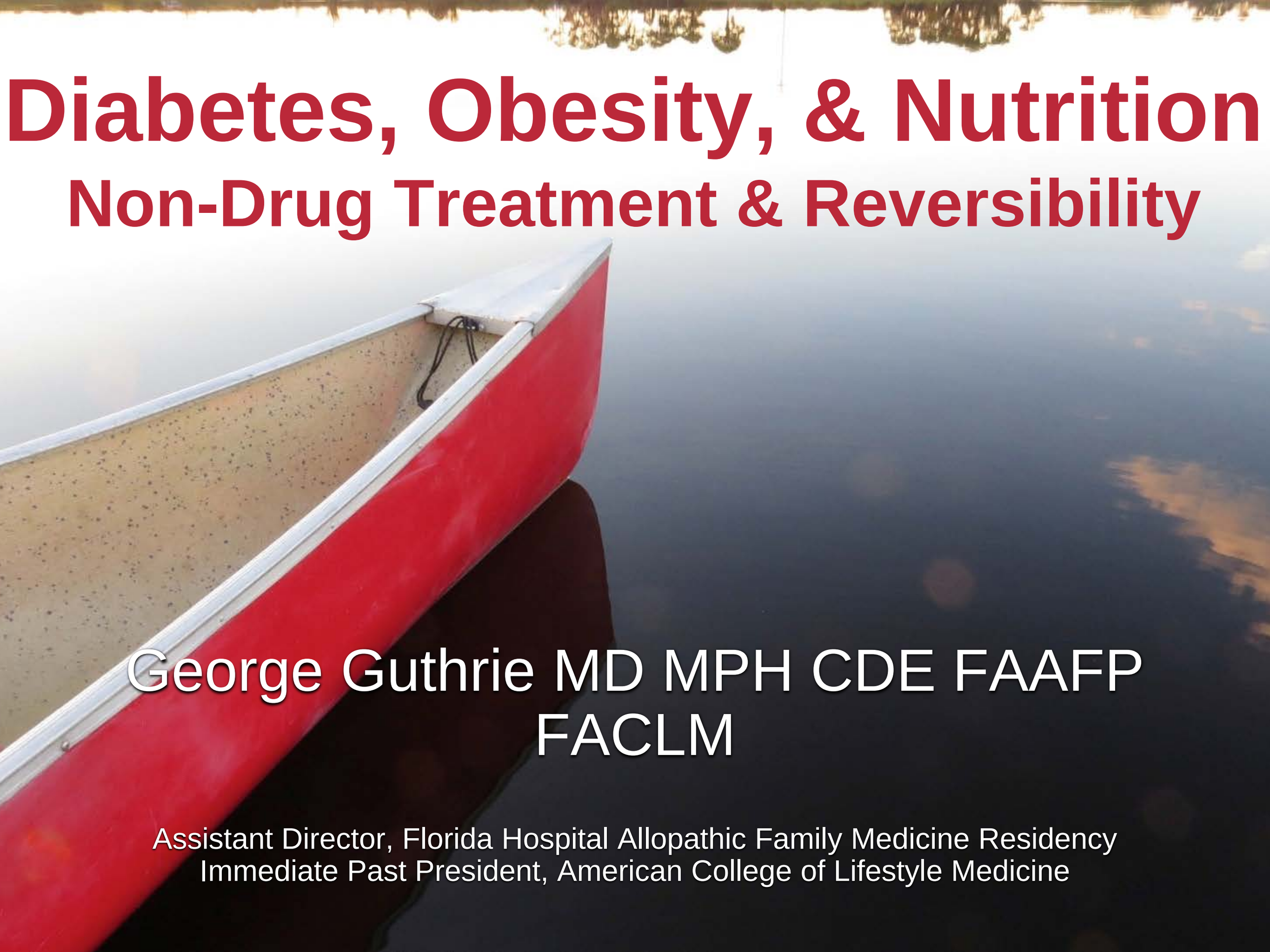
Diabetes, Obesity, & Nutrition

Non-Drug Treatment & Reversibility



George Guthrie MD MPH CDE FAAFP FACLM

Assistant Director, Florida Hospital Allopathic Family Medicine Residency
Immediate Past President, American College of Lifestyle Medicine

Stimulation of
Glucose Transport

GLUT-4

Exercise

Insulin

Cell Membrane

Chromium

Insulin Receptor

ATP

tyrosine phosphorylation

5'-AMP-activated
kinase

?

?

Protein
Kinase B

Phosphoinositide
Dependent
Kinase

P110 P85

IRS

Phosphoinositide-3
kinase

SH2 Domains

?

Atypical
Protein
Kinase C

Inulin
Responsive
Glute-4 containing
vesicle

Inulin
Responsive
Glute-4 containing
vesicle

Cytoplasm

Olefsky JM, Ciaraldi TP, Kolterman OG. Mechanisms of insulin resistance in non-insulin-dependent (type II) diabetes. Am J Med. 1985 Sep 20;79(3B):12-22.

Reversibility? - 1988

Metabolic Syndrome - Deadly Quartet

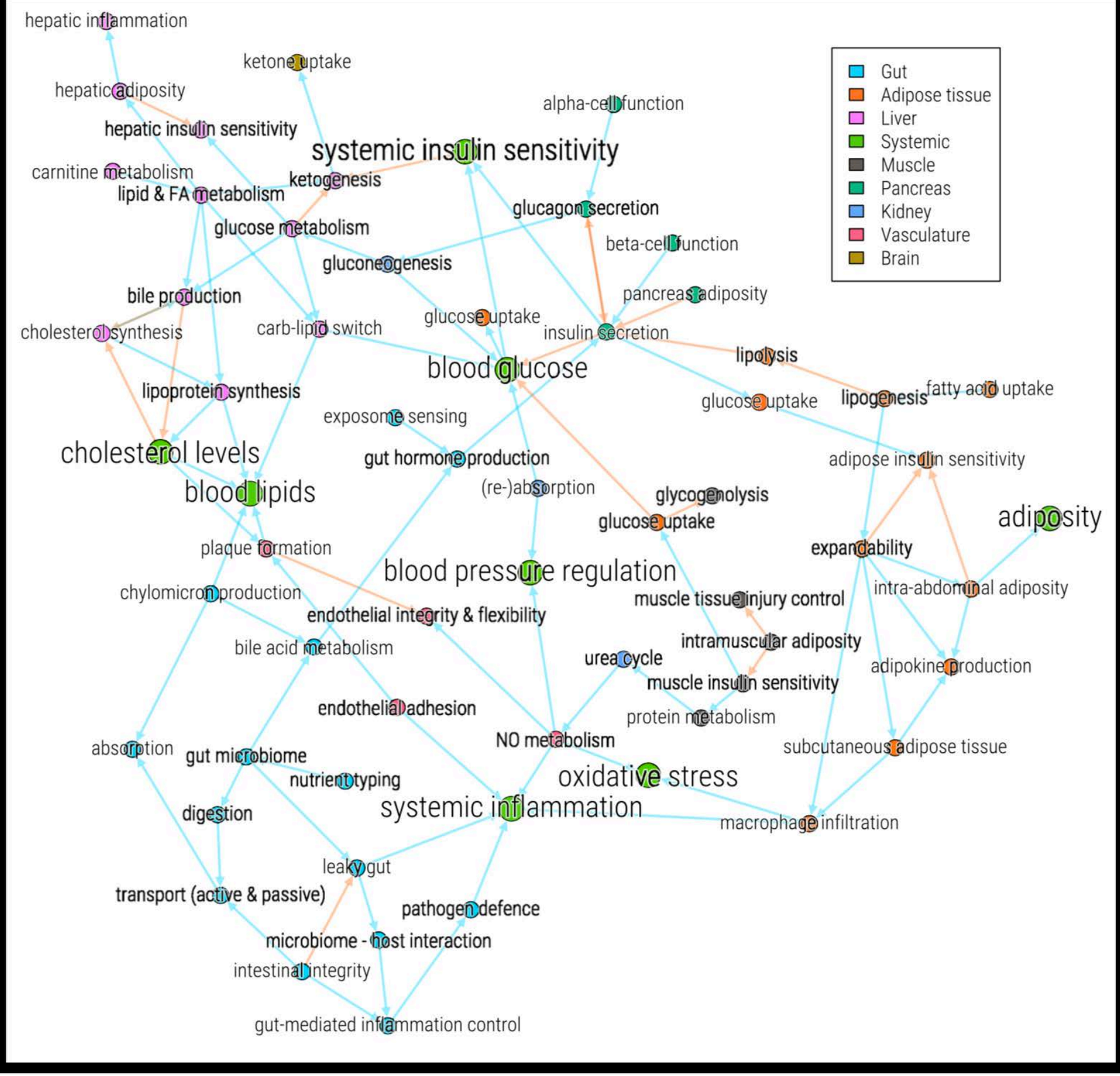
- Obesity
- Hypertension
- Coronary Artery disease - Atherosclerotic Vascular Disease
- Diabetes

Reaven GM. Banting lecture 1988. Role of insulin resistance in human disease. *Diabetes* 1988;37:1595-607. PMID 3056758

Ominous Octet - 2008

- Decreased Muscle Glucose uptake
- Increased Hepatic Glucose production
- Decreased Insulin Secretion
- Increased Lipolysis
- Decreased Incretins
- Increased Kidney Glucose reabsorption
- Increased Glucagon Secretion
- Neurotransmitter Dysfunction

DeFronzo R. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes 2009 Apr; 58(4): 773-795. http://dx.doi.org/10.2337/db09-9028



van Ommen B1, et al. From Diabetes Care to Diabetes Cure-The Integration of Systems Biology, eHealth, and Behavioral Change. Front Endocrinol (Lausanne). 2018 Jan 22;8:381. doi: 10.3389/fendo.2017.00381. eCollection 2017.

Data-driven Cluster Analysis - (k-means and hierarchical clustering)

according to differing disease progression and risk of diabetic complications.

Finland, DIREVA=Diabetes Registry Vaasa

Sweden - ANDIS=All New Diabetics in Scania.

1. SAID=severe autoimmune diabetes.
2. SIDD=severe insulin-deficient diabetes.
3. SIRD=severe insulin-resistant diabetes. - Kidney prone
4. MOD=mild obesity-related diabetes. - Retinopathy
5. MARD=mild age-related diabetes.

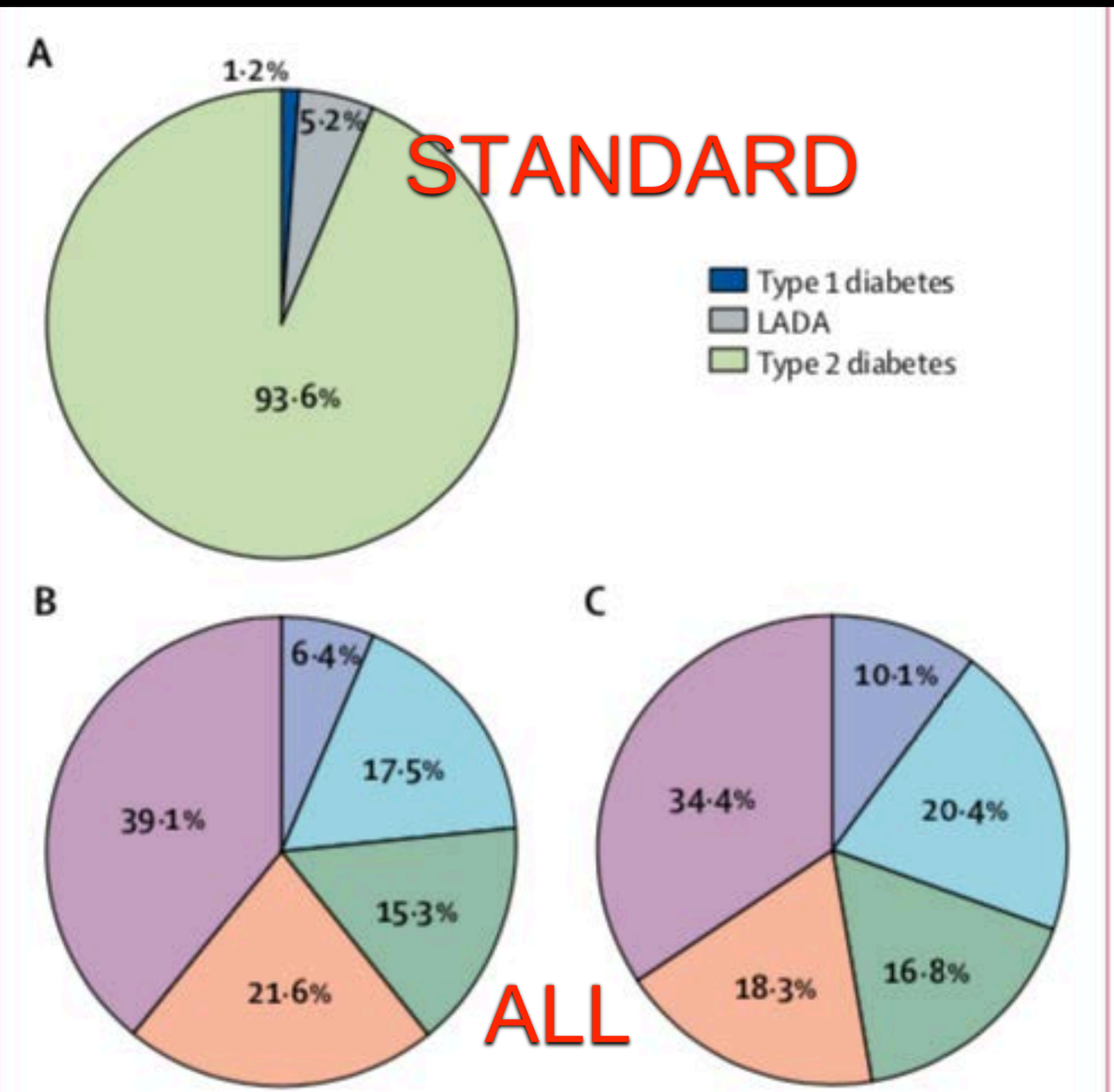
Clusters were based on six variables:

1 glutamate decarboxylase antibodies (GAD-65) 2. age at diagnosis, 3. BMI, 4. HbA1c, 5. HOMA-2 β, 6. HOMA-2 IR

Ahlqvist E, et al, Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018 Mar 1. pii: S2213-8587(18)30051-2. doi: 10.1016/S2213-8587(18)30051-2. [Epub ahead of print]

Figure 1: **Patient distribution according to method of classification**

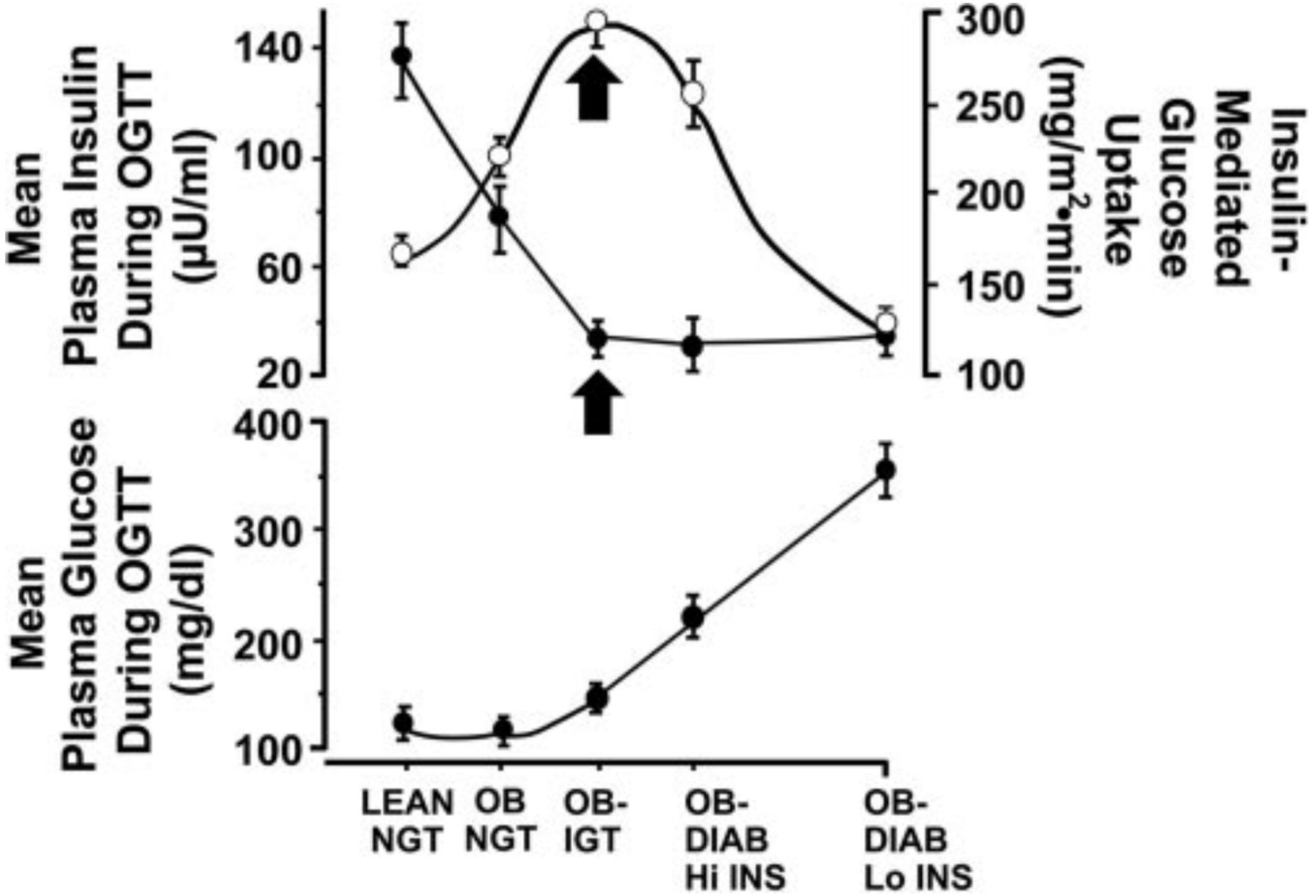
Ahlqvist E, et al, Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018 Mar 1.



3. SIRD

4. MOD

Natural Hx of NIDDM



DeFronzo R. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes 2009 Apr; 58(4): 773-795. http://dx.doi.org/10.2337/db09-9028

3. SIRD

4. MOD

Pancreatic Cell Failure

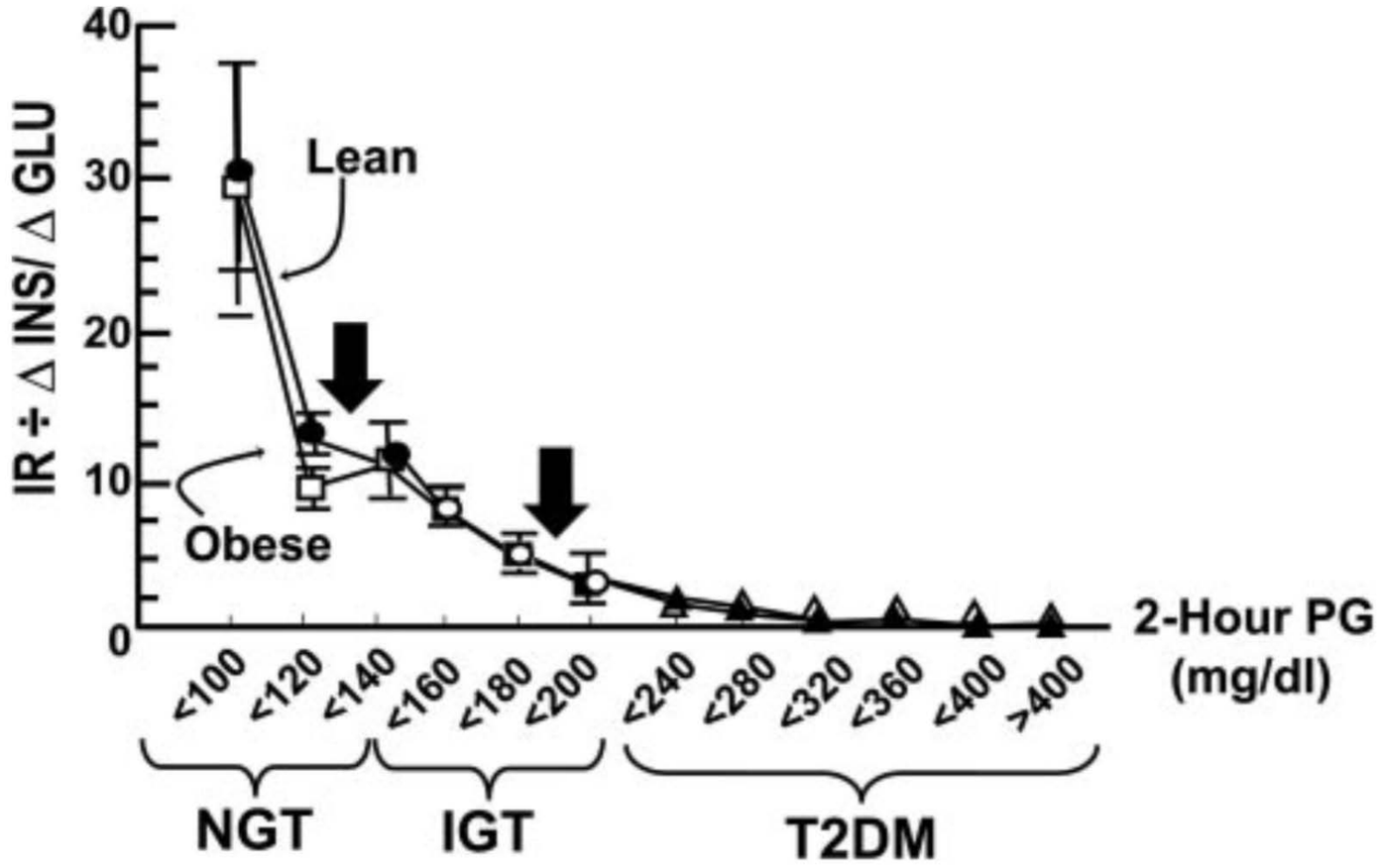


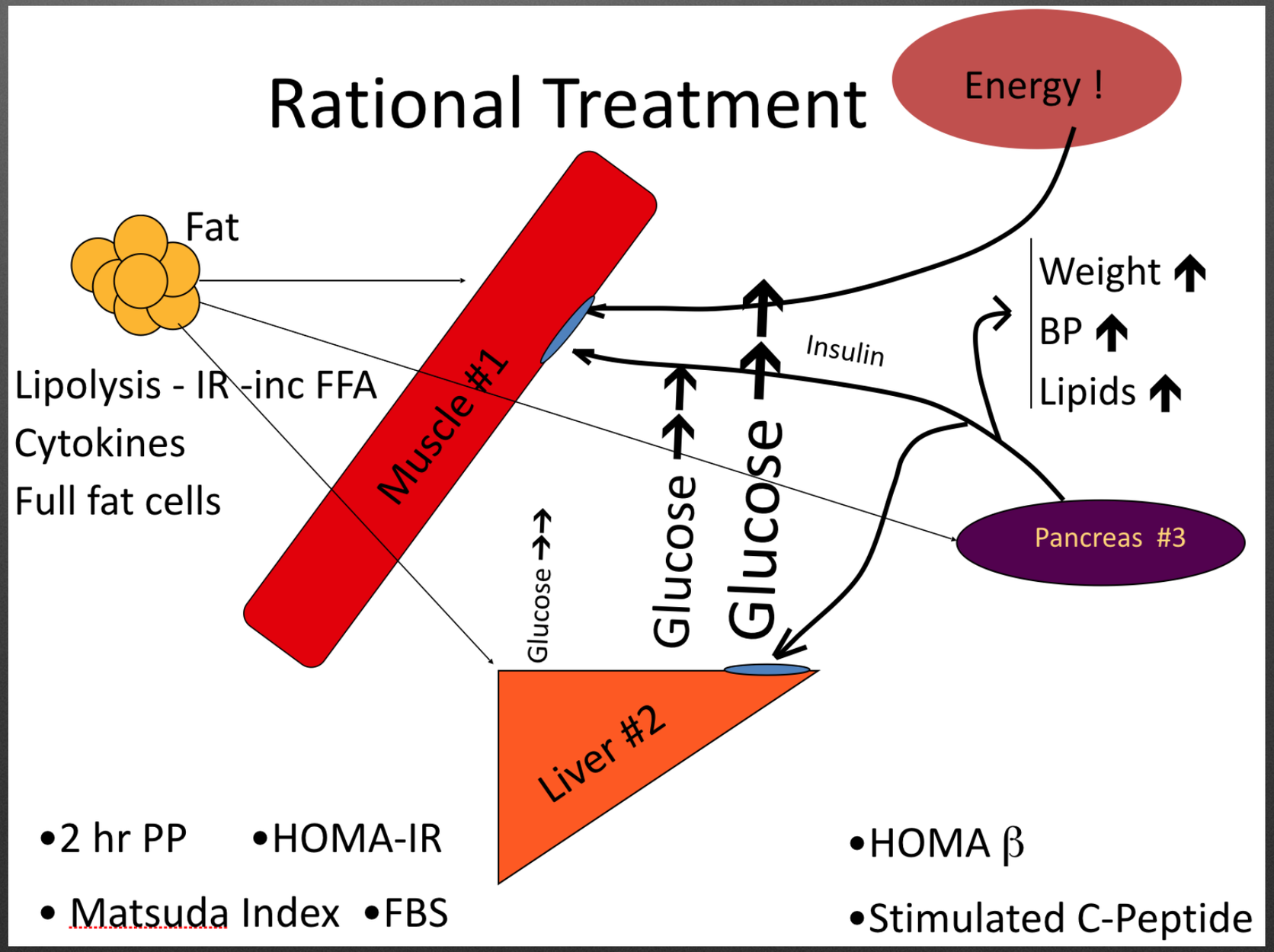
FIG. 3. Insulin secretion/insulin resistance (disposition) index (ΔI/ΔG ÷ IR) in individuals with NGT, IGT, and type 2 diabetes (T2DM) as a function of the 2-h plasma glucose (PG) concentration in lean and obese subjects (39–42).

DeFronzo R. From the Triumvirate to the Ominous Octet: A New Paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes 2009 Apr; 58(4): 773-795. http://dx.doi.org/10.2337/db09-9028

The Patient in Front of You.

Insulin Resistance

- Muscle
- Fat
- Liver
- Pancreas



Reversibility - 2012

- Counterpoint Study - Counteracting Pancreatic Inhibition by Triglycerides

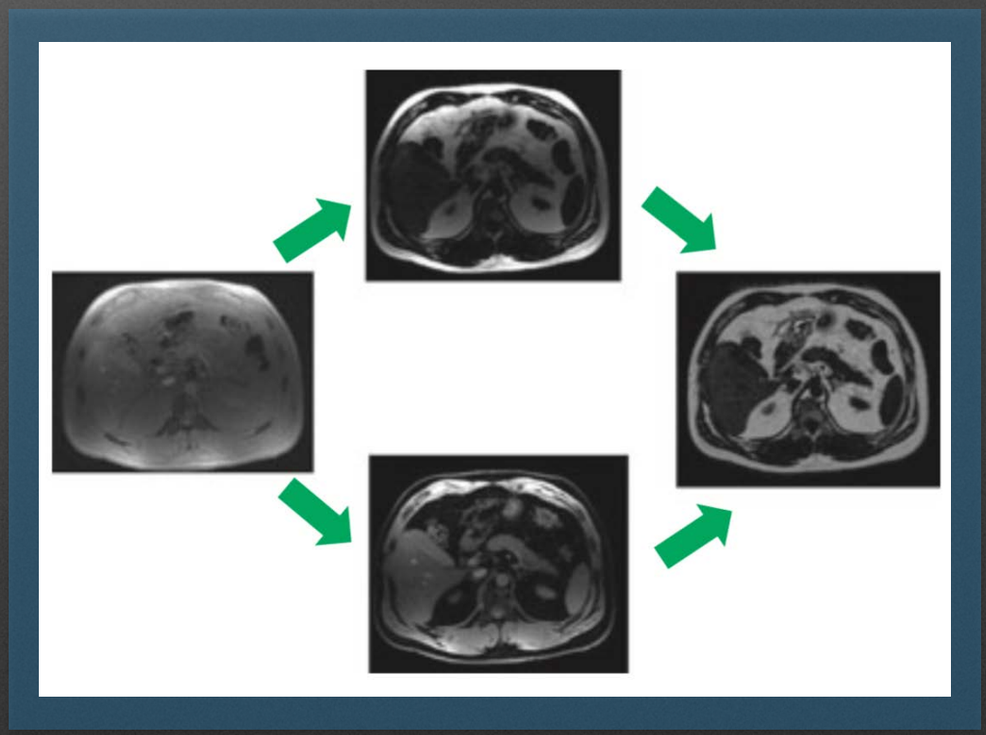
- Excess Calories leads to fat accumulation in the liver, increased ALT, VLDL, & insulin resistance

- Fat in the pancreas - decreased ins production & increased apoptosis.

Taylor R. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabetes

Counterpoint Study

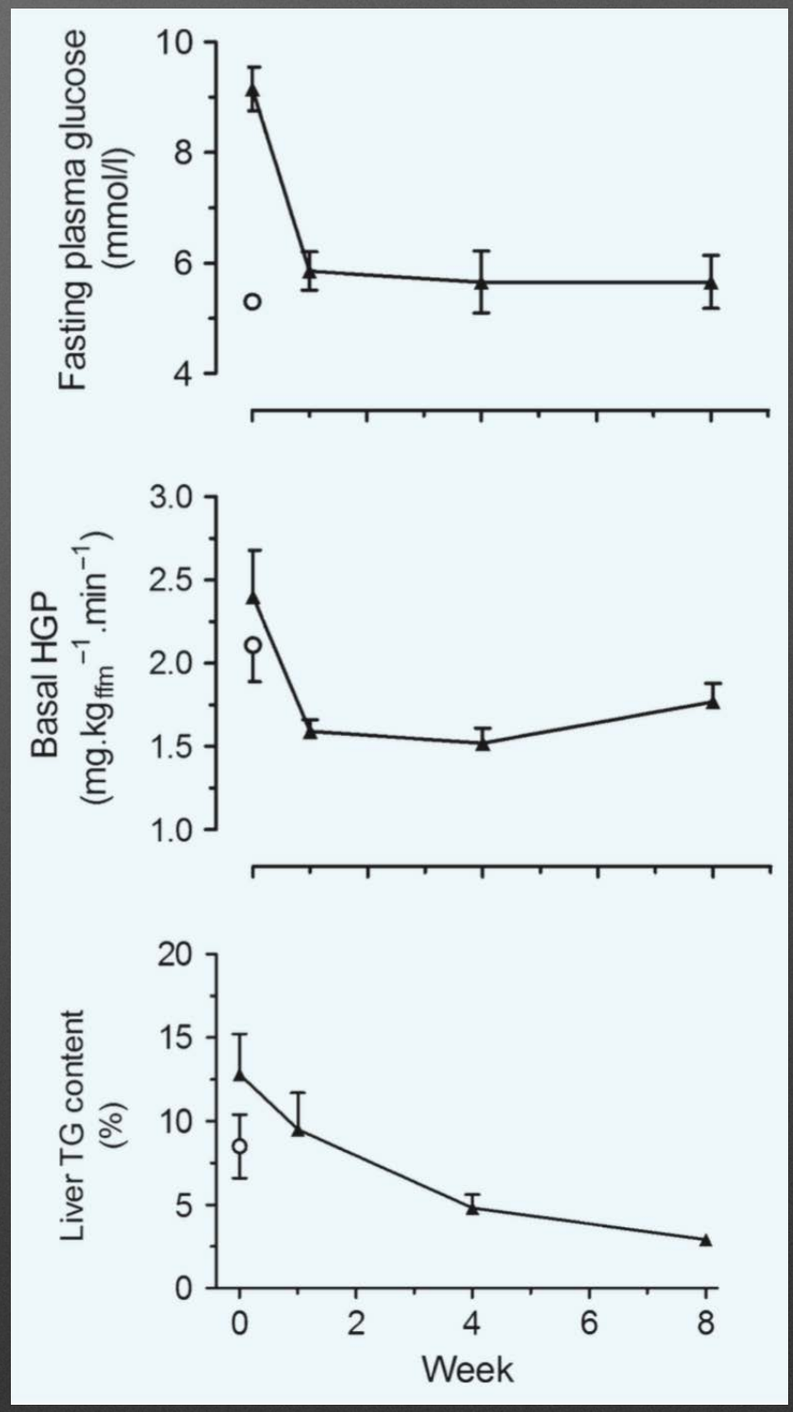
- Type 2 diabetes and normal controls
- 25% of Usual Calories — 600 kcal optifast meal replacement and non-starchy vegetables
- MRI to measure organ fat % - 10 sec breath hold. Hydrogen ions in fat and water.



Taylor R1. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabete

Results

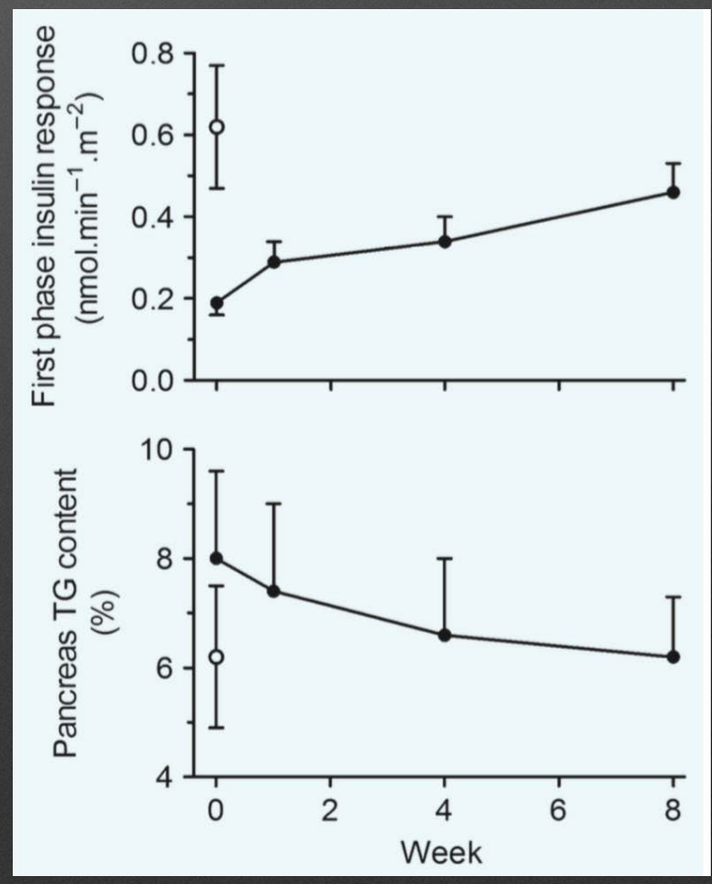
- Base line - insulin suppression of liver glucose release
  - Normal - 70%
  - Type 2 Diabetes - 43%
  - Normalized in 7 days
- liver fat fell by 30%
- No change in Muscle Insulin Sensitivity - Long Term Promotor
- Stepped Insulin Secretion Test



Taylor R1. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabete

Results

- Stepped Insulin Secretion Test (SIST)
  - Glucose increased by 2.8mM (50gm/dl)
  - Repeat another 2.8 mM plus IV Arginine
- Results
  - Baseline -
    - first phase insulin absent -
    - Peak insulin 60%
  - 8 weeks - First Phase insulin = control
    - Fat in pancreas decreased

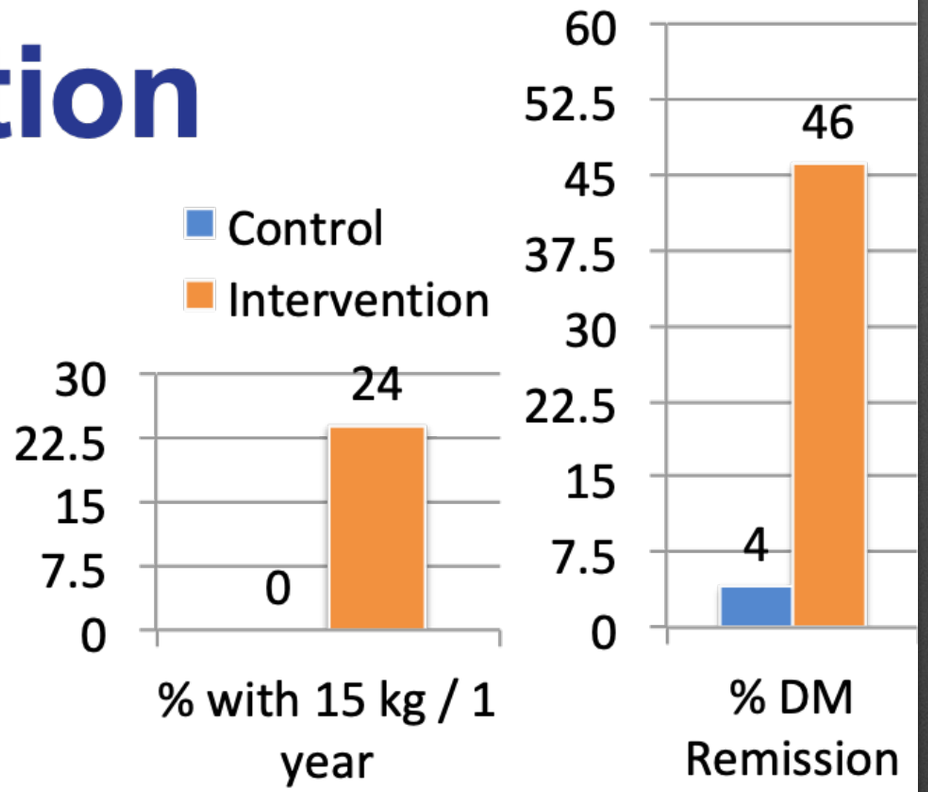


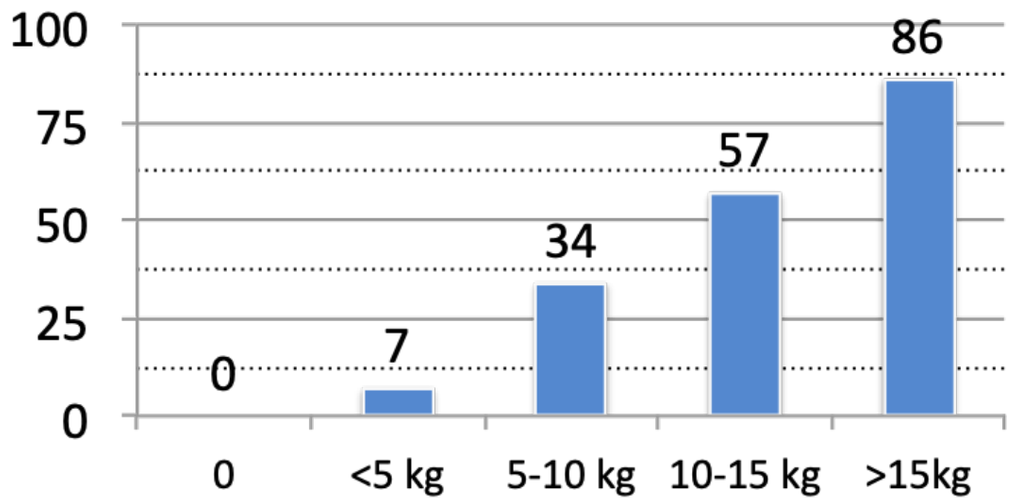
Taylor R1. Banting Memorial lecture 2012: reversing the twin cycles of type 2 diabete

The DiRECT Trial

Chronic Caloric Restriction

- DiRECT Trial - 1 year
- 49 general practices - 306 individuals
- RCT - intervention vs best practice
- Dx T2DM ≤ 6years; age 20-65 yrs; BMI 27-45
- 825-853 kcal/day formula for 3-5 months with stepped food introduction 2-8 weeks
- Withdrawal of DM & HTN Medications





Lean MEJ, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial *Lancet* 2018; 391: 541–51

frontiers in Endocrinology

REVIEW
published: 22 January 2018
doi: 10.3389/fendo.2017.00381

Individualization

From Diabetes Care to Diabetes Cure—The Integration of Systems Biology, eHealth, and Behavioral Change

Ben van Ommen[1], Suzan Wopereis[1], Pepijn van Empelen[2], Hilde M. van Keulen[2], Wilma Otten[2], Marise Kasteleyn[3], Johanna J. W. Molema[4], Iris M. de Hoogh[1], Niels H. Chavannes[3], Mattijs E. Numans[3], Andrea W. M. Evers[5,6] and Hanno Pijl[7]*

[1] Netherlands Organization for Applied Scientific Research (TNO), Department of Microbiology and Systems Biology, Leiden, Netherlands, [2] Netherlands Organization for Applied Scientific Research (TNO), Department of Child Health, Leiden, Netherlands, [3] Leiden University Medical Center (LUMC), Department of Public Health and Primary Care, Leiden, Netherlands, [4] Netherlands Organization for Applied Scientific Research (TNO), Department of Work Health Technology, Leiden, Netherlands, [5] Department of Health, Medical and Neuropsychology, Leiden University Medical Centre, Leiden University, Leiden, Netherlands, [6] Department of Psychiatry, Leiden University Medical Centre, Leiden University, Leiden, Netherlands, [7] Leiden University Medical Center (LUMC), Department of Internal Medicine, Leiden, Netherlands

van Ommen B1, et al. From Diabetes Care to Diabetes Cure-The Integration of Systems Biology, eHealth, and Behavioral Change. Front Endocrinol (Lausanne). 2018 Jan 22;8:381. doi: 10.3389/fendo.2017.00381. eCollection 2017.

TABLE 1 | Type 2 diabetes subgroup (process) dependent diagnosis–intervention strategies.

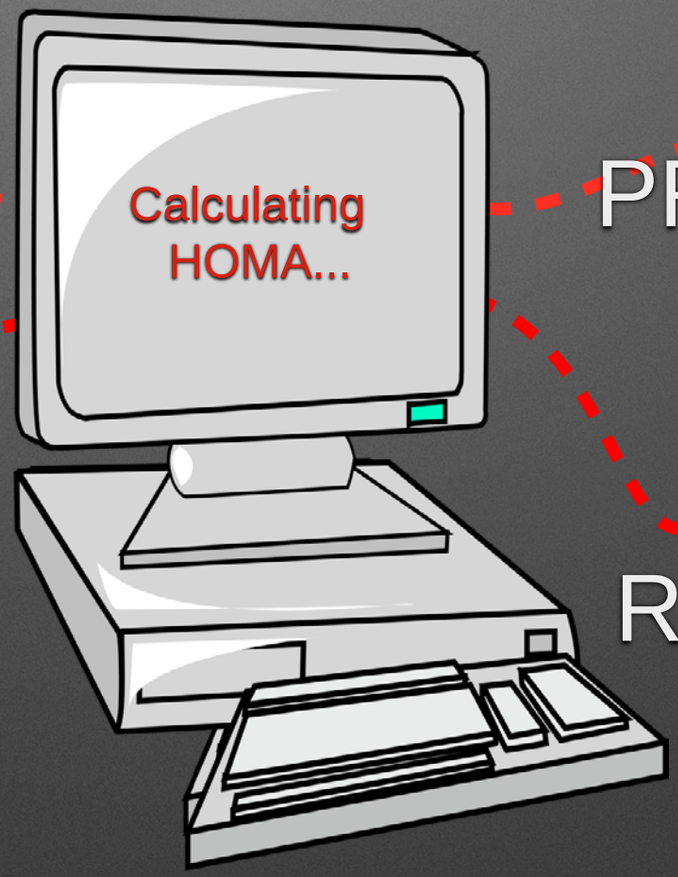
T2D subgroups (see Figure 2, based on processes involved)	Diagnosis (i.e., parameters of the biopassport)	Potential interventions
1. Pancreatic β-cell function (impaired insulin secretion)	Oral glucose tolerance test (OGTT) or challenge test: disposition index	Fasting-mimicking diet (FMD); β-cell protective nutrients (MUFA, protein, vit. K, Mg, leucine); β-cell protective drugs (TZDs, GLP-1 analogs, DPP4-inhibition)
2. Muscle insulin resistance (decreased glucose uptake)	OGTT or challenge test: muscle IR index, HbA1C, 2-h glucose	Physical activity (resistance training); Mediterranean diet; low-glycemic index diet; low-carb diet; low refined sugar; fiber (arabinoxylan, alpha-cyclodextrin, resistant starch, beta-glucans)
3. Hepatic insulin resistance (decreased glucose uptake, but increased production and release)	OGTT or challenge test: hepatic IR index, fasting glucose	Low (saturated) fat diet; weight loss; very low-caloric diet; intermittent fasting; wholegrain; choline; carnitine; resveratrol; cinnamon extract; metformin
4. Adipocyte insulin resistance and lipotoxicity	Basal adipocyte insulin resistance index, non-esterified fatty acids, visceral and ectopic fat percentage	Intermittent fasting; FMD; α-lipoic acid; poly-unsaturated fatty acid/SFA balance; omega-3 FAs; TZDs; acipimox
5. Vasculature	Blood pressure, LDL-cholesterol, HDL-cholesterol, fasting, and post-prandial triglycerides	DASH diet; low-sodium diet; wholegrain; fiber (pectin, β-glucan); beet root (extract); lycopene; Vit. C; Vit. K; cocoa flavonols; hydroxytyrosol (olive oil); monacolin K; coenzyme Q10; grape seed extract; chitosan/phytosterols; *L. reuteri* NCIMB 30242; statins; blood pressure lowering medication
6. Chronic low-grade inflammation	CRP, total leukocytes, cytokines	Physical activity; fish oil/n-3 fatty acids; Vit. D; Vit E.; Mg; flavonoids; curcuminoids; salicylates; TNF-α inhibitors

Currently, six processes involved in T2D are identified, and for each of them a biomarker approach to quantify the process, and an intervention strategy to optimize/restore, is suggested.

van Ommen B1, et al. From Diabetes Care to Diabetes Cure-The Integration of Systems Biology, eHealth, and Behavioral Change. Front Endocrinol (Lausanne). 2018 Jan 22;8:381. doi: 10.3389/fendo.2017.00381. eCollection 2017.

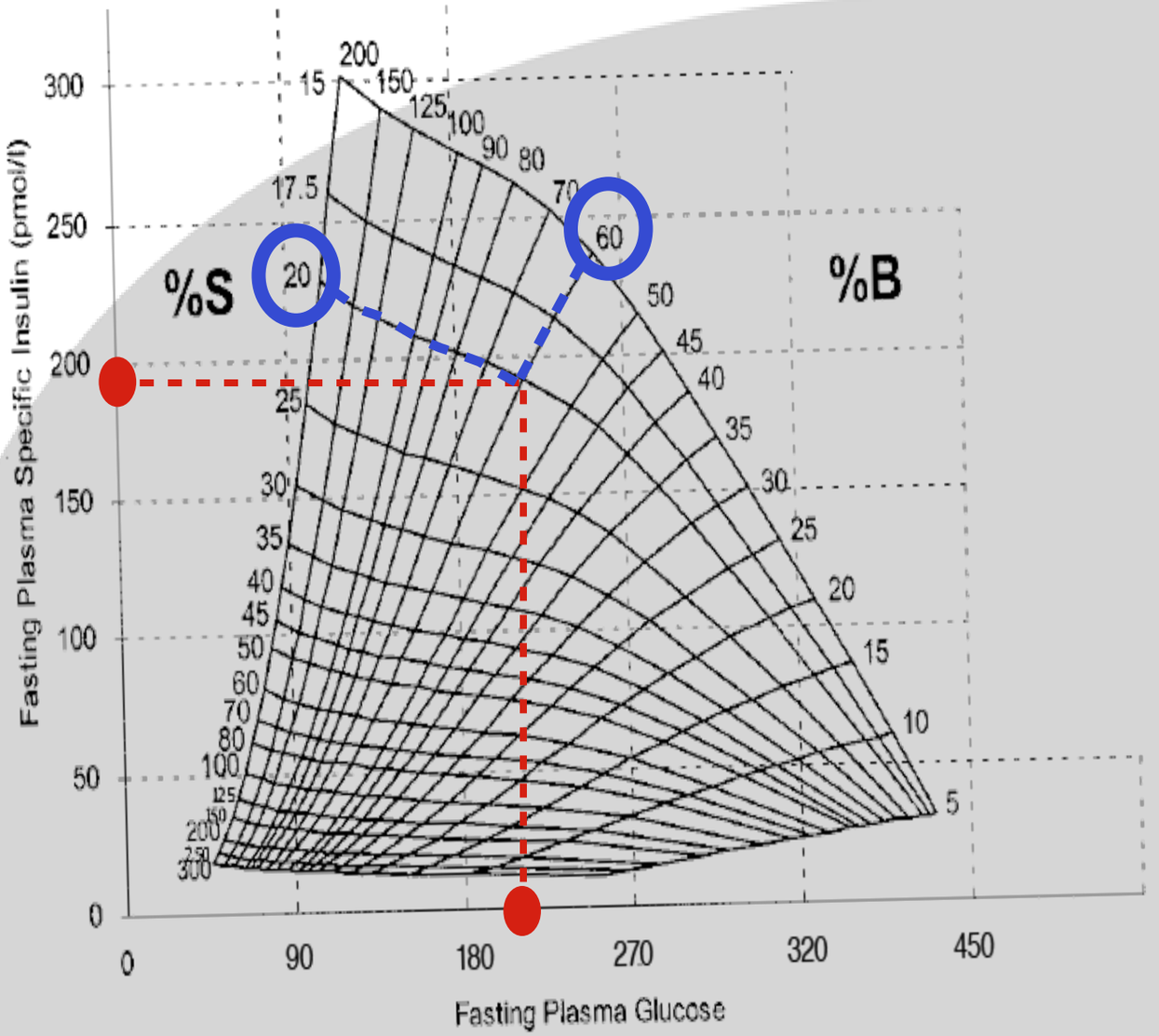
Fasting insulin or c-peptide

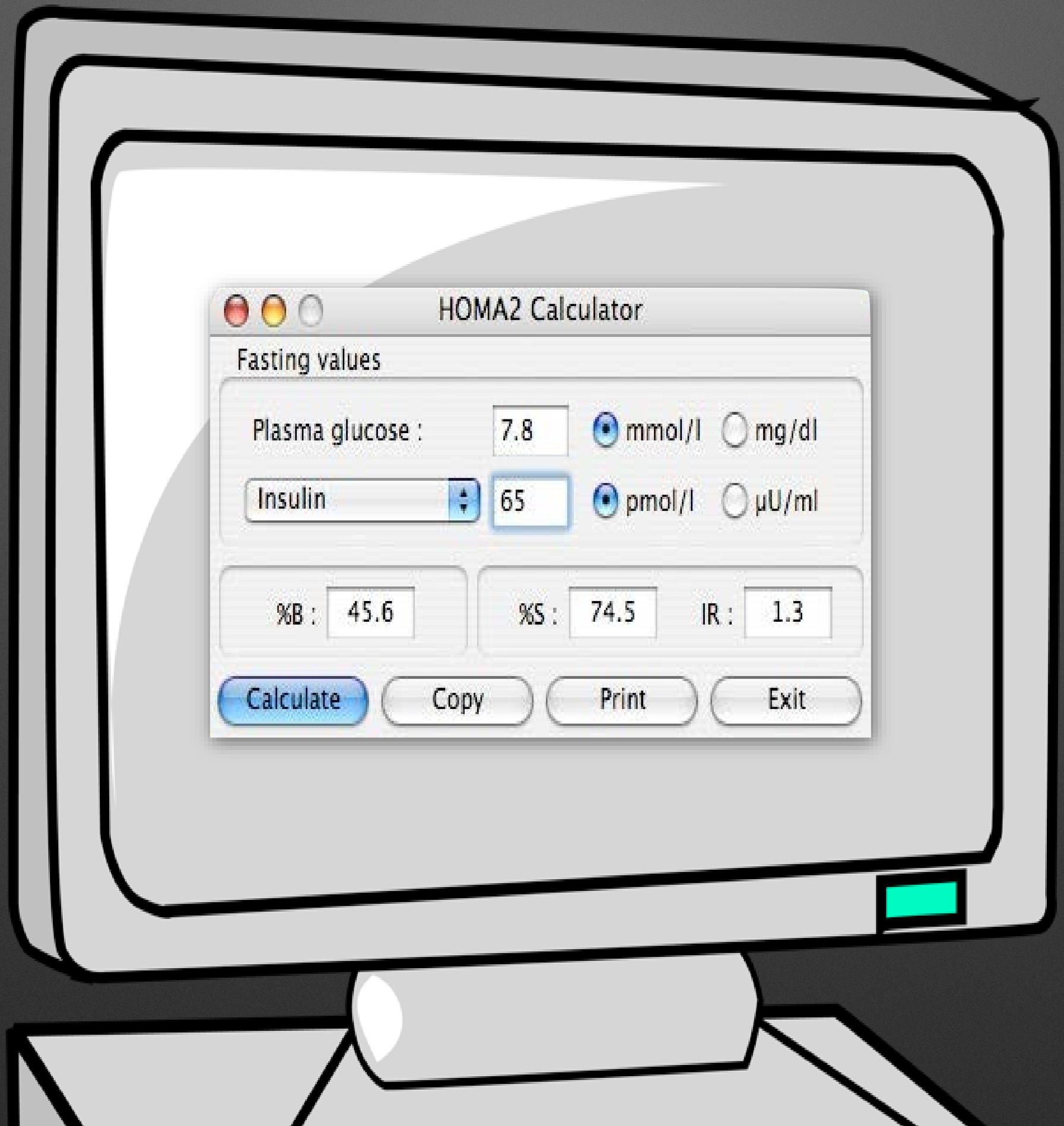
Fasting glucose



Insulin PRODUCTION (%B)

Body RESISTANCE (%S)


%S
%B
Fasting Plasma Specific Insulin (pmol/l)
Fasting Plasma Glucose
0
90
180
270
320
450
300
250
200
150
100
50
0
200
150
125
100
90
80
70
60
50
45
40
35
30
25
20
15
10
5
17.5
20
25
30
35
40
45
50
60
70
80
100
125
150
200
250
300


HOMA2 Calculator
Fasting values
Plasma glucose :
7.8
mmol/l
mg/dl
Insulin
65
pmol/l
µU/ml
%B :
45.6
%S :
74.5
IR :
1.3
Calculate
Copy
Print
Exit

Appropriate and Inappropriate use of HOMA

HOMA-2 - Computer Model

- Inappropriate use - measuring β-cell function is isolation
- "…the HOMA model has become a widely used clinical an epidemiological tool, and when used appropriately, it can yield valuable data."
- correlation:
- r=0.78 (computer model) Sensitivity (Euglycemic clamp)
- r=0.87 (computer model) Resistance (Hyperglycemic clamp)

Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004 Jun;27(6):1487-95. Review.

Appropriate and Inappropriate use of HOMA

HOMA-2 - Computer Model

- “HOMA can be used to track changes in insulin sensitivity and β-cell function longitudinally in individuals. The model can also be used in individuals to indicate whether reduced insulin sensitivity or β-cell failure predominates.”
- When used in individuals, triplicate insulin samples should be used to improve the CV (coefficient of variation).”

Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care. 2004 Jun;27(6):1487-95. Review.

Beyond Diet & Exercise

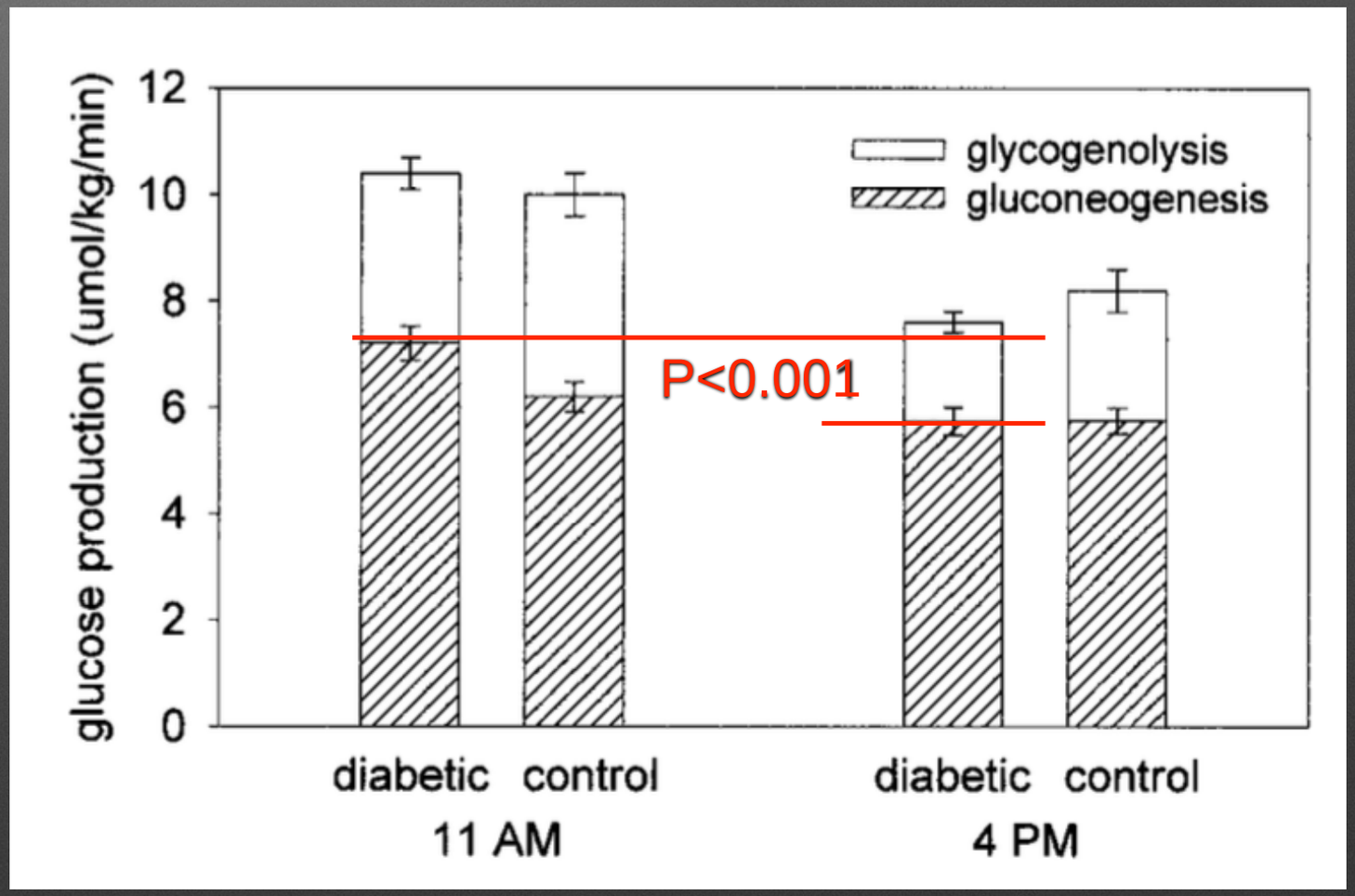
- Behavior Change - Coaching
- Social Support - Supportive Culture
- Fasting & Meal Timing
- Hydration

Learning Activity

- Download the HOMA2 calculator from the Oxford UKPDS website (look for “ox” in the URL)
- You may down load it as a calculator or as a Excel spread sheet
- Open it and use it

Fasting & Gluconeogenesis

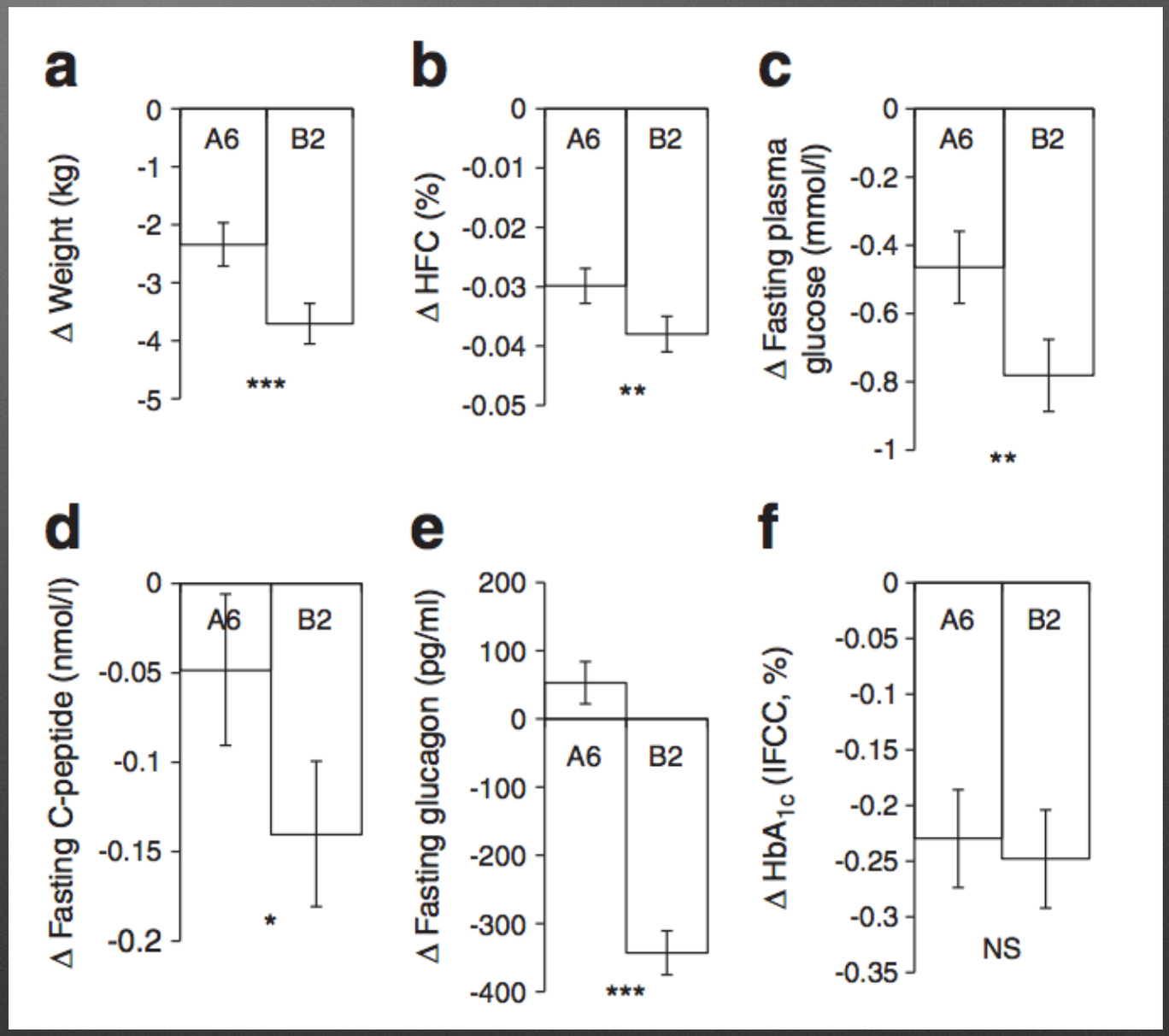
- Deuterated Water to track Gluconeogenesis vs lysis
- Decrease in Gluconeogenesis



Wajngot A, et al. Quantitative Contributions of Gluconeogenesis to Glucose Production During Fasting in Type 2 Diabetes Mellitus. Metabolism, Vol 50, No 1 (January), 2001: pp 47-52

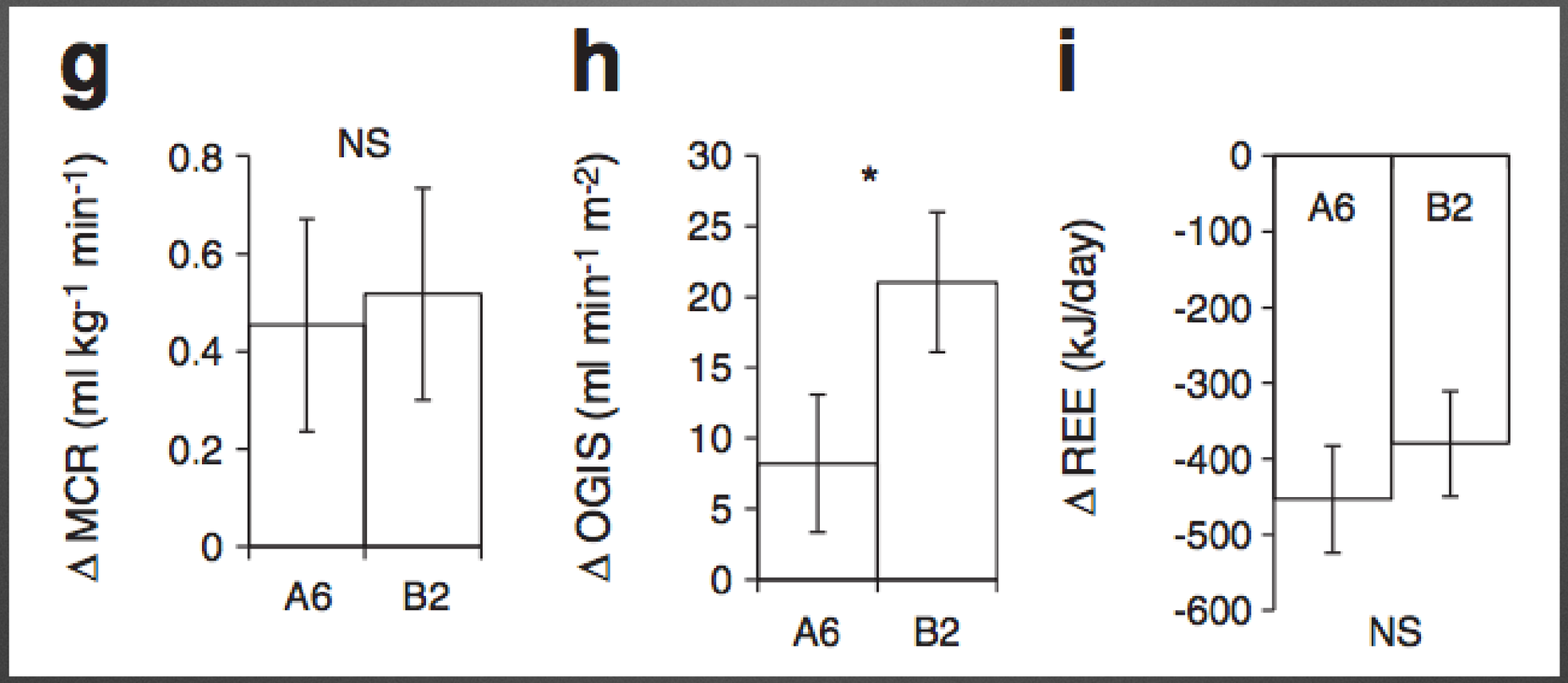
Six vs Two Meals a day

- Weight - p<0.001
- Hepatic Fat Content p<.01
- Fasting Glucose p<.01
- Fasting C Peptide - p<0.05
- Fasting Glucagon - p<0.001
- A1C change NS



Hana Kahleova et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia. DOI 10.1007/s00125-014-3253-5

Six vs Two Meals a Day



- MCR - Metabolic Clearance Rate of Glucose NS
- Oral Glucose Insulin Sensitivity $p<0.05$
- REE - Resting Energy Expenditure - NS

Hana Kahleova et al. Eating two larger meals a day (breakfast and lunch) is more effective than six smaller meals in a reduced-energy regimen for patients with type 2 diabetes: a randomised crossover study. Diabetologia. DOI 10.1007/s00125-014-3253-5

Breakfast: Managing appetite

Methods: In this study 193 obese (BMI 32.2), sedentary non diabetic adult men and women (4 7 ± 7 years) were randomized to a low carbohydrate breakfast (LCb) or an isocaloric diet with high carbohydrate and protein breakfast (HCPb),

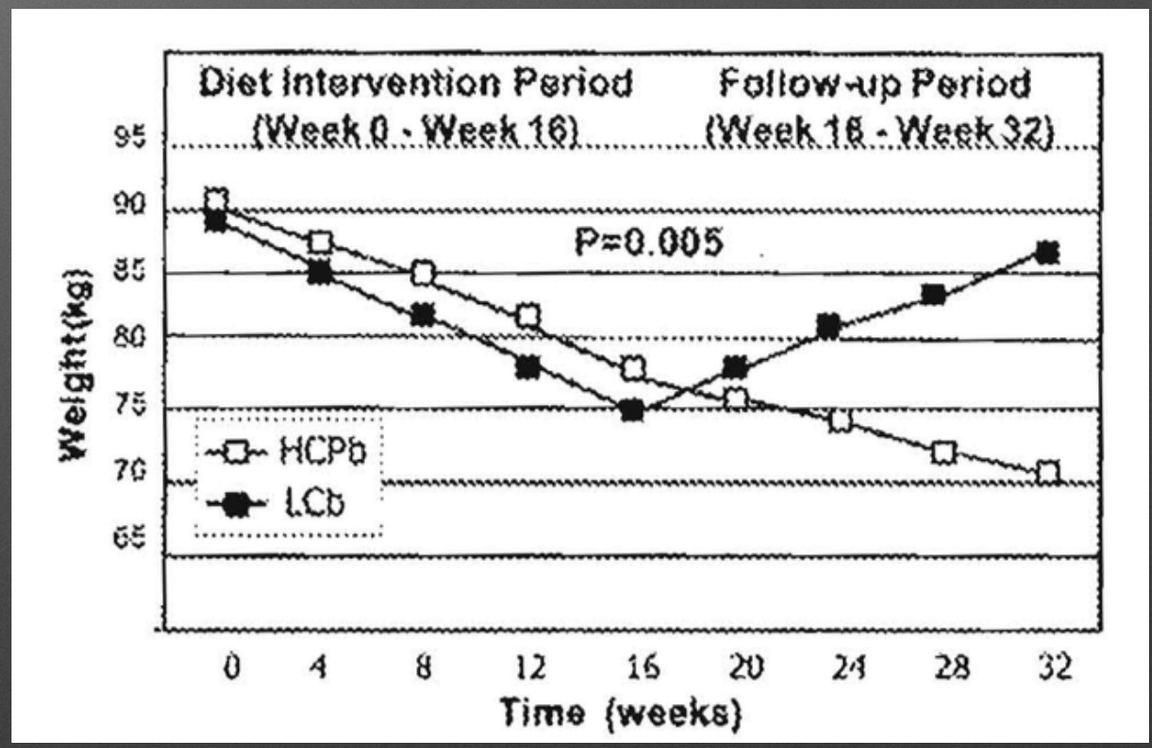
Anthropometric measures were assessed every 4 weeks. Fasting glucose, insulin, ghrelin. lipids, craving scores and breakfast meal challenge assessing hunger, satiety, insulin and ghrelin responses, were performed at baseline, after a Diet Intervention Period (Week 16) and after a Follow-up Period (Week 32).

Jakubowicz D , et al. Meal timing and composition influence ghrelin levels, appetite scores and weight loss maintenance in overweight and obese adults. J.Steroid (2011) doi 10.1016/j.steroids.2011:12.006

Breakfast: Managing appetite

Results: A high carbohydrate and protein breakfast may prevent weight regain by reducing diet induced compensatory changes in hunger, cravings and ghrelin suppression.

To achieve long-term weight loss, meal timing and macronutrient composition must counteract these compensatory mechanisms which encourage weight regain after weight loss .



Jakubowicz D , et al. Meal timing and composition influence ghrelin levels, appetite scores and weight lo

Hydration

Stanford A TO Z weight loss intervention on 173 premenopausal overweight women (aged 25–50 years) who reported <1 l/day drinking water at baseline.

Adkins, Zone, LEARN, Ornish

Weight loss

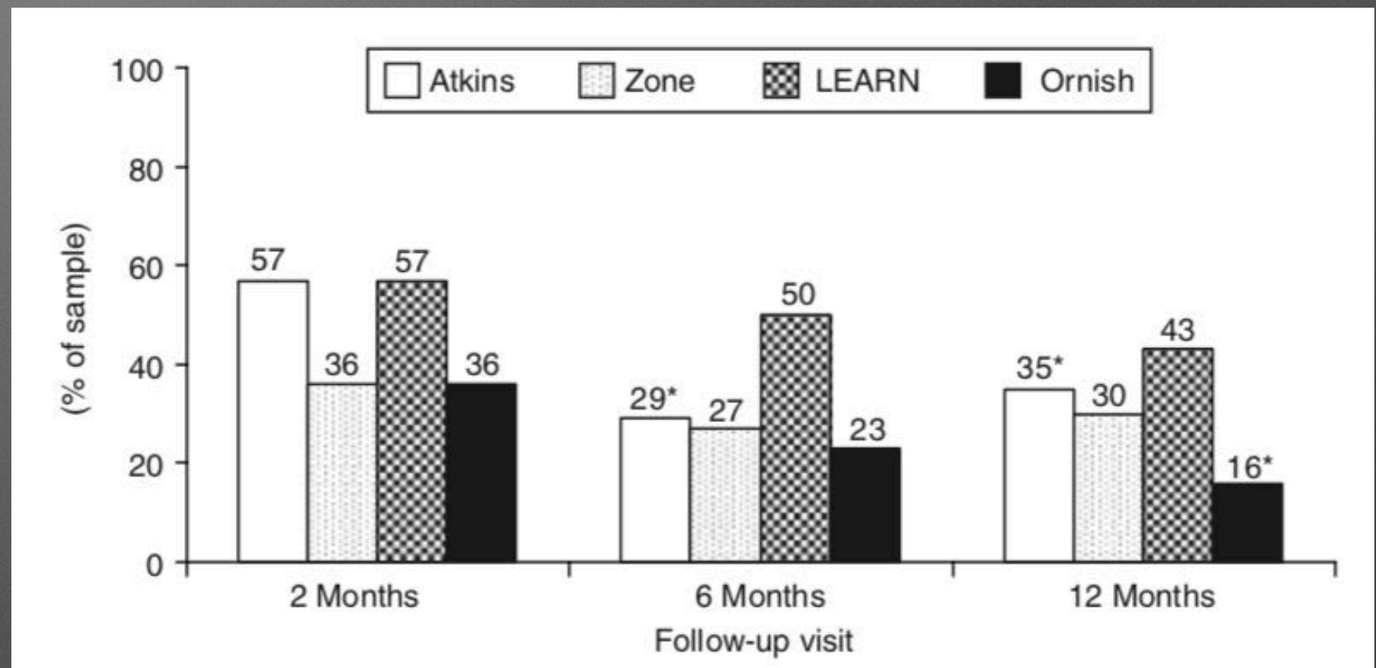


Figure 1 Proportion of the sample reporting ≥1 l/day drinking water at 2, 6, and 12 months by diet group. At baseline and 2 months, water intake data were available for all 173 women. All 173 women reported <1 l of drinking water per day at baseline. At 6 months, water intake data were available for 41, 44, 38, and 39 women in the Atkins, Zone, LEARN, and Ornish groups, respectively. At 12 months, water intake data were available for 40, 37, 35, and 31 women in each diet group, respectively. *P value <0.05 for comparison with the corresponding value at 2 months using random effects logistic regression models (xtlogit command in stata).

Stookey JD, Constant F, Popkin BM, Gardner CD. Drinking water is associated with weight loss in overweight dieting women independent of diet and activity. *Obesity* 2008;16(11):2481-2488.

Hydration

Model 1 included non-time-varying variables only.
Model 2 added control for time-varying variables that covary with changes in beverage intake during weight loss diets: energy expenditure, energy intake from food, and food macronutrient and water composition.
Model 3 added control for energy intake from beverages.
Compare Models 2 and 3 to determine whether change in beverage calories mediated or explained observed associations between drinking water and weight change.

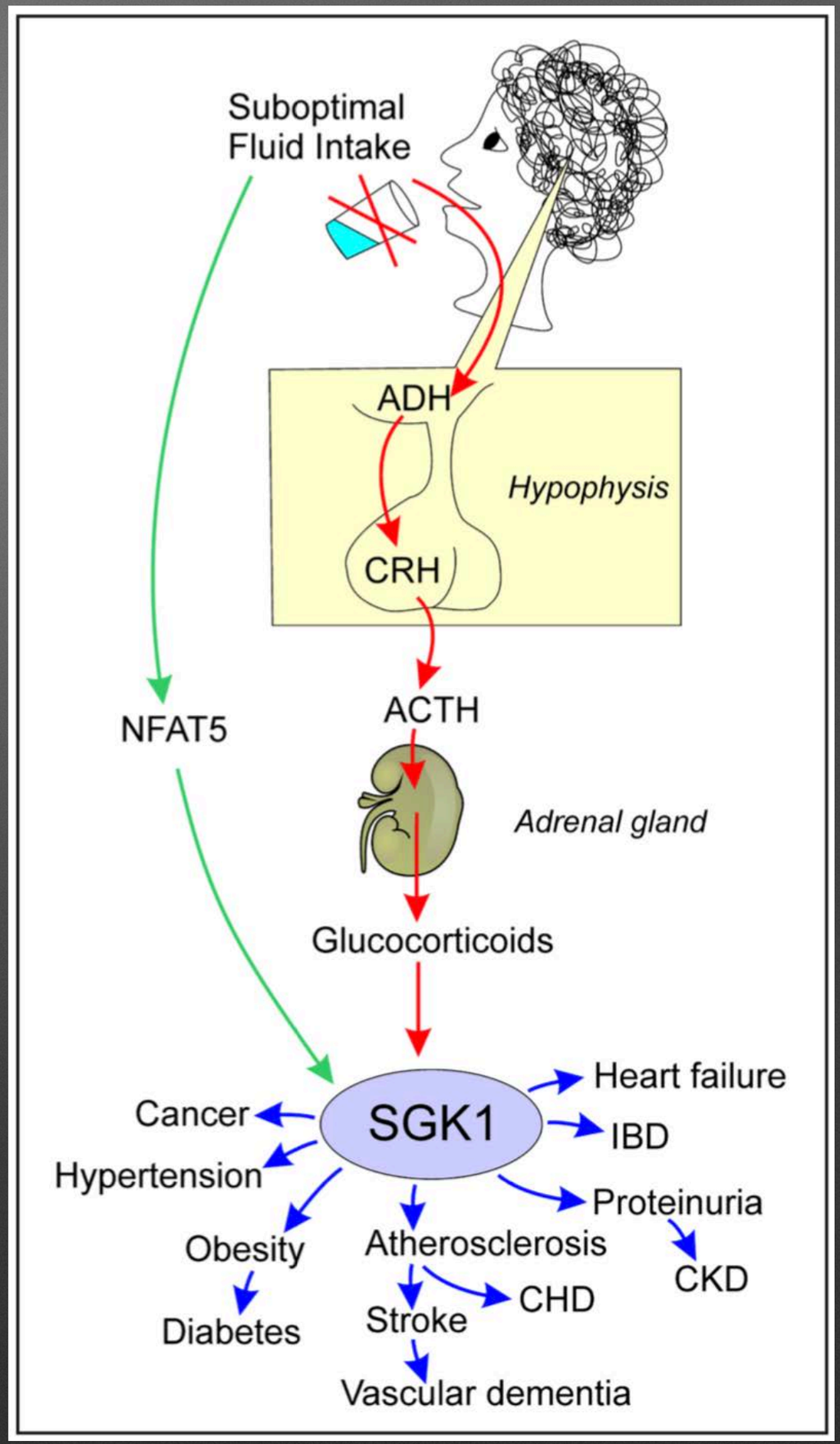
Hydration Conclusion

- Absolute and relative increases in drinking water were associated with decreases in body weight, waist circumference, and percent body fat in overweight women assigned to four popular weight loss diets.
- Independent of diet group, food composition, physical activity, and sociodemographic variables.
- Intake of unsweetened and noncaloric (diet) beverages was not associated with comparable benefit.
- Absolute increase in drinking water to **≥1 liter/day** was associated with ~**2 kg weight loss** over 12 months.

Dehydration Mechanisms

- Indirect - glucocorticoid
- Direct - NAFT5 Transcription factor

- SGK1 negative effects



Lang F, Guelinckx I Guillaume Lemetais IG, Melander O. Two Liters a Day Keep the Doctor Away? Considerations on the Pathophysiology of Suboptimal Fluid Intake in the Common Population. Kidney Blood Press Res 2017;42:483-494 DOI: 10.1159/000479640

Summary

- Know Your Patient's Diabetes Type
- Customize the treatment to the patient - Physiology, Psychology, Social, Spiritual
- Team to Create supporting culture
- Optimize all areas of the lifestyle for best results

The Gold Standard
Reversing Type 2 Diabetes