Clinical Trial Evidence for Type 2 Diabetes Remission and Reversal through Dietary Approaches

Hallberg Legacy Course

February 24, 2024

Laura Saslow, PhD

Associate Professor, University of Michigan

Speaker Disclosure

Laura Saslow, PhD

- Funded by the National Institutes of Health and the Baszucki Group for dietary clinical trials
- Intellectual bias? I've been studying the impact of a very low-carbohydrate way of eating for over a decade

The Problem: Prevalence

- 15% of US adults have diabetes (95% type 2 diabetes)
- A third of US adults have prediabetes
- **About 50% of US adults have prediabetes or type 2 diabetes**

1. CDC. National Diabetes Statistics Report. Available at *https://www.cdc.gov/diabetes/data/statistics-report/index.html* Accessed February 12, 2024.
2. NIDDK. Diabetes Statistics. Available at *https://www.niddk.nih.gov/health-information/health-statistics/diabetes-statistics* Accessed February 12, 2024.

The Problem: Cost

New American Diabetes Association Report Finds Annual Costs of Diabetes to be $412.9 Billion

November 1, 2023 | Arlington, Virginia

- People with diagnosed diabetes now account for **1/4 health care dollars** spent in the U.S.

American Diabetes Association. Press release. Available at *https://diabetes.org/newsroom/press-releases/new-american-diabetes-association-report-finds-annual-costs-diabetes-be* Accessed February 12, 2024.

What is it going to take for the collective to care?

Spontaneous Combustion?

Image from: *Carbohydrate Diet for Type 2 Diabetes Reversal,* Sarah Hallberg, 2019
https://www.youtube.com/watch?v=Q_6dKfHApC0

Type 2 Diabetes Remission vs. Reversal

- **Remission** = Sub-diabetes level of glycemia (HbA1c <6.5%) achieved with at least 3 months without glucose-lowering medications
- **Reversal** = Sub-diabetes level of glycemia (HbA1c <6.5%) achieved without glucose-lowering medications or only with metformin.

Riddle MC, et al. *Diabetes Care*. 2021;44(10):2438-2444. Available at https://diabetesjournals.org/care/article/44/10/2438/138556/Consensus-Report-Definition-and-Interpretation-of

Remission from Type 2 Diabetes is Infrequent without Intervention

- In US-based study of 122,781 people of remission over 7 years:
  - 1.6% overall remission
  - 4.6% remission if the duration of their type 2 diabetes was less than 2 years

Karter AJ, et al. *Diabetes Care*. 2014;37(12):2188-3195. Available at https://pubmed.ncbi.nlm.nih.gov/25231895/

Many Possible Dietary Patterns

- Low-fat
- Low-calorie
- Total meal replacement
- Intermittent fasting
- Continuous glucose monitoring
- Vegetarian/vegan
- Mediterranean
- DASH
- Low-carbohydrate
- Very low-carbohydrate/ketogenic

I will discuss randomized controlled trial results, if available

- Randomized controlled trials
- Non-randomized controlled trials (participants could choose whether to be in the active intervention)
- Pre-post trials and clinic audits (no comparison group)

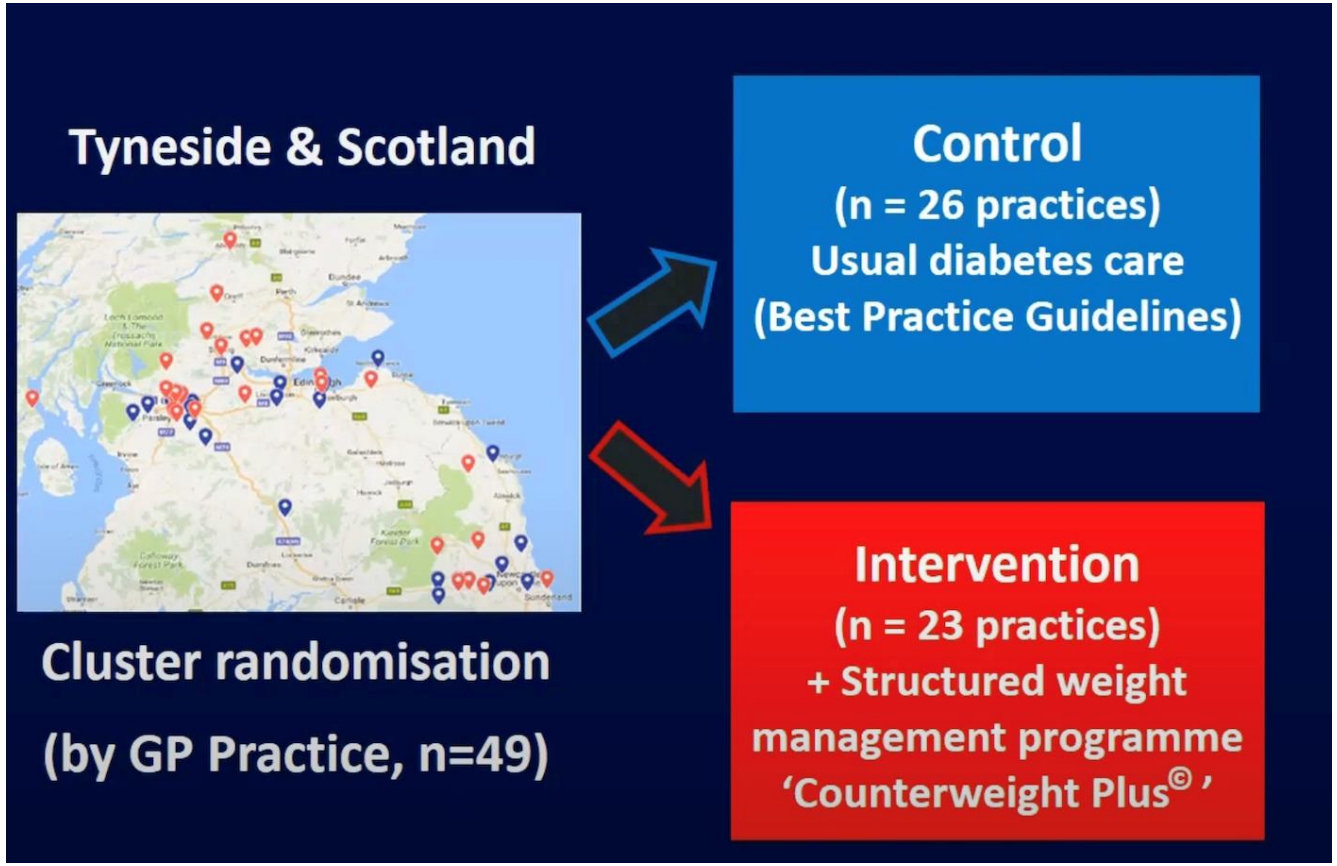
- Outcomes tracked out to at least 1 year
- At least 50 people in each group

Two Clinically Tested Ways to Reverse Type 2 Diabetes Using Dietary Approaches

- Formula total diet replacement (about 850 kcal/day)
- Very low-carbohydrate/ketogenic diet – real food, not calorie-restricted

Formula Total Diet Replacement

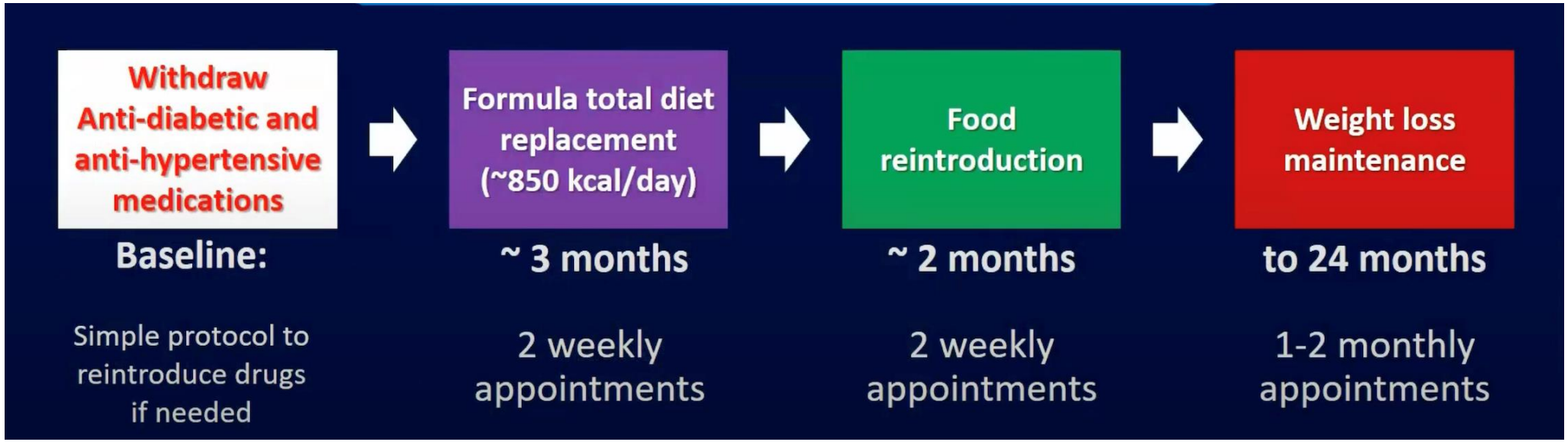
Total Diet Replacement +: DiRECT (RCT)



- 149 people in intervention, 149 in control
- "The invitation includes a written information sheet providing details of the treatment arm to which their GP practice is randomised."
- 3 years mean duration of diabetes
- 0% taking insulin (exclusion criteria)
- 7.7% mean baseline HbA1c

DiRECT = Diabetes Remission Clinical Trial
Leslie WS, et al. *BMC Fam Pract.* 2016;17:20. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4754868/
Image from the seminar on: *Diabetes No More: lessons from the DiRECT trial and beyond.* Michael Lean, 2023. Seminar recording available at: https://www.youtube.com/watch?v=GcdMtIXQpRo

Total Diet Replacement +: DiRECT (RCT)



- INTERVENTION: Very low-calorie total diet replacement liquid formula diet (Counterweight Plus, 825-853 kcal/day, 59% carbohydrate (about 122-126 g/carb per day), 13% fat, 26% protein, 2% fiber) plus 7 g/day fiber supplement for average of 14 weeks. Then, food reintroduction and exercise. If weight gain of greater than 4.4 pounds, another 2-4 weeks of liquid meal replacements (50% used this at least once) or orlistat (weight loss drug – only 3 used). **Follow-up diet unknown/not tracked.**
- CONTROL: Diabetes education control

DiRECT = Diabetes Remission Clinical Trial
Image from the seminar on: *Diabetes No More: lessons from the DiRECT trial and beyond.* Michael Lean, 2023. Seminar recording available at: *https://www.youtube.com/watch?v=GcdMtIXQpRo*

Total Diet Replacement +: DiRECT (RCT)

- Intervention:
  - **46%** (68/149) remission after 1 year
  - **36%** (53/149) remission after 2 years
  - **11%** (16-17/149) remission after 5 years
- **If people lost at least 10 kg of weight, they had about a 60-80% chance of going into remission at years 1 or 2.**
- Control: between 2-4% remission between years 1-5

Lean MEJ, et al. *Lancet Diabetes Endocrinol.* 2019;7(5):344-355. Available at https://pubmed.ncbi.nlm.nih.gov/30852132/
Thom G, et al. *Diabet Med.* 2021;38(8):e14395. Available at https://onlinelibrary.wiley.com/doi/10.1111/dme.14395
Managing Type 2 Diabetes with Diet: Evidence from the Direct Trial. Roy Taylor, 2024. Video available at: https://www.youtube.com/watch?v=iaQ16lzJZEI

Total Diet Replacement +: DIADEM-I (RCT)

- Intervention: Total diet replacement (800–820 kcal/day; 57% carbohydrate (about 117 g/day of carbohydrate), 14% fat, 26% protein, and 3% fiber) for 12 weeks, fiber supplement if needed for constipation. Then, food reintroduction. Dietitian visits every 2-4 weeks. **Follow-up diet not tracked.**
- Control: Usual care with meetings with physician every 3 months and access to diabetes educators and dietitians
- Qatar, 2017-2018
- 79 in intervention, 79 in control, about 2 years mean duration of diabetes, 1% taking insulin, mean baseline HbA1c 6.95%
- Impact:
  - **Intervention: 54% (43/79) remission after 1 year**
  - **Control: 11% (9/79) remission after 1 year**

Taheri S, et al. *Lancet Diabetes Endocrinol.* 2020;8(6):477-489. Available at https://pubmed.ncbi.nlm.nih.gov/32445735/

Total Diet Replacement: Direct-Aus (Pre-post Intervention, Non-randomized)

- Intervention: 13 weeks of total diet replacement with 2 cups low-starch vegetables, 1 teaspoon of oil, daily, with fiber supplement if constipated. If later weight gain, return to the diet replacement. Dietitian visits every 2-4 weeks. **Follow-up diet not tracked.**
- Australia, 2020-2021
- 173 people in intervention, 3 years mean duration of diabetes, none on insulin, mean baseline HbA1c 7.1%
- Impact:
  - **Intervention: 49% (85/173) remission after 1 year**

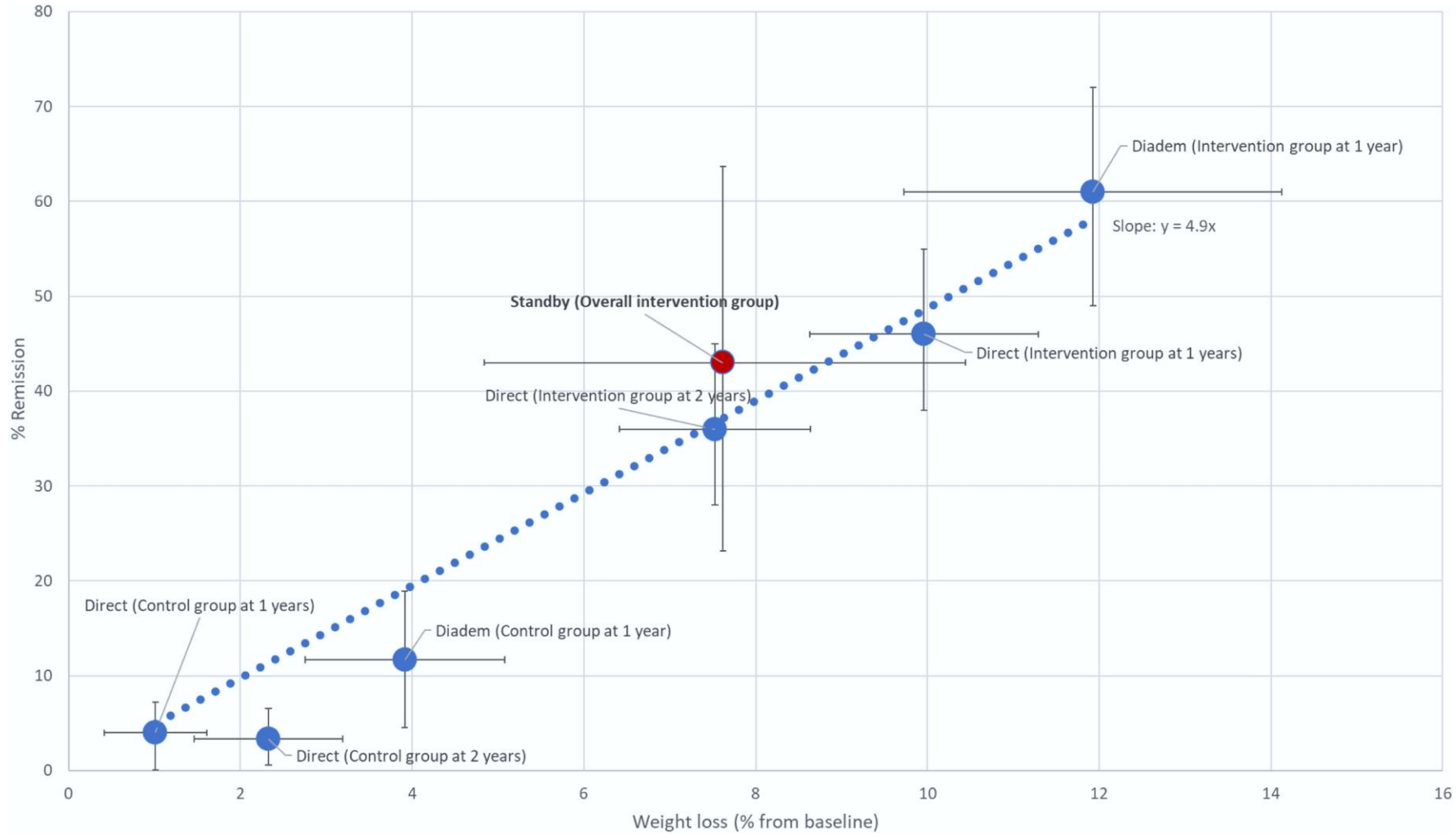
Hocking S, et al. *Diabetes Care*. 2024;47(1):66-70. Available at https://diabetesjournals.org/care/article/47/1/66/153542/Intensive-Lifestyle-Intervention-for-Remission-of

Total Diet Replacement: STANDby (Small RCT)

- Intervention: 12 weeks of total diet replacement
- United Kingdom, 2019-2021
- **People of South Asian descent**. 13 people in intervention, 12 in control, ≤4 years duration of diabetes, none on insulin, mean baseline HbA1c 7.7%
- Impact:
  - **Intervention 38% (5/13) remission after 1 year**
  - **Control: 0% (0/12) after 1 year**

Sattar N, et al. *Lancet Reg Health Southeast Asia*. 2023;Feb 9:100111. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9904218/

Percent Remission Correlates With Relative Weight Loss



Sattar N, et al. *Lancet Reg Health Southeast Asia*. 2023;Feb 9:100111. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9904218/

Formula Total Diet Replacement

- About 50% remission after 1 year
- About 10% remission after 5 years
- Greater weight loss, more likely to go into remission
- Only tested on people with type 2 diabetes for a few years and NOT on insulin

Very Low-carbohydrate

Very Low-carbohydrate Diets

- The “total amount of carbohydrate eaten is the primary predictor of glycemic response”
- Carbohydrate sources:
  - Non-starchy vegetables
  - Nuts and seeds
  - Limited berries
  - Dairy

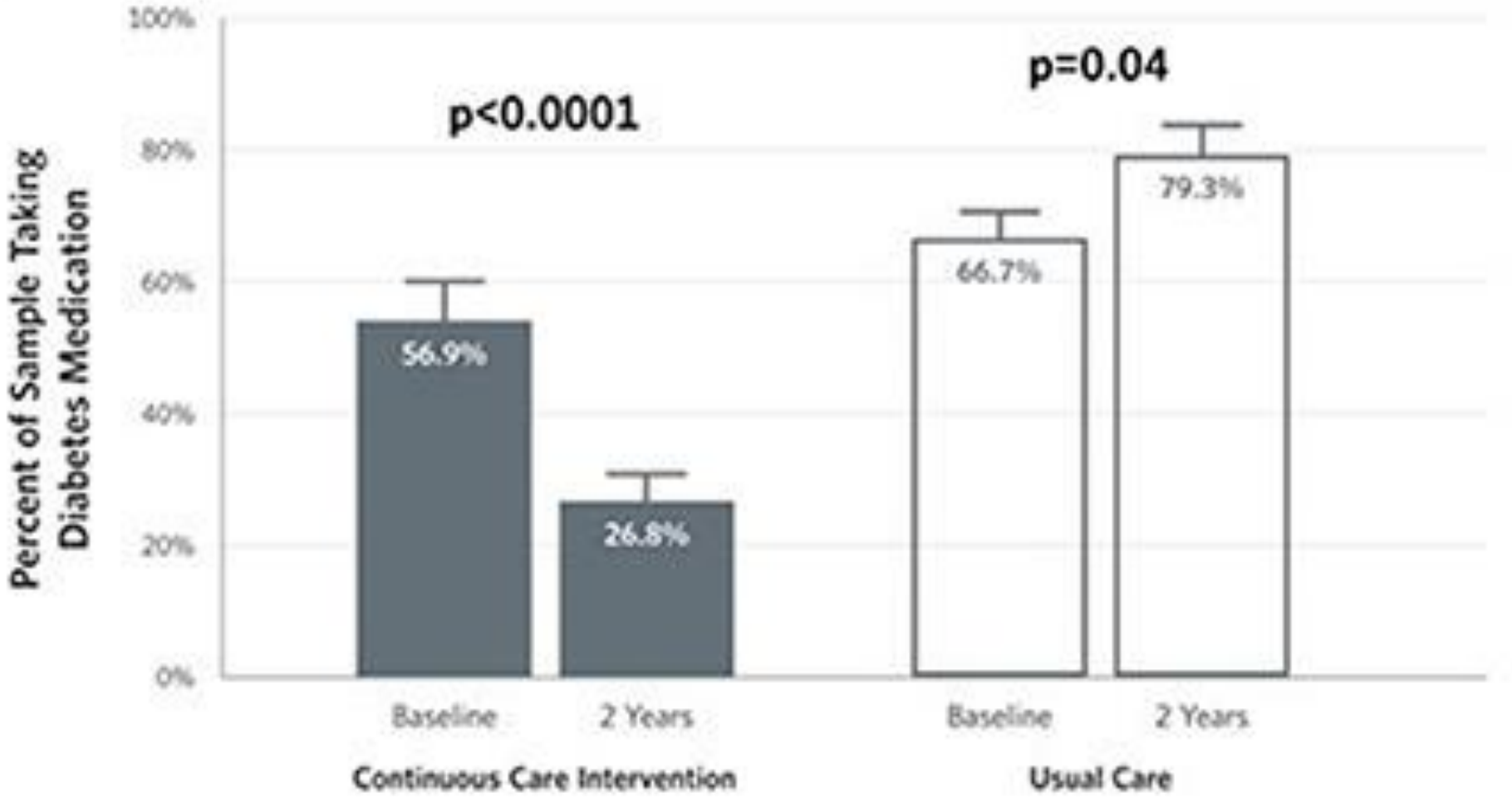
Evert AB, et al. *Diabetes Care*. 2013;36(11):3821-3842. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3816916/

Very Low-carb/Keto: Indiana U (Non-randomized)

- Intervention: Very low-carb/keto with (either on-site n = 136 or virtual/online n = 126), called continuous care or CCI
  - "participants were advised to achieve and sustain nutritional ketosis (blood BHB level of 0.5–3.0 mmol/L) through sufficient carbohydrate restriction (initially <30 g/day but gradually increased… protein intake was initially targeted at a level of 1.5 g/kg of a medium-frame ideal weight body…. Participants were instructed to include sufficient dietary fat in meals to achieve satiety without tracking energy intake."
- Control: usual care (n = 87)
- Indiana 2015-2018
- 8.4 years mean duration of diabetes, 46% on insulin, mean baseline HbA1c 7.6%

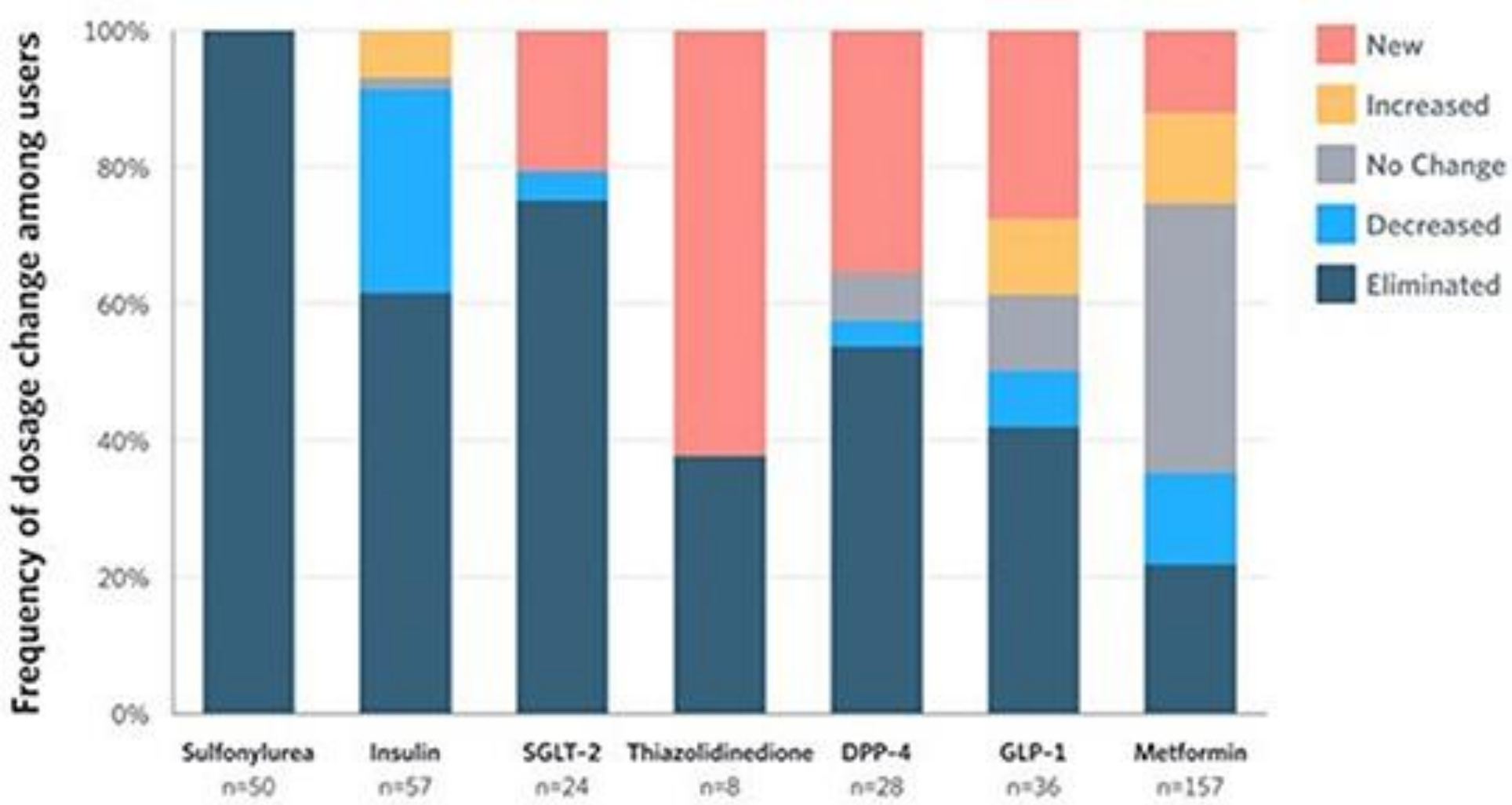
Athinarayanan S, et al. *Front Endocrinol* (Lausanne). 2019;10:348. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6561315/
Brown A, et al. *J Hum Nutr Diet*. 2022;35(1):165-178. Available at *https://onlinelibrary.wiley.com/doi/10.1111/jhn.12938*

Very Low-carb/Keto: Indiana U



Athinarayanan S, et al. *Front Endocrinol* (Lausanne). 2019;10:348. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6561315/
Brown A, et al. *J Hum Nutr Diet*. 2022;35(1):165-178. Available at *https://onlinelibrary.wiley.com/doi/10.1111/jhn.12938*

Very Low-carb/Keto: Frequency of Medication Dose and Use Change by Diabetes Medication Class



Athinarayanan S, et al. *Front Endocrinol* (Lausanne). 2019;10:348. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6561315/

Very Low-carb/keto: Results from Indiana U

- Intervention (Reversal or Remission):
  - **47%** (123/262) after 1 year
  - **38%** (99/262) after 2 years
  - **15%** (39/262) after 5 years
- Intervention (Remission):
  - **20%** (52/262) after 1 year
  - **17%** (45/262) after 2 years
  - **9%** (24/262) after 5 years
- Control: between 7-10% remission or reversal between years 1-2, between 2-5% remission between years 1-2

Athinarayanan S, et al. *Front Endocrinol* (Lausanne). 2019;10:348. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6561315/
Brown A, et al. *J Hum Nutr Diet*. 2022;35(1):165-178. Available at https://onlinelibrary.wiley.com/doi/10.1111/jhn.12938

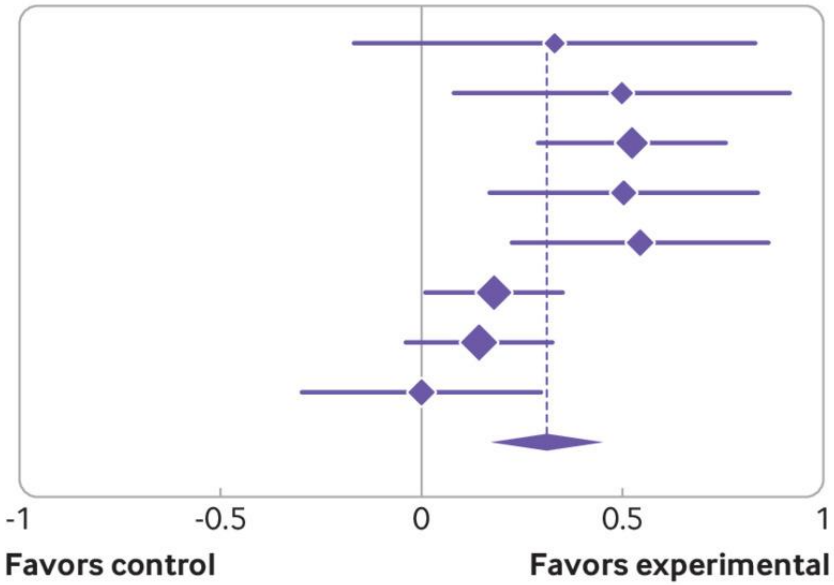
Low-carbohydrate… ish (RCT)

- Intervention: goal of 20-30 g/day carbohydrates, increased over time (to about 114 g/day carbohydrates by the end of year 1)
- Control: medication management control group (189-176 g/carbs a day throughout year 1)
- Group medical visits
- North Carolina, 2015-2017
- 127 in intervention, 136 in control, about 15 years mean duration of diabetes, 62% taking insulin, mean baseline HbA1c 9.1%
- **IMPACT: 9% (12/127) reversal at 1 yr, control: 0%**

Yancy WS Jr, et al. *JAMA Intern Med*. 2020;180(1):70-79. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6830502/

Meta-analysis of Small RCTs

Study or subgroup	No of events/total Experimental	Control	Risk difference, IV, random (95% CI)	Weight (%)	Risk difference, IV, random (95% CI)
Dyson 2010	3/6	1/6		6.5	0.33 (-0.17 to 0.83)
Jönsson 2009	6/6	3/6		8.3	0.50 (0.08 to 0.92)
Morris 2019	11/21	0/12		15.0	0.52 (0.29 to 0.76)
Saslow 2014	8/9	5/13		10.8	0.50 (0.17 to 0.84)
Saslow 2017	6/11	0/8		11.4	0.55 (0.23 to 0.86)
Sato 2017	4/22	0/27		18.2	0.18 (0.01 to 0.35)
Tay 2014	36/46	30/47		17.5	0.14 (-0.04 to 0.33)
Yamada 2014	2/12	2/12		12.2	0.00 (-0.30 to 0.30)
Total (95% CI)	76/133	41/131		100.0	0.32 (0.17 to 0.47)
Test for heterogeneity: τ^2=0.02; χ^2=16.50, df=7, P=0.02; I^2=58%					
Test for overall effect: Z=4.15, P<0.001					



- Low-carbohydrate or very low-carbohydrate diets were more likely to lead to an HbA1c <6.5% than comparison diets: 76/133 (57%) v 41/131 (31%), I^2=58%.
- Studies that included patients using insulin had lower remission rates

Goldenberg JZ, et al. *BMJ*. 2021;13:372:m4743. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7804828/

Carb Reduction: David Unwin's Practice (Clinic Audit, Pre-post Intervention, Non-randomized)

- Intervention: Carbohydrate reduction taught with general practitioner visits and optional group sessions
- England, 2013+
- 186 in intervention (39% of total patients who see the GP), mean baseline HbA1c 8.9%
- **Impact: 51% remission**
  - **77% achieved remission if ≤ 1 yr duration of type 2 diabetes, 20% achieved remission if > 15 yrs of type 2 diabetes**
  - None achieved remission without weight loss

Unwin D, et al. What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss. *BMJ Nutr Prev Health.* 2023;6(1):46-55. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10407412/

Very Low-carbohydrate/Low-carb

- About 50% remission or reversal after 1 year
- About 15% remission or reversal after 5 years
- People with a longer duration of diabetes are less likely to go into remission

What else is promising?

Continuous Glucose Monitoring + (RCT)

- Intervention: Participants wore CGM, received AI-created nudges several times a day. Also requested to increase aerobic activity and resistance exercise, get sufficient sleep, and daily deep breathing meditation. AI nudges largely recommended increased intake of vegetables and protein, to reduce glucose elevations. Carbohydrate intake reduced from average of 307 to 150 g/day, protein intake increased from 36 to 73 g/day.
- Control: Standard calorie-restricted diet. Also requested to increase aerobic activity and resistance exercise.
- India, 2020-2021
- 242 people in intervention, 86 in control, mean baseline HbA1c 8.5-9%, 3.4 years mean duration of type 2 diabetes
- Impact:
  - **Intervention: 63% (152/242) remission at yr 1**
  - **Control: 0% (0/86) at yr 1**

Joshi S, et al. Endocr Pract. 2023;29(12):960-970. Available at https://pubmed.ncbi.nlm.nih.gov/37778441/

What doesn’t work that well?

Low-calorie, Low-fat: Look AHEAD (RCT)

- Intervention: “The energy goal for persons < 114 kg (250 lb) is 1200–1500 kcal/d and is 1500–1800 kcal/d for individuals ≥ 114 kg…. < 30% of calories from fat, with < 10% from saturated fat.” “patients encouraged to replace two meals and one snack daily with liquid shakes and meal bars.” Weekly group and individual meeting in the first 6 months, followed by 3 per month for the second 6 months and twice-monthly in years 2 to 4.
- Control: 3/yr group sessions about diabetes support and education
- US-wide, 2001-2008
- > 2000 in intervention, > 2000 in control, 5 years mean duration of type 2 diabetes, 15% taking insulin, mean baseline HbA1c about 7.3%
- Impact:
  - **Intervention: 11% (247/2157) remission at yr 1, 7% (150/2157) at yr 4**
  - **Control: 2% (43/2170) at yr 1, 2% (41/2170) remission at yr 4**

Gregg EW, et al. *JAMA*. 2012;308(23):2489-2496. Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4771522/

Mediterranean vs. Low-Fat: RCT

- Intervention: Calorie-reduced 1500-1800 kcal/day, Mediterranean (about 43% calories from carbs)
- Control: Low-fat (about 53% calories from carbs)
- How: Monthly visits with staff first year, then every two months
- Naples, Italy, 2004-2012
- 108 in Mediterranean, 107 in low-fat, newly diagnosed with diabetes, mean baseline HbA1c 7.8-7.7%
- Impact:
  - **Mediterranean: 14% (15/108) remission at yr 1, 1% (1/108) at yr 6**
  - **Low-fat: 4% (4/107) remission at yr 1, 0% at yr 6**

Esposito K, et al. *Diabetes Care*. 2014;37(7):1824-1830. Available at https://pubmed.ncbi.nlm.nih.gov/24722497/

What’s missing?

What's Missing? Vegan, Vegetarian, DASH, Intermittent Fasting

- *Remission of Type 2 Diabetes After Treatment With a High-Fiber, Low-Fat, Plant-Predominant Diet Intervention: A Case Series.* Panigrahi G, et al. *Am J Lifestyle Med*. 2023;839-846. Available at https://journals.sagepub.com/doi/full/10.1177/1559827623118157 4
- *Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial.* Yang X, et al. *J Clin Endocrinol Metab*. 2023;108(6):1415-1424. Available at https://pubmed.ncbi.nlm.nih.gov/36515429/
- *Efficacy and Safety of Intermittent Fasting in People With Insulin-Treated Type 2 Diabetes (INTERFAST-2)—A Randomized Controlled Trial.* Obermayer A, et al. *Diabetes Care*. 2023;46(2):463-468. Available at https://pubmed.ncbi.nlm.nih.gov/36508320/

What's Missing? Other Diabetes Self-management Programs

- **For all: No description of medication changes or remission.**
  - **Omada Health**: *Long-Term Results of a Digital Diabetes Self-Management and Education Support Program Among Adults With Type 2 Diabetes: A Retrospective Cohort Study.* Pre-post examination of 1,322 people.[1]
  - **Livongo Health** (bought by Teladoc Health): *Evaluation of a Diabetes Remote Monitoring Program Facilitated by Connected Glucose Meters for Patients With Poorly Controlled Type 2 Diabetes: Randomized Crossover Trial.* Randomized crossover trial of 119 people. No difference between their program and standard of care for HbA1c over the complete trial (6 months of intervention or control).[2]
  - **Cecelia Health**: No trial published, just description of results on their website.
  - **HeLP-Diabetes***: Web-based self-management support for people with type 2 diabetes (HeLP-Diabetes): randomised controlled trial in English primary care.*[3]

1. Berthoumieux A, et al. *Sci Diabetes Self Manag Care*. 2024;50(1):19-31. Available at https://pubmed.ncbi.nlm.nih.gov/38240247/
2. Amante DJ, et al. *JMIR Diabetes*. 2021;6(1):e25574. Available at https://diabetes.jmir.org/2021/1/e25574/
3. Murray E, et al. *BMJ Open*. 2017;7(9):e016009.. Available at https://pubmed.ncbi.nlm.nih.gov/28954789/

Two-Three Clinically Tested Ways to Reverse Type 2 Diabetes Using Dietary Approaches

- Formula total diet replacement (about 850 kcal/day)
- Very low-carbohydrate/ketogenic diet – real food, not calorie-restricted
- Emerging evidence for multi-component intervention based on continuous glucose monitoring

Percent of participants in remission or reversal

- After 1 year:
  - About half in remission in formula diet or CGM program
  - About half in remission or reversal (20% in remission) with very low-carbohydrate/ketogenic diet
- After 5 years:
  - About 11% in remission with formula diet
  - About 15% reversal or remission (9% in remission) with very low-carbohydrate/ketogenic diet

Challenges to Remission

- Taking insulin
- Not losing weight
- Longer duration of type 2 diabetes
- Higher starting HbA1c

- Be patient… it may take time for the pancreas to improve its morphology and improve β-cell capacity

Al-Mrabeh A, et al. *Lancet Diabetes Endocrinol.* 2020;8(12):939-948. Available at https://pubmed.ncbi.nlm.nih.gov/33031736/

History! About 100 years ago… 1910s-1920s:

- Frederick Allen and Elliott Joslin advocated for very low-calorie diets

- Louis Newburgh and Phil Marsh studied very low-carbohydrate diets, without having to fast or follow a low-calorie diet

Image from Sarah Hallberg

Laura Saslow, U Michigan

Thank you to the organizers of this course and to Sarah Hallberg, who was truly a firecracker, an inspiration to us all!

“This amazing woman changed my life with this 18 minute video. I reversed type 2 diabetes over 3 years ago and I am in the best shape I have ever been in. I even hiked the 2194 mile Appalachian Trail... Thank you Dr. Sarah! I’m never going back to obesity and diabetes!”
- comment from Sarah Hallberg’s talk, “Reversing Type 2 diabetes starts with ignoring the guidelines” with 11 million views