Weight Management and Diabetes

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Agenda

- The Current Standard of Care
- Goals: Control vs. Remission
- Nutritional Treatment of Diabetes for remission
- Pharmacotherapy for Diabetes
- Combining Therapies

Conflicts of Interest

- Speakers Bureau—Novo Nordisk
- Medical Advisory Panel--Robard

Diabetes “Standard of Care”

words of wisdom

‘ The fallacy that eating fat will make you fat is about as scientifically logical as saying that eating tomatoes will turn you red.’

Dr Richard Bernstein

The HERNRIED CENTER
Medical Weight Loss

American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for Developing a Diabetes Mellitus Comprehensive Care Plan

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ENDOCRINE PRACTICE Vol 21 No. 4 April 2015

Q4. How are glycemic targets achieved for T2D?

Healthful Eating Recommendations

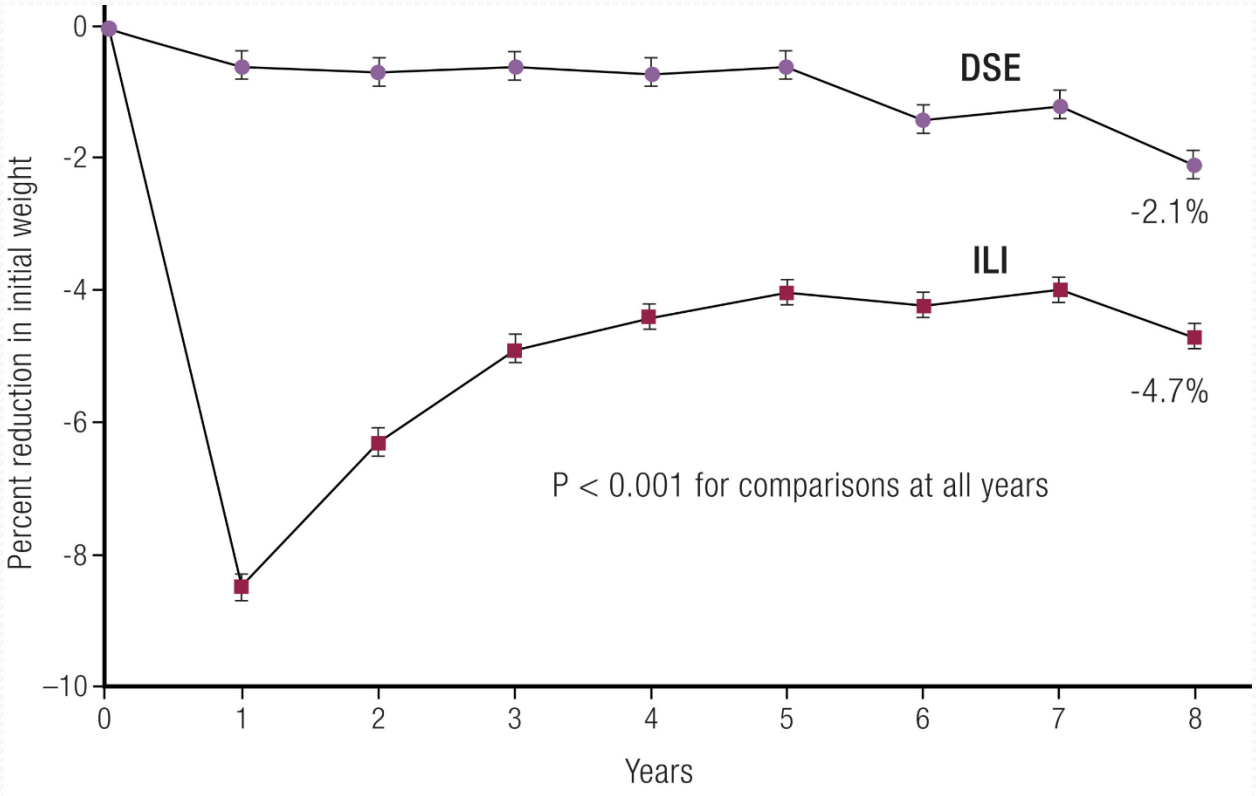
Carbohydrate	Specify healthful carbohydrates (fresh fruits and vegetables, legumes, whole grains); target 7-10 servings per day Preferentially consume lower-glycemic index foods (glycemic index score <55 out of 100: multigrain bread, pumpernickel bread, whole oats, legumes, apple, lentils, chickpeas, mango, yams, brown rice)
Fat	Specify healthful fats (low mercury/contaminant-containing nuts, avocado, certain plant oils, fish) Limit saturated fats (butter, fatty red meats, tropical plant oils, fast foods) and trans fat; choose fat-free or low-fat dairy products
Protein	Consume protein in foods with low saturated fats (fish, egg whites, beans); there is no need to avoid animal protein Avoid or limit processed meats
Micronutrients	Routine supplementation is not necessary; a healthful eating meal plan can generally provide sufficient micronutrients Chromium; vanadium; magnesium; vitamins A, C, and E; and CoQ10 are not recommended for glycemic control Vitamin supplements should be recommended to patients at risk of insufficiency or deficiency

What About the ADA?

Objective 2: Support Patient Self-management

- Implement a systematic approach to support patient behavior change efforts, including:
  - Healthy lifestyle
  - Disease self-management
  - Prevention of diabetes complications
  - Identification of self-management problems and development of strategies to solve those problems

American Diabetes Association Standards of Medical Care in Diabetes.
Promoting Health and Reducing Disparities in Populations. *Diabetes Care* 2017; 40 (Suppl. 1): S6-S10



Abbreviations: DSE, diabetes support and education; ILI, intensive lifestyle intervention

From: The Science of Obesity Management: An Endocrine Society Scientific Statement
Endocr Rev. 2018;39(2):79-132. doi:10.1210/er.2017-00253

Recommendations: Nutrition (4)

Eating patterns & macronutrient distribution:

- Macronutrient distribution should be individualized while keeping total calorie and metabolic goals in mind. E
- Carbohydrate intake from whole grains, vegetables, fruits, legumes, and dairy products, with an emphasis on foods higher in fiber and lower in glycemic load, should be advised over other sources, especially those containing sugars. B
- A varietv of eating patterns are acceptable for the management of type 2 diabetes and prediabetes including Mediterranean, DASH, and plant-based diets. B
- Diets should be individualized, as those that provide the same caloric restriction but differ in protein, carbohydrate, and fat content are equally effective in achieving weight loss. A

American Diabetes Association Standards of Medical Care in Diabetes.

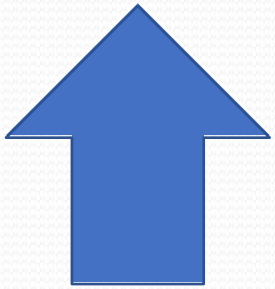
Recommendations: Metabolic Surgery

- Metabolic surgery *should be recommended* to treat T2DM for all appropriate surgical candidates with BMIs ≥ 40 (37.5*) and those with BMIs 35.0-39.9 (32.5-37.4*) when hyperglycemia is inadequately controlled despite lifestyle & optimal medical therapy. A
- Metabolic surgery *should be considered* for the treatment of T2DM in adults with BMIs 30-34.9 (27.5-32.4*) when hyperglycemia is inadequately controlled despite optimal medical control by either oral or injectable medications (including insulin). B

American Diabetes Association Standards of Medical Care in Diabetes. 2017

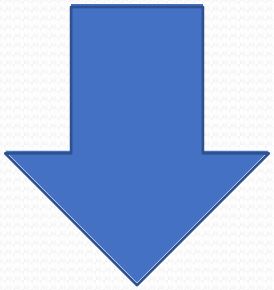
Associated weight changes with T2DM meds

Weight gain: sulfonylureas, TZDs, insulin



Neutral: DPP IV inhibitors

Weight loss: metformin, SGLT-2 inhibitors, GLP-1 RA



Start with Monotherapy unless:

A1C is greater than or equal to 9%, **consider Dual Therapy.**

A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, **consider Combination Injectable Therapy** (See Figure 8.2).

Monotherapy — Metformin — Lifestyle Management

EFFICACY*	high
HYPO RISK	low risk
WEIGHT	neutral/loss
SIDE EFFECTS	GI/lactic acidosis
COSTS*	low

If A1C target not achieved after approximately 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Dual Therapy — Metformin + — Lifestyle Management

	Sulfonylurea	Thiazolidinedione	DPP-4 inhibitor	SGLT2 inhibitor	GLP-1 receptor agonist	Insulin (basal)
EFFICACY*	high	high	intermediate	intermediate	high	highest
HYPO RISK	moderate risk	low risk	low risk	low risk	low risk	high risk
WEIGHT	gain	gain	neutral	loss	loss	gain
SIDE EFFECTS	hypoglycemia	edema, HF, fxs	rare	GU, dehydration, fxs	GI	hypoglycemia
COSTS*	low	low	high	high	high	high

If A1C target not achieved after approximately 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference — choice dependent on a variety of patient- & disease-specific factors):

Triple Therapy — Metformin + — Lifestyle Management

Sulfonylurea +	Thiazolidinedione +	DPP-4 inhibitor +	SGLT2 inhibitor +	GLP-1 receptor agonist +	Insulin (basal) +
TZD	SU	SU	SU	SU	TZD
or DPP-4-i	or DPP-4-i	or TZD	or TZD	or TZD	or DPP-4-i
or SGLT2-i	or SGLT2-i	or SGLT2-i	or DPP-4-i	or SGLT2-i	or SGLT2-i
or GLP-1-RA	or GLP-1-RA	or Insulin[§]	or GLP-1-RA	or Insulin[§]	or GLP-1-RA
or Insulin[§]	or Insulin[§]		or Insulin[§]		

If A1C target not achieved after approximately 3 months of triple therapy and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin, or (3) on optimally titrated basal insulin, add GLP-1 RA or mealtime insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessarily complex or costly regimens (i.e., adding a fourth antihyperglycemic agent).

Combination Injectable Therapy (See Figure 8.2)

PROFILES OF ANTIDIABETIC MEDICATIONS

	MET	GLP-1 RA	SGLT-2i	DPP-4i	AGi	TZD	SU / GLN	COLSVL	BCR-QR	INSULIN	PRAML
HYPO	Neutral	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate/ Severe / Mild	Neutral	Neutral	Moderate to Severe	Neutral
WEIGHT	Slight Loss	Loss	Loss	Neutral	Neutral	Gain	Gain	Neutral	Neutral	Gain	Loss
RENAL/ GU	Contra-indicated CKD Stage 3B,4,5	Exenatide Contra-indicated CrCl < 30	Genital Mycotic Infections	Dose Adjustment May be Necessary (Except Linagliptin)	Neutral	May Worsen Fluid Retention	More Hypo Risk	Neutral	Neutral	More Hypo Risk & Fluid Retention	Neutral
GI Sx	Moderate	Moderate	Neutral	Neutral	Moderate	Neutral	Neutral	Mild	Moderate	Neutral	Moderate
CHF	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral	Neutral	Neutral
CVD	Benefit		Increased LDL			Neutral	?		Safe		
BONE	Neutral	Neutral	Neutral	Neutral	Neutral	Moderate Bone Loss	Neutral	Neutral	Neutral	Neutral	Neutral

Few adverse events or possible benefits — Use with caution — Likelihood of adverse effects

Glycemic Control Algorithm

LIFESTYLE MODIFICATION
(Including Medically Assisted Weight Loss)

Entry A1c < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ✓ AGi
- ⚠ TZD
- ⚠ SU/GLN

If not at goal in 3 months proceed to Double Therapy

Entry A1c ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1c > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

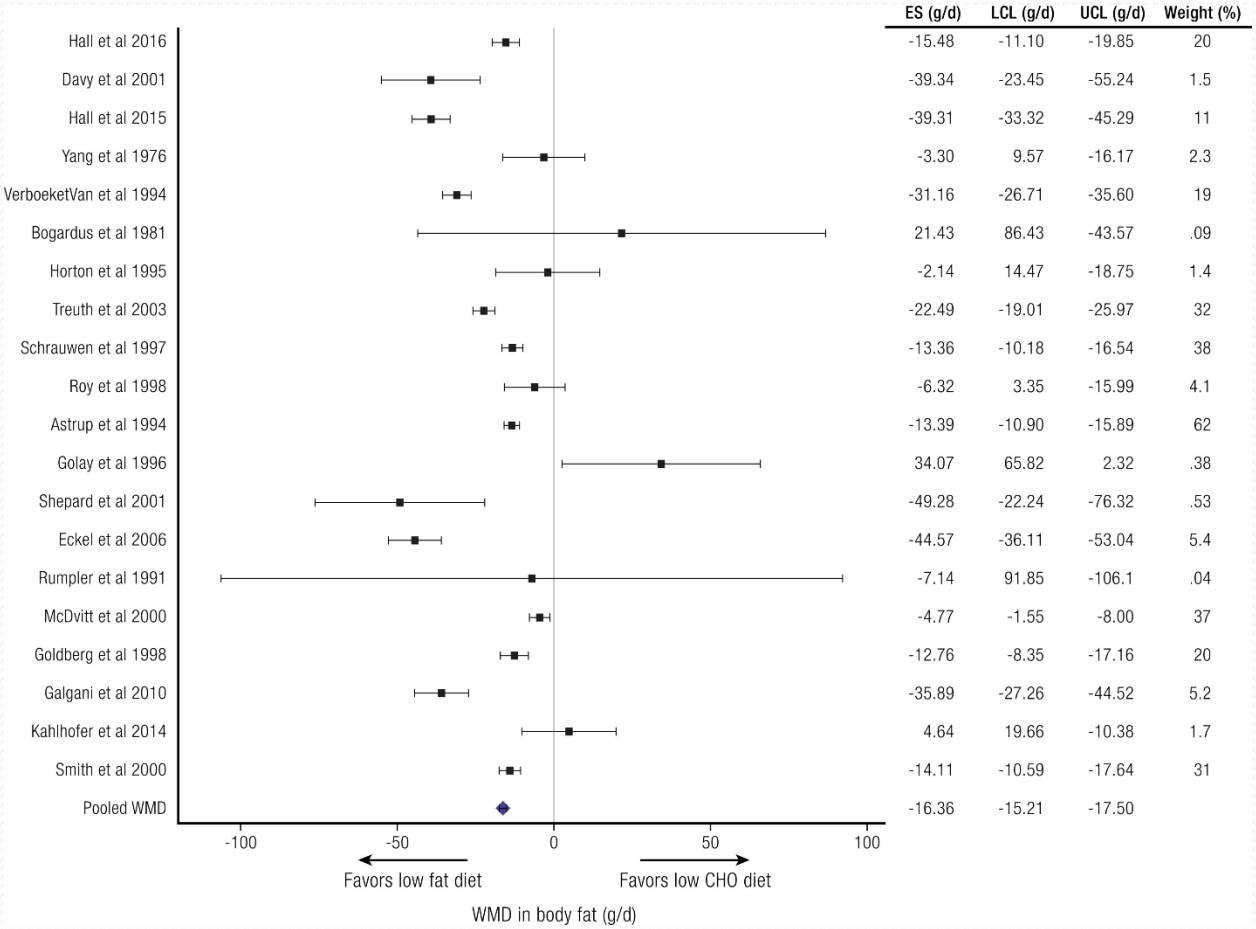
ADD OR INTENSIFY INSULIN
Refer to Insulin Algorithm

LEGEND
- ✓ Few adverse events or possible benefits
- ⚠ Use with caution

* Order of medications listed represents a suggested hierarchy of usage

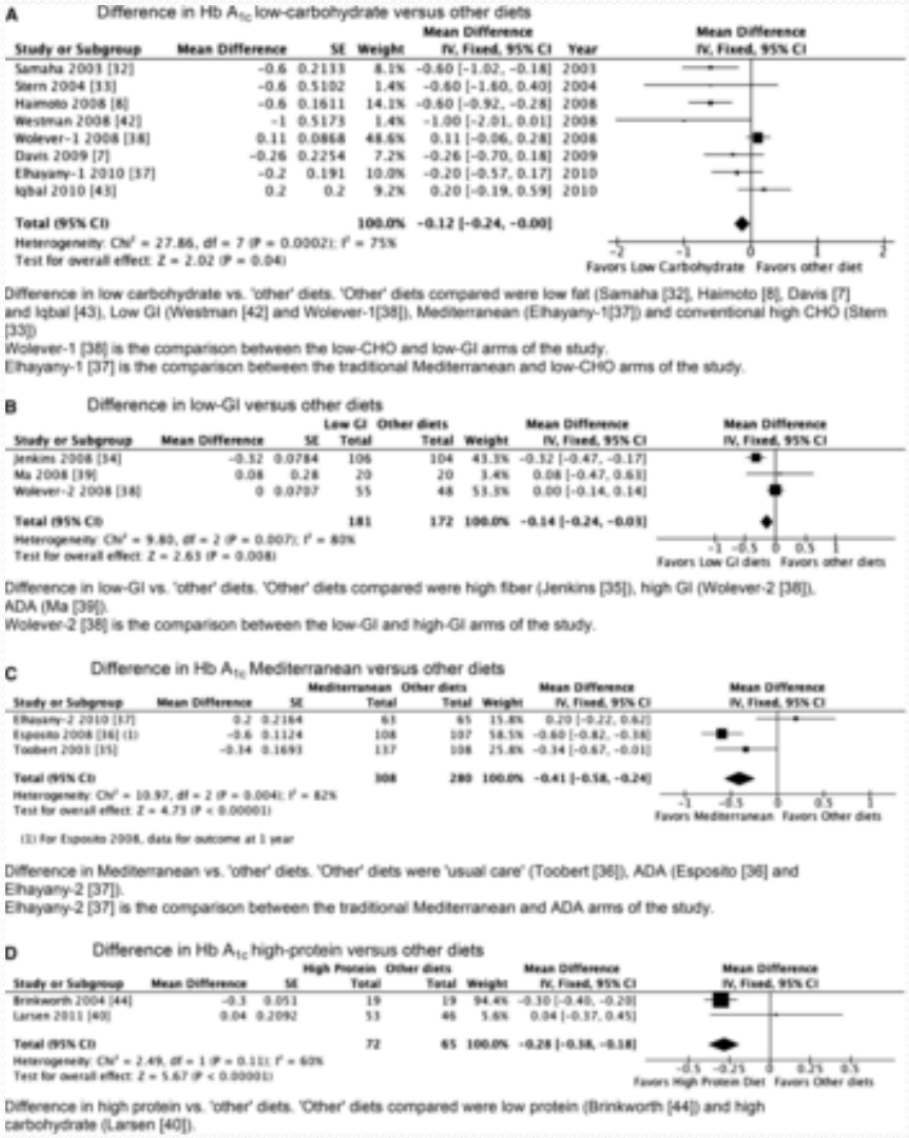
PROGRESSION OF DISEASE

Any Diet Will Do?



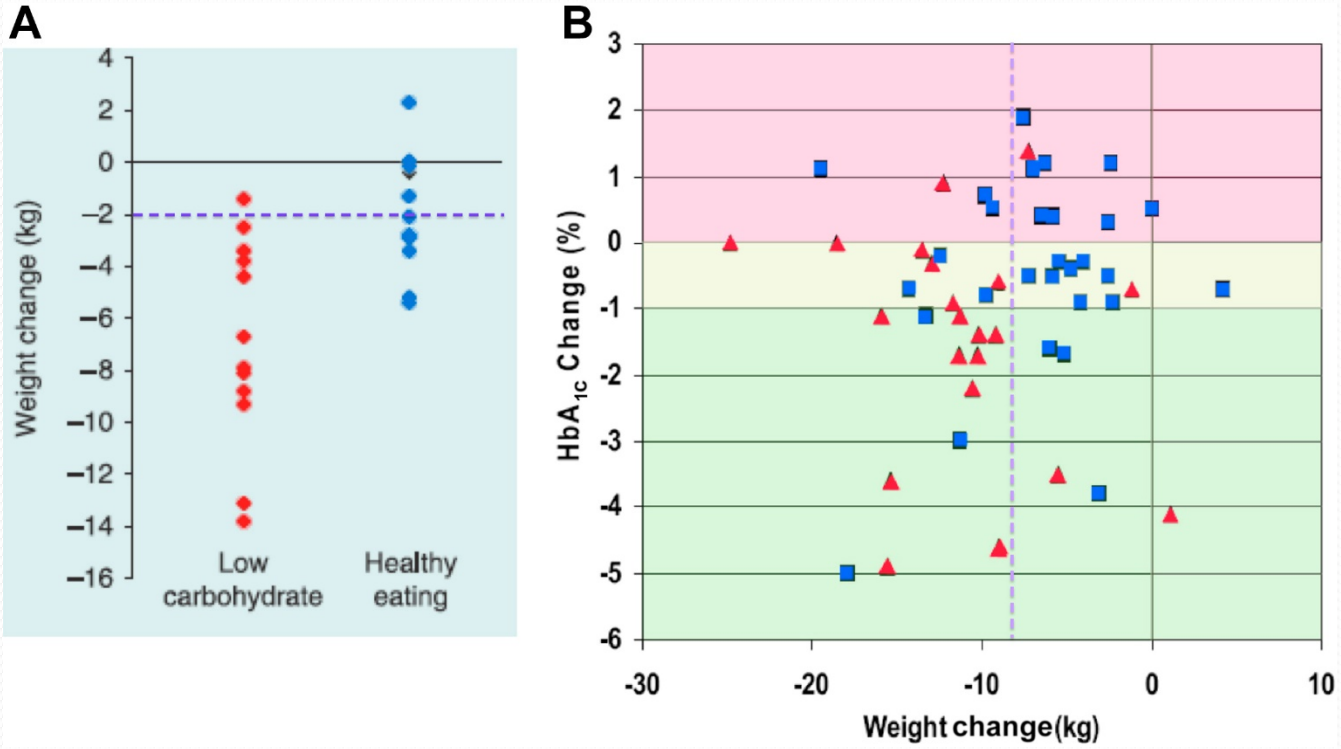
From: The Science of Obesity Management: An Endocrine Society Scientific Statement
Endocr Rev. 2018;39(2):79-132. doi:10.1210/er.2017-00253

Any Diet Will Do?



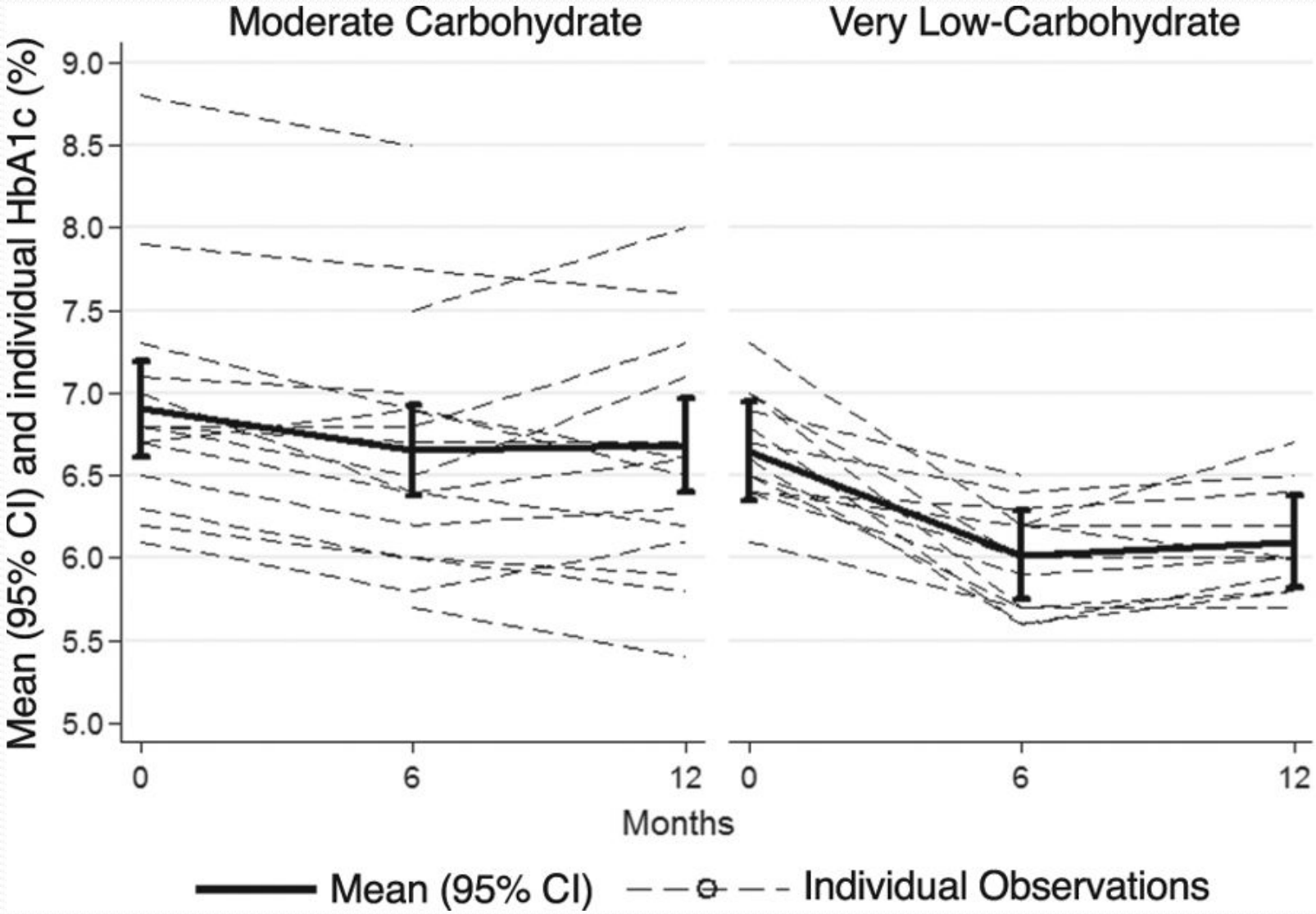
From: Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes
Am J Clin Nutr. 2013;97(3):505-516. doi:10.3945/ajcn.112.042457

Dietary carbohydrate restriction as the first approach in diabetes management: Critical review and evidence base



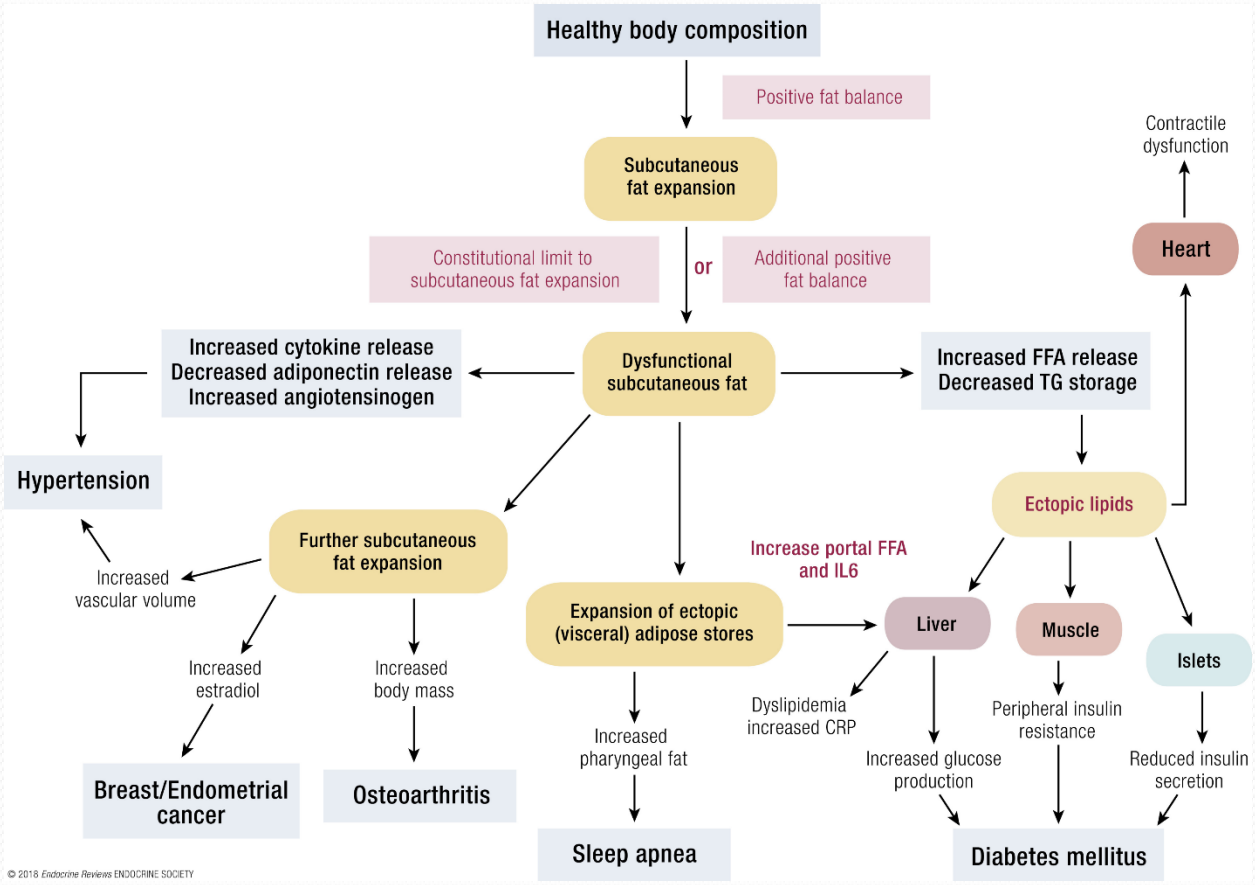
Nutrition 2015 31, 1-13DOI: (10.1016/j.nut.2014.06.011)

CARBS MATTER



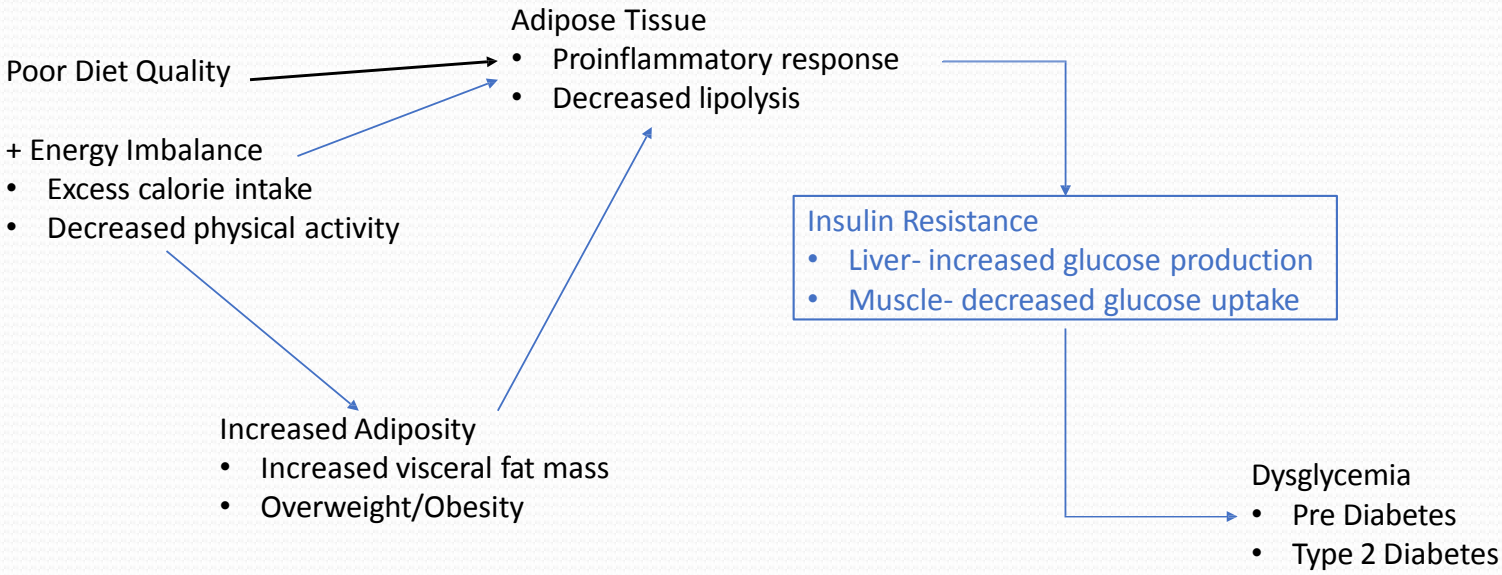
Saslow, J Med Internet Res. 2017 Feb; 19(2): e36.

Obesity as a Metabolic Disease

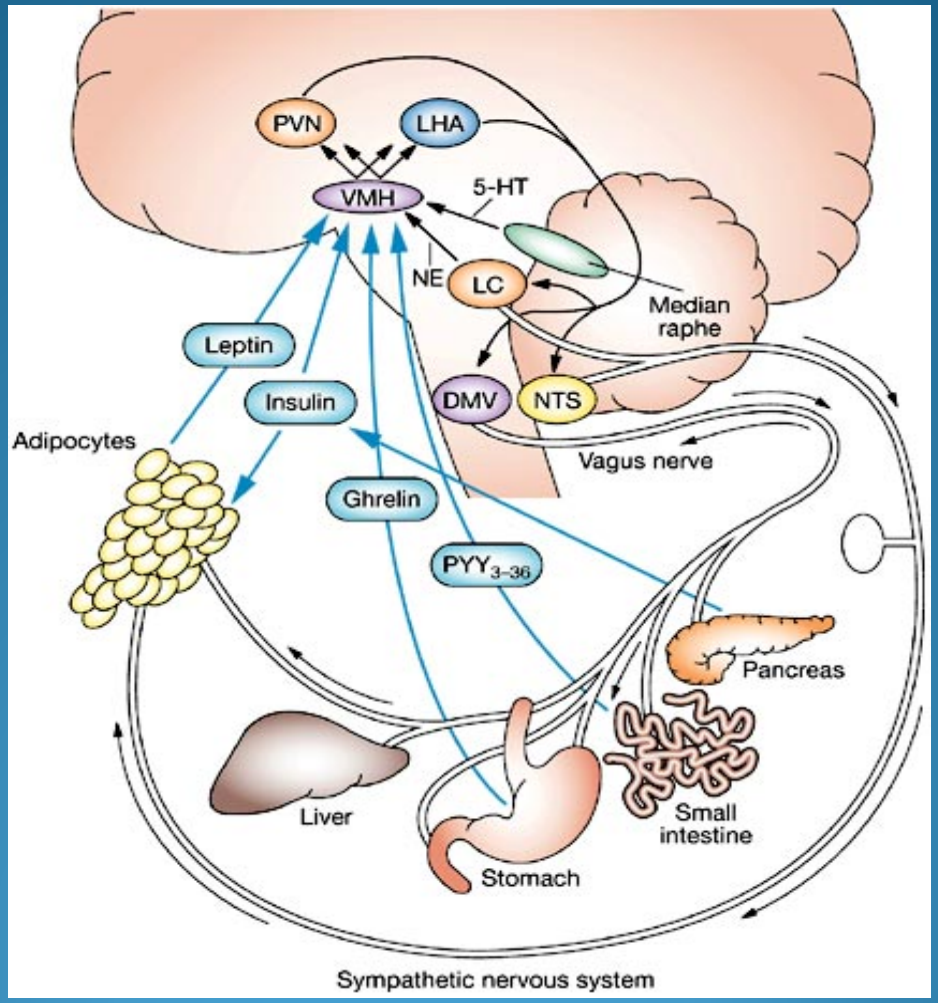


From: The Science of Obesity Management: An Endocrine Society Scientific Statement
Endocr Rev. 2018;39(2):79-132. doi:10.1210/er.2017-00253

The Link is Insulin Resistance



The homeostatic pathway of energy balance



Lustig RH (2006) Childhood obesity: behavioral aberration or biochemical drive? reinterpreting the first law of thermodynamics *Nat Clin Pract Endocrino Metabol* 2: 447–458 doi:10.1038/ncpendmet0220

Key Messages to Patients

- Energy Storage Disease— A chronic condition of "Savers"
- A Disease of Carbohydrate Intolerance
- Weight Loss is NOT the Cure for Obesity—it is a chronic condition
- Relapse and Retreatment is to be expected and not shameful

Goals: Management or Remission?

Definition of Remission

Achieving glycemia below the diabetic range in the absence of active pharmacologic or surgical (ongoing procedures such as repeated replacements of endoluminal devices) therapy.

Buse et al. *Diabetes Care November 2009 vol. 32 no. 11 2133-2135*

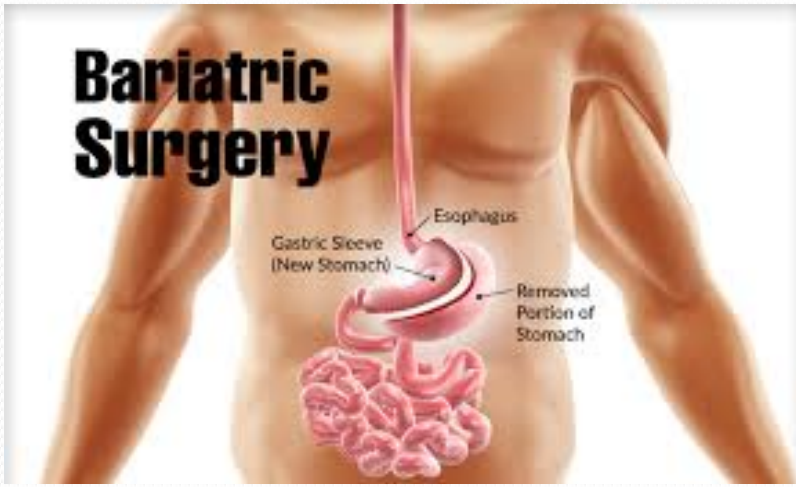
Subcategories

1. Partial Remission: Hba1c < 6.5
2. Complete Remission Hba1c < 5.7 for 1 year
3. Prolonged Remission: Hba1c<5.7 for 5 years

Diabetes Remission & Bariatric Surgery

3. years median disease free period following RYGB

   Obes Surg 2013;23:93–102
   Diabetologia 2015;58:1448–1453

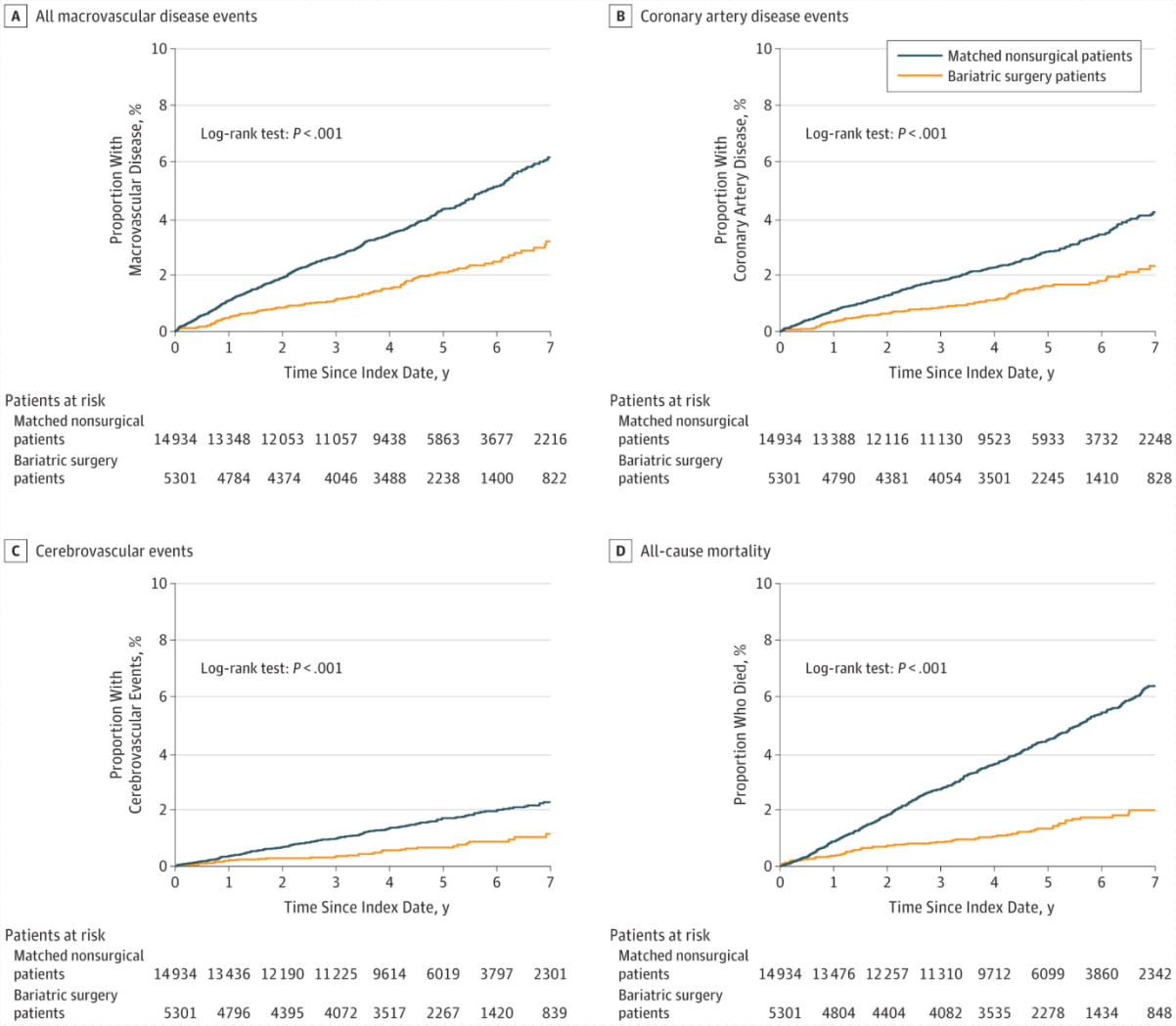


Predictors of response

- Younger age
- Shorter duration of diabetes (<8 years)
- Not on insulin
- Greater weight loss

  Diabetes Care 2017;40(Suppl. 1):S1–S2

From: **Association Between Bariatric Surgery and Macrovascular Disease Outcomes in Patients With Type 2 Diabetes and Severe Obesity**



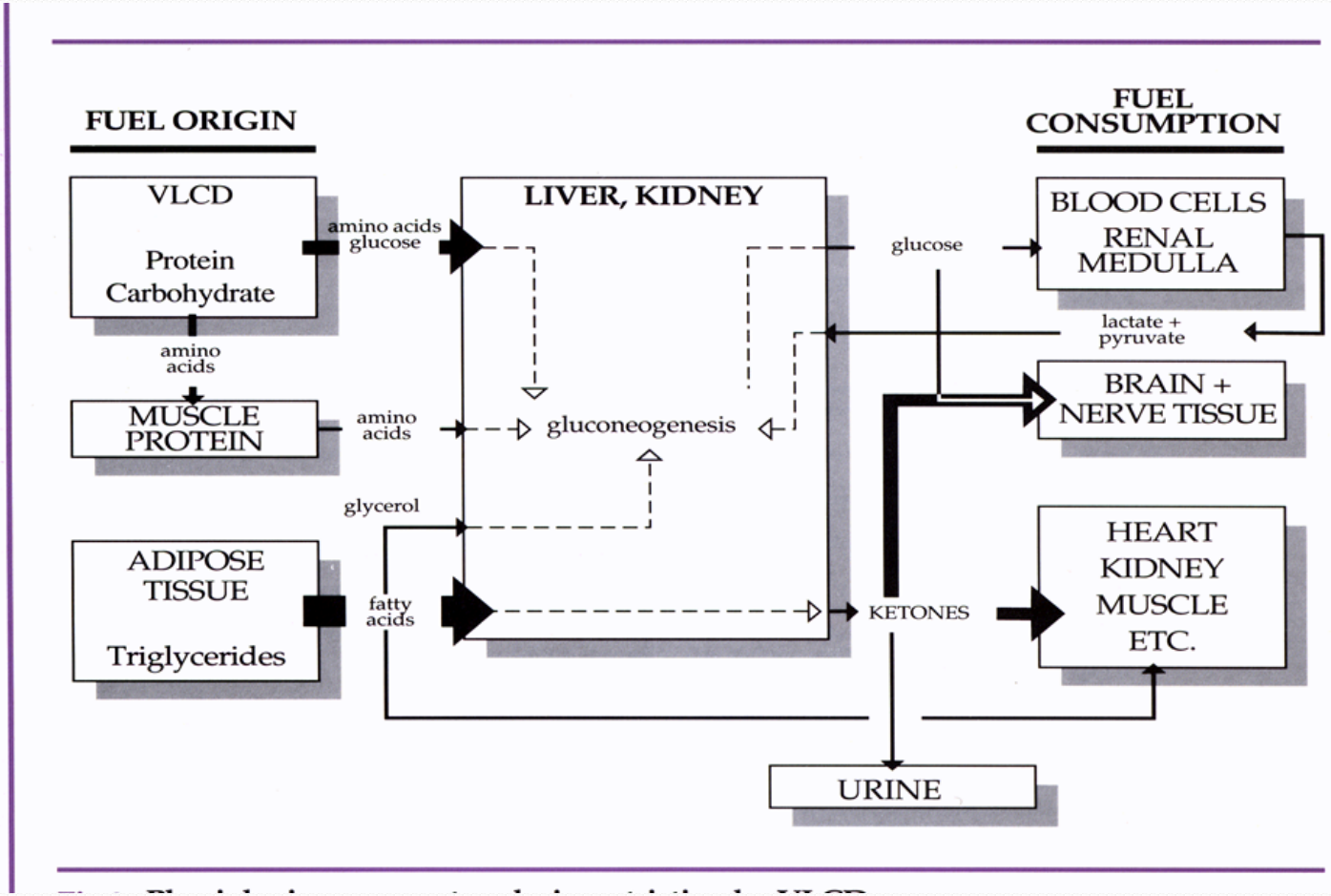
JAMA. 2018;320(15):1570-1582. doi:10.1001/jama.2018.14619

Nutritional Intervention For Diabetes: Remission is Achievable!

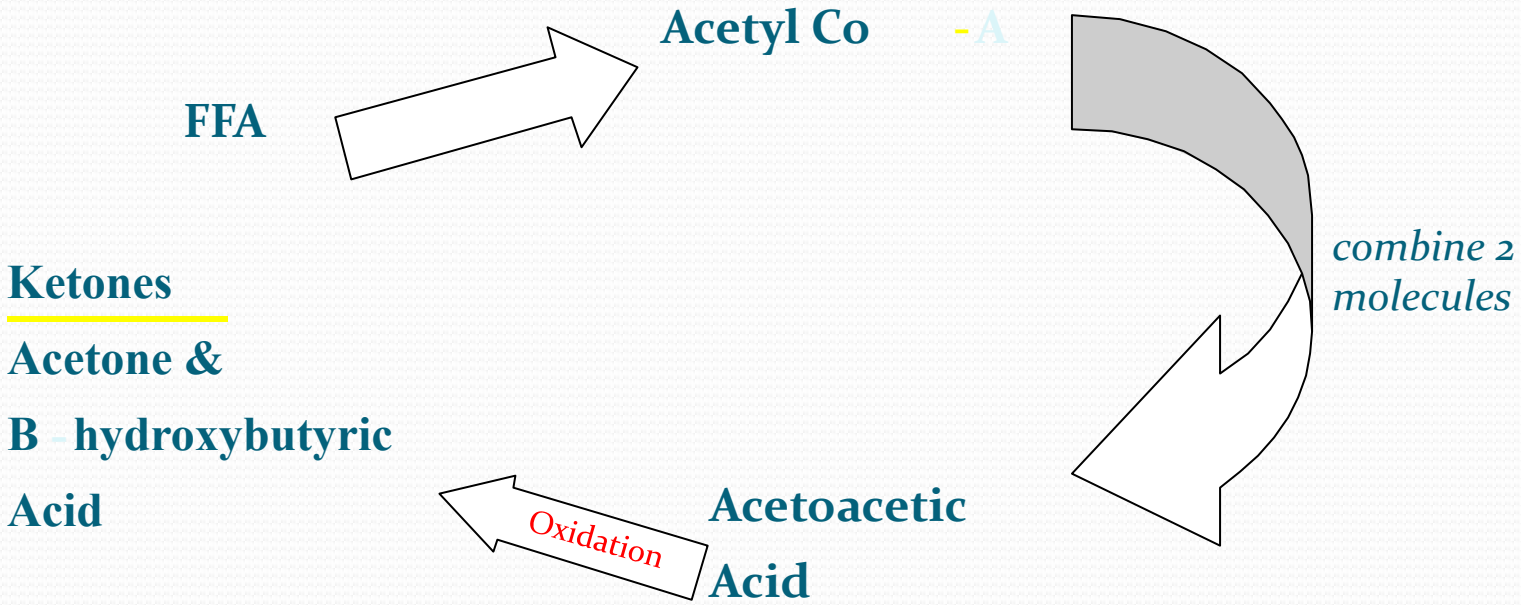
What is a VLCD?

- **Very low calorie diet (VLCD)**
  - Meal Replacement Diet of 600-1000 calories
  - nutritionally complete,
  - contain the recommended daily requirements for vitamins, minerals, trace elements, fatty acids and protein.
- Developed at Harvard around 1970—long since perfected
- Nutritional Ketosis—patients are not hungry
- Weight Loss of 3-5 pounds per week
- Requires Medical Supervision
- Obesity Related Medical Conditions Improve Rapidly
- NOT THE CURE—MUST BE ACCOMPANIED BY LIFESTYLE CHANGE

Physiological Response to VLCD



Ketosis and Ketogenesis



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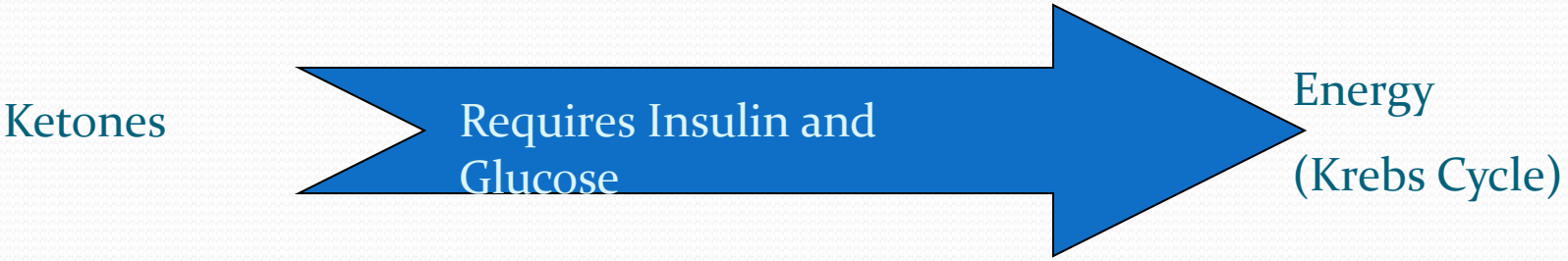
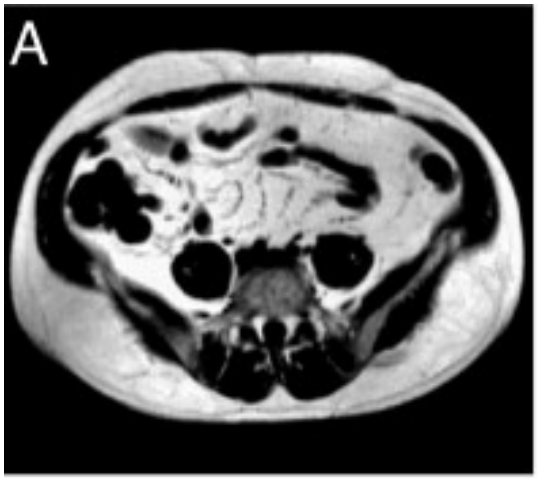
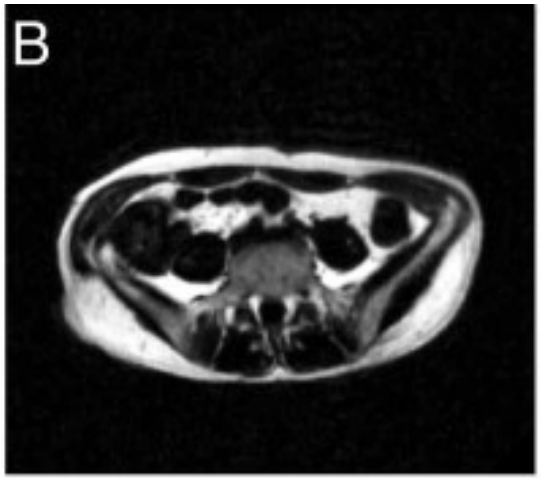
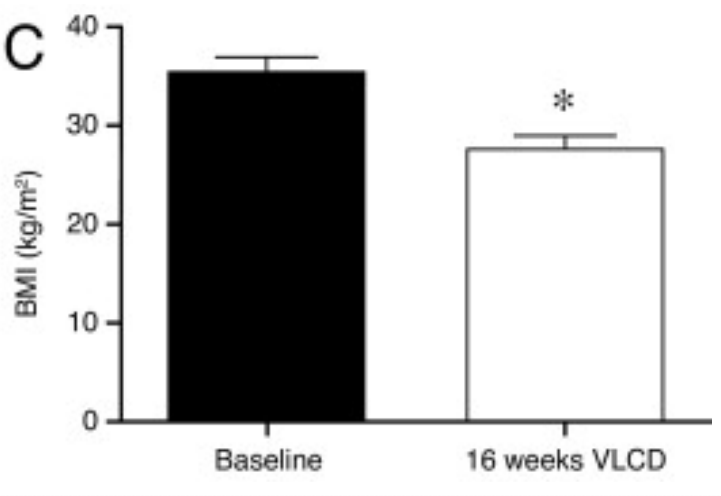


Fat Stores After 16 weeks on a VLCD



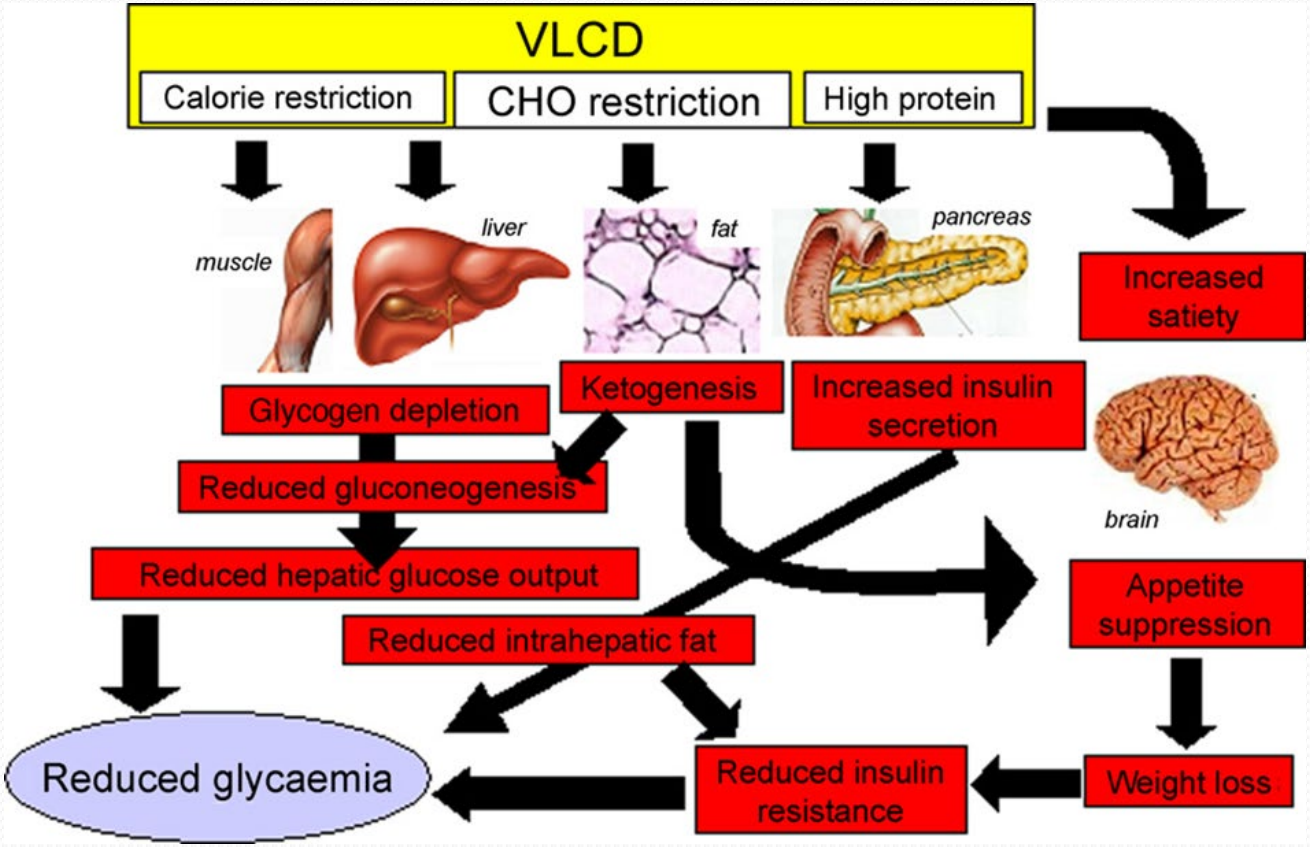




: Journal of the American College of Cardiology 2008; 52:1006-1012 (DOI:10.1016/j.jacc.2008.04.068)

VLCD's and Diabetes

VLCD's Improve Diabetes



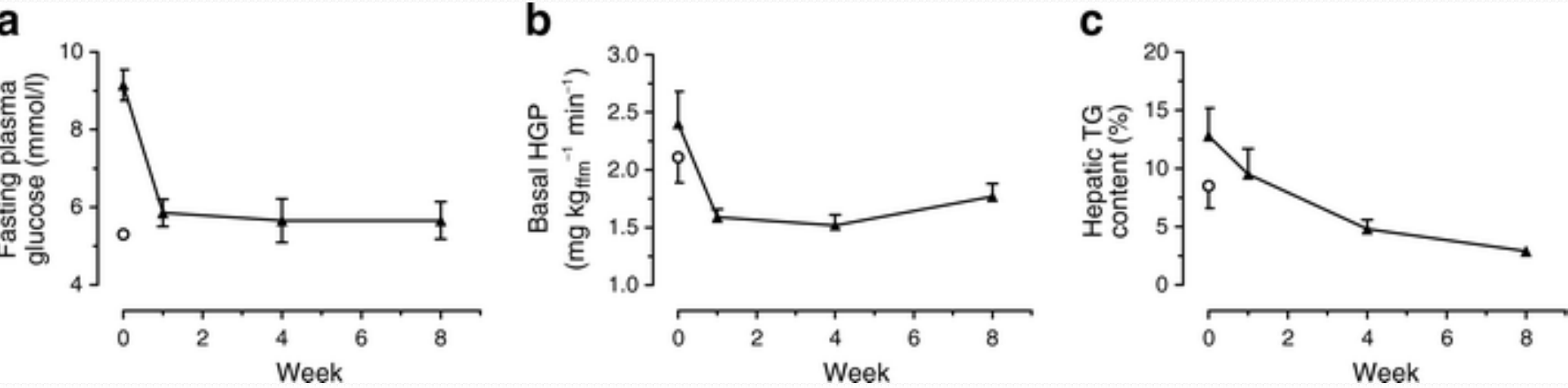
S. Baker, et al., Effects and clinical potential of very-low-calorie diets (VLCDs) in type 2 diabetes, Diab. Res. Clin. Pract. (2009), doi:10.1016/j.diabres.2009.06.002

What is Happening?

1. Nearly immediate improvement in hepatic insulin sensitivity
2. Normalization of Beta Cell Function

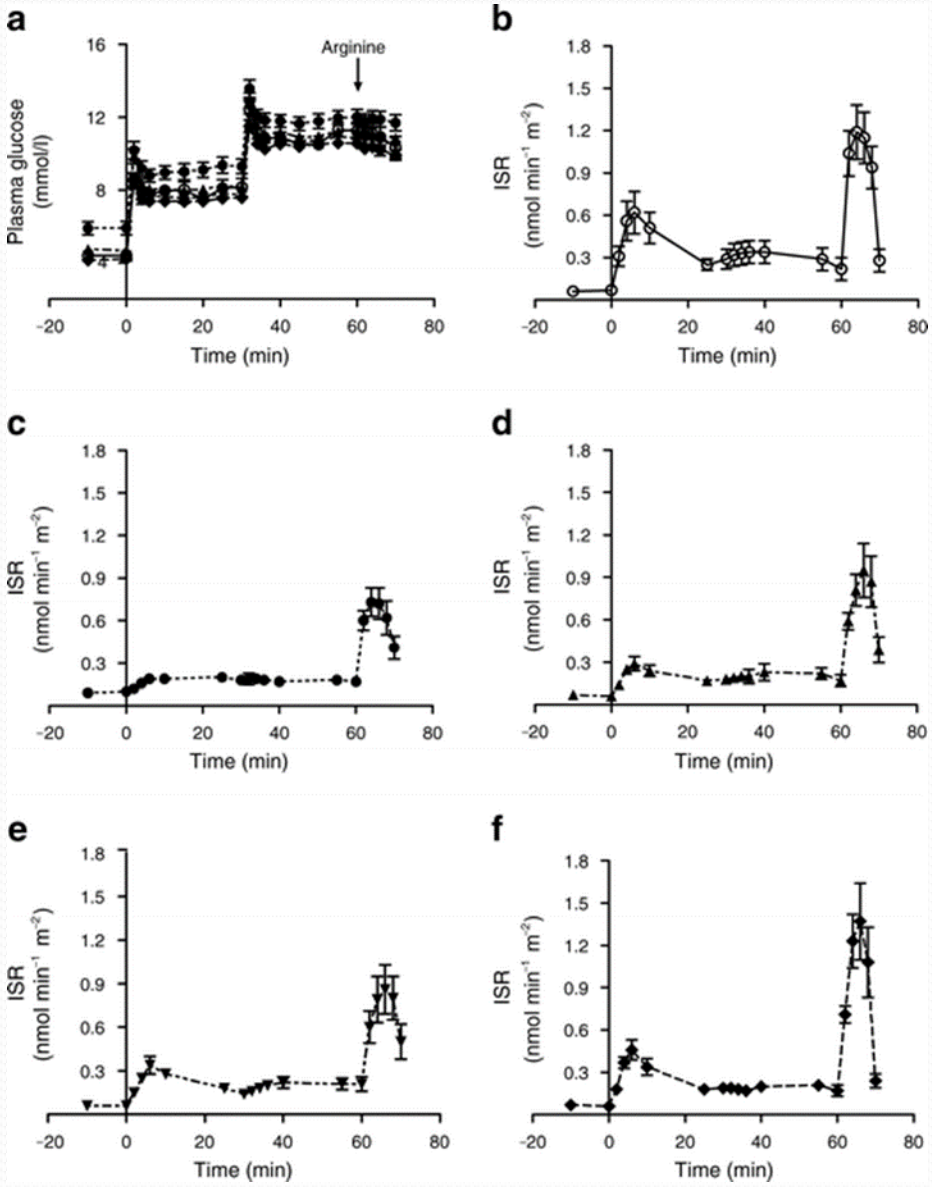
Mechanism: Reduction of lipid accumulation in the liver and pancreas (also in the heart)

VLCD's and the liver



Lim et al, "Reversal of type 2 diabetes: normalisation of beta cell function in association with decre4ased pancreas and liver triaglycerol" *Diabetologia*, June 2011

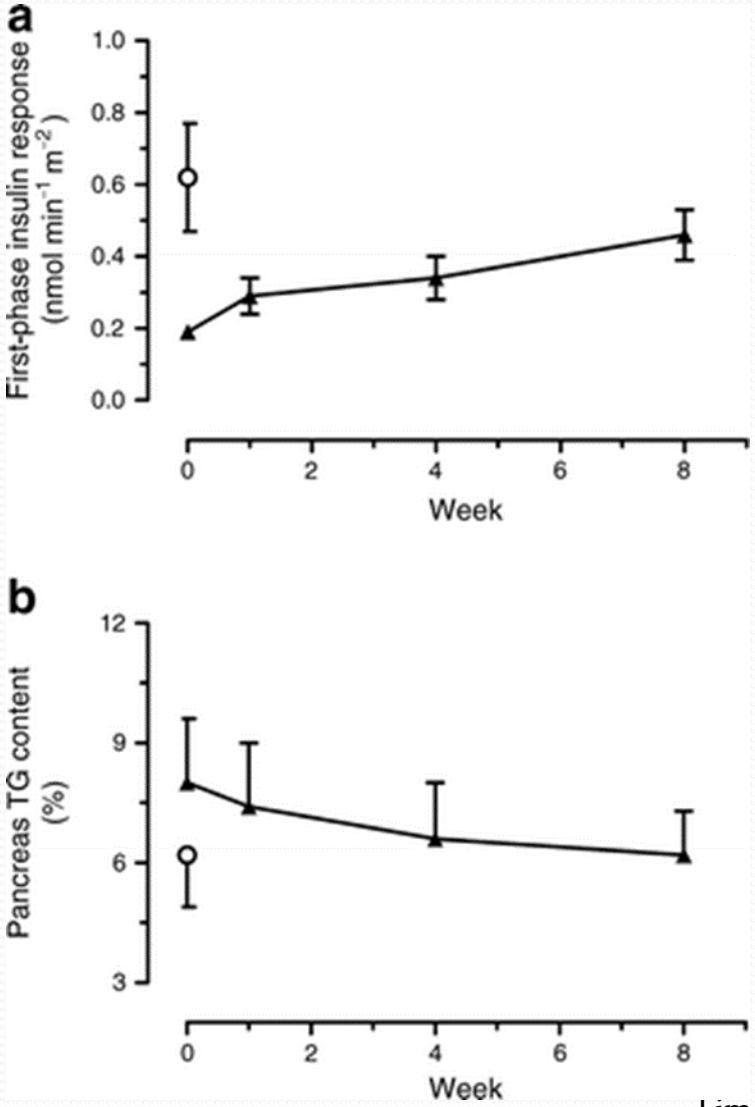
Beta Cell Function Improves



Key
a-glucose levels
b-non diabetic
c-diabetic baseline
d-1 week VLCD
e-4 week VLCD
f-8 week VLCD

Lim et al, "Reversal of type 2 diabetes: normalisation of beta cell function in association with decre4ased pancreas and liver triaglycerol" *Diabetologia*, June 2011

First-phase Insulin Response Normalizes



Lim et al, "Reversal of type 2 diabetes: normalisation of beta cell function in association with decre4ased pancreas and liver triaglycerol" *Diabetologia*, June 2011

Weight Management Program Significantly Improves Glycemic Control and Cardiovascular Disease Risk Factors in Patients with Type 2 Diabetes

	Baseline	Final	Mean % Change
Weight	283 lbs	195	-31%
Fasting Glucose	166	99	-39.8%
Cholesterol	160	138	-13.5%
HDL-C	45.6	47.3	+3.7%
LDL-C	87.4	74.6	-14.6%
Triglycerides	199	88	-55.6%

Average Hba1c Reduction of 2.04% (Baseline 7.86%)

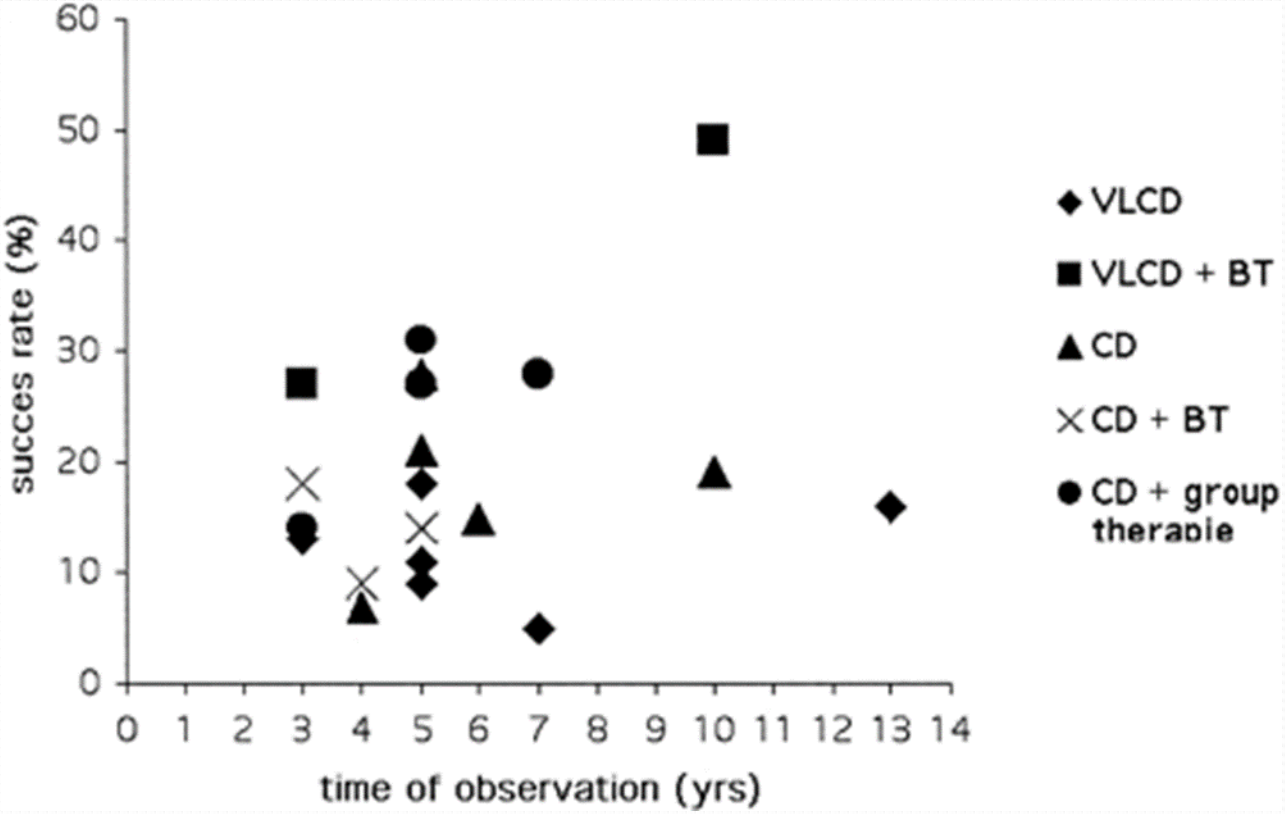
C. Case, Endocrine Society

Other Clinical Improvements

- Blood Pressure Drops
- Renal Function Improves
- Cardiac function improves-CHF
- Edema is reduced
- Sleep improves
- Depression and Quality of Life improves
- Arthritis pain is reduced
- GERD resolves or is improved

What Drug Can Can Do All This?!

Long-Term VLCD Benefits

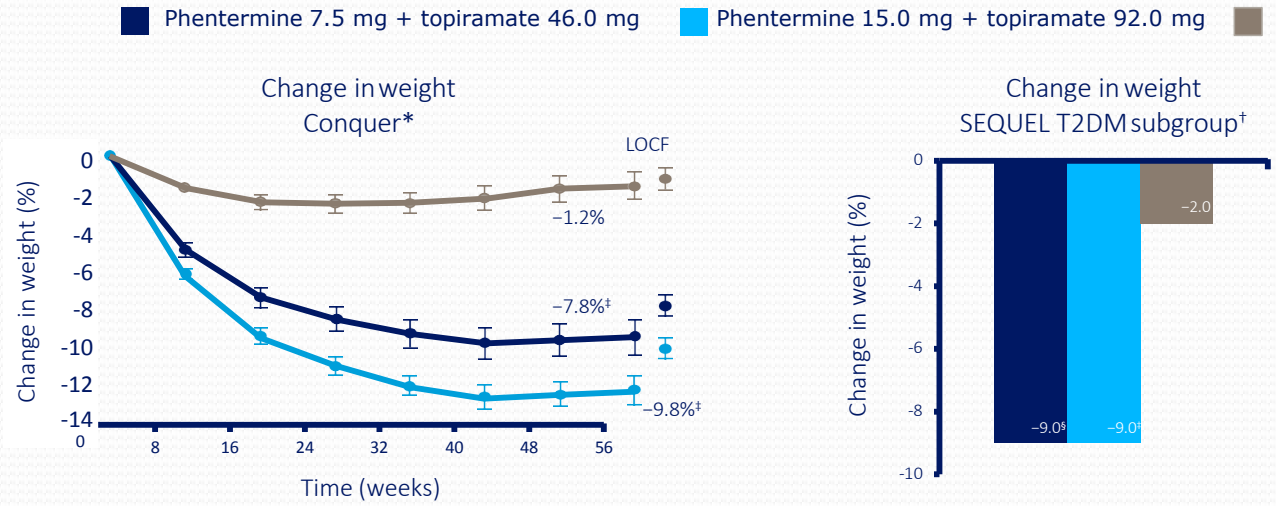


Success rate defined as maintenance of all weight (100%) initially lost, or maintenance of at least 9 to 11 kg of the initial weight loss and time of observation in 21 study groups. VLCD, very-low-calorie diet; BT, behavior therapy; CD, conventional diet. Adapted from Ayyad and Andersen Obesity Research 2001

Obesity Pharmacotherapy and Diabetes

Effect of phentermine and topiramate ER on weight in patients with and without T2DM

Conquer: 56-week data and SEQUEL T2DM subgroup: 2-year data

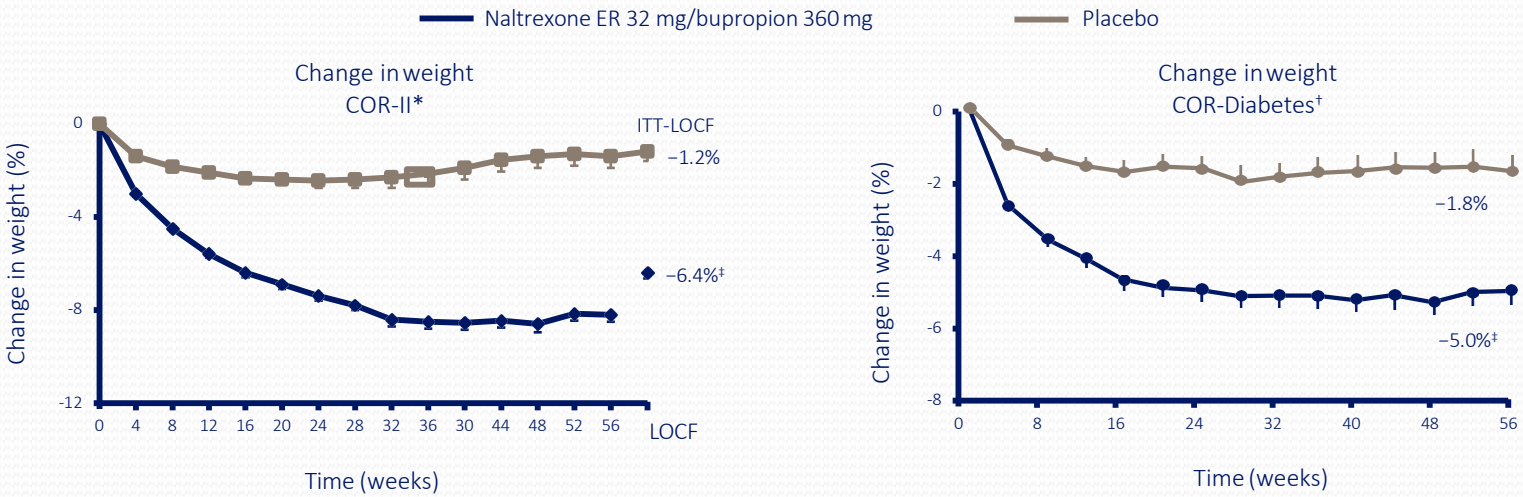


- Mean reduction in HbA_{1c} at week 108 was greater in T2DM phentermine and topiramate ER treated groups compared with placebo

Gadde KM *et al. Lancet* 2011;377:1341–52; Garvey WT *et al.* Am J Clin Nutr 2012;95:297–308

Effect of naltrexone ER/bupropion on weight in patients with and without T2DM

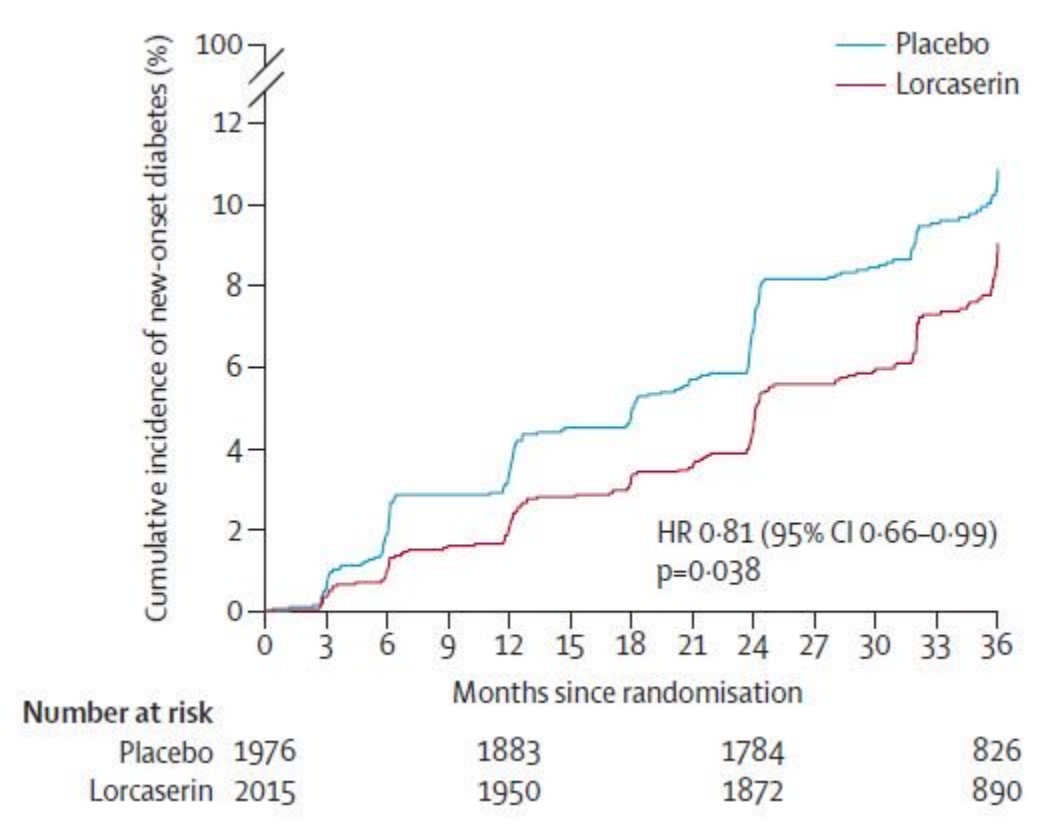
COR-II and COR-Diabetes: 56-week data



- Mean reduction in HbA_{1c} was significantly greater in the T2DM naltrexone ER/bupropion treated group compared with placebo

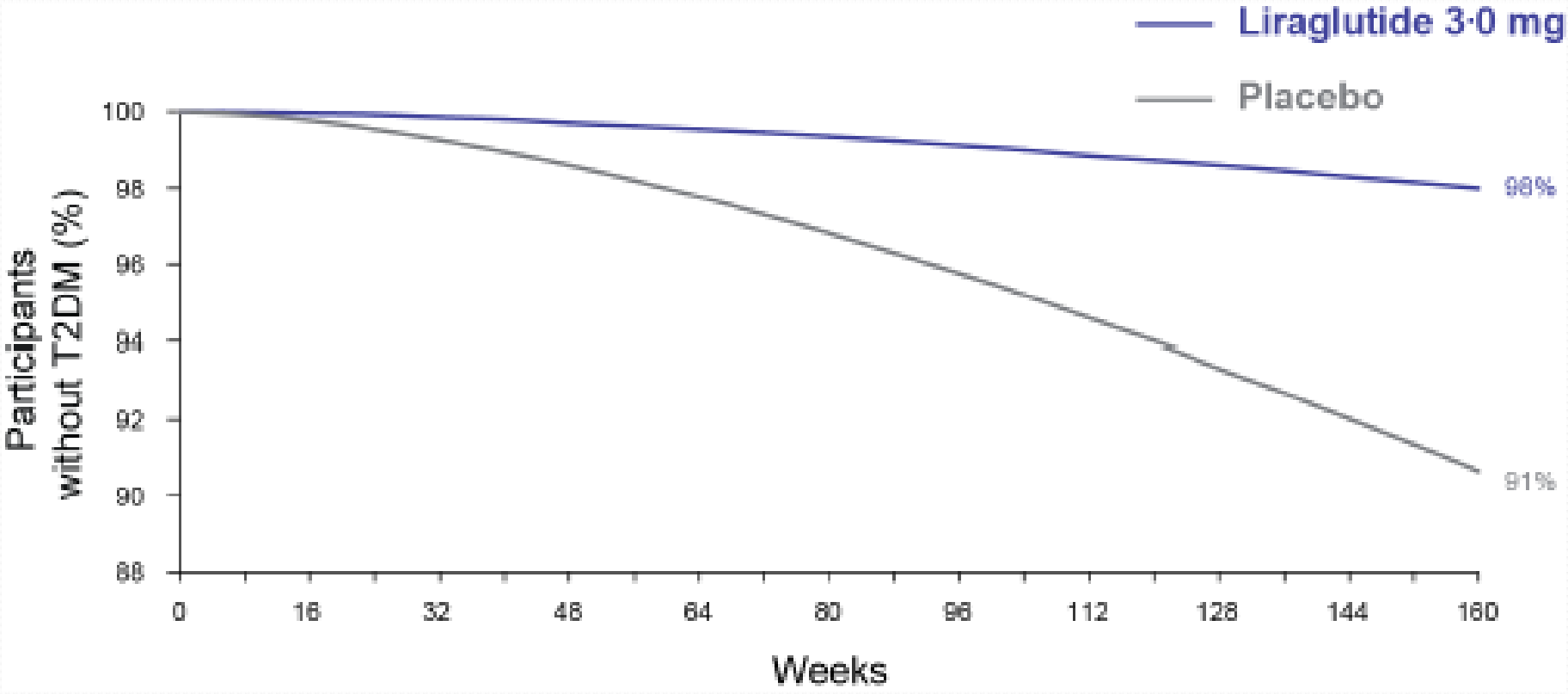
Apovian CM *et al. Obesity (Silver Spring)* 2013;21:935–43; Hollander P *et al. Diabetes Care* 2013;36:4022–9

Effect of lorcaserin on prevention and remission of type 2 diabetes in overweight and obese patients (CAMELLIA-TIMI 61): a randomised, placebo-controlled trial



Lancet October 2018, https://doi.org/10.1016/S0140-6736(18)32328-6

Liraglutide: SCALE 3 Year



Lancet, Lr Rous et al, February 2017

Remission Combo Therapies That Work!

VLCD and Behavioral Care

Prediabetes

	Baseline	Final	Mean % Change
Hemoglobin A1c	7.9%	6.1%	22.8%
Body Weight	256.4 lbs	196.7 lbs	23.3%
Waist Circumference	119 cm	97 cm	18.5%
Triglycerides (mg/dl)	169.5	114.8	32%
LDL-C (mg/dl)	97.1	95	2.2%
HDL-C (mg/dl)	55.7	46.6	16.3%
SBP	133.9	119	11.1%
DBP	73.5	68.6	6.7%

Diabetes

	Baseline	Final	Mean % Change
Hemoglobin A1c	5.9%	5.5%	6.8%
Body Weight	235.7 lbs	178.9 lbs	24.1%
Waist Circumference	112.2 cm	90.8 cm	19%
Triglycerides (mg/dl)	138.2	96.8	30%
LDL-C (mg/dl)	110.9	101.6	8.4%
HDL-C (mg/dl)	54	54.3	0.6%
SBP	128.1	116.6	9%
DBP	74.9	69.1	7.7%

Soure: The Hernried Center, In Publication 2018

Virta/UI: Nutritional Ketosis and Behavioral Care

60% OF PATIENTS REVERSED THEIR TYPE 2 DIABETES

94% OF PATIENTS REDUCED OR ELIMINATED INSULIN

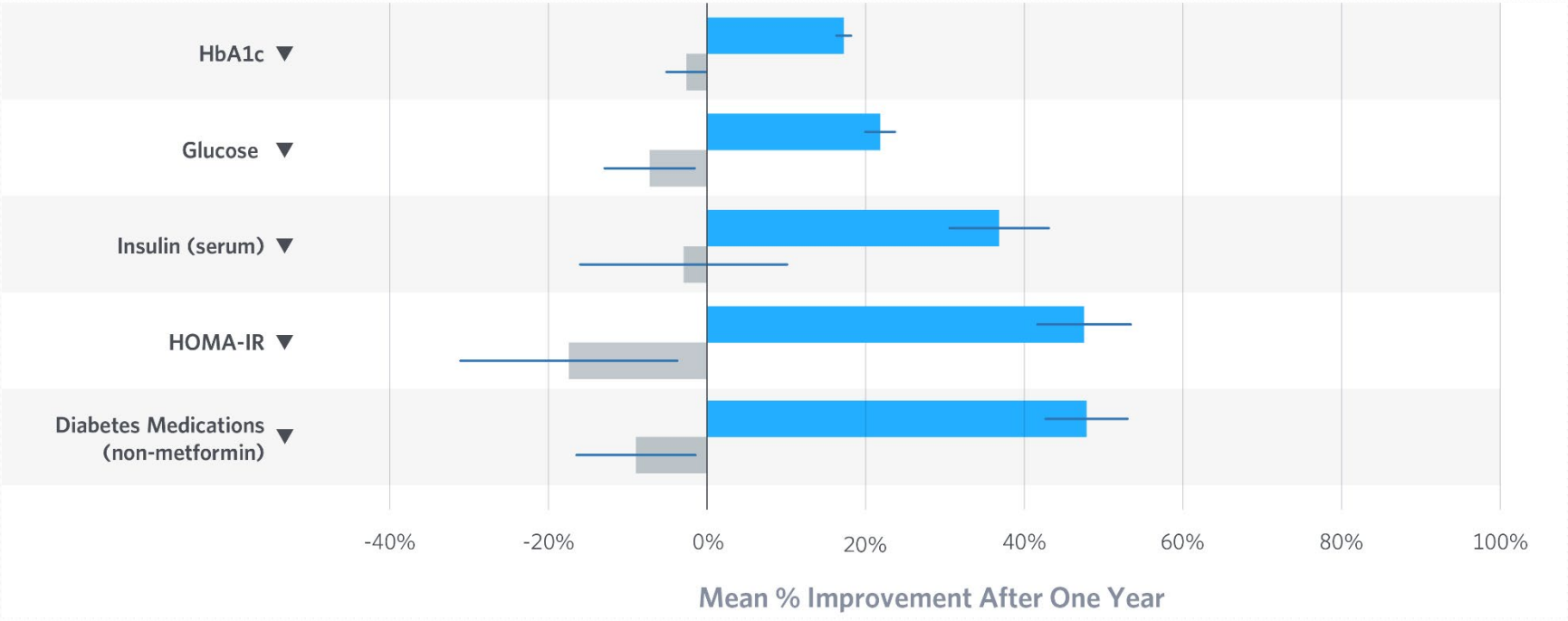
1.3% AVERAGE HBA1C REDUCTION AT ONE YEAR

30 lbs AVG WEIGHT LOSS AT ONE YEAR (12%)

83% CLINICAL TRIAL RETENTION AT ONE YEAR

Hallberg SJet al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at One Year:. Diabetes Therapy. 2018;

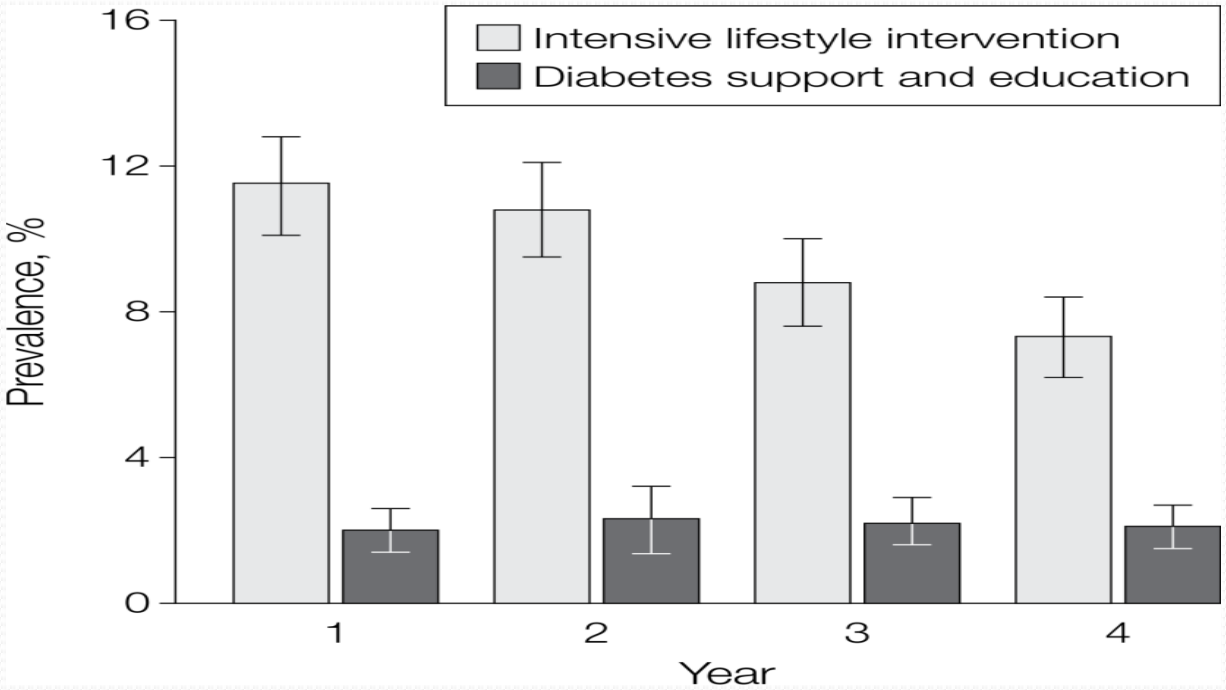
Virta: Ketogenic Diet (long-term) and Behavioral Care



Hallberg SJet al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at One Year:. Diabetes Therapy. 2018;

ILI and Meal Replacements

- Behavioral weight loss intervention
- From The Look AHEAD (Action for Health for Diabetes) study



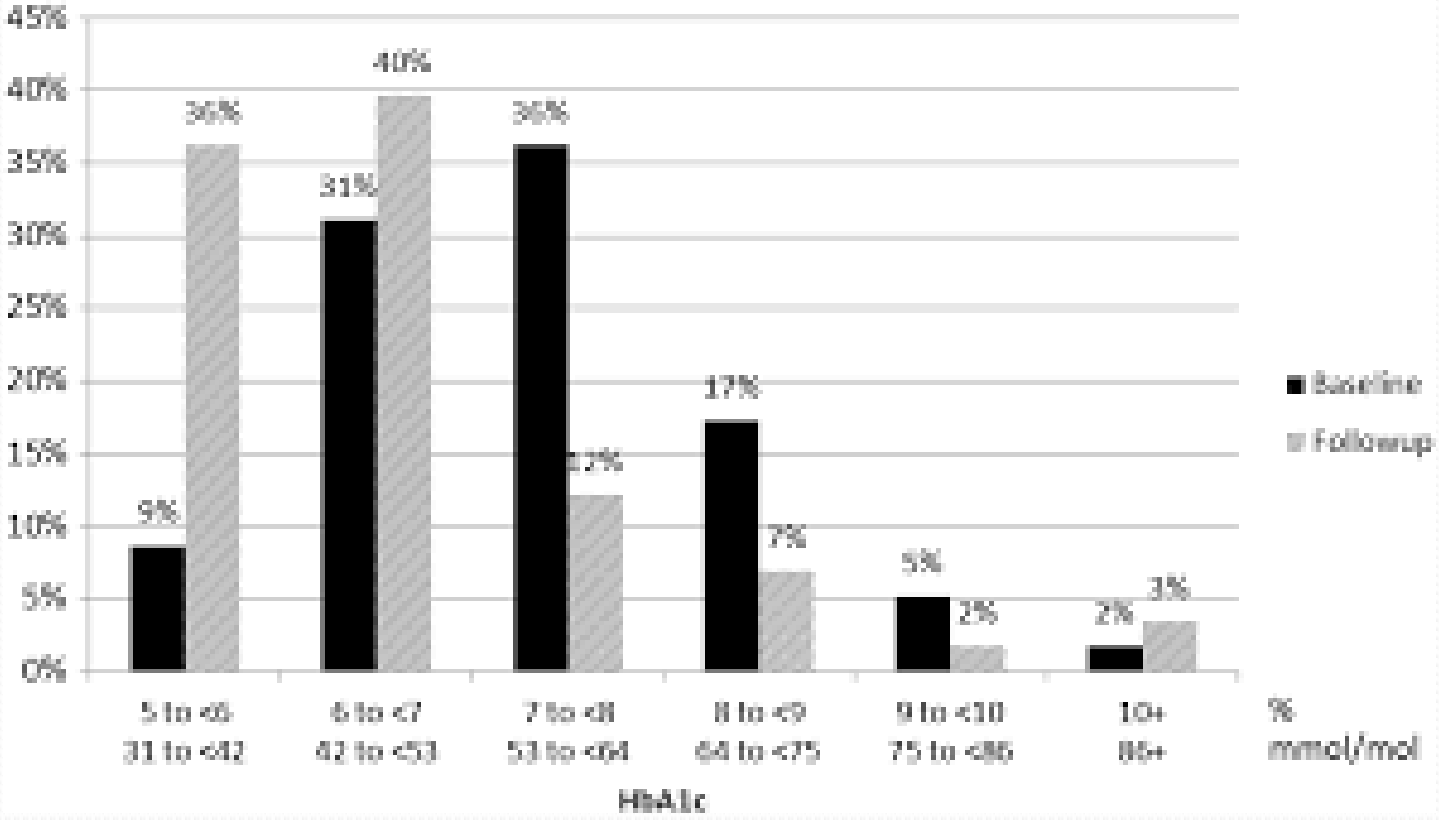
The ILI group was significantly more likely to experience any remission (partial or complete), with prevalences of 11.5% (95% CI, 10.1%-12.8%) during the first year and 7.3% (95% CI, 6.2%-8.4%) at year 4, compared with 2.0% for the DSE group at both time points. *JAMA.* 2012;308(23):2489-2496

Results of the DIRECT trial

- RCT of intensive medical weight loss with total diet replacement (825-853 kcal/d) in primary care offices in England
- Comparison intervention- guideline driven practice
- N= 149 per group
  - 23 intervention practices
  - 29 control practices
- Endpoint- HbA1c < 6.5% after 2 months off diabetes meds = remission
- 46% of intervention group achieved remission
  - 86% of those who lose 15 kg achieved remission
- Average weight loss at 1 year= 10 ± 8 kg in active intervention vs 1 ± 3.7 kg in control

Lancet. 2017 Dec 4. pii: S0140-6736(17)33102-1

VLCD and Diabetes Remission



Lancet. 2017 Dec 4. pii: S0140-6736(17)33102-1

Summary

- Current Standard of Care Disease Management is hampering focus on disease remission
- Remission has surgical and medical options
- Nutrional Therapies for Diabetes Remision are evidence-based and achievable.
- Anti-Obesity Medications all show benefit in Metabolic Disease
- Combination of Therapies/Tools: diet, ILI,MR's pharmacotherapy have shown benefit in diabetes remission and should be utilized aggressively.

Thanks For Listening?

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