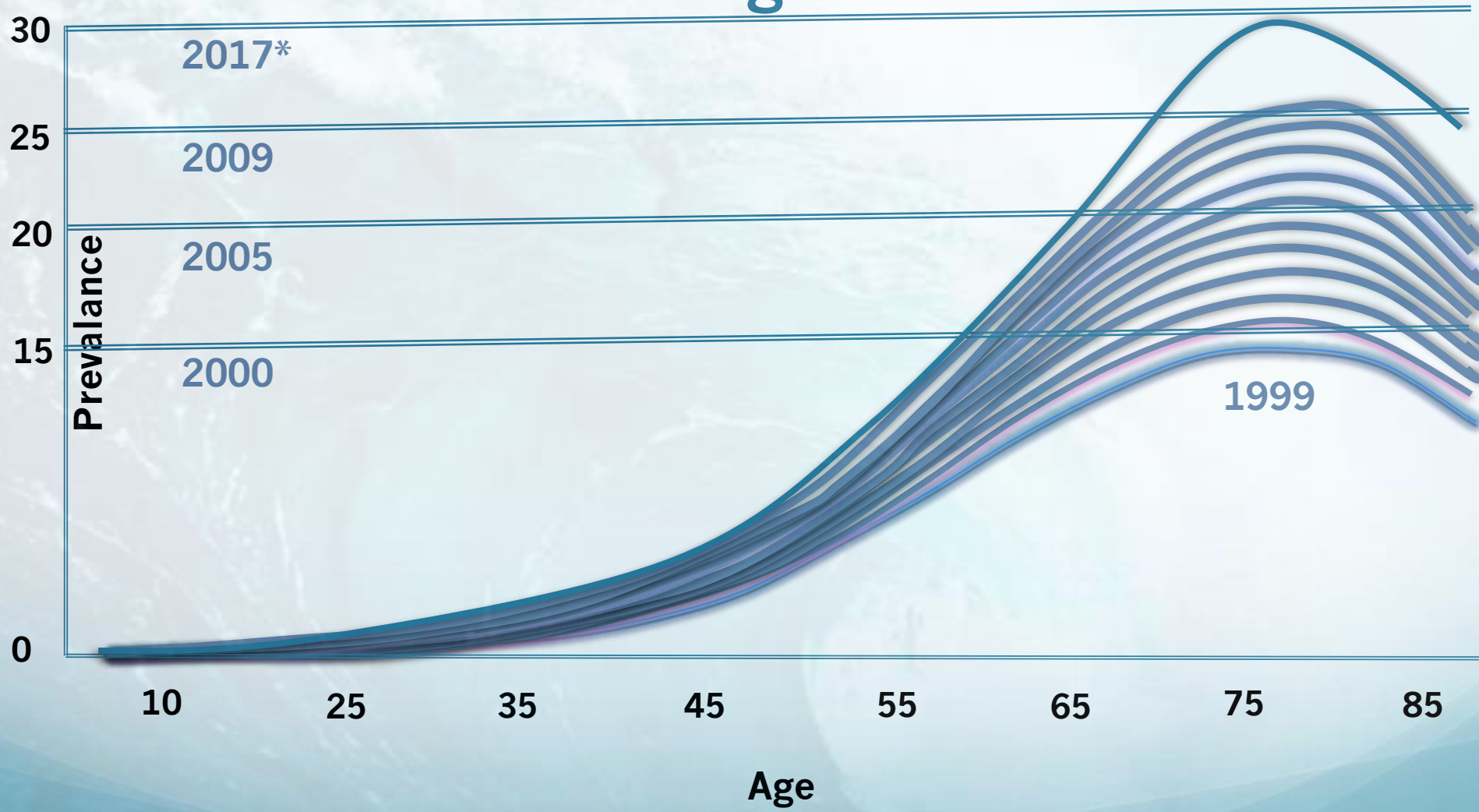


Blundell, J, R Stubbs, C Golding, F Croden, R Alam, S Whybrow, J Lenoury, and C Lawton. "Resistance and Susceptibility to Weight Gain: Individual Variability in Response to a High-Fat Diet." *Physiology & Behavior* 86, no. 5 (December 15, 2005): 614–22. https://doi.org/10.1016/j.physbeh.2005.08.052.

TYPE 2 DM IS A DISEASE OF “ADIPOSOPATHY”

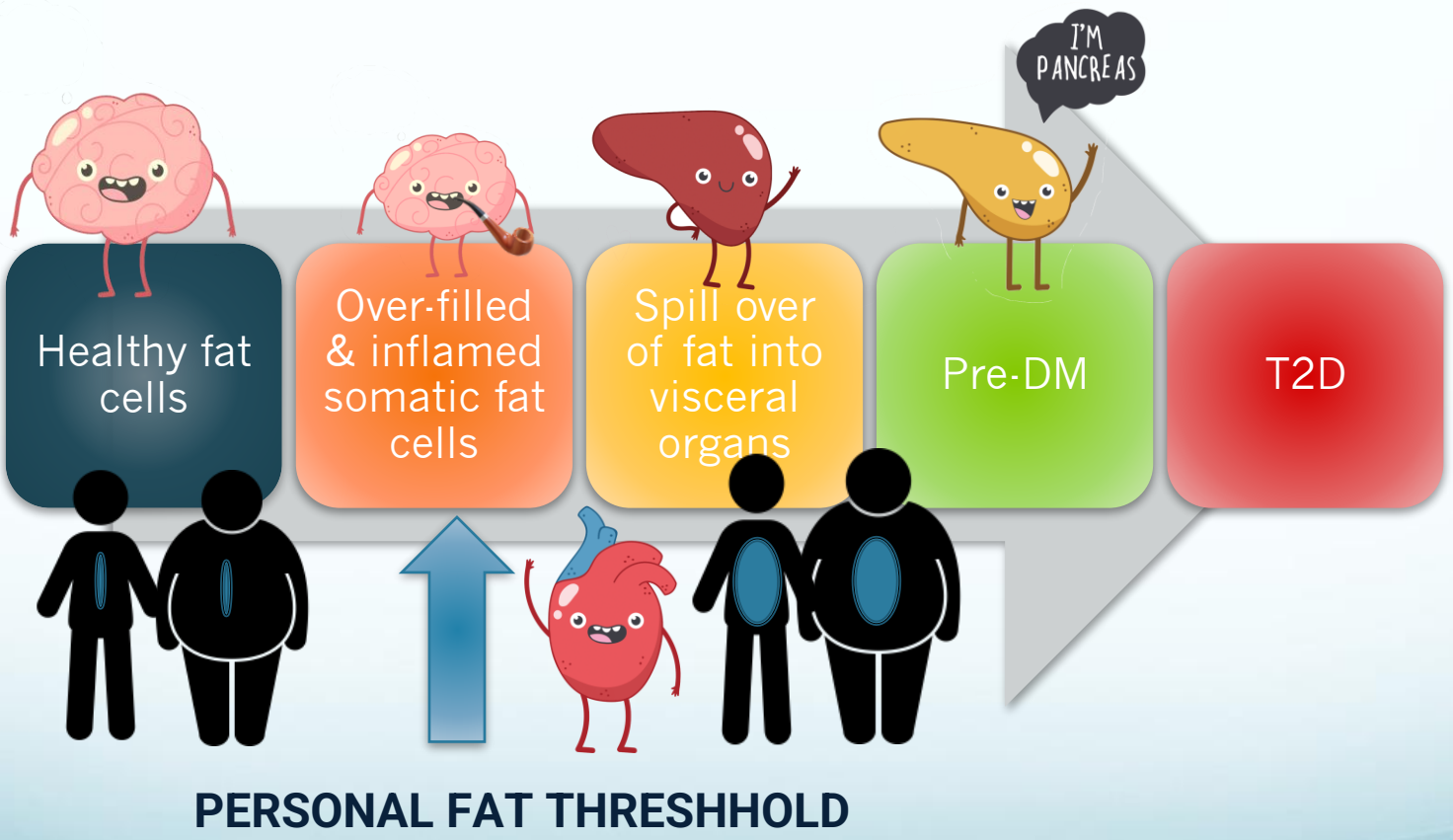


Type 2 diabetes prevalence: a rising tide

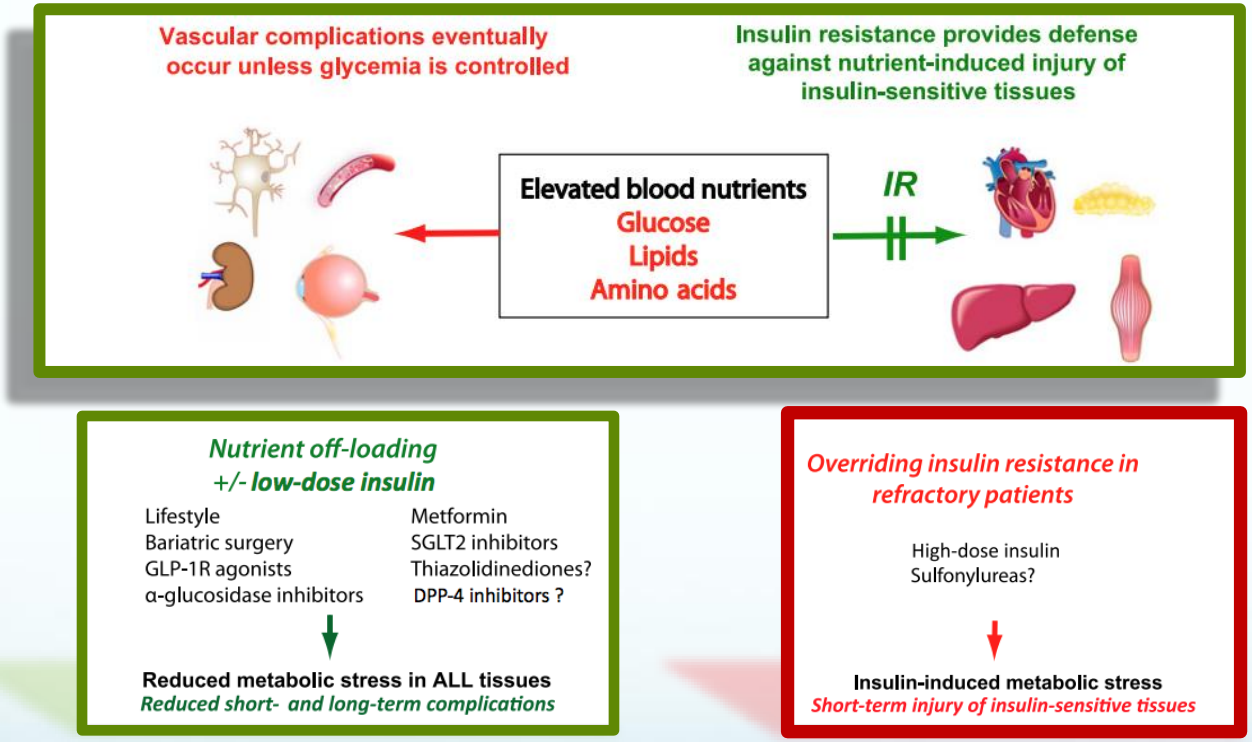


Turin TC, Saad N, Jun M, et al. *Lifetime risk of diabetes among First Nations and non-First Nations people.* CMAJ. 2016; 188(16):1147-53. .
https://www.canada.ca/en/public-health/services/chronic-diseases/reports-publications/diabetes/diabetes-canada-facts-figures-a-public-health-perspective/chapter-1.html;
*2017 curve generated from 2016/2017 diabetes prevalence from Nova Scotia DCPNS registry data

TYPE 2 DIABETES AS A MODEL DISEASE OF ADIPOSOPATHY

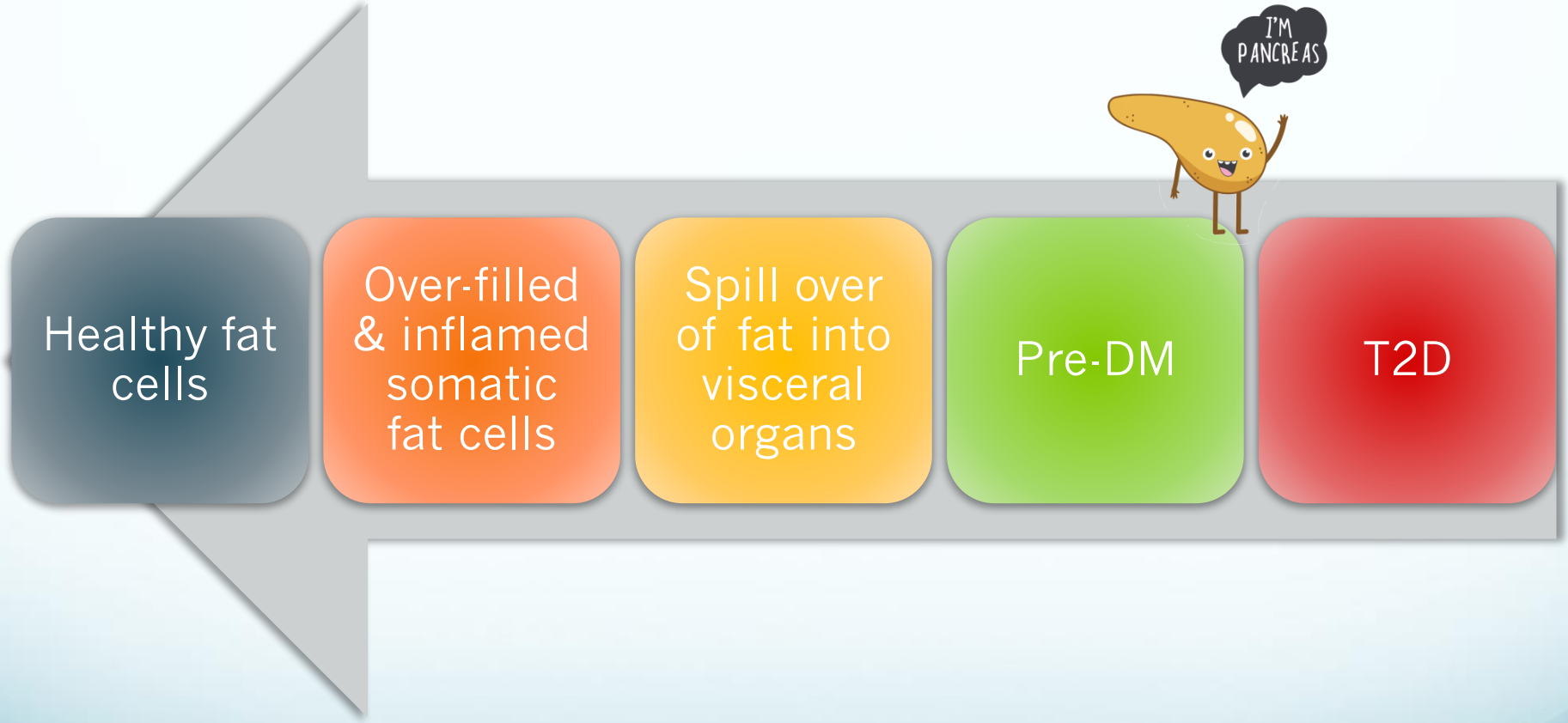


PARADIGM SHIFT IN CARE OF TYPE 2 DIABETES



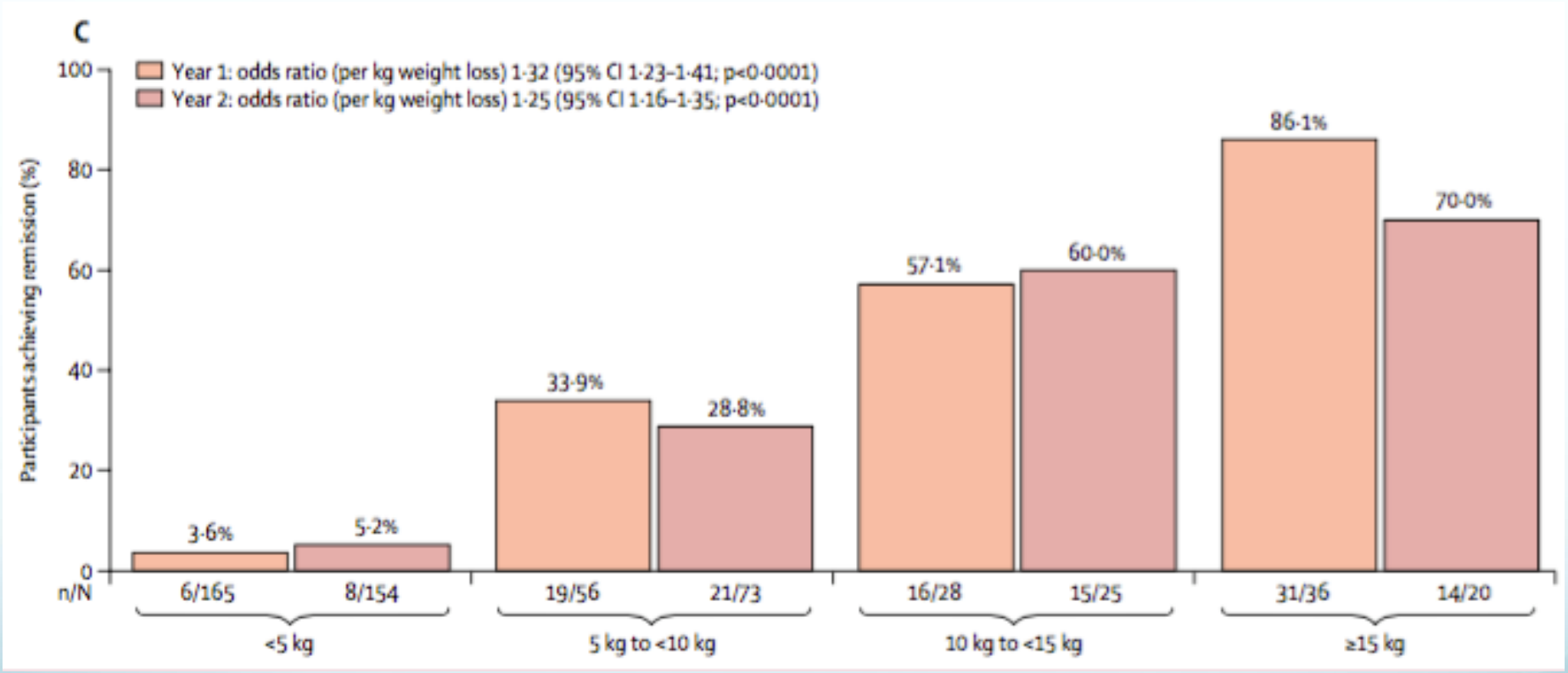
Nolan, Christopher J., Neil B. Ruderman, Steven E. Kahn, Oluf Pedersen, and Marc Prentki. "Insulin Resistance as a Physiological Defense Against Metabolic Stress: Implications for the Management of Subsets of Type 2 Diabetes." *Diabetes* 64, no. 3 (March 2015): 673–86. https://doi.org/10.2337/db14-0694.

Type 2 diabetes remission



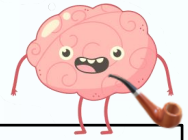
For further details see “twin cycle hypothesis” by Taylor, R., Al-Mrabeh, A., Endocrinology, N. S. T. L. D., 2019. (n.d.). Understanding the mechanisms of reversal of type 2 diabetes. *Elsevier*

DiRECT Trial:
T2D remission & weight loss



Lean, M. E., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., et al. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *The Lancet*, *391*(10120), 541–551. http://doi.org/10.1016/S0140-6736(17)33102-1

TWIN CYCLE HYPOTHESIS



Positive calorie balance

Pre-existing muscle insulin resistance

+ +

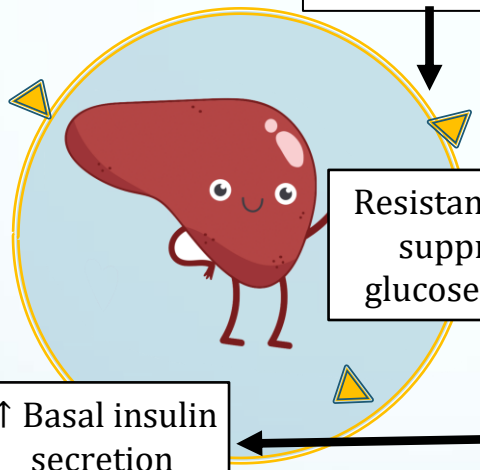
↑ Liver Fat

↑ VLDL

Subcutaneous fat storage capacity exceeded

↑ Islet triglyceride

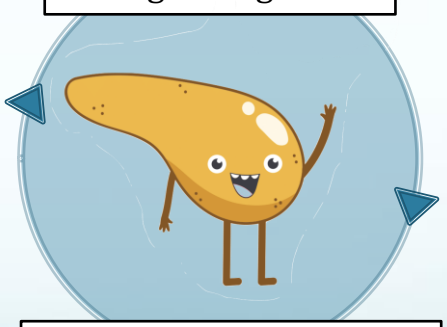
↓ insulin response to ingested glucose



Resistance to insulin suppression of glucose production

↑ Basal insulin secretion

↑ Plasma Glucose



↑ Post – prandial glucose

Taylor, R, A Al-Mrabeh, N Sattar The Lancet Diabetes Endocrinology, and 2019. "Understanding the Mechanisms of Reversal of Type 2 Diabetes." *Elsevier*, n.d. https://doi.org/10.1016/S2213-8587(19)30076-2.

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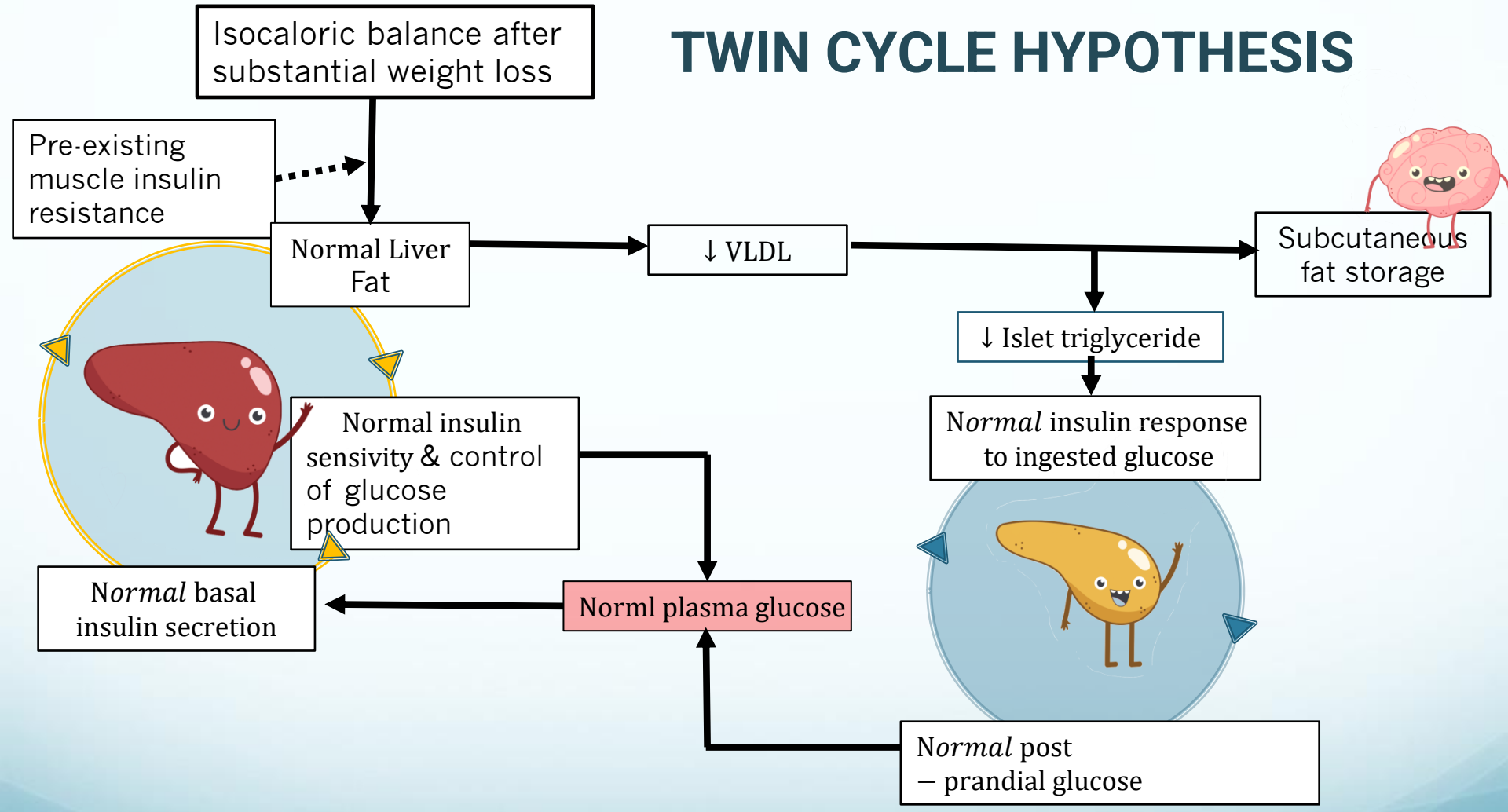
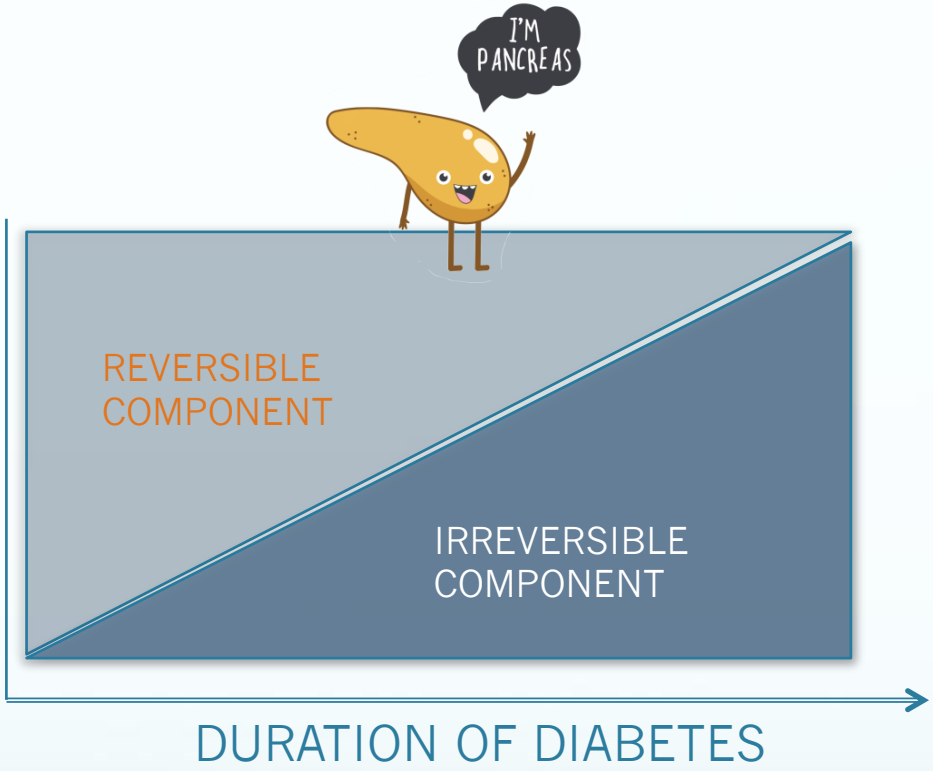


Taylor, R, A Al-Mrabeh, N Sattar The Lancet Diabetes Endocrinology, and 2019. "Understanding the Mechanisms of Reversal of Type 2 Diabetes." *Elsevier*, n.d. https://doi.org/10.1016/S2213-8587(19)30076-2.

BETA CELL DYSFUNCTION



Beta-cell exposure to glucotoxicity, lipotoxicity and inflammation

Retnakaran, R. (2014, December 1). Joe Doupe lecture: emerging strategies for the preservation of pancreatic beta-cell function in early type 2 diabetes. *Clinical and Investigative Medicine. Medecine Clinique Et Experimentale*.

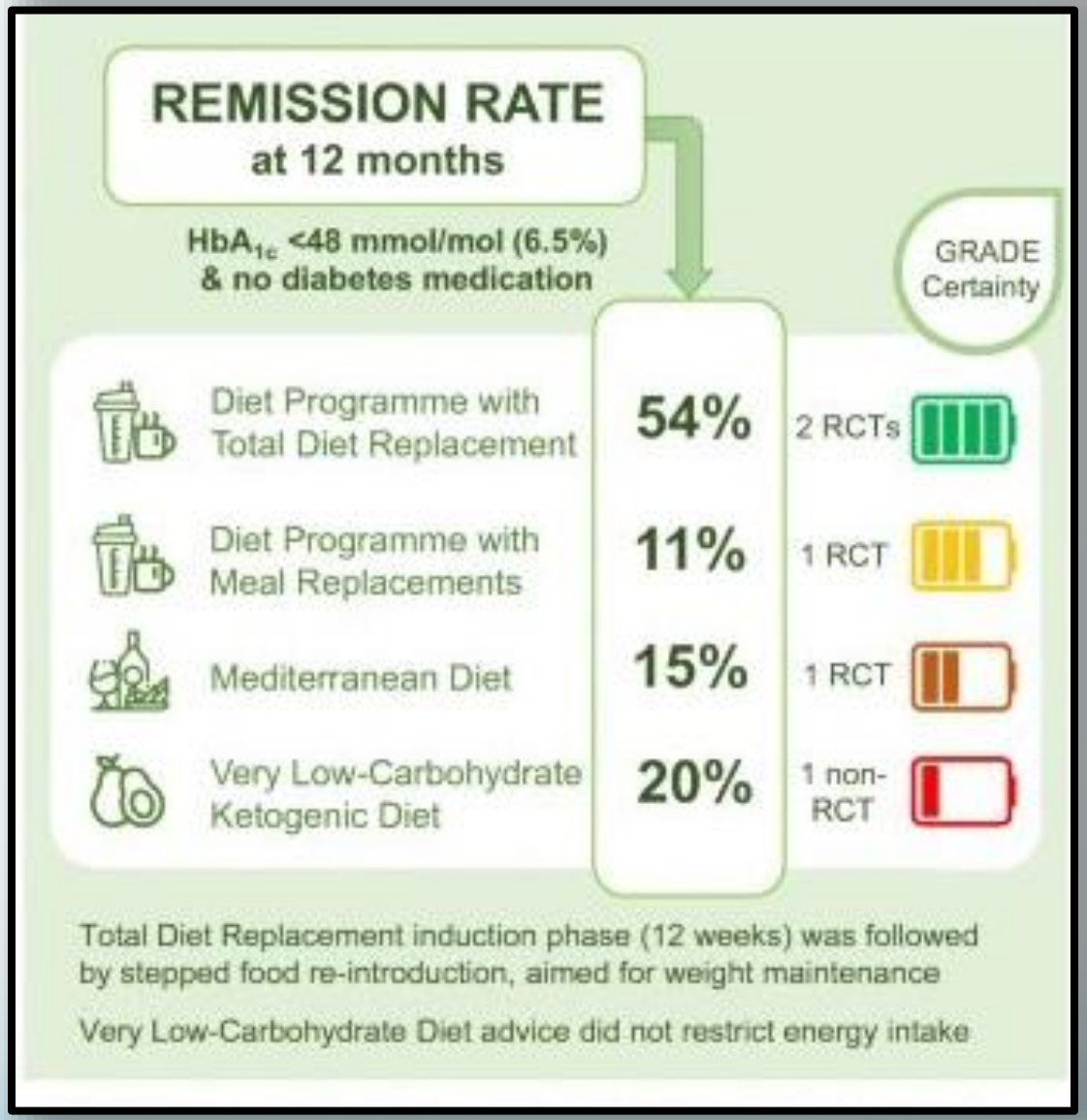
Churuangsuk, Chaitong, Julien Hall, Andrew Reynolds, Simon J. Griffin, Emilie Combet, and Michael E. J. Lean. "Diets for Weight Management in Adults with Type 2 Diabetes: An Umbrella Review of Published Meta-Analyses and Systematic Review of Trials of Diets for Diabetes Remission." *Diabetologia*, November 17, 2021. https://doi.org/10.1007/s00125-021-05577-2.

BEST WEIGHT

NO SIGNIFICANT DIFFERENCE IN VARIOUS HEALTHY DIETARY APPROACHES

--- Goal weight for metabolic health

--- Best weight with lifestyle therapies



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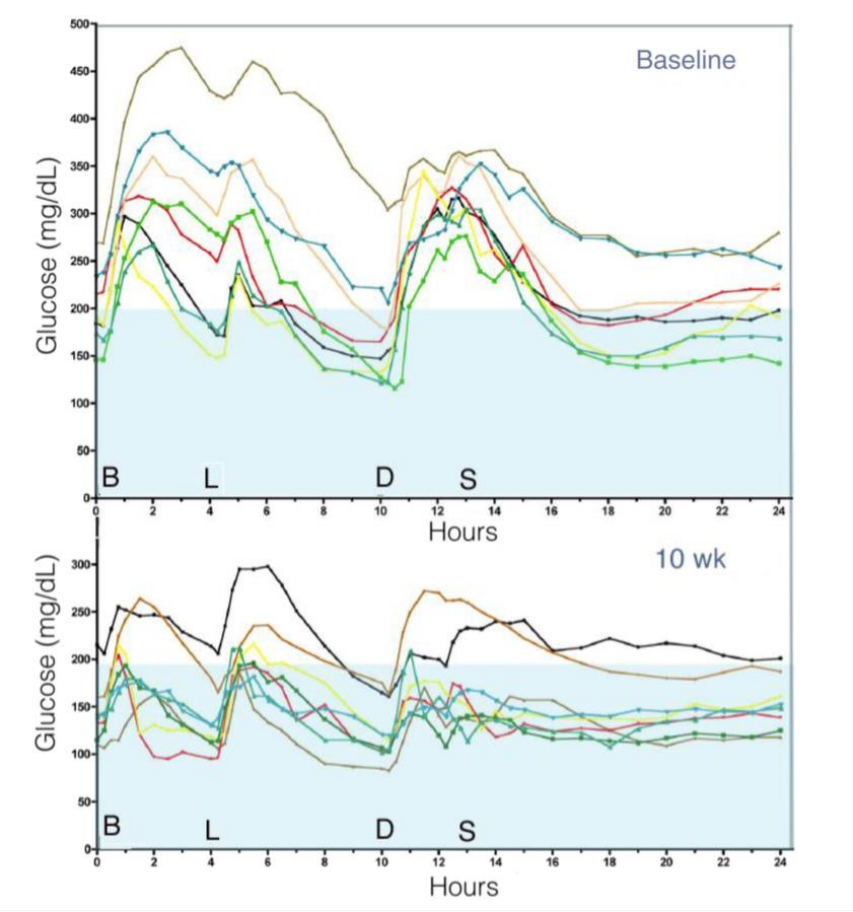
Carbohydrate Restriction
Glucose variability independent of weight loss



Gannon, Mary C, Heidi Hoover, and Frank Q Nuttall. "Further Decrease in Glycated Hemoglobin Following Ingestion of a LoBAG30 Diet for 10 Weeks Compared to 5 Weeks in People with Untreated Type 2 Diabetes." *Nutrition & Metabolism* 7, no. 1 (July 29, 2010): 64. https://doi.org/10.1186/1743-7075-7-64.

Carbohydrate Restriction for Glycemic Control Independent of Weight Loss

Confounders

- Weight loss, calorie restriction
- Protein content
- Definition of low carbohydrate diet

Study

- 12 patients, cross over study
- Eucaloric
- Protein equal
- Dose response of 10, 15 20 25, & 30% Carb on Glycemic control

Conclusion

- No difference in glucose
- Need 5% comparator
- Ketone effect?
- Reduce EGP?
- Protein effect?

Ozairi, Ebaa Al, Muhammad Abdul-Ghani, Nick Oliver, Brandon Whitcher, Reem Al Awadi, Abeer El Samad, Etab Taghadom, Jumana Al-Kandari, and Nicola Guess. "A Randomised Crossover Trial: Exploring the Dose-Response Effect Of Carbohydrate Restriction on Glycaemia in People with Type 2 Diabetes (D-ROC2)." Preprint. Nutrition, June 1, 2021. https://doi.org/10.1101/2021.05.30.21258049.

Obesogenic Environment

Inherited appetite system

Calories over tolerance

Increased adiposity

Genetics of adiposopathy

Eat carbs over tolerance

Excess visceral fat

Release more insulin

Need even more insulin

Insulin Resistance

Less sensitive to insulin

virta

In considering Paul's case, which of the following is true:

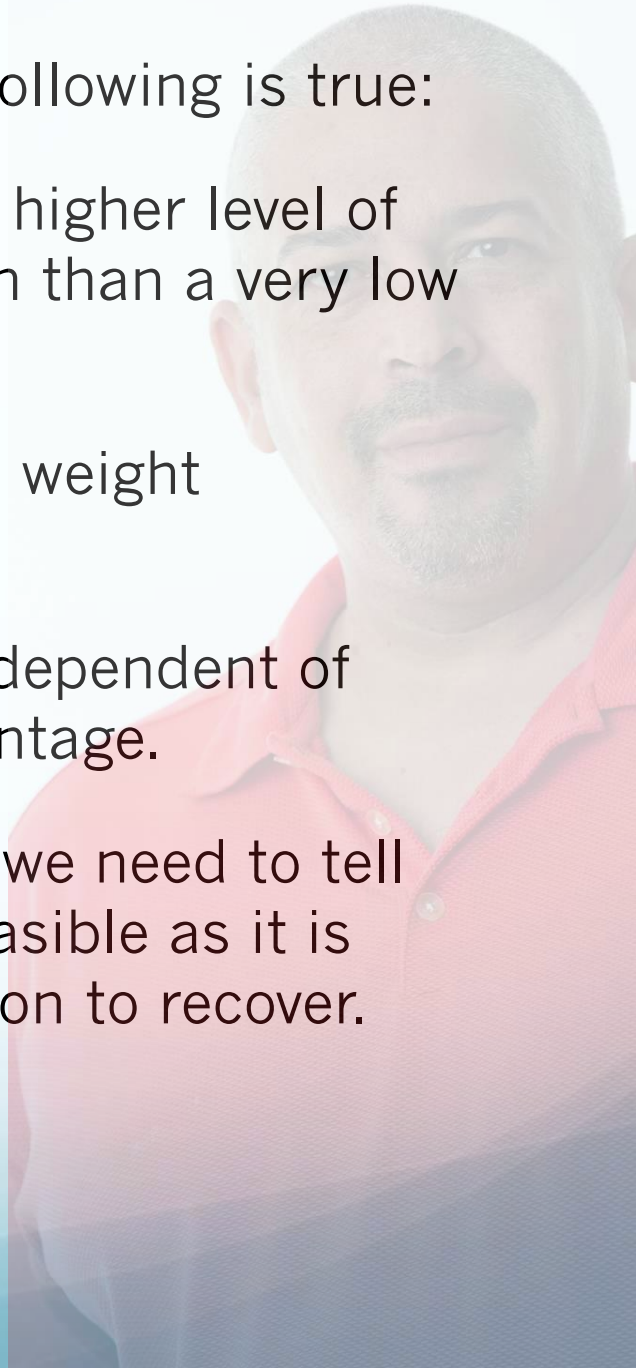
A. Studies demonstrate that LCHF has a higher level of evidence for type 2 diabetes remission than a very low energy diet.

B. LCHF is the most effective way to lose weight compared to other diets.

C. LCHF works for diabetes remission independent of weight loss which is a particular advantage.

D. Since he is 5 years into his diagnosis we need to tell Paul that diabetes remission is not feasible as it is unlikely for pancreatic beta-cell function to recover.

E. None of the above are true.



Sam is a 30 year old with a 7 year history of type 2 diabetes. His BMI is 36 and lost 25 lbs after starting semaglutide, a SGLT2i, and buproprion/naltrexone. He eats ~250 g of CHO/day. His BP is 126/80.

- ✓ glargine 120 units at night
- ✓ aspart 30 units qAC (insulin:carb ratio of 1:3),
- ✓ Metformin 1000 mg BID
- ✓ semaglutide 1 mg SQ weekly
- ✓ hydrocholorothiazide 25 mg
- ✓ Perindopril 4 mg a day
- ✓ Naltrexone/Buproprion 8/90 2 tabs BID.

Fasting glucose is 10, glycemic variability is 40%; A1c recently was 8.6.

He is feeling at wits end with regards to diabetes distress, frustrated by highs and lows. Sam has excellent family support, access to a dietitian, already read

With regards to medication management which of the following recommendations do you **disagree** with in this case?

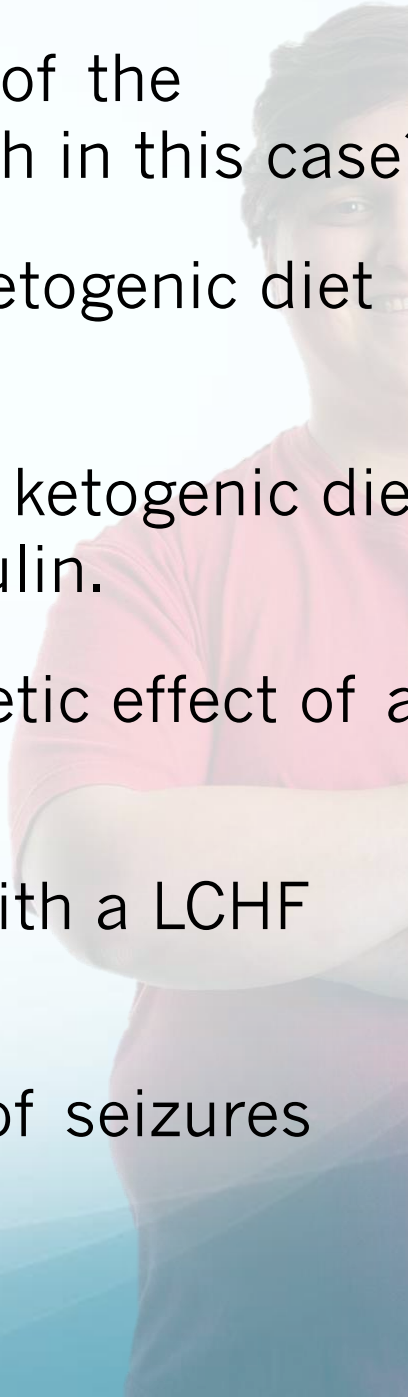
A. Discontinue SGLT2i three days prior to the ketogenic diet due to risk of euglycemic DKA.

B. Reduce glargine by 50% the night before the ketogenic diet and discontinue routine use of the rapid insulin.

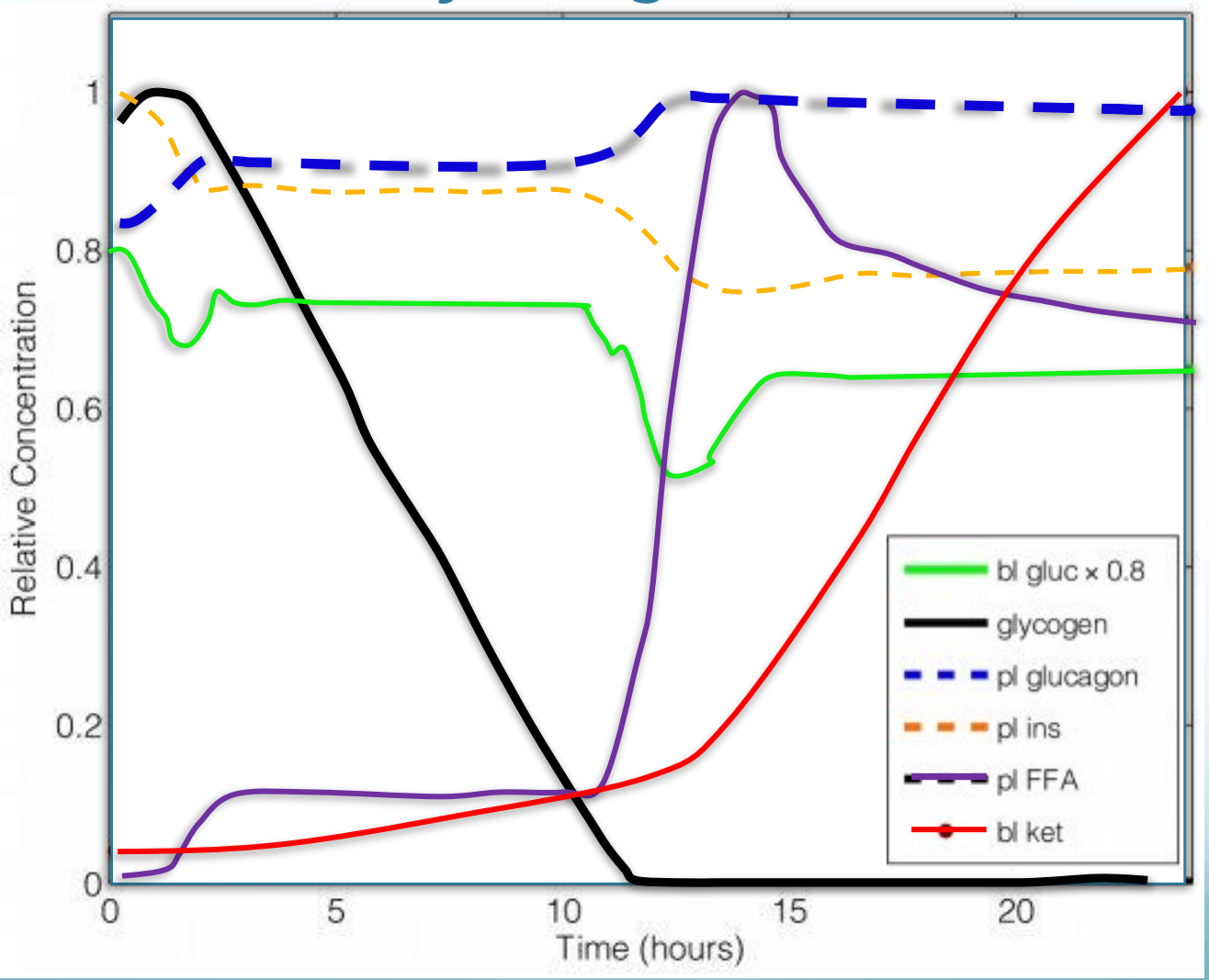
C. Stop his hydrochlorothiazide due to the diuretic effect of a ketogenic diet.

D. Stop the GLP1a due to risk of pancreatitis with a LCHF diet.

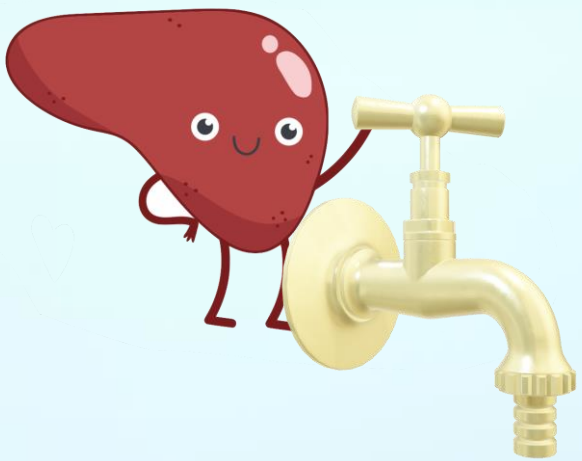
E. Stop the Naltrexone/buproprion due to risk of seizures when taken with a high fat diet.



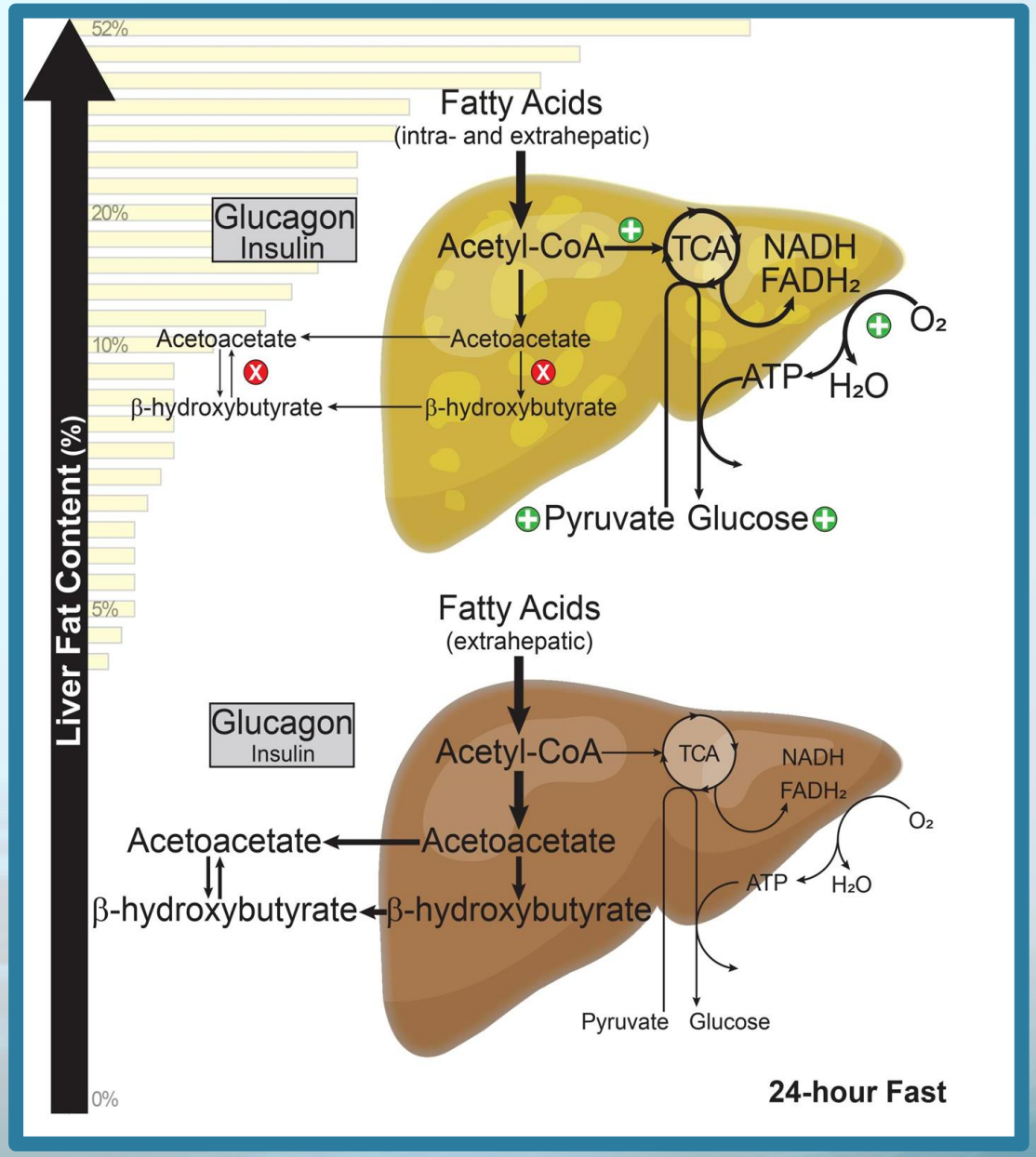
Carbohydrate Restriction
Physiologic effects



Xu, Ke, Kevin T. Morgan, Abby Todd Gehris, Timothy C. Elston, and Shawn M. Gomez. "A Whole-Body Model for Glycogen Regulation Reveals a Critical Role for Substrate Cycling in Maintaining Blood Glucose Homeostasis." Edited by Nathan D. Price. *PLoS Computational Biology* 7, no. 12 (December 1, 2011): e1002272. https://doi.org/10.1371/journal.pcbi.1002272.

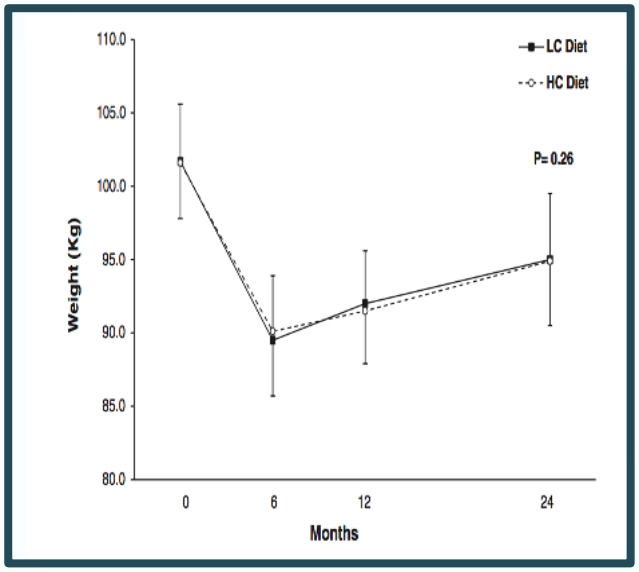


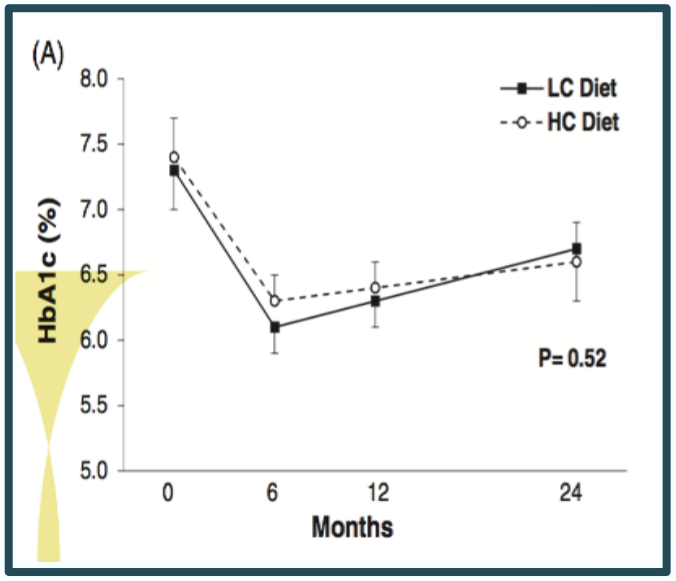
Endogenous Glucose Production

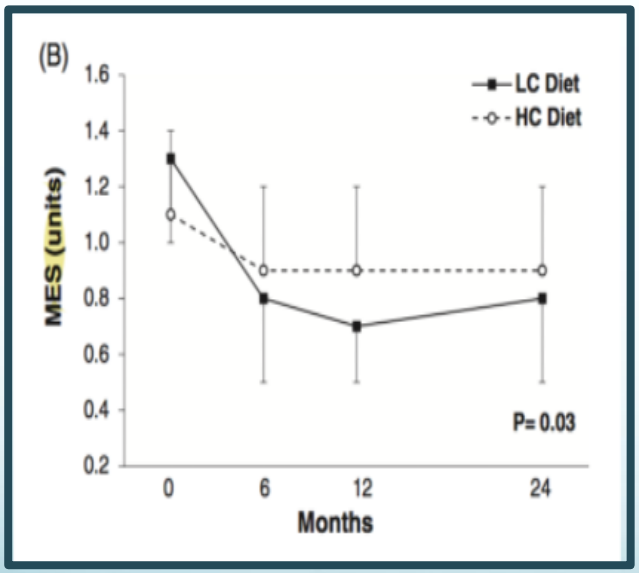


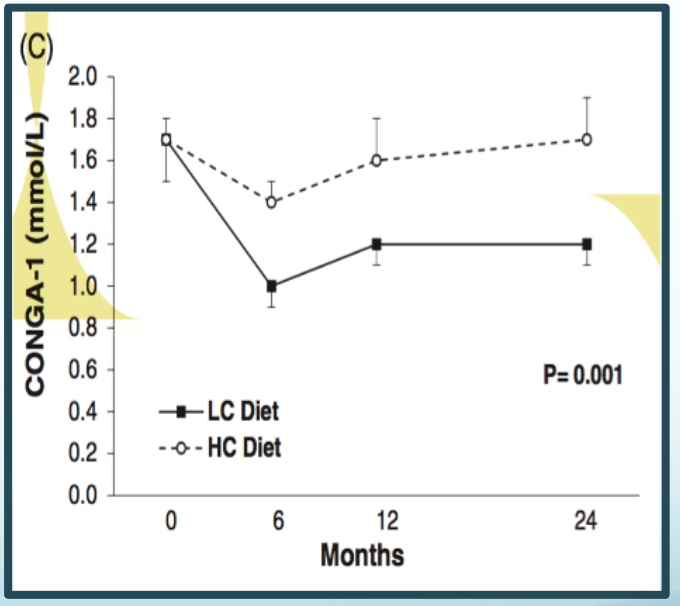
Fletcher, Justin A., Stanisław Deja, Santhosh Satapati, Xiaorong Fu, Shawn C. Burgess, and Jeffrey D. Browning. "Impaired Ketogenesis and Increased Acetyl-CoA Oxidation Promote Hyperglycemia in Human Fatty Liver." *JCI Insight* 4, no. 11 (June 6, 2019): e127737. https://doi.org/10.1172/jci.insight.127737.

CSIRO



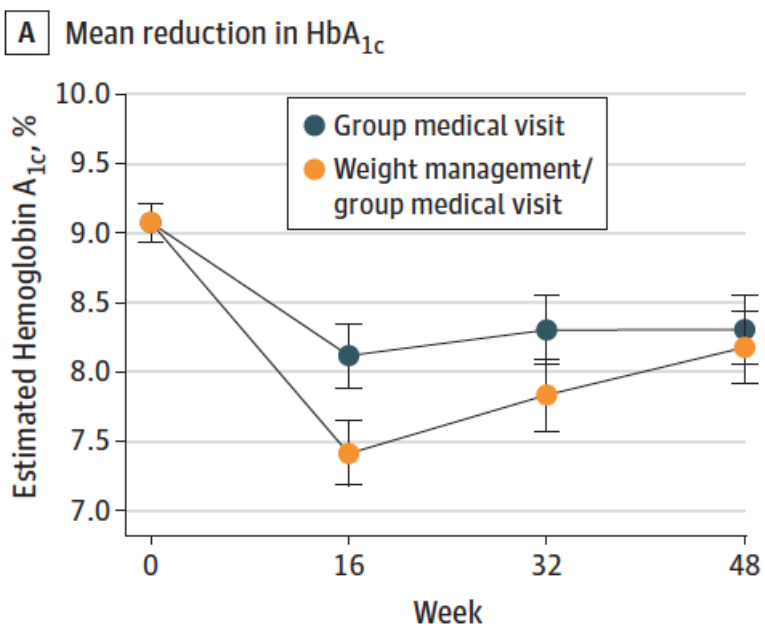


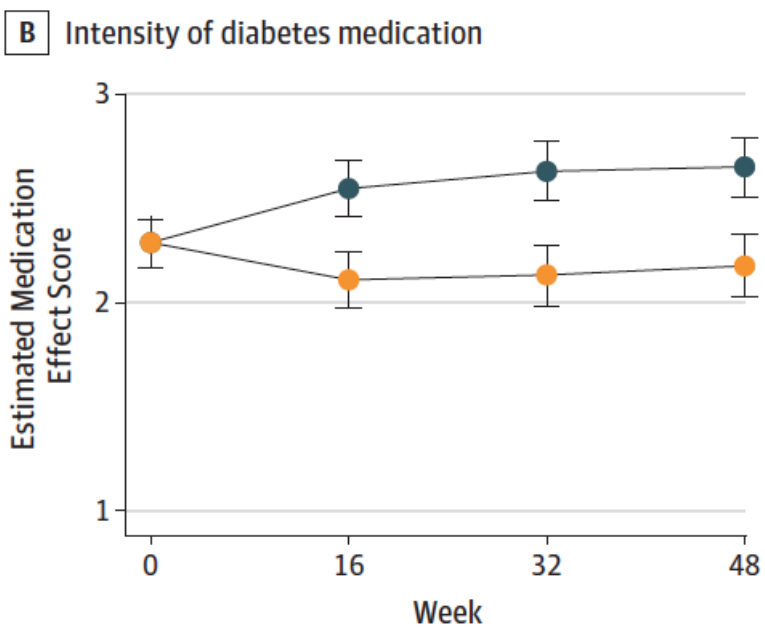




Tay, Jeannie, et al. "Effects of an Energy-Restricted Low-Carbohydrate, High Unsaturated Fat/Low Saturated Fat Diet versus a High-Carbohydrate, Low-Fat Diet in Type 2 Diabetes: A 2-Year Randomized Clinical Trial." *Diabetes, Obesity and Metabolism* 20, no. 4 (April 1, 2018): 858–71. https://doi.org/10.1111/dom.13164.

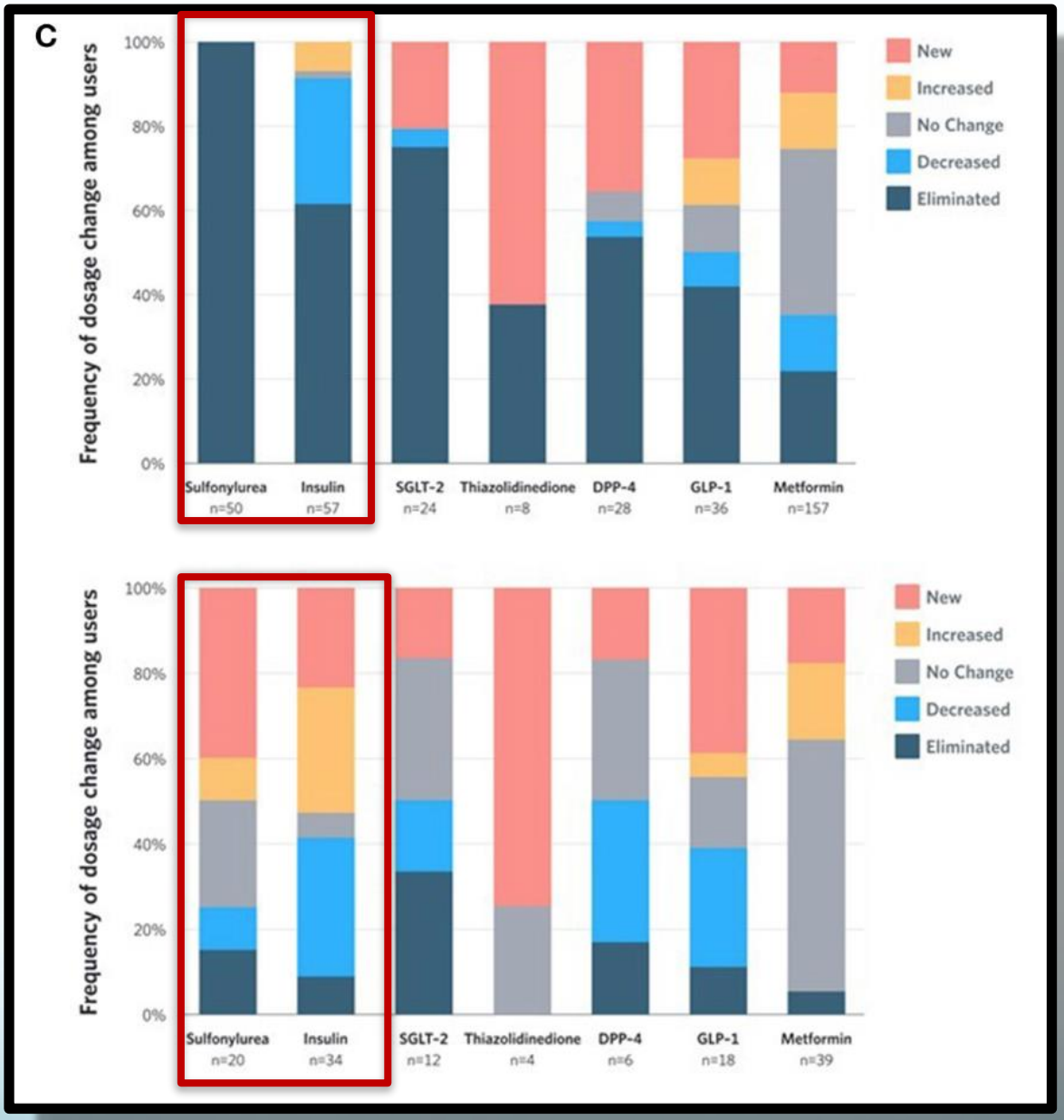
JAMA
LCHF, A1c and Medication Reduction





Yancy, William S., Matthew J. Crowley, Moahad S. Dar, Cynthia J. Coffman, Amy S. Jeffreys, Matthew L. Maciejewski, Corrine I. Voils, Anna Barton Bradley, and David Edelman. "Comparison of Group Medical Visits Combined With Intensive Weight Management vs Group Medical Visits Alone for Glycemia in Patients With Type 2 Diabetes: A Noninferiority Randomized Clinical Trial." *JAMA Internal Medicine*, November 4, 2019. https://doi.org/10.1001/jamainternmed.2019.4802.

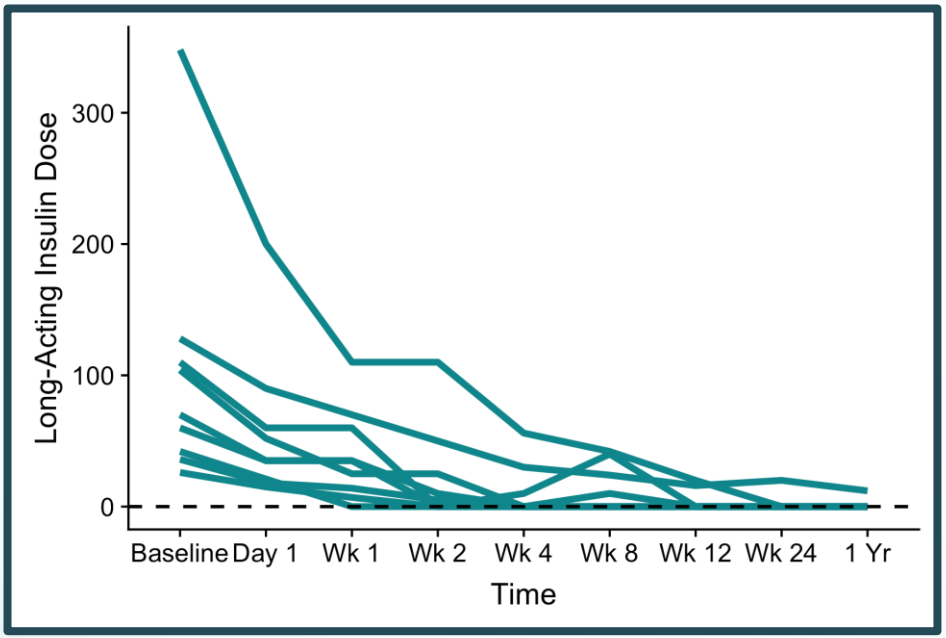
VIRTA

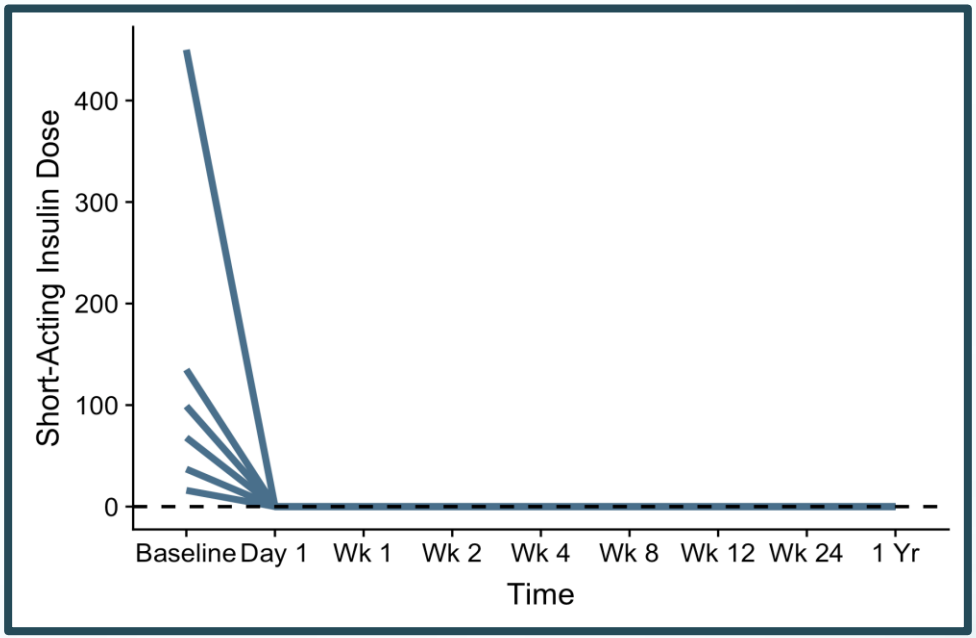


Athinarayanan, S. J., Adams, R. N., Hallberg, S. J., McKenzie, A. L., Bhanpuri, N. H., Campbell, W. W., et al. (2019). Long-Term Effects of a Novel Continuous Remote Care Intervention Including Nutritional Ketosis for the Management of Type 2 Diabetes: A 2-Year Non-randomized Clinical Trial. *Frontiers in Endocrinology*, *10*, 348. http://doi.org/10.3389/fendo.2019.00348

PERSONAL EXPERIENCE

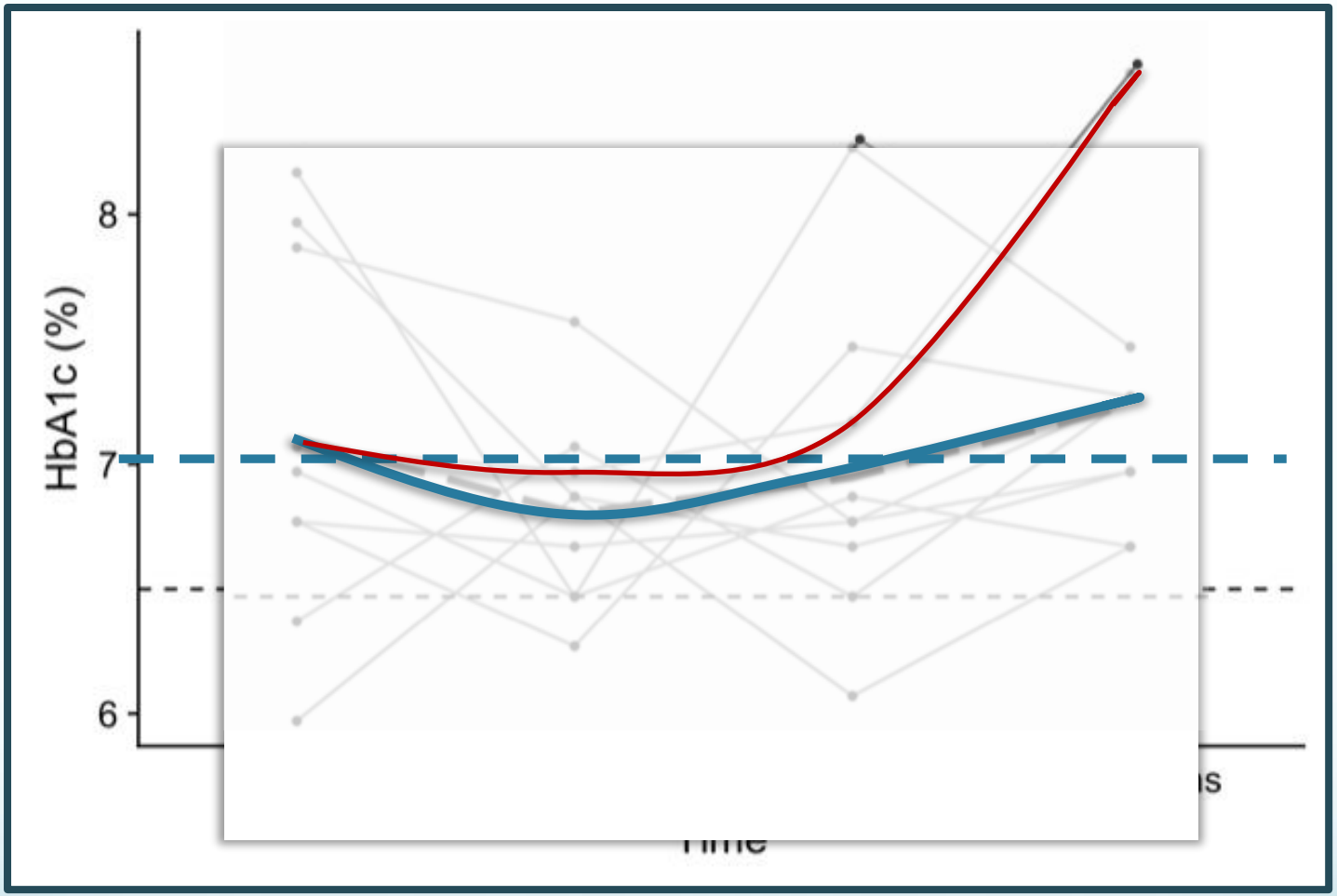
INSULIN DE-ESCALATION





Neudorf, Helena, Michael Mindrum, Christa Mindrum, Cody Durrer, and Jonathan P. Little. "A Low-Carbohydrate High-Fat Ketogenic Diet Program Implemented by an Interdisciplinary Primary Care Team Improves Markers of Cardiometabolic Health in Adults with Type 2 Diabetes: A Retrospective Secondary Analysis." *Canadian Journal of Diabetes*, September 2021, S1499267121002458. https://doi.org/10.1016/j.jcjd.2021.09.001.

A1c for Insulin Users



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Medication De-Prescribing

Drug group	Hypo Risk?	Suggestion
Sulfonylureas	Yes	Reduce/stop (if gradual CHO restriction wean by 50%)
Insulins	Yes	Typically wean by 30 to 50% successively depending on baseline glucose and CHO level*
SGLT2i	No	Stop. Risk of euglycemic DKA
Biguanides	No	Individualize, often maximize
DPP-4	No	Individualize, consider stopping
GLP1a	No	Individualize
Thiazidolones	No	Usually stop
Suggest glucose target of 7 to 10 while weaning down on hypoglycemic agents of insulin or sulfonylurea. Consider diagnosis of LADA prior to de-prescribing insulin.		

Adapted from: Murdoch, C., Unwin, D., Cavan, D., Cucuzzella, M., & Patel, M. (2019). Adapting diabetes medication for low carbohydrate management of type 2 diabetes: a practical guide. *British Journal of General Practice*, *69*(684), 360–361. http://doi.org/10.3399/bjgp19X704525

With regards to medication management which of the following recommendations do you **disagree** with in this case?

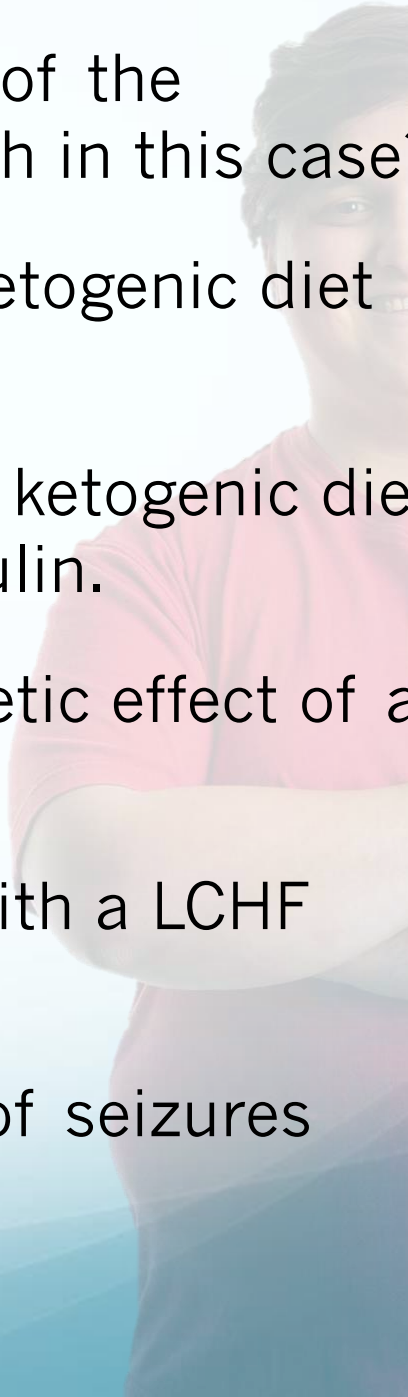
A. Discontinue SGLT2i three days prior to the ketogenic diet due to risk of euglycemic DKA.

B. Reduce glargine by 50% the night before the ketogenic diet and discontinue routine use of the rapid insulin.

C. Stop his hydrochlorothiazide due to the diuretic effect of a ketogenic diet.

D. Stop the GLP1a due to risk of pancreatitis with a LCHF diet.

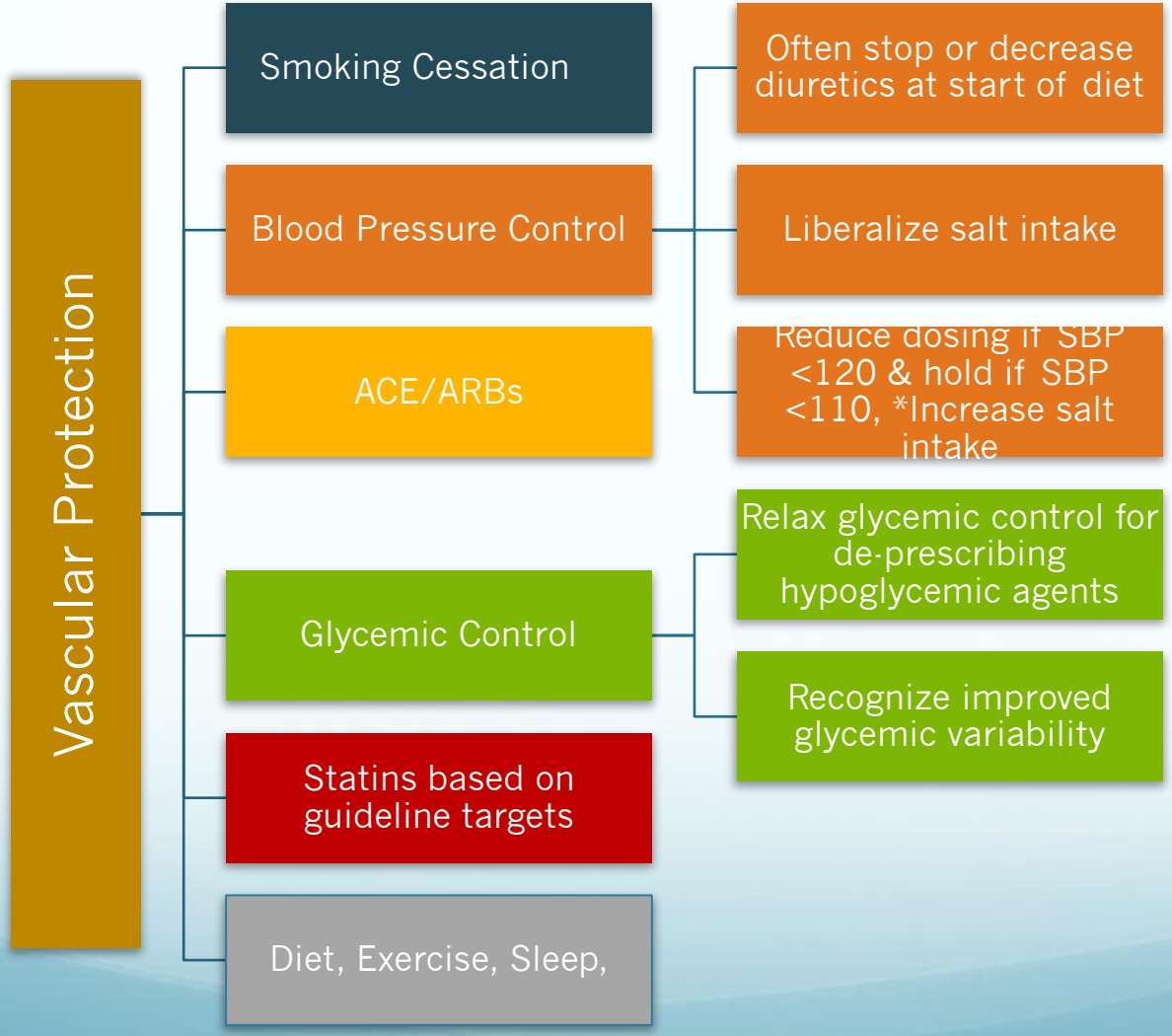
E. Stop the Naltrexone/buproprion due to risk of seizures when taken with a high fat diet.



Key Points
Carbohydrate restriction for Type 2 DM

- Act early if possible.
- The less the carbohydrate the more effective (modest changes lead to modest results). Protein likely matters.
- Can achieve similar to better glycemic control on less medications that other dietary patterns.
- Leads to improved glucose variability and less hypoglycemia.
- Improvement in blood pressure and dyslipidemia.*
- It's a team sport.

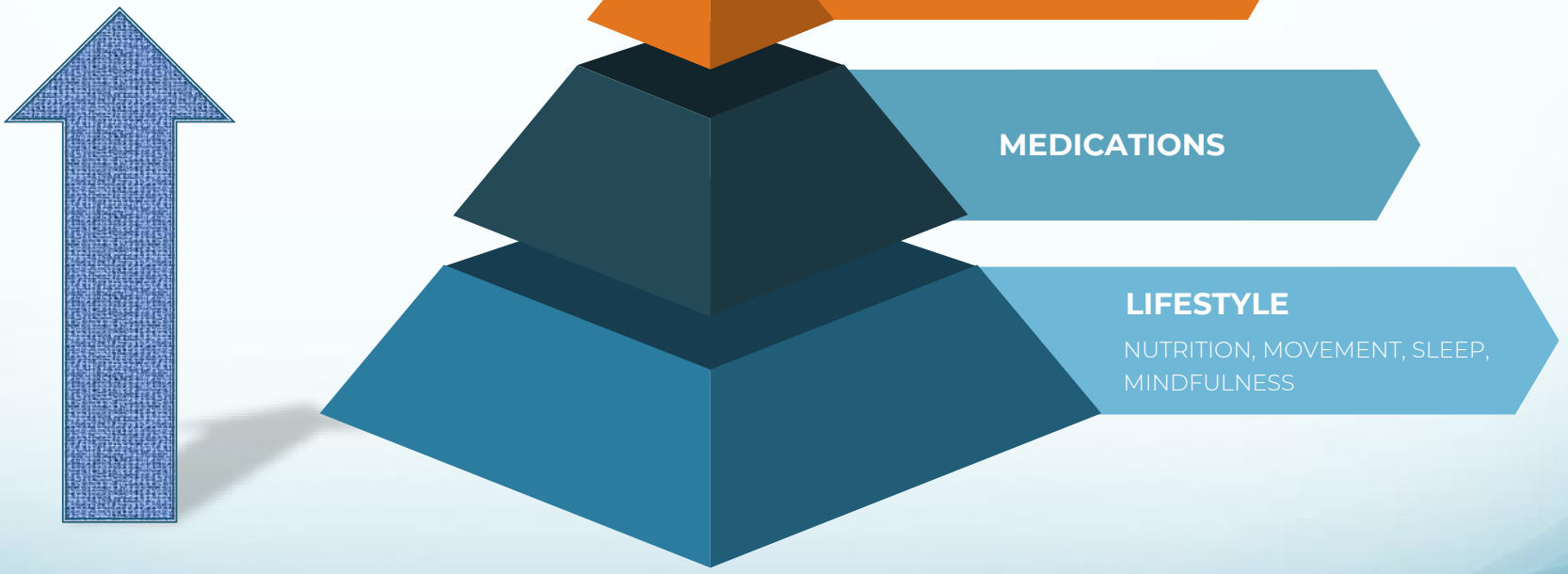
T2D management with therapeutic nutrition: don't forget the other guidelines

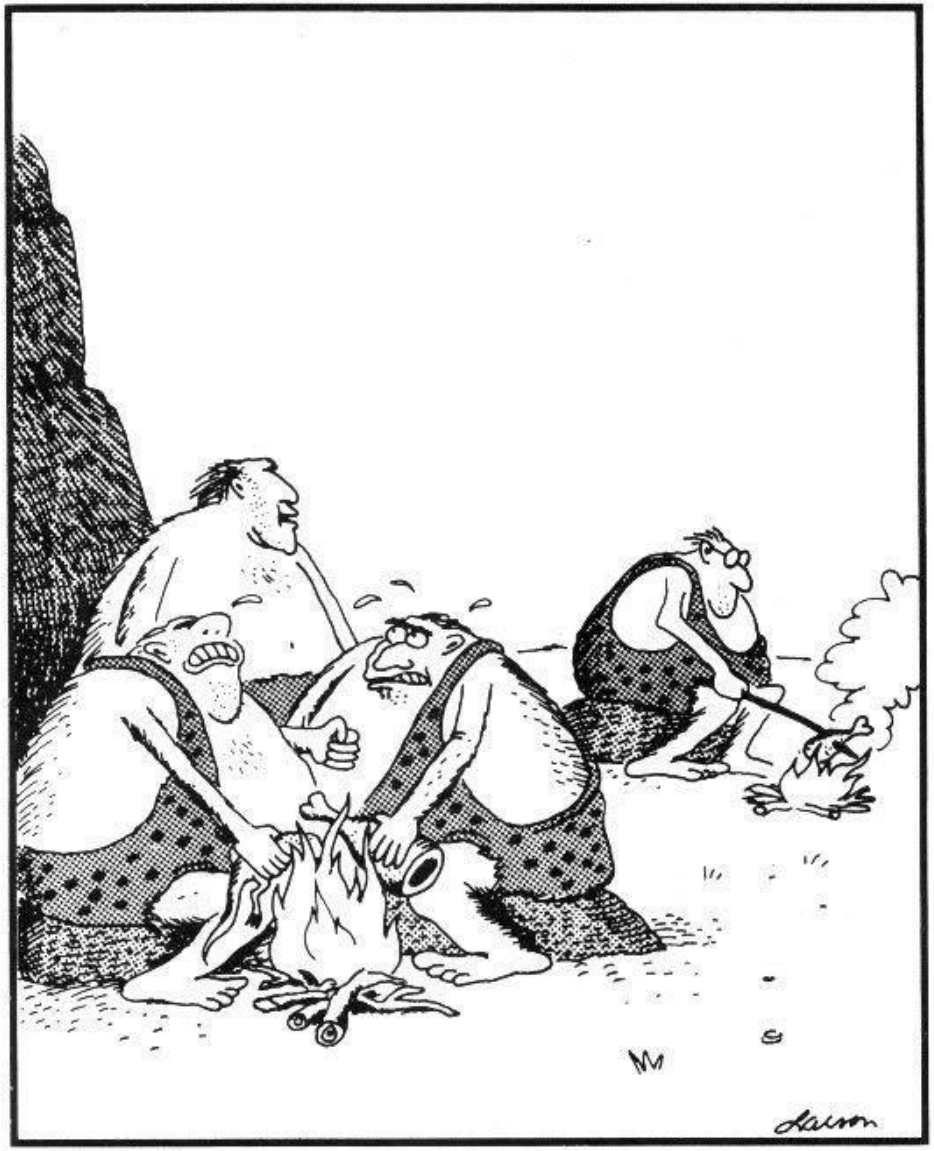


APPROACHING METABOLIC HEALTH

ACHIEVING SYMPTOM RESOLUTION

- ✓ Treatment is escalated until symptom control is reached.
- ✓ Balance risks/benefits of each step
- ✓ Guided by patient preferences





"Hey! Look what Zog do!"