VLCKD E INSULINO-RESISTENZA: UNA TERAPIA? VLCKD E NAFLD, NASH: EPATOPROTEZIONE?

Simona Valeria Ferrero

ISTITUTO AUXOLOGICO ITALIANO

Ketogenic Diet Academy
Bologna, 24 febbraio 2018

VLCKD e LCKD:
Definizione e caratteristiche biochimiche

- Contenuto calorico molto ristretto o ristretto
  VLCKD: 450-800 kcal
  LCKD: 800-1200 kcal

- Normale apporto proteico: 1 gr/kg peso ideale
- Ridotto contenuto di grassi: 15-20 gr/die
- Ridotto contenuto di carboidrati: 40 gr/die,
  (frazionati in almeno 4 o 5 porzioni nel corso della giornata)

- Richieste vitaminiche e micronutrizionali totalmente soddisfatte

TANTI NOMI E SIGLE CONFONDENTI: ATTENZIONE AL CONTENUTO

- VLCKD E LCKD (very low calory ketogenic diet, low calory ketogenic diet)
- VLCD e LCD (very low calory diet, low calory diet;

  ….ma attenzione a volte utilizzati anche per very low e low carbohydrate diet)
- VLED e LED (very low energy diet e low energy diet)
- Low Carbohydrate Protein Sparing Modified Fast Diet
- Dieta proteinata (Francia)
- Dieta proteica (Italia)

LE 3 CARATTERISTICHE CHE DEFINISCONO LA VLCKD

1. La composizione biochimica
2. L'utilizzo di prodotti sostitutivi specificatamente formulati
3. La progressione in fasi ben distinte

VLCKD e LCKD:
Definizione e caratteristiche biochimiche

Le vie metaboliche coinvolte si esplicano attraverso la regolazione del rapporto insulina/glucagone e consentono:

- La mobilizzazione rapida e selettiva della massa corporea grassa
- Il risparmio della massa magra e muscolare
- L'induzione di uno stato di *chetogenesi controllata (mild ketosis)*, che attenua fortemente il senso di fame e di astenia, abituali effetti collaterali della forte restrizione calorica

ADVANTAGES of USING a VLED approach in obese subjects

- Rapid weight loss is a motivating factor.
- Ketosis slows the rate of muscle loss.
- VLED results in diuresis wich improves patients feeling of wellness early.
- Patients become mildly ketotic and mild ketosis results in reduced hunger.
- The form of meal replacements improves adherence and compliance.

Delbridge E, J Clin Nutr 2006

ADVANTAGES:
Adherence and Compliance

- Fixed and reduced calories
- Ensures Protein intake = > LBM maintenance
- Reduced SFAs intake
- Contributes to micronutrient intake => avoids deficiencies
- Reduces decision-making process = > no frustration
- Reduces measuring or weighing.
- Simple plans: “this is the basis of what you eat/drink.”
- Part-of-a-Meal Replacements = flexibility

VLCD: CRITICITA’

- Tempi di dimagramento
- Mantenimento nel medio/lungo termine
- Qualità del dimagramento
- Effetti collaterali
- Tollerabilità e sostenibilità del metodo
- Rapporto costo/beneficio

VLCD: RISULTATI A BREVE TERMINE

Rolland C et al – Cholesterol 2011

TABLE 1: Studies investigating the use of VLCD only.

Study	N	Number of males	Intervention	Duration of intervention	Weight at baseline (Kg)	Weight at end of intervention (Kg)
Clément et al. [13]	21	0	800 kcal/d	28 days	94 (3.0)	88 (3.0) *
Clément et al. [13]	8	0	650 kcal/d	2 days	120 (7.7)	119 (8)
Haugaard et al. [14]	13	4	600–800 kcal/d	8 weeks	106.4 (SE: 4.1)	97.0 (SE: 4.3) *
Hong et al. [12]	152	0	Black participants 500–800 kcal/d + BT + exercise.	12 weeks	105 (21)	95 (28)*
Hong et al. [12]	152	0	White participants 500–800 kcal/d + BT + exercise.	12 weeks	104 (28)	94 (25)*
Laaksonen et al. [15]	20	9	800 kcal/d	9 weeks	101.3 (12.0)	86.4 (9.6) *
Lin et al. [16]	66	24	1200 kcal/d + 450 kcal/d	14 weeks (2 weeks LCD followed by 12 weeks VLCD)	92.5 (14.1)	Δ −8.37 (0.7) *
Lin et al. [16]	66	21	1200 kcal/d + 800 kcal/d	14 weeks (2 weeks LCD followed by 12 weeks VLCD)	98.1 (15.6)	Δ −8.42 (0.7) *

All values are reported as means (standard deviation) unless stated otherwise.
N: number of participants
*$P < .05$ compared to baseline
Δ Values reported as change
SE: standard error.

Durata mediana dell'intervento settimane: n 10
Calo ponderale mediano 10 kg (1-15)

Review Article

State of the science: VLED (Very Low Energy Diet) for obesity

Elizabeth Delbridge BSc (Hons) MND, MPH and Joseph Proietto MB BS FRACP PhD

University of Melbourne, Department of Medicine(AH/NH), Repatriation Hospital, Heidelberg, Victoria 3081, Australia

Diet	Weight loss 1-2 years	Weight loss > 2 years
Ad lib low fat	-3.9 kg	-2.7 kg
Low energy	-6.7 kg	-1.1 kg
Very low energy	-11.8 kg	-4.1 kg
Meal replacement	-5.5 kg	-6.5 kg
'Popular' diets	Not known	Not known

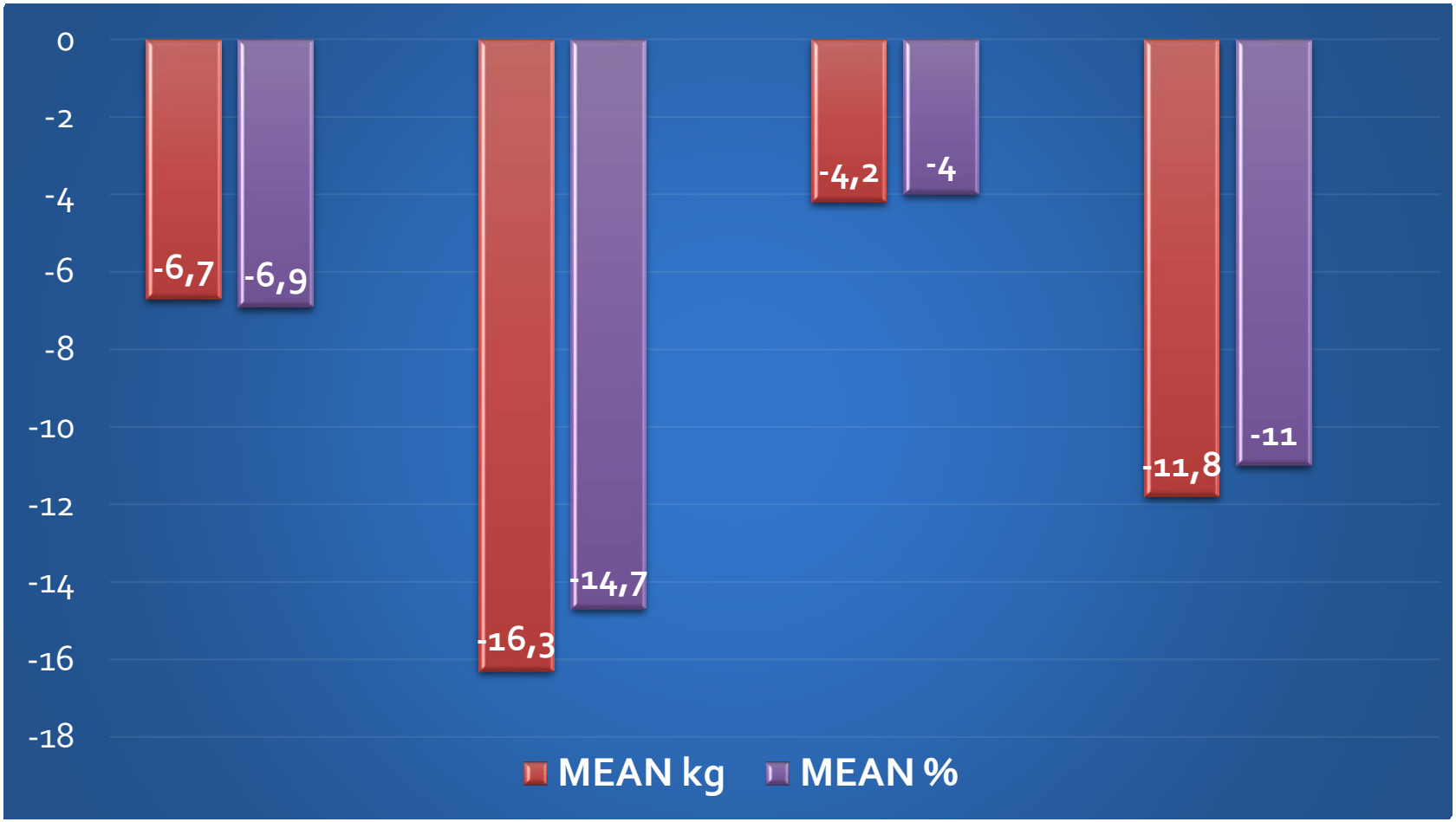
	End of program weight loss	1-2 year follow up weight loss
VLED	9.2-19.3kg	7.2-12.9kg
Non-VLED	6.2-14.3kg	5.7-9.5kg

VLCD: effetti a breve e lungo termine

Reference	Length of treatment	Post-treatment weight loss in kg (%)	Follow-up weight loss after VLED in (kg)
Ryttig K, 1997	2 months	-18.9	-10.9 after 2 years[a]
Apfelbaum M,1999	4 weeks		+0.5 (+0.5%) after 1 year
Torgerson JS, 1997	12 weeks		-9.2 (-7.9%) after 2 years[a]
Torgerson JS, 1999	16 weeks	-13.8 (-12.4%)	-12.3 (-11.0%) after 1 year[a]
Miura J, 1989	1-2 months	-8.6 (-8.0%)	-4.1 (~ -3.8%) after 2 years
Sikand G, 1988	16 weeks	-17.5 (-17.0%)	-0.8 (-0.8%) after 2 years
Wadden TA, 1986 Wadden TA, 1988	4 months	-14.1 (~ -12.9%)	-4.6 (~ -4.2%) after 1 year -12.9 (~ -11.8%) after 1 year[a]
Wadden TA, 1989	16 weeks	-13.1 (-12.4%)	-4.7 (-4.4%) at 1 year +1.0 (+0.9%) at 5 years
Wadden TA, 1994	16 weeks	-10.9 at 1.5 yearsa	
Wing R, 1991	20 weeks	-18.6 (-17.9%)	-8.6 (-8.3%) after 1 year
Wing R, 1994	2 x 12-week periods over 50 weeks		-14.2 (-13.4%) after 1 year[a] -7.2 (-6.8%) after 2 years
Fogelhom M, 2000	12 weeks	-13.1 (-14.2%)	-10.0 (~ -10.9%) at 1 year[a] -2.3 (~ -2.5%) at 3 years
Wadden TA, 1992	12 weeks	-25.6 (-23.1%)	-7.9 (-6.2%) at 5 years

Clinical Practice Guidelines for Management of Overweight and Obesity in Adults, NHMRC 2003

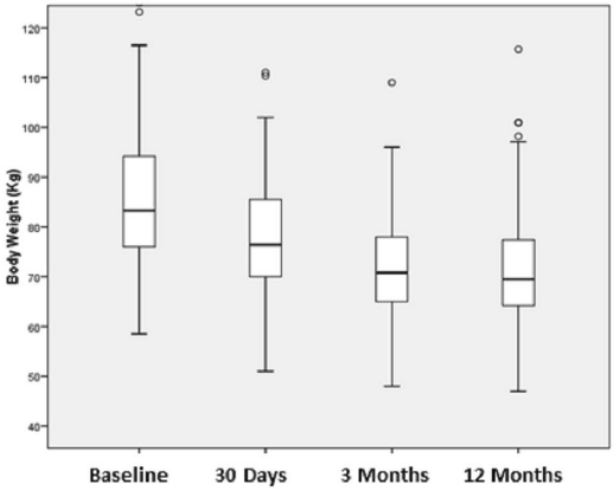
LCD *vs* VLCD

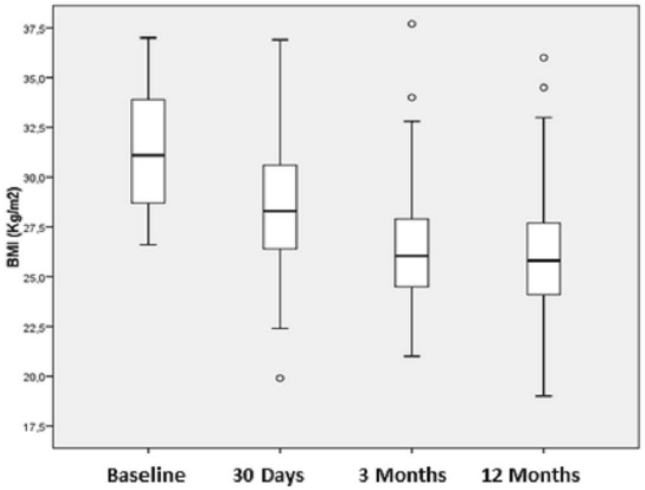


Clinical Practice Guidelines for Management of Overweight and Obesity in Adults, NHMRC 2003, modified

Middle and Long-Term Impact of a Very Low-Carbohydrate Ketogenic Diet on Cardiometabolic Factors: A Multi-Center, Cross-Sectional, Clinical Study

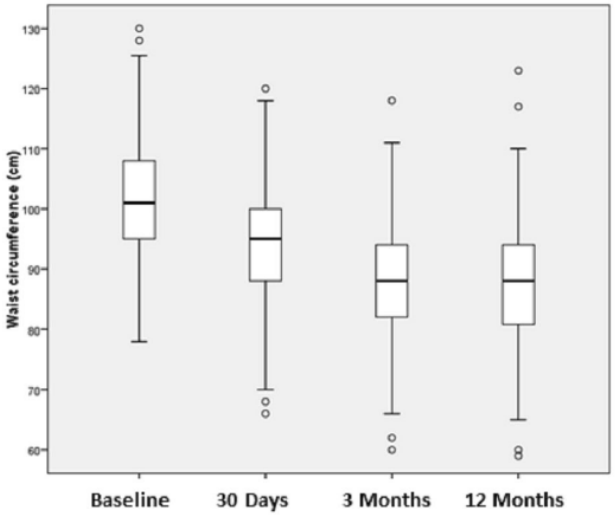
Body Weight

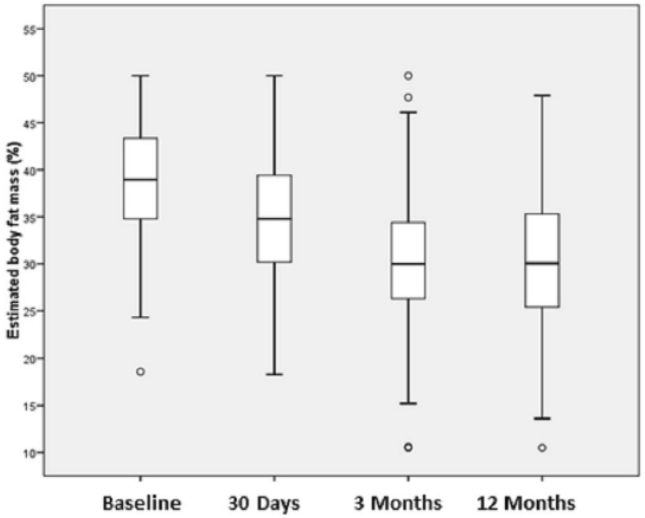




BMI

Waist

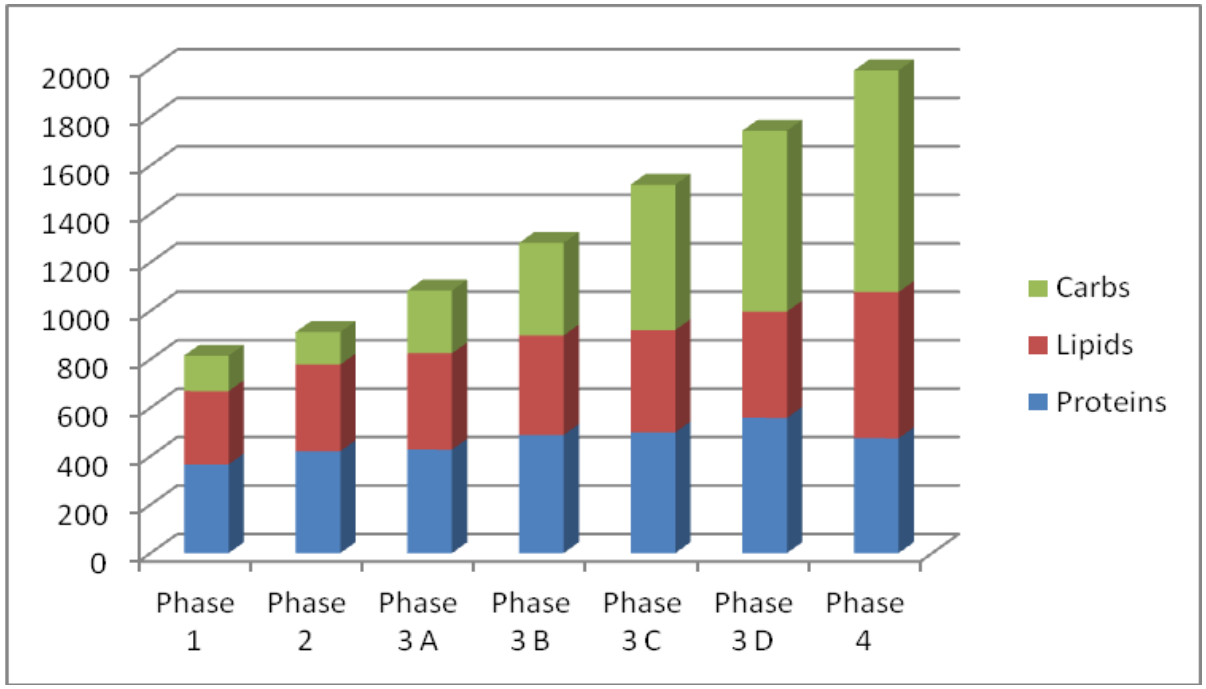




Estimated body FM% changes

A. F. G. Cicero, High Blood Press Cardiovasc Prev 2015

REINTRODUCTION OF CARBS AFTER A VLCKD



"… It may not be appropriate to return to a HC intake for weight maintenance. ***A gradual reintroduction while still limiting the intake of carbohydrate may be more appropriate****."*

Hession M., Rolland C., Kulkarni U., et al. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obesity Reviews 2009 10 (1)

VLCD DECREASE FAT MASS and SPARE LEAN BODY MASS

STUDY	YEAR	DIET	SUBJECTS	DURATION (DAYS)	ENERGY (KCAL)	CHO (G)	BODY MASS CHANGE (KG)	FAT MASS CHANGE (KG)	LEAN BODY MASS CHANGE (KG)	METHOD
Benoit et al[11]	1965	Fasting	7 M, obese	10	0	0	−9.6	−3.4	−6.2	UWW
		VLCD		10	1,000	10	−6.6	−6.4	−0.2	
Young et al[9]	1971	VLCD	2 M, obese	63	1,800	104	−11.2	−8.4	−2.8	K40
		VLCD	3 M, obese	63	1,800	60	−12.3	−10.2	−2.1	
		VLCD	3 M, obese	63	1,800	30	−15.6	−14.9	−0.7	
Phinney et al[22]	1980	VLCD	5 F, 1 M, obese	42	500–750	0	−10.6	−7.1	−3.5	UWW
Willi et al[12]	1998	VLCD	6, obese	56	650–725	25	−15.4	−16.8	1.4	DXA
Volek et al[13]	2002	VLCD	12 M, lean	42	2,335	46	−2.2	−3.3	1.1	DXA
		Control	8 M, lean	42	2,190	330	0.4	0.0	0.4	DXA

Very-low-carbohydrate weight-loss diets revisited , Volek J.S et al. Clev Clin J Med 2002

Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review

TB Chaston, JB Dixon Int J Obesity 2008

Summary of studies of visceral and subcutaneous fat distribution before and after weight loss using:

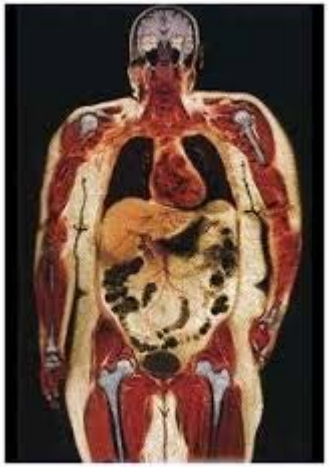
- LCD
- LCD+Exercise
- VLCD
- Exercise alone
- LCD+Orlistat
- LCD+Sibutramina
- LAGB

Effetti delle VLCD sulla composizione corporea

Factors associated with percent change in visceral versus subcutaneous abdominal fat during weight loss: findings from a systematic review preferential loss of visceral fat
Chaston TB et al. Int J Obesity 2008

Table 3 Summary of studies of visceral and subcutaneous abdominal fat distribution before and after weight loss using LCD+exercise, VLCDs and exercise alone

Author	*Year*	n	*Intervention*	*%δV/%δS*	*sex*	*BMI*	*%WL*	*Weeks*	*%SAT loss*	*%VAT loss*	*VAT/SAT*
Colles	2006	37	VLCD	0.95		47.3	10.6	12	17.7	16.9	0.762
Conway[43]	1995	8	VLCD	1.02	F	40.0	15.7	12	12.8	13.0	0.234
Stallone[44]	1991	11	VLCD	1.08	F	37.0	19.8	13	33.1	35.7	0.321
Conway[43]	1995	10	VLCD	1.24	F	38.2	16.7	12	17.9	22.2	0.359
Goodpaster[45]	1999	15	VLCD	1.29	M	34.5	16.1	12	34.0	44.0	0.359
Goodpaster[45]	1999	17	VLCD	1.30	F	34.0	13.2	12	23.0	30.0	0.283
Laaksonen[46]	2003	20	VLCD	1.85		35.8	14.5	9	17.0	31.5	0.523
Gray[47]	1991	10	VLCD	2.13	F	35.3	11.7	10	12.7	27.1	0.197
Zamboni[48]	1993	16	VLCD	2.80	F	38.2	6.4	2	7.5	21.0	0.280
Bosello[49]	1990	19	VLCD	3.71	F	40.0	6.3	3	5.5	20.4	0.228
Zamboni[50]	1996	11	VLCD	4.09	F	34.8	5.3	2	7.7	31.5	0.264
Chowdhury[51]	1993	9	VLCD	6.08	M	35.1	3.9	1	2.6	15.8	0.466
De Pergola[52]	1998	21	VLCD	8.06	F	38.8	8.1	3	6.2	50.0	0.197



TB Chaston, JB Dixon
Int J Obesity 2008

- Visceral adipose tissue is lost preferentially with modest weight loss.
- Acute caloric restriction, using VLCD, produces early preferential loss of VAT.
- Very-low-calorie diets (VLCDs) provided exceptional short-term (<4 weeks) preferential VAT loss, but this effect was lost by 12-14 weeks.

Body composition changes after very low-calorie-ketogenic diet in obesity evaluated by three standardized methods

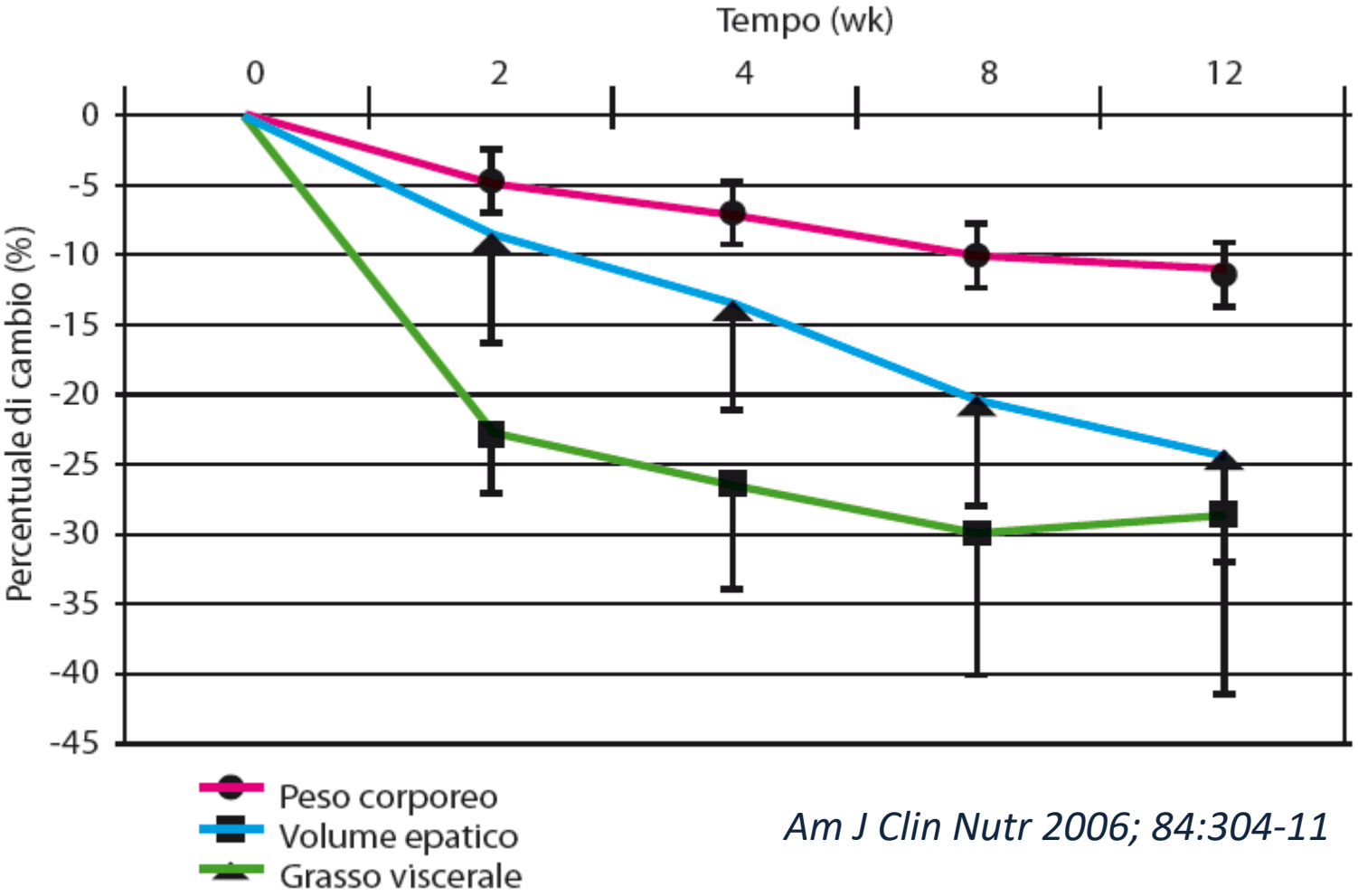
D. Gomez-Arbelaez et al, J Clin Endocrinol Metab 2016

- Dual-energy X-ray Absorptiometry (DXA)
- Multifrequency Bioelectrical Impedance (MF-BIA)
- Air displacement Plethysmography (ADP)

1. Significant wight loss, mostly explaned by reduction in FM and visceral fat tissue (VF)
2. A mild initial loss of FFM followed by a partial subsequent recovery
3. Adequate preservation of muscle strength
4. Less expensive MF-BIA showed an acceptable agreement with DXA in estimating body composition

Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging

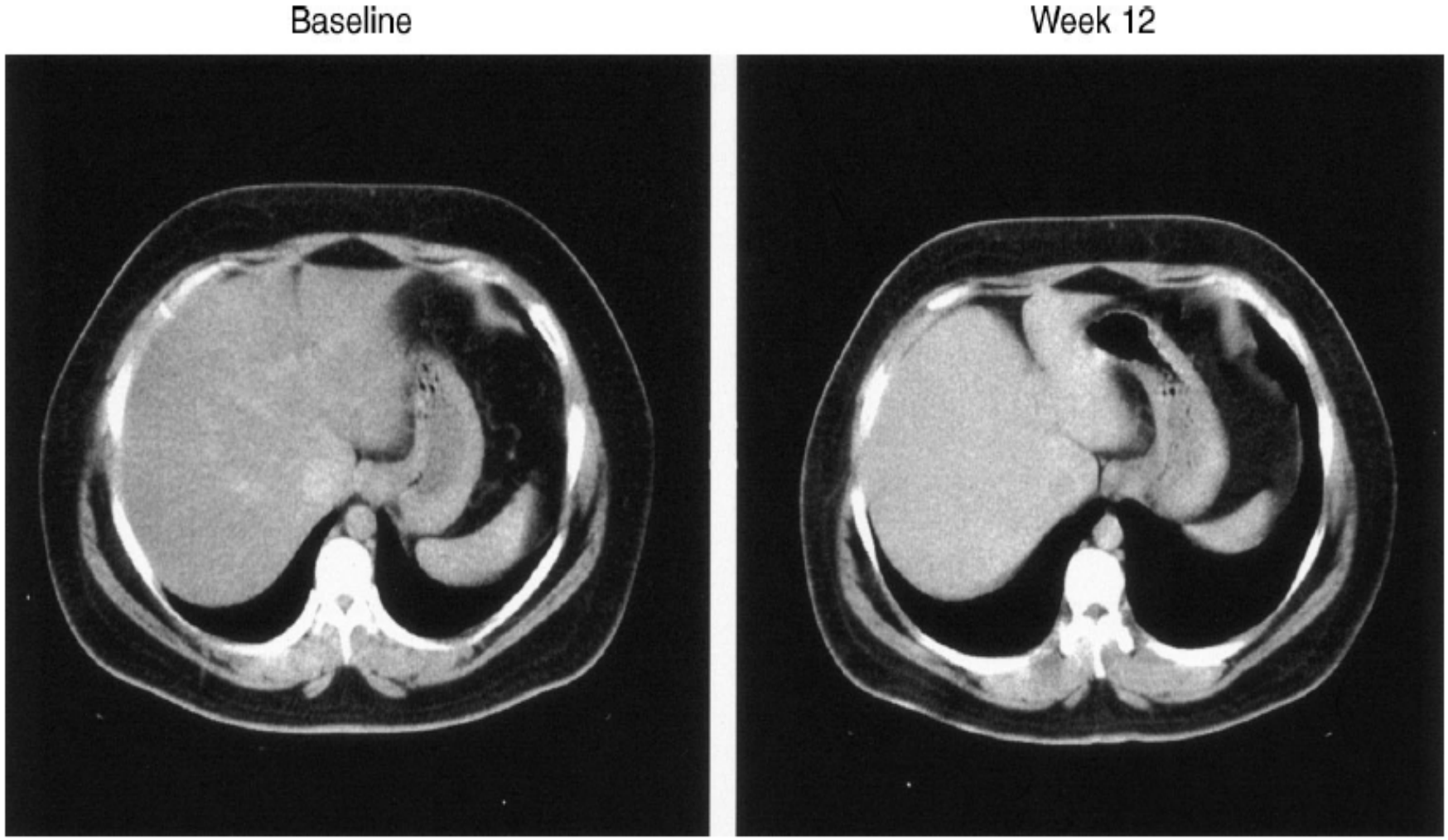
Susan L. Colles, John B. Dixon, Paul Marks, Boyd J Strauss and Paul E. O'Brien



Am J Clin Nutr 2006; 84:304-11

Preoperative weight loss with a very-low-energy diet: quantitation of changes in liver and abdominal fat by serial imaging

SL Colles, ***Am J Clin Nutr 2006***



ELSEVIER

Surgery for Obesity and Related Diseases ▮ (2017) 00–00

SURGERY FOR OBESITY AND RELATED DISEASES

Controversies in Bariatric Surgery

Effects of very low calorie diets on liver size and weight loss in the preoperative period of bariatric surgery: A systematic review

Mariana Holderbaum, R.D., M.Sc.[a,b], Daniela Schaan Casagrande, R.D., M.Sc., Ph.D.[b], Samanta Sussenbach, R.D., M.Sc., Ph.D.[b], Caroline Buss, R.D., M.Sc., Ph.D.[a,c,*]

1. VLCDs are effective for weigh loss and hepatic liver decrease in BS preoperative period.
2. Benefits are shown to be maximized in the 2- to 4-week timeframe.
3. The effect on the reduction of surgical risks is still uncertain.
4. Standardization of dietary characteristics is needed (no change in weigh loss and liver volume in higher caloric restriction).

Diete chetogeniche e sindrome metabolica

Diversi studi dimostrano che le VLCKD, oltre alla riduzione dell'adiposità viscerale, portano ad una significativa riduzione di TG, Col totale e LDL e aumento di HDL in 8-12 settimane e che durante le VLCKD la glicemia a digiuno si normalizza rapidamente e si riduce l'emoglobina glicata e i livelli di insulinemia.

Raitakari M. et al. Arterioscler. Thromb. Vasc. Biol. 2004; Westman EC, Am J Clin Nutr 2007; Dunlap BS Metabolic Syndrome e related Disorders 2008; Paoli A. Nutr J 2011

Sindrome metabolica

Reaven, 1988:
Sindrome X, Deadly Quartet, Metabolic Syndrome

1. Insulin resistance (and by definition, hyperinsulinemia)
2. Impaired Glucose Tollerance
3. Abnormalities of Plasma Lipids
4. Hypertension

Reaven GM: Banting lecture: role of insulin resistance in human desease. Diabetes 37, 1988

The Effects of Low-Carbohydrate versus Conventional Weight Loss Diets in Severly Obese Adults: One-Year Follow-up of a Randomized Trial

Partecipants:

132 obese adults with a body mass index of 35 kg/m2 or greater; 83% had diabetes or the metabolic syndrome

Partecipants on a low-carbohydrate diet had more favorable overall outcomes at 1 year than did those on a conventional diet.

Weight loss was similar between groups, but effects on atherogenic dyslipidemia and glycemic control were still more favorable with a low-carbohydrate diet after adjustment for differences in weight loss.

Linda Stern et al, Annals of Internal Medicine, 2004

VLCKD vs. LOW GI WITH A PMR STRATEGY

	LCKD (n=31)			LGID (n=32)		
	Week 0	Week 22	Mean change	Week 0	Week 22	Mean change
Weight (Kg)	109.74±20.73	93.81±19.13	-15.93*	103.50±14.84	98.54±14.64	-4.96
Waist (cm)	131.28±12.70	100.93±13.42	-30.35*	126.66±9.34	114.60±7.79	-12.06
Fat mass (kg)	47.41±11.35	34.70±10.40	-12.71*	44.38±10.49	42.05±8.9	-2.33
HbA1c (%)	8.8±1.8	7.3±1.5	-1.5*	8.3±1.9	7.8±2.1	-0.5
TC (mg/dl)	182.55±36.62	161.14±33.07	-21.41*	183.33±34.63	176.58±26.19	-9.65
LDL (mg/dl)	112.44±33.83	108.24±35.17	-4.2	111.73±24.51	113.07±24.47	+1.34
HDL (mg/dl)	41.38±6.81	45.67±3.21	+4.29*	42.25±4.57	43.20±4.52	+0.95
TG (mg/dl)	142.93±51.78	114.85±33.71	-28.08*	137.66±78.00	121.39±40.56	-16.27
SBP (mm Hg)	131.6±15.8	127.3±14.5	-4.3	129.8±14.2	126.4±13.4	-3.4
DBP (mm Hg)	82.9±9.7	76.3±10.1	-6.6*	82.1±11.0	79.8±8.7	-2.3

A. Koutsovasilis, D. Vlachos, A. Ganotopoulou, C. Stathi, E. Diakoumopoulou, D. Doulgerakis, N. Tentolouris, A. Melidonis, N. Katsilambros; A VERY LOW-CARBOHYDRATE KETOGENIC DIET COMPARED WITH A LOW GLYCEMIC INDEX REDUCED CALORIE DIET IN OBESE TYPE 2 DIABETIC PATIENTS. Poster ECO 2012

67 patients	Initial time	Final time (6 weeks)
Weight (Kg)	100.5 ± 18.0	89.5±16.6
Body mass index (Kg/m^2)	35.2 ± 5.4	31.4± 5.2
Waist circumference (cm)	110 ± 14	99 ±13
Hip circumference (cm)	118 ±11	110 ± 10
Waist-to-hip-ratio	0.93 ± 0.08	0.90 ± 0.08
Systolic blood pressure (mm HG)	142 ± 18	130 ± 19.0
Diastolic blood pressure (mm HG)	90 ±18.0	81 ± 11
Glucose (mmol/L)	5.53 ± 0.69	5.06 ± 0.60
Insulin (mU/L)	11.1 ± 8.3	6.3 ± 5.6 - 36%
Total cholesterol (mmol/L)	5.45 ± 1.09	4.19 ± 0.87
HDL cholesterol (mmol/L)	1.40 ± 0.38	1.34 ± 0.37
Tryglicerides (mmol/L)	1.46 ± 0.79	0.96 ± 0.42
LDL cholesterol (mmol/L)	3.43 ± 0.99	2.43 ± 0.76
C-reactive protein (mg/L)	**3.3 ± 3.3**	**1.9 ± 2.1**

Raitakari M. et al. Arterioscler. Thromb. Vasc. Biol. 2004

CARDIOVASCULAR DISEASE

Central obesity and/or hyperleptinemia

Microalbuminuria

Low-grade inflammation

Prothrombotic state (PAI-1,FBG,vW,fX,plt)

PCOS

IGT, T2DM Ins Resistance

↑PAI-1

↓Adiponectina

↑Lattato

↑Adipsina

↑Leptina

↑Resistina

↑TNF-α

Dyslipidemia (↑ TG e/o ↓ HDL)

↑FFA

↑CRP

↑Insulina

↑Angiotensinogeno

↑IL-6

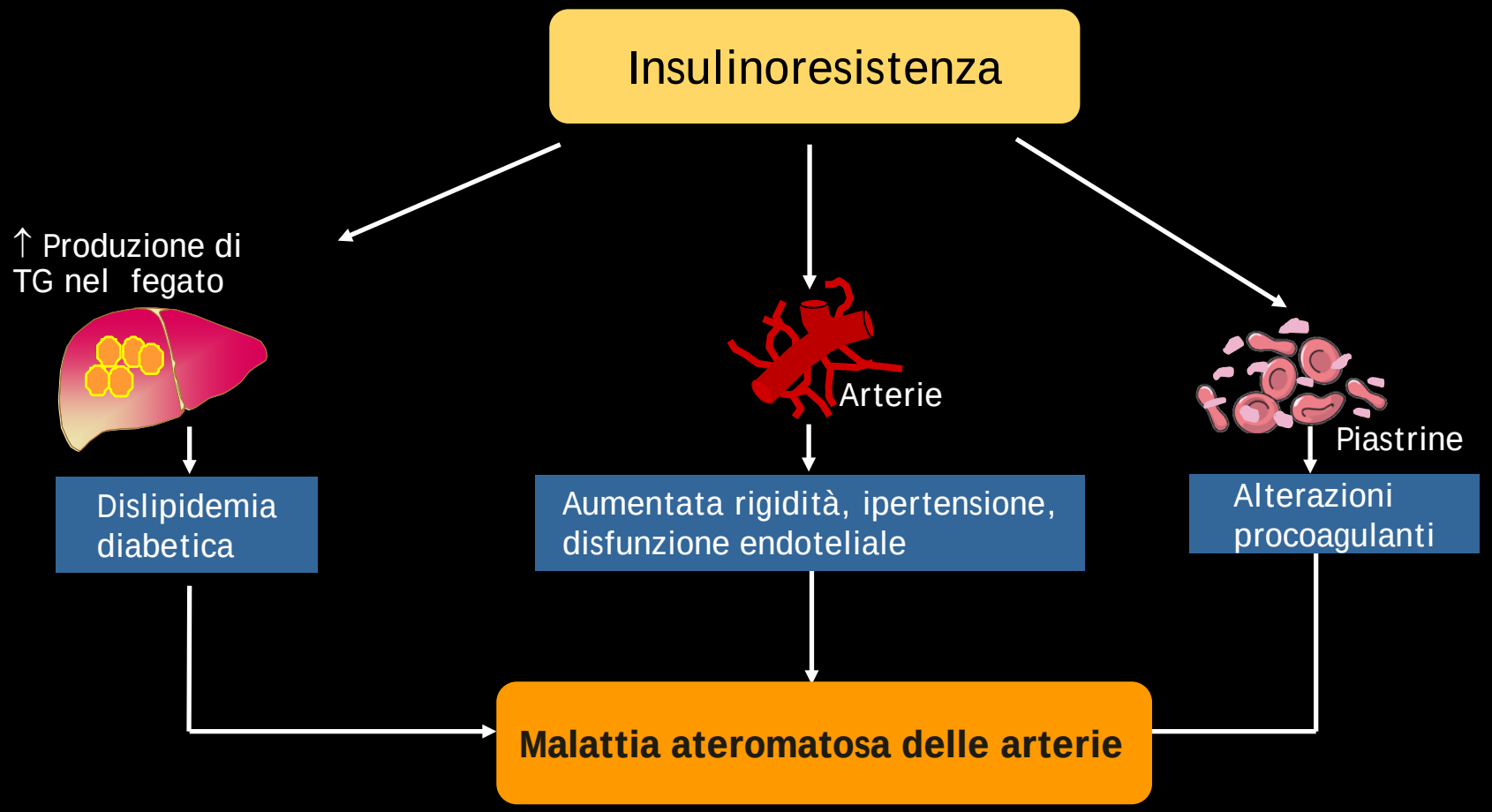
↑Lipasi lipoproteica

Hypertension

GENETIC AND LIFE STYLE

Trayhurn P, Wood IS. Br J Nutr 2004; 347-55; Eckel RH et al. Lancet 2005: 365: 1415-1428

Altre conseguenze dell'insulinoresistenza



TG=trigliceridi.
Adattata da Yki-Järvinen H. In: *Textbook of Diabetes 1.* 3rd ed. Oxford, UK: Blackwell; 2003:22.1–22.19.

Ruolo dell'adiposità centrale nella fisiopatogenesi delle complicanze metaboliche e cardiovascolari

Adiposità addominale

Fattori genetici

Fattori ambientali

Adipocita

FFA liberi

Leptina
Adiponectina
Resistina
} Adipochine

Citochine { TNF-α, IL-6

Markers infiammatori

Insulino-resistenza
epatica, muscolare, adipocitaria
SINDROME METABOLICA
↑ TG ↑ PA ↓ HDL

⇄ Iperinsulinemia compensatoria

Diabete tipo 2

Eventi cardiovascolari

Muredach P. R et al. The metabolic Syndrome More than the sum of its parts? ***Circulation 2003***

EVIDENCE LINKING OBESITY TO TYPE 2 DIABETES

1. Epidemiological
2. Genetic
3. Mechanistic
4. Clinical
5. Reversibility

1. BMI is the dominant risk factor for type 2 diabetes. With BMI 30-35, RRs for CVD tend to be twofold to threefold; whereas RRs for diabetes approaching 50-80 times at BMI 35 vs BMI 21.
2. Genes linked to higher BMI, in particular thr FTO gene, have been clearly shown to predict T2DM.
3. Ectopic fat in key organs that are relevant to glucose metabolism appears to be crucial for tissue insulin resistance.
4. BMI or waist size make up around half of the weighting in diabetes risk scores, regardless of ethnicity. Moreover, around half of all patients with diabetes are obese.
5. Weight loss via dietary or surgical methods can reverse T2DM and even some patients previously on insulin can show remission, suggesting improvements in ßcell.

BMC Medicine 2014, **12**:123

BMC Medicine
BMC Medicine 2014, **12**:123

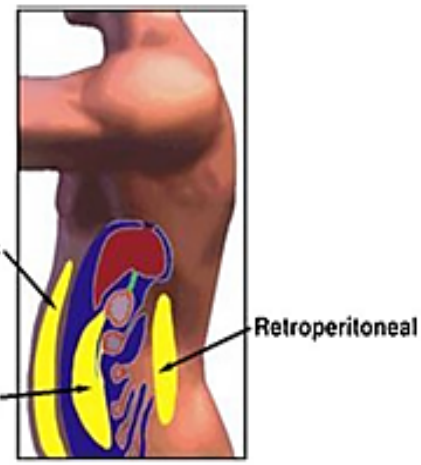
Type 2 diabetes as a disease of ectopic fat?

Naveed Sattar* and Jason MR Gill

Obesity is the major risk factor for T2DM and appears to drive tissue insulin resistance in part via gain of ectopic fat, with the best-studied organ being the liver. However, ectopic fat in the pancreas may contribute to β-cell disfuction. **In line with this observation, rapid resolution of diabetes linked to a preferential and rapid reduction in liver fat has been noted with significant caloric reduction.**

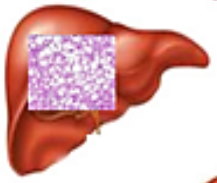
Whether these observations can help develop **better cost-effective and sustainable lifestyle/medical interventions** in patients with T2DM requires further study

Excess calories
(increased intake +/-
reduced energy expenditure)



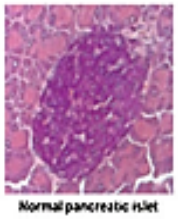
Subcutaneous stores
overwhelmed
(genes, ethnicity, ageing)

FAT
'Spill over'

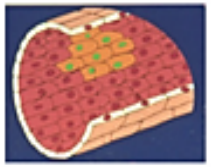


Hepatic lipid
accumulation

muscle



pancreatic
beta cell



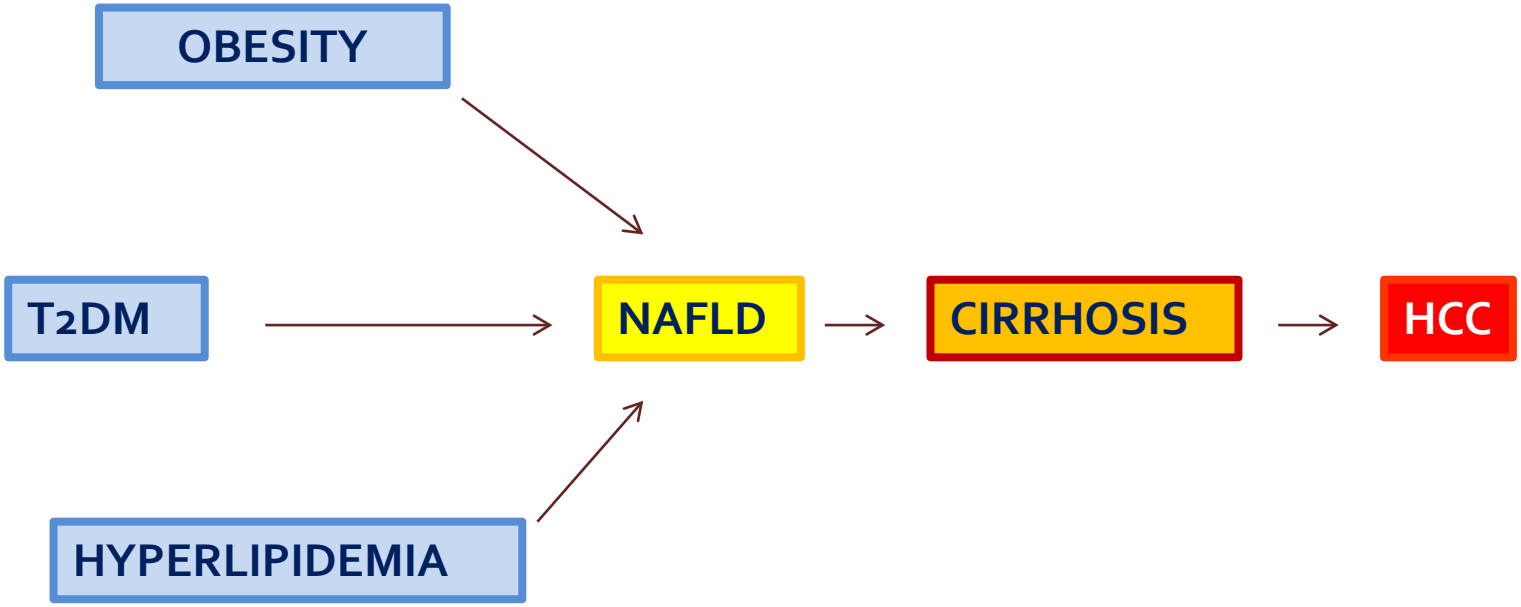
Perivascular fat ⇒
Endothelial dysfunction (altered blood flow)

Insulin resistance

β cell dysfunction?

Hyperglycaemia

DIABETE E MALATTIE EPATICHE



DIABETE E MALATTIE EPATICHE

1. DMT2 come fattore di rischio per NAFLD e HCC

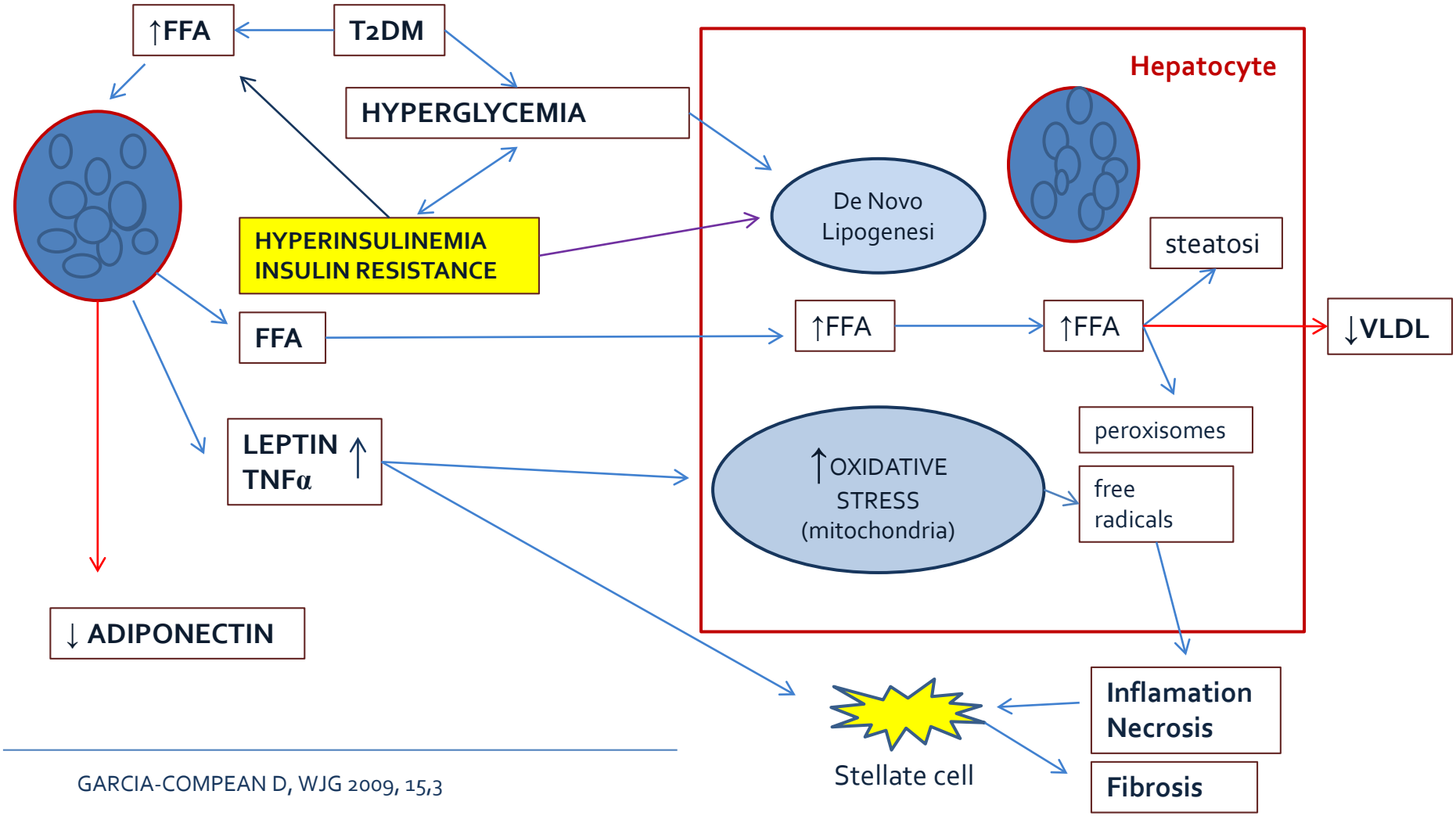
2. DM come una complicanza della cirrosi epatica
   (Hepatogenous Diabetes)

Spectrum of Liver Disease in Type 2 Diabetes

- NAFLD: nel 34-74% DMT2, nel 100% DM+OB. Alla diagnosi, 50% di NASH e 19% di cirrosi epatica.
- CIRROSI: indipendentemente associata ad insulinoresistenza, importante causa di morte nel diabetico (The Verona Study: SMR 2,52 vs 1.34 per CVD, se insulinotrattati: SMR 6.84).
- HCC: è la terza causa di morte neoplastica al mondo, molti studi confermano la sua prevalenza aumentata di circa 4 volte nel diabetico. La prevalenza di DM nell'HCC è superiore al 30%.
- INSUFFICIENZA EPATICA ACUTA: 2.31 per 10.000/anno tra i diabetici vs 1.44 nella popolazione generale.
- EPATITE C: HCV ab: 4,2% nei diabetici vs 1,6% controlli. DM dal 20 al 50% di pazienti HCV.

Spectrum of Liver Disease in Type 2 Diabetes K. G. Tolman et al, Diabetes Care 2007

INSULINORESISTENZA E MALATTIE EPATICHE



GARCIA-COMPEAN D, WJG 2009, 15,3

Diabetes: Have We Got It All Wrong?

Hyperinsulinism as the culprit: surgery provides the evidence

WALTER J. PORIES, MD, FACS
G. LYNIS DOHM, PHD

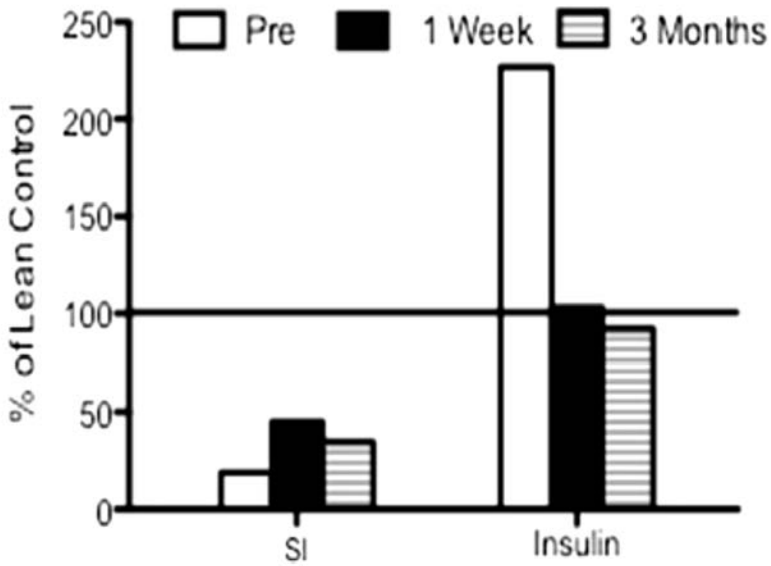


Fig 2. A new figure of previously published data (Reed et al[3]) showing that Roux-en-Y gastric bypass corrects hyperinsulinemia immediately after surgery. This normalization of insulin levels coincides with the remission of T2DM within 1 week of surgery. However, insulin sensitivity (SI), which is indicative of insulin resistance, is not normalized even 3 months after surgery, suggesting that hyperinsulinemia is not dependent on insulin resistance.

Hyperinsulinemic syndrome: The metabolic syndrome is broader than you think

Christopher T. Kelly, BA,[a] Janet Mansoor, BS,[a] G. Lynis Dohm, PhD,[b] William H. H. Chapman III, MD, FACS,[c] John R. Pender IV, MD, FACS,[c] *and* **Walter J. Pories, MD, FACS,[c]** *Greenville, NC*

Background. *Type 2 diabetes mellitus (T2DM) is characterized by hyperinsulinemia. In 2011 we showed that gastric bypass (RYGB) corrects these high levels even though insulin resistance remains high, ie, the operation "dissociates" hyperinsulinemia from insulin resistance. RYGB produces reversal of T2DM along with other diseases associated with the metabolic syndrome. This observation led us to examine whether these illnesses also were characterized by hyperinsulinemia.*
Methods. *A systematic review was performed to determine whether hyperinsulinemia was present in disorders associated with the metabolic syndrome. We reviewed 423 publications. 58 were selected because of appropriate documentation of insulin measurements. Comparisons were based on whether the studies reported patients as having increased versus normal insulin levels for each metabolic disorder.*
Results. *The presence (+) or absence (−) of hyperinsulinemia was documented in these articles as follows: central obesity (4+ vs 0−), diabetes (5+ vs 0−), hypertension (9+ vs 1−), dyslipidemia (2+ vs 0−), renal failure (4+ vs 0−), nonalcoholic fatty liver disease (5+ vs 0−), polycystic ovary syndrome (7+ vs 1−), sleep apnea (7+ vs 0−), certain cancers (4+ vs 1−), atherosclerosis (4+ vs 0−), and cardiovascular disease (8+ vs 0−). Four articles examined insulin levels in the metabolic syndrome as a whole (4+ vs 0−).*
Conclusion. *These data document that disorders linked to the metabolic syndrome are associated with high levels of insulin, suggesting that these diseases share a common etiology that is expressed by high levels of insulin. This leads us to propose the concept of a "hyperinsulinemic syndrome" and question the safety of insulin as a chronic therapy for patients with T2DM. (Surgery 2014;156:405-11.)*

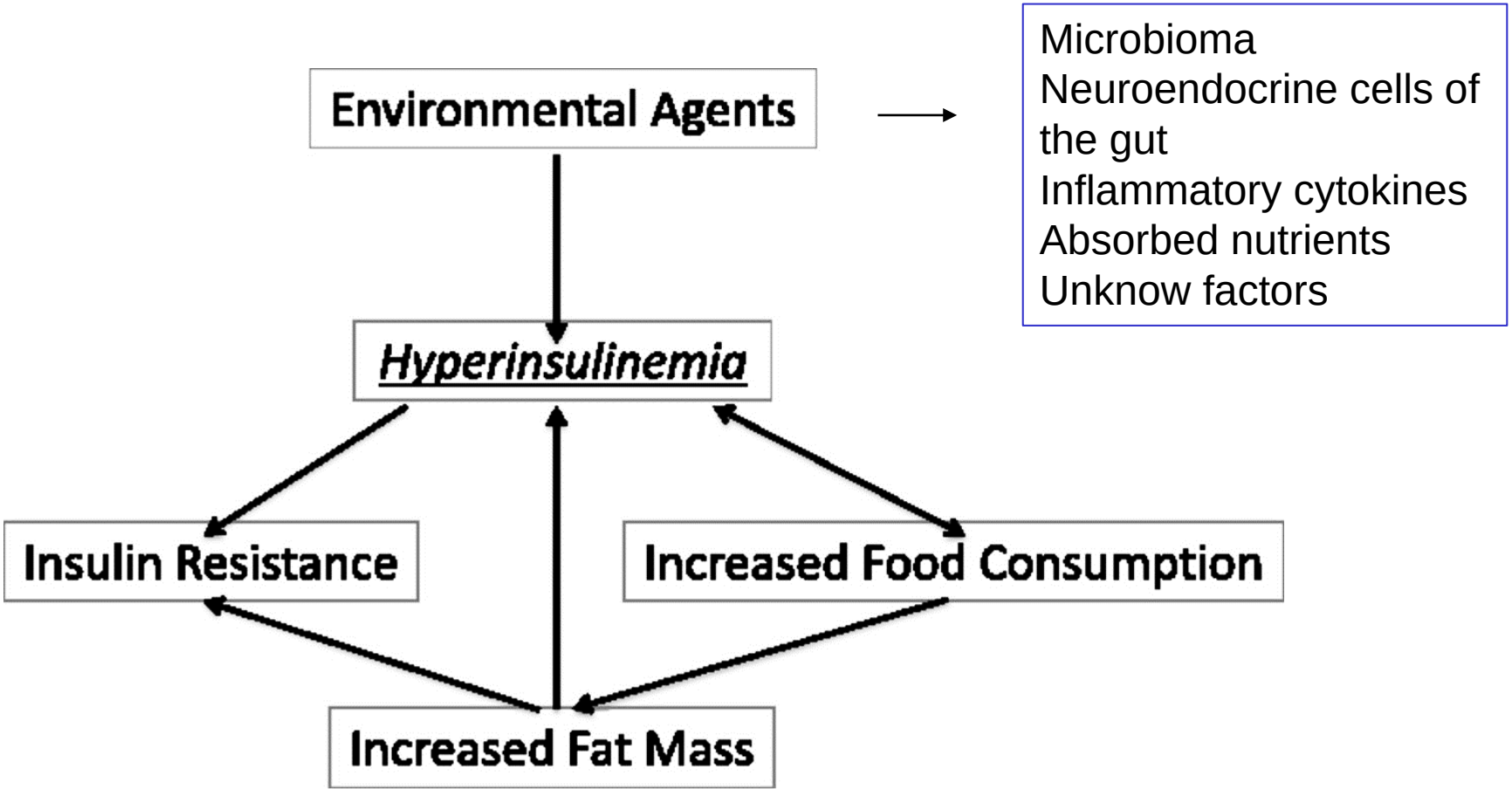
From the MD Program,[a] Department of Physiology,[b] and Department of Surgery,[c] Brody School of Medicine, East Carolina University, Greenville, NC

The Hyperinsulinemic syndrome extends beyond the Metabolic syndrome

- Central Obesity
- Diabetes
- Hypertension
- Dyslipidemia
- Renal Failure
- NAFD
- Polycystic ovary syndrome
- Certain Cancers
- Sleep Apnea
- Atherosclerosis
- Cardiovascolar disease
- Metabolic Syndrome

A systematic review performed to determine whether hyperinsulinemia was present in disorders associated with the metabolic syndrome

Model of environmental agent–induced hypersecretion of insulin.

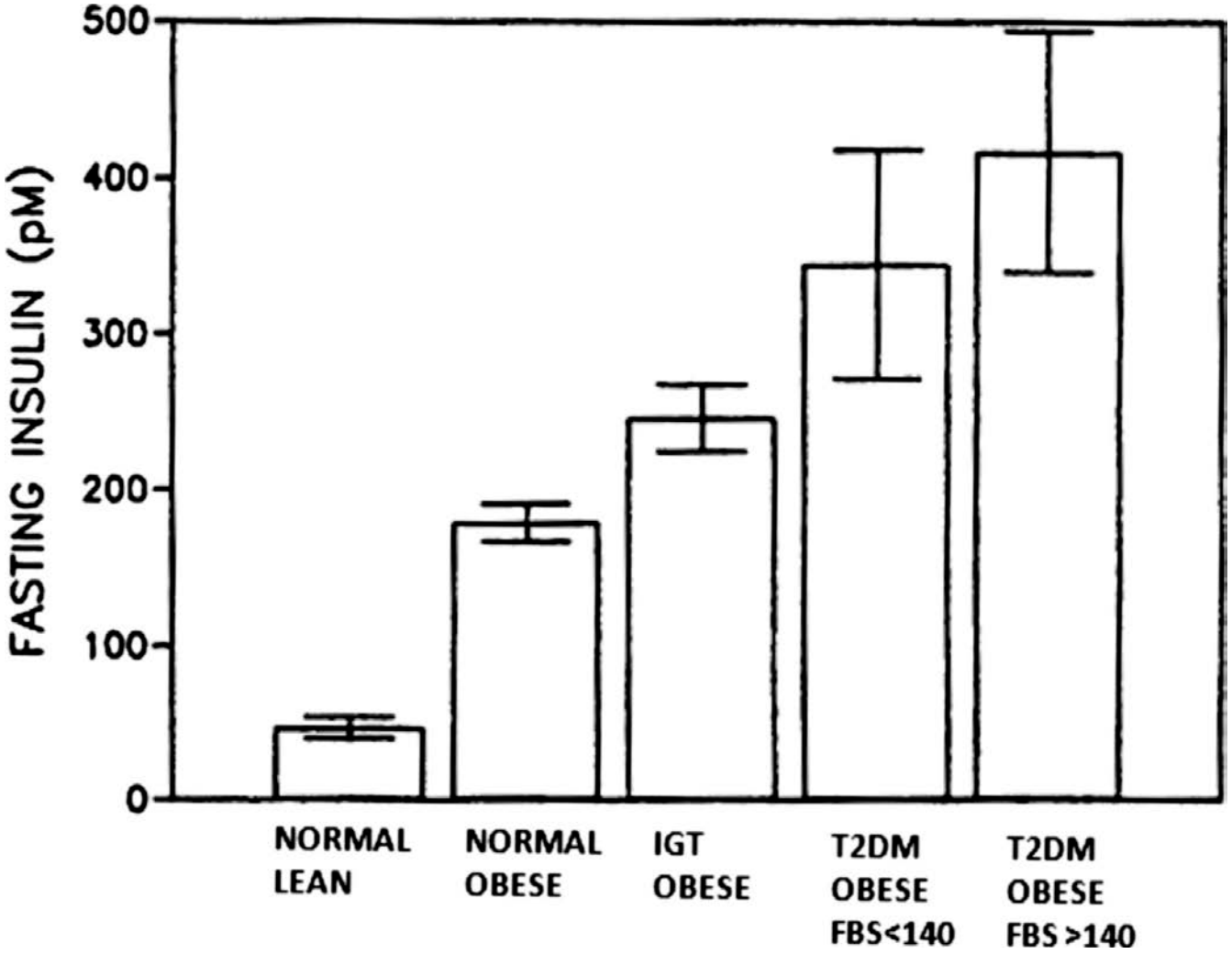


Barbara E. Corkey Dia Care 2012;35:2432-2437
C.T: Kelly Surgery 2014, 156: 405-411

©2012 by American Diabetes Association

American Diabetes Association

Fasting insulin in normal lean, normal obese, IGT, early T2DM, and advanced T2DM (data previously published [5]).

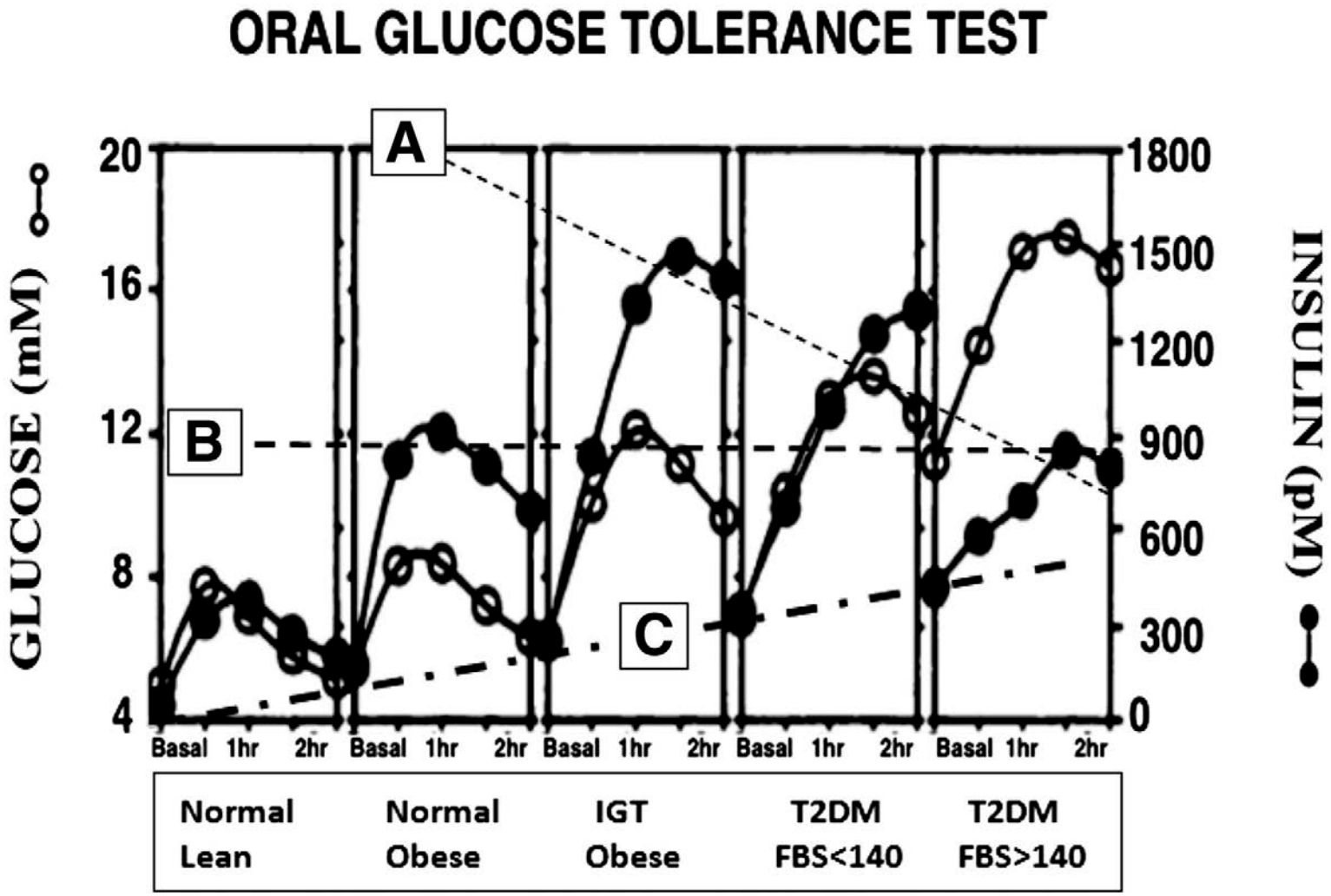


Walter J. Pories, and G. Lynis Dohm Dia Care 2012;35:2438-2442

©2012 by American Diabetes Association

American Diabetes Association

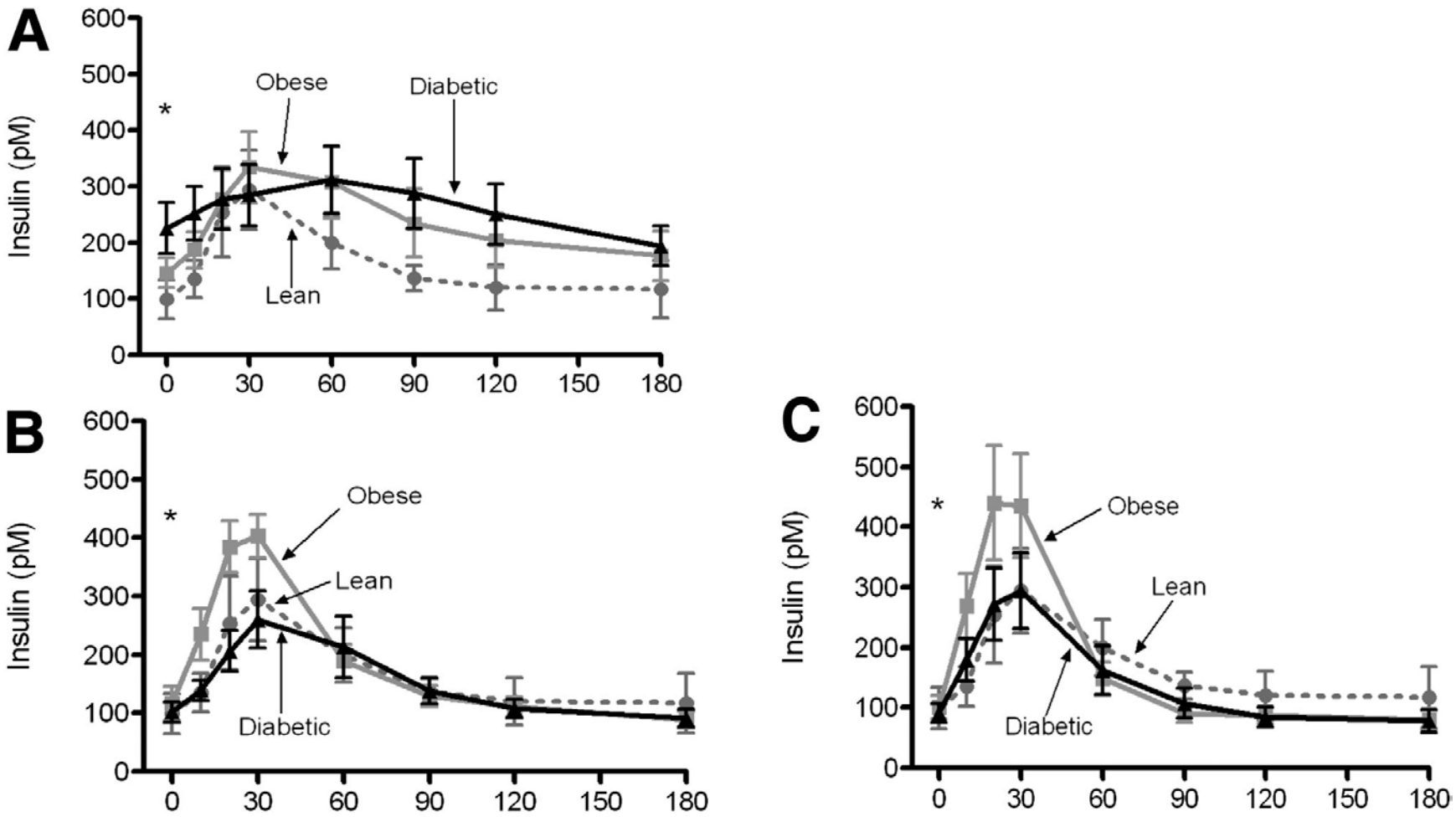
Glucose tolerance curves in five cohorts: normal lean, normal obese, IGT, early T2DM, and advanced T2DM (data previously published [5]).



Walter J. Pories, and G. Lynis Dohm Dia Care 2012;35:2438-2442

©2012 by American Diabetes Association

Plasma insulin in obese nondiabetic and diabetic patients after a mixed-meal challenge.



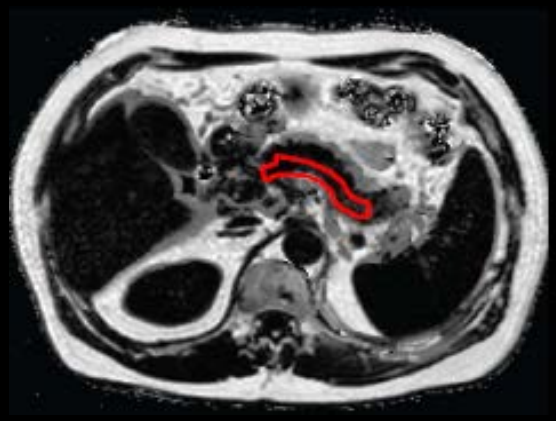
Walter J. Pories, and G. Lynis Dohm Dia Care 2012;35:2438-2442

©2012 by American Diabetes Association

American Diabetes Association

Counterpoint Study

Lim et al. Diabetologia 2011; 54 (10):2506-2514



a) Pancreas: beta cell function using an incremental insulin secretion test

b) Liver: insulin sensitivity by isoglycaemic hyperinsulinaemic clamp

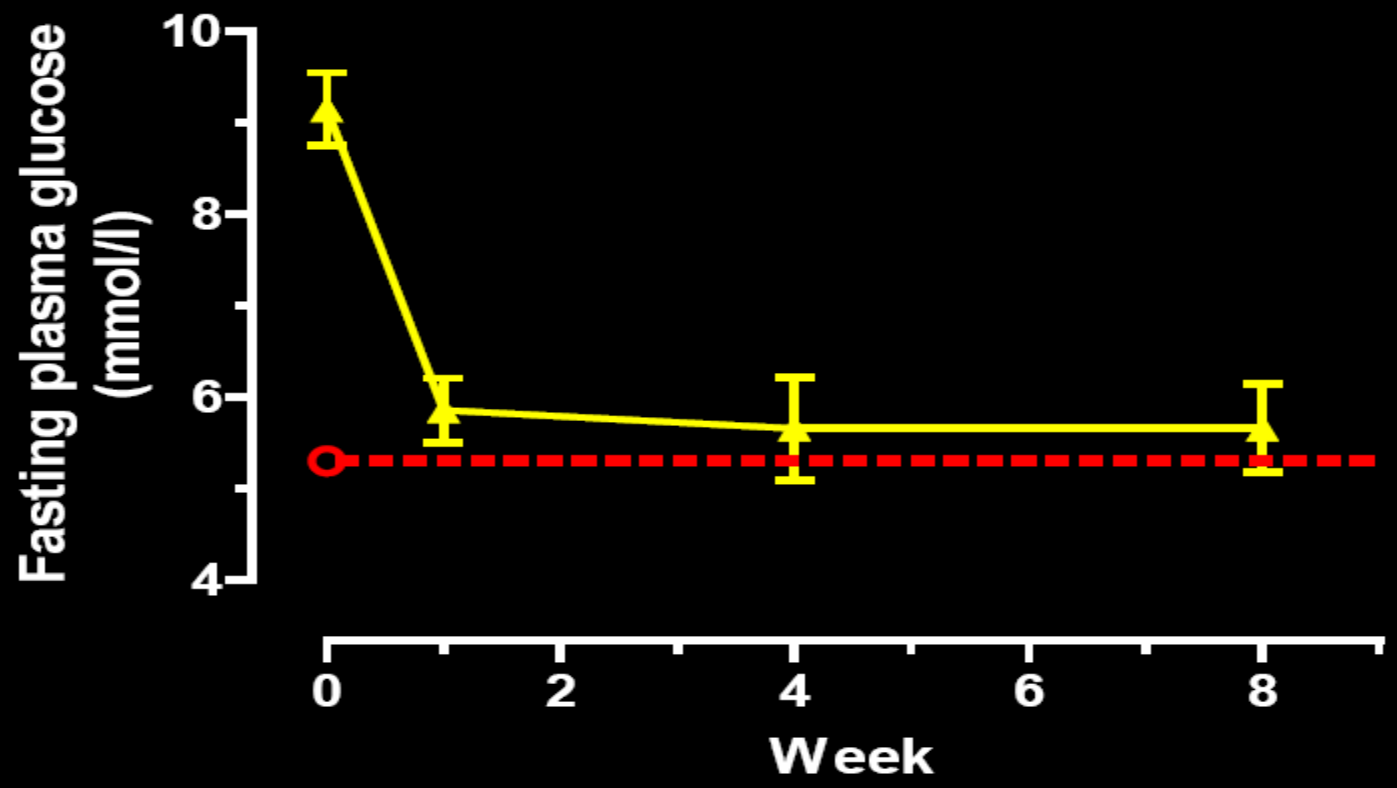
c) Liver and pancreatic fat levels: 3 point Dixon MR method

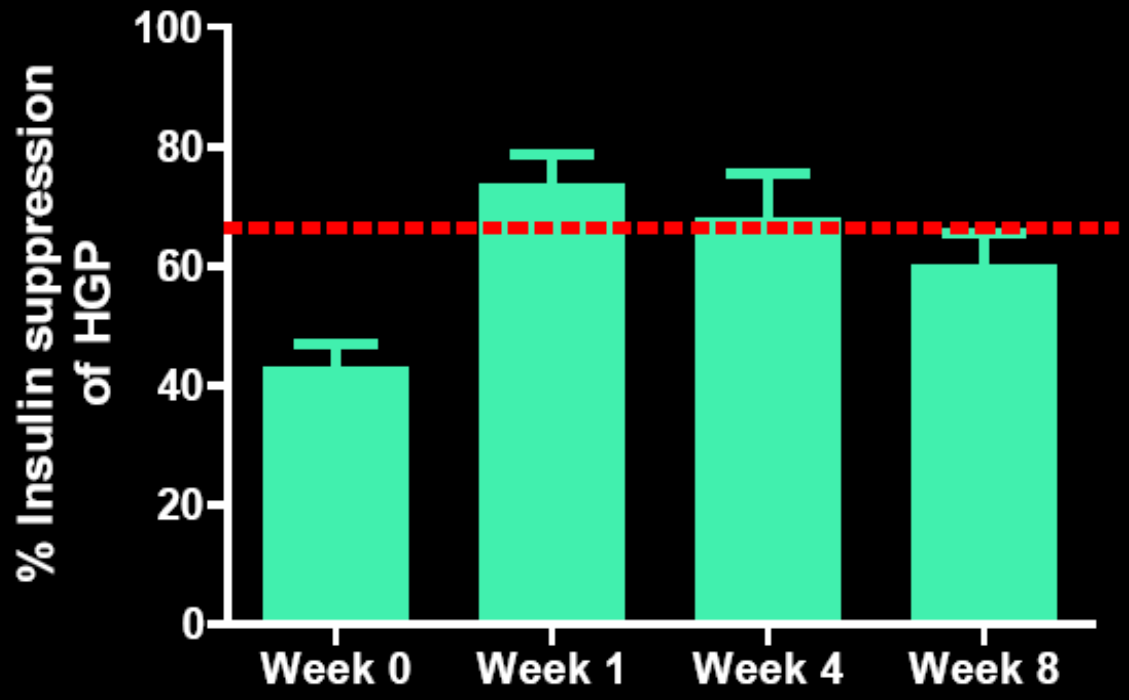
Counterpoint Study

Lim et al. Diabetologia 2011; 54 (10):2506-2514

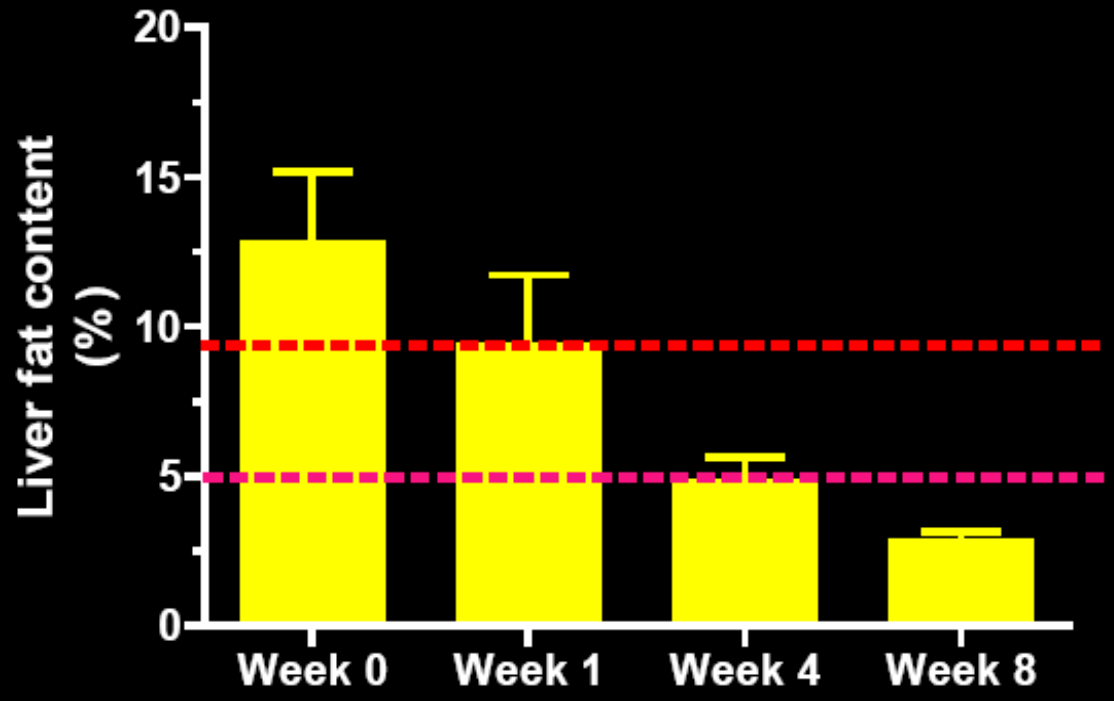
Plasma glucose

9.2 ± 0.4 → 5.9 ± 0.4 mmol/l; p = 0.003

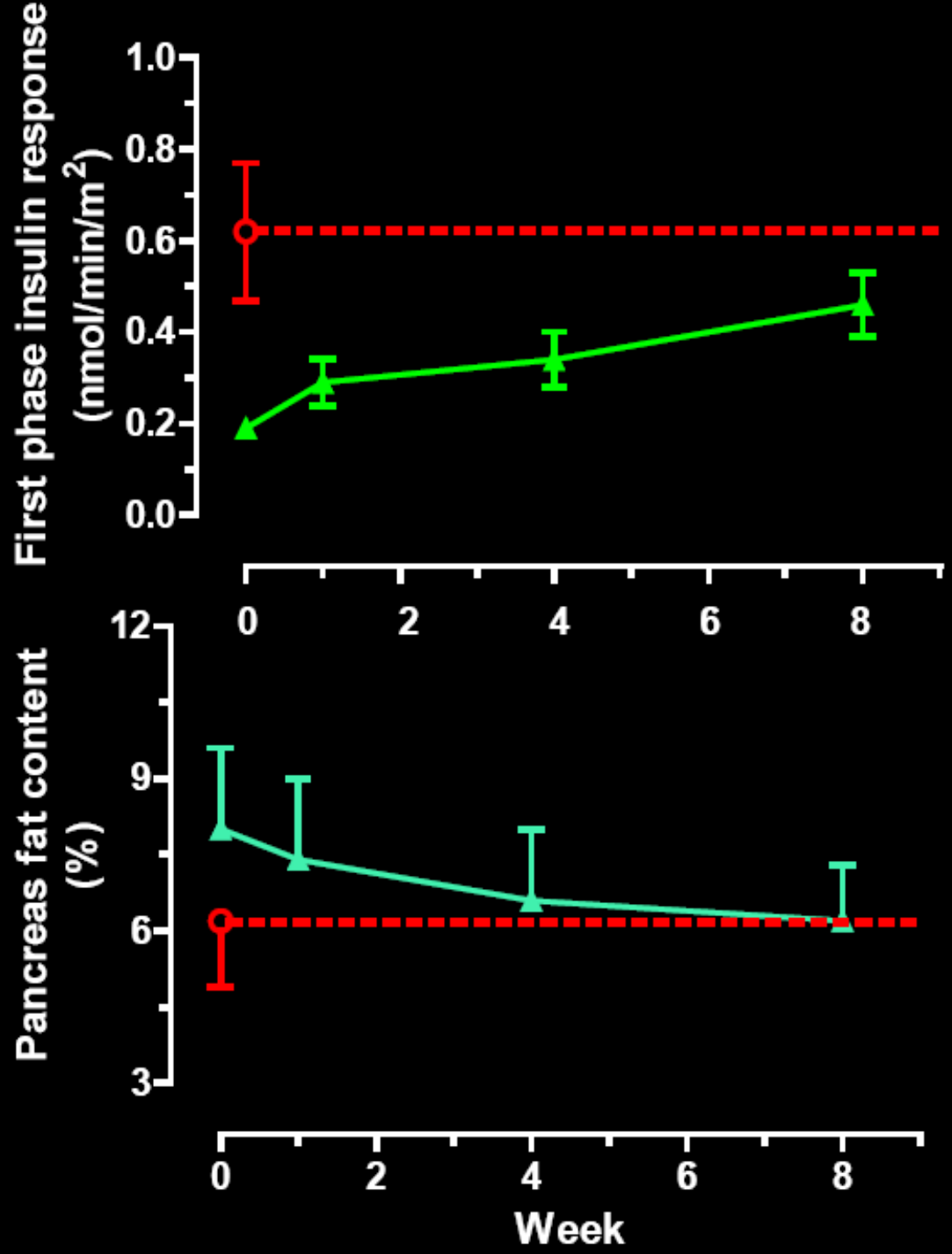




- CON: 68 ± 5%
  DM: 43 ± 4%
  (p = 0.001)
- Marked ↑ after 1 week of diet (74 ± 5%, p = 0.003)

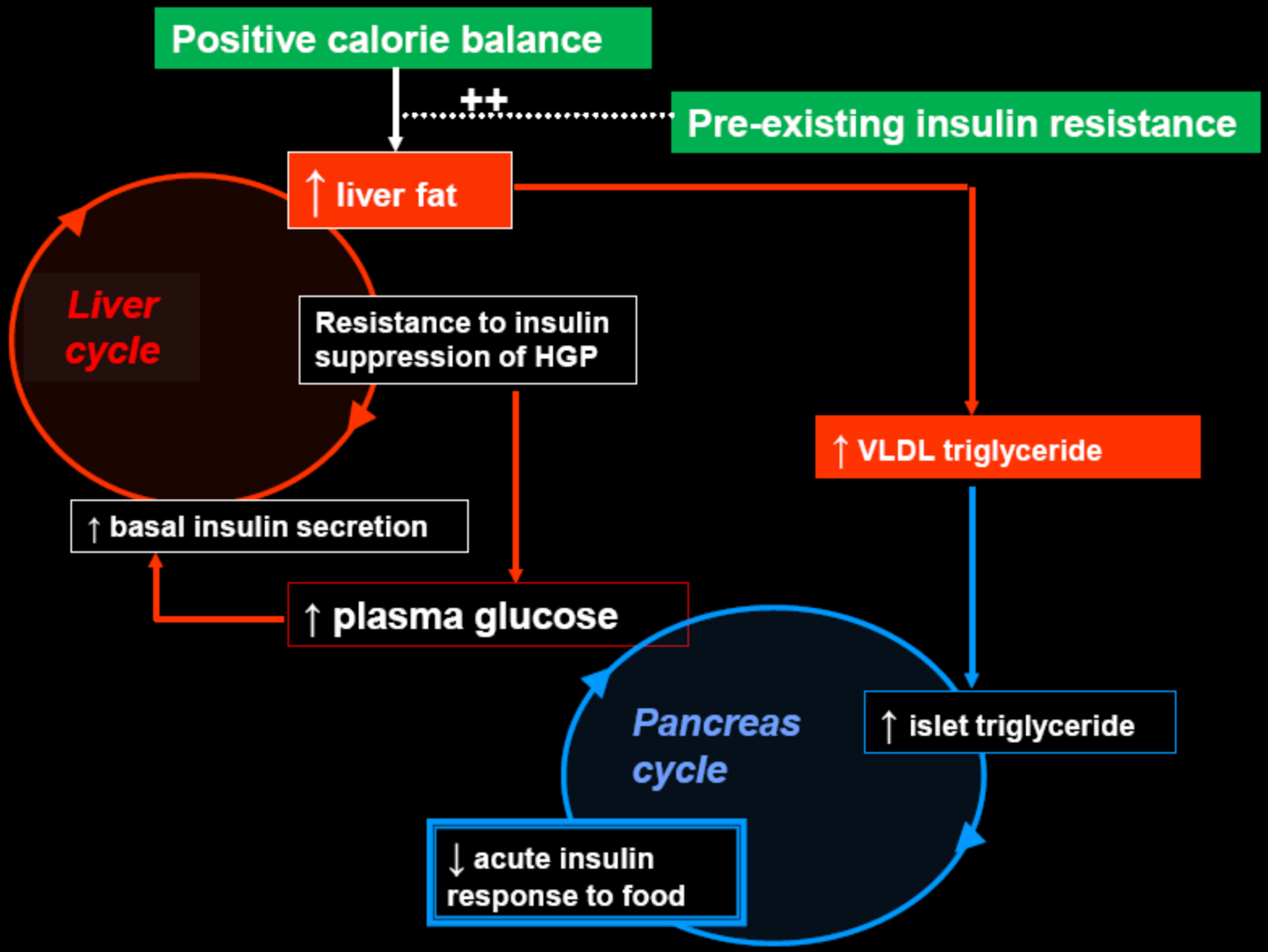


- CON: 8.5 ± 1.9%
  DM: 12.8 ± 2.4%
- Reduced by 30% during 1st week; 70% by 8 weeks



- Insulin secretion ↑ steadily
- At 8 weeks, similar to control values
- Pancreatic fat content fell gradually over 8 weeks

Aetiology of Type 2 Diabetes: Twin Cycle Hypothesis



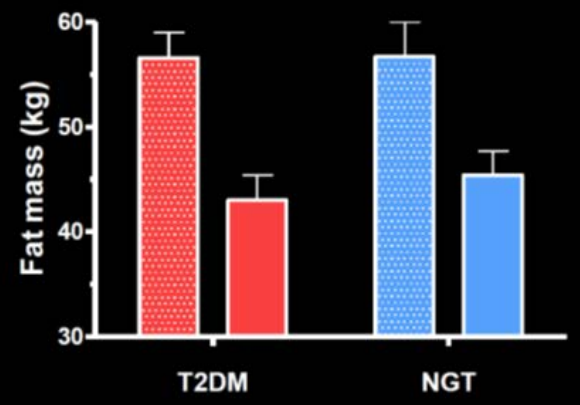
Taylor, Diabetologia 2008

The Pancreas Study

Question:
Is the decrease in triglyceride content of the pancreas specifically related to type 2 diabetes and it reversal?
Or is it merely a generalised effect of loss of fat from the body?

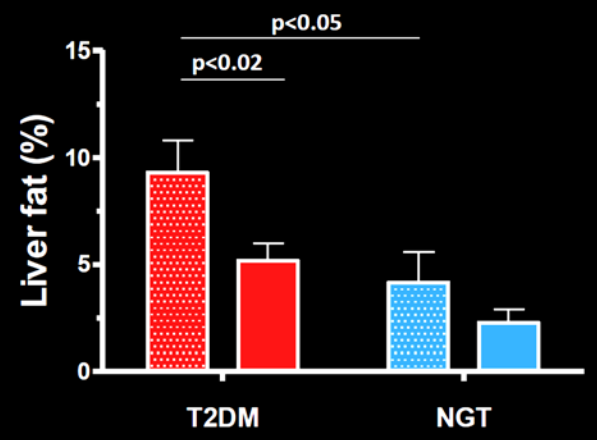
Design:
Compare pancreas triglyceride in matched groups of people with and without type 2 diabetes undergoing identical weight loss

Fat mass in type 2 diabetic and normal glucose tolerance groups – before and after weight loss



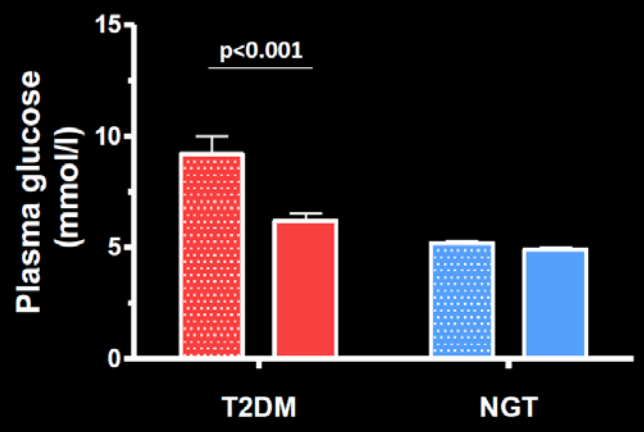
Decrease body weight 13.6±0.7% 12.8 ± 0.8%

Liver fat in T2DM and NGT – before and after weight loss

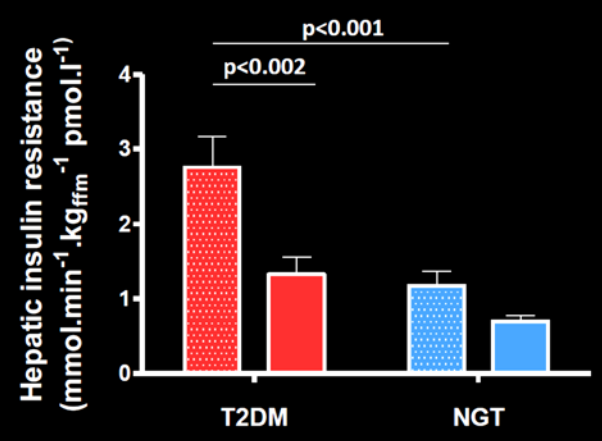


Steven et al, Diabetes Care 39(1):158-65; *2016*

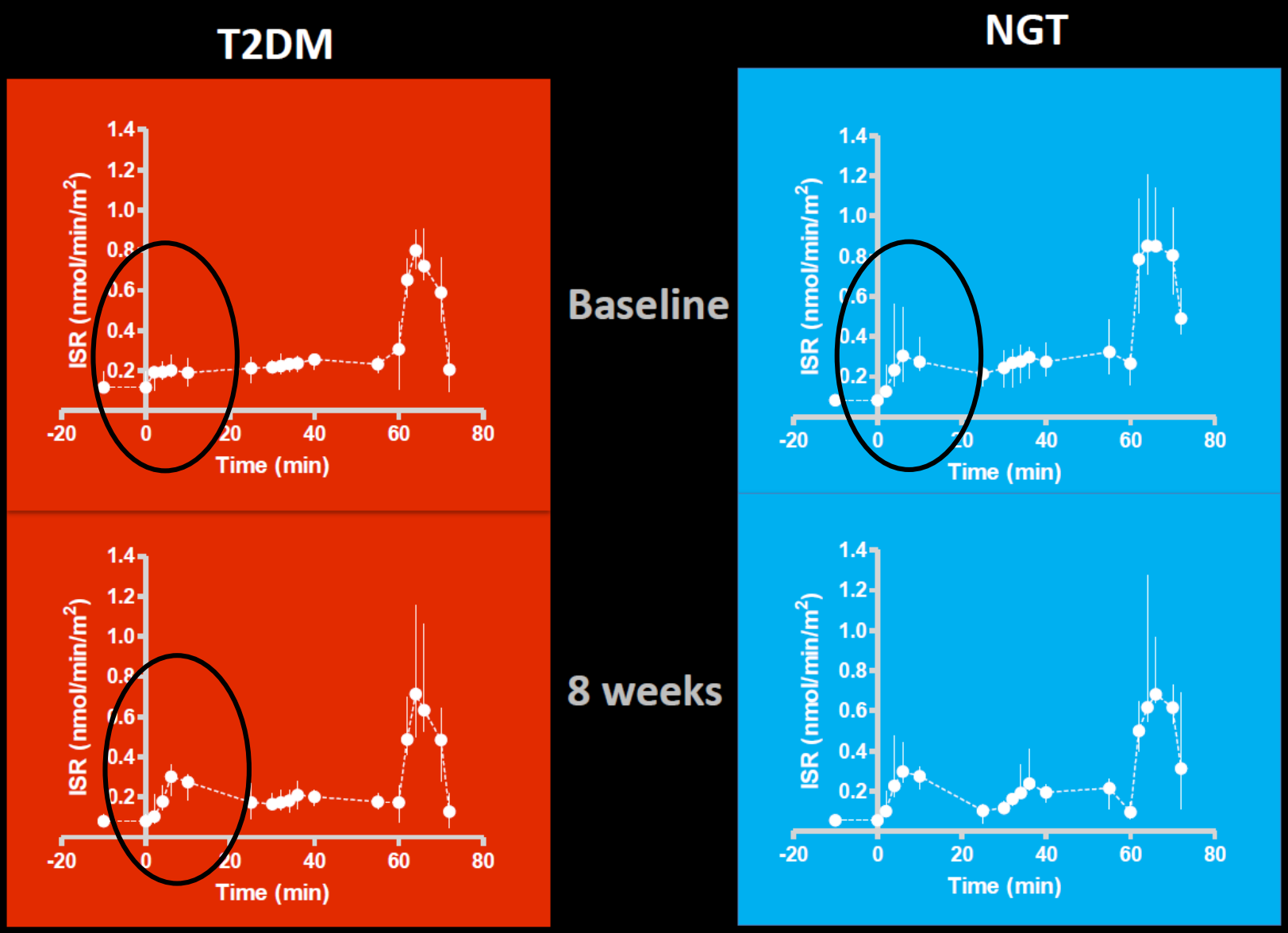
Fasting plasma glucose in T2DM and NGT – Before and after weight loss



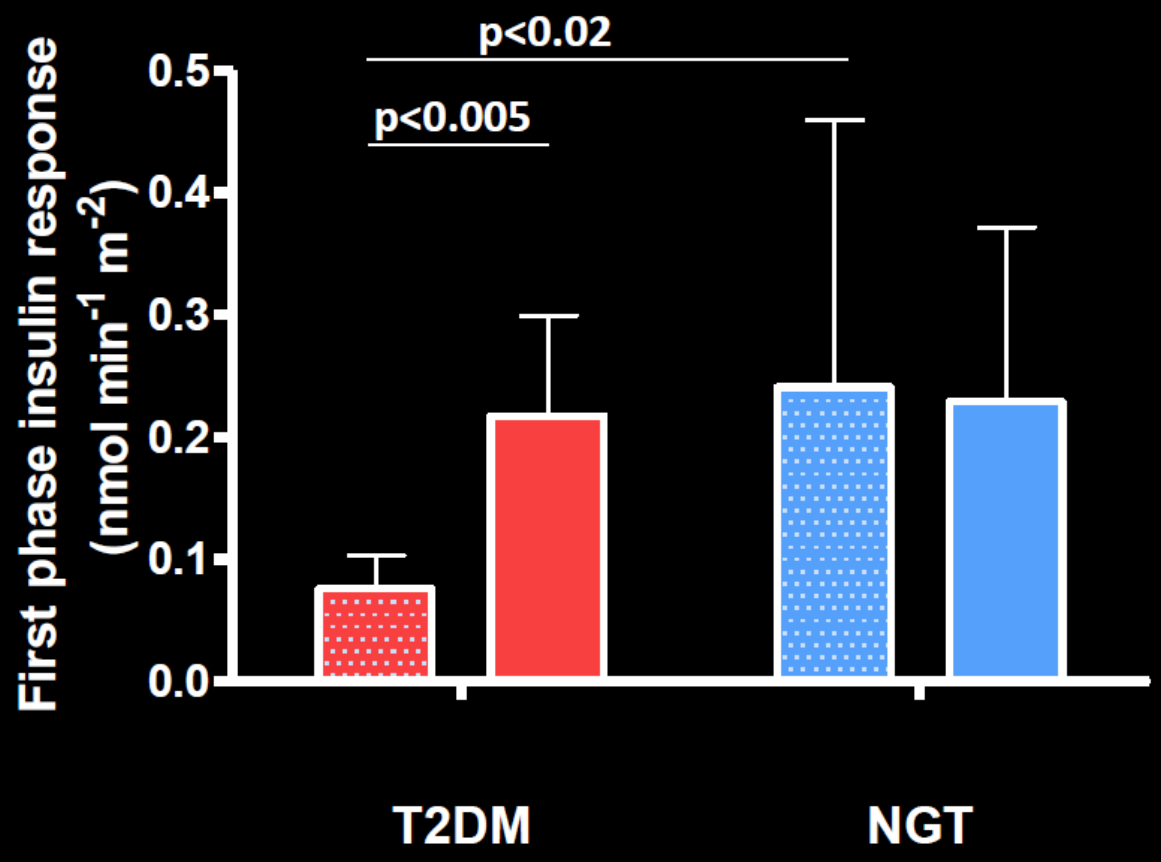
Hepatic insulin resistance in T2DM and NGT – before and after weight loss



Insulin secretion before and after weight loss

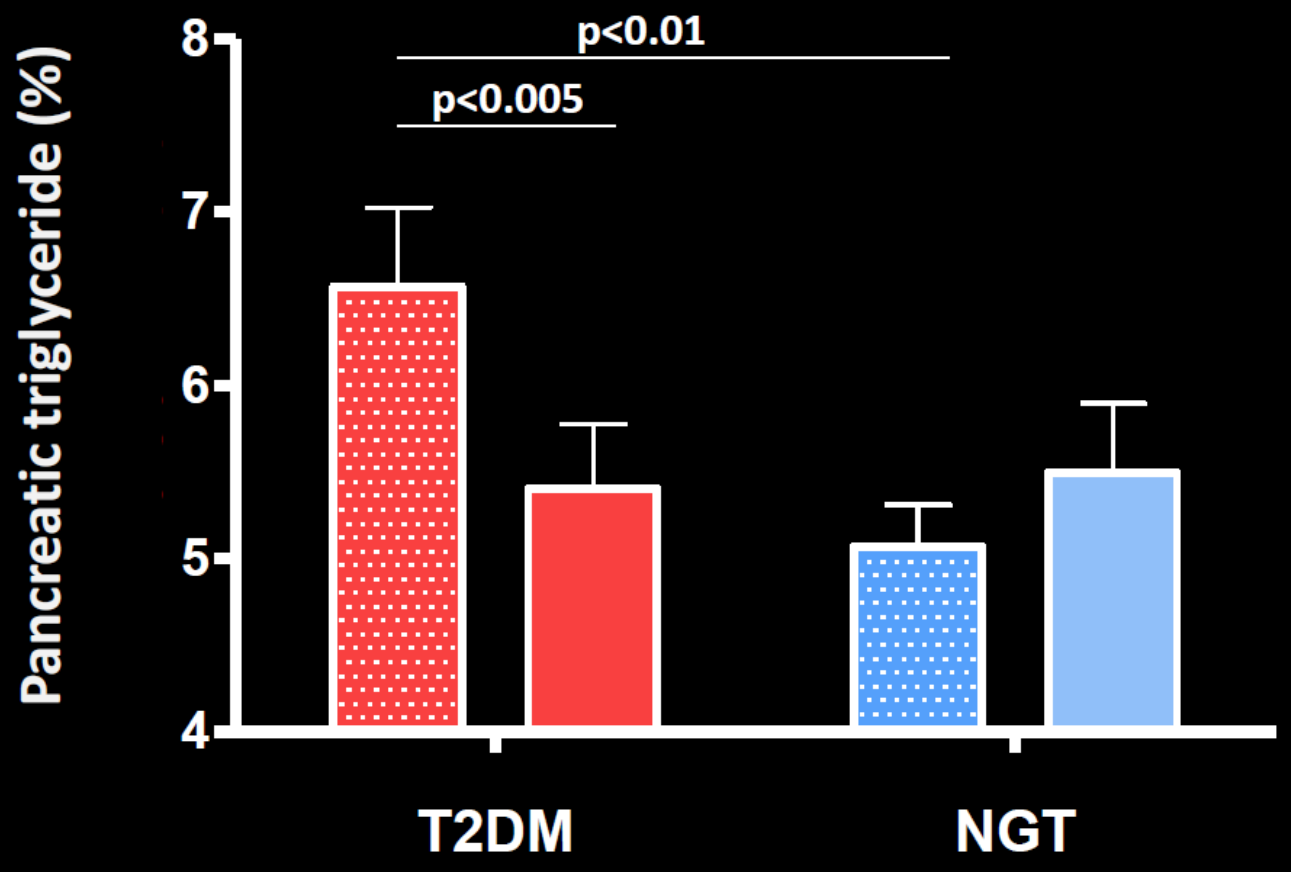


First phase insulin secretion in T2DM and NGT – before and after weight loss



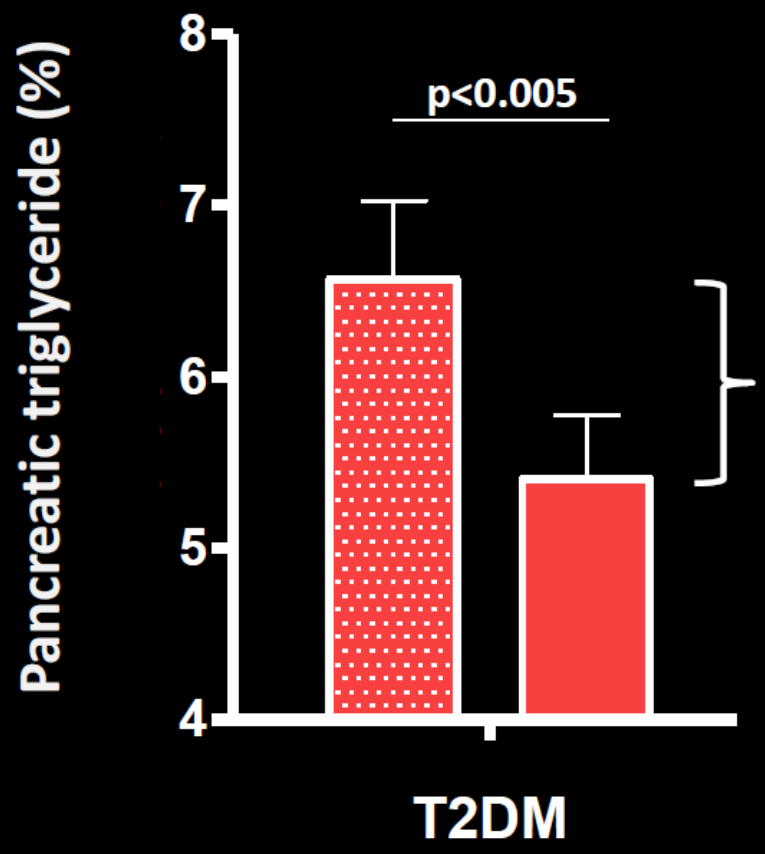
Steven et al, Diabetes Care 39(1):158-65; *2016*

Pancreatic triglyceride in T2DM and NGT – before and after weight loss



Steven et al, Diabetes Care 39(1):158-65; *2016*

Pancreatic triglyceride in T2DM before and after weight loss



Decrease of 1.2%
Mean pancreas volume ~50ml

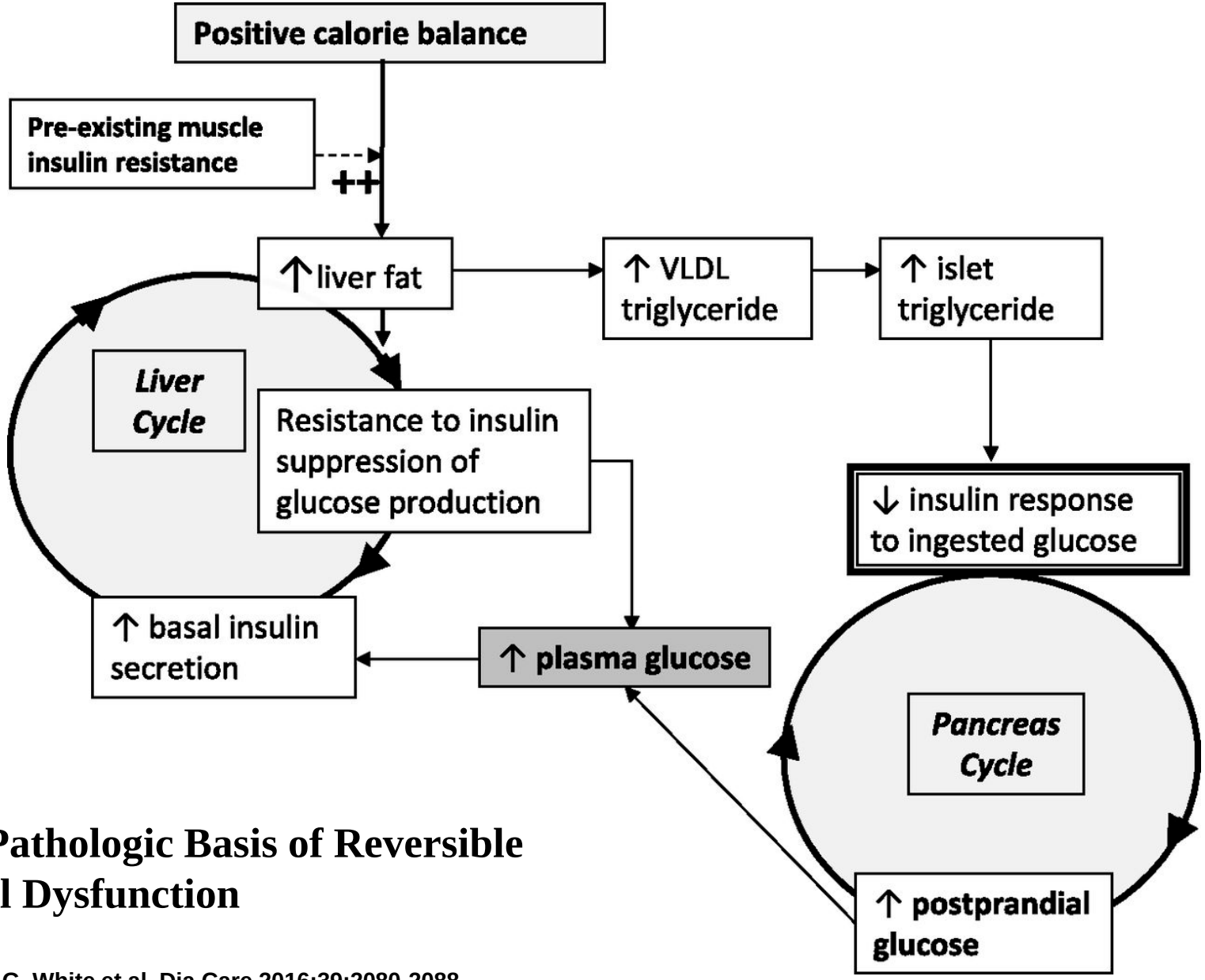
This represents ~0.6 grams of fat

Steven et al, Diabetes Care 39(1):158-65; *2016*

Conclusions:

Weight loss over 8 weeks brings about loss of pancreatic triglyceride specifically in type 2 diabetes

It is likely that type 2 diabetes is caused by less than 1 gram of fat in the pancreas



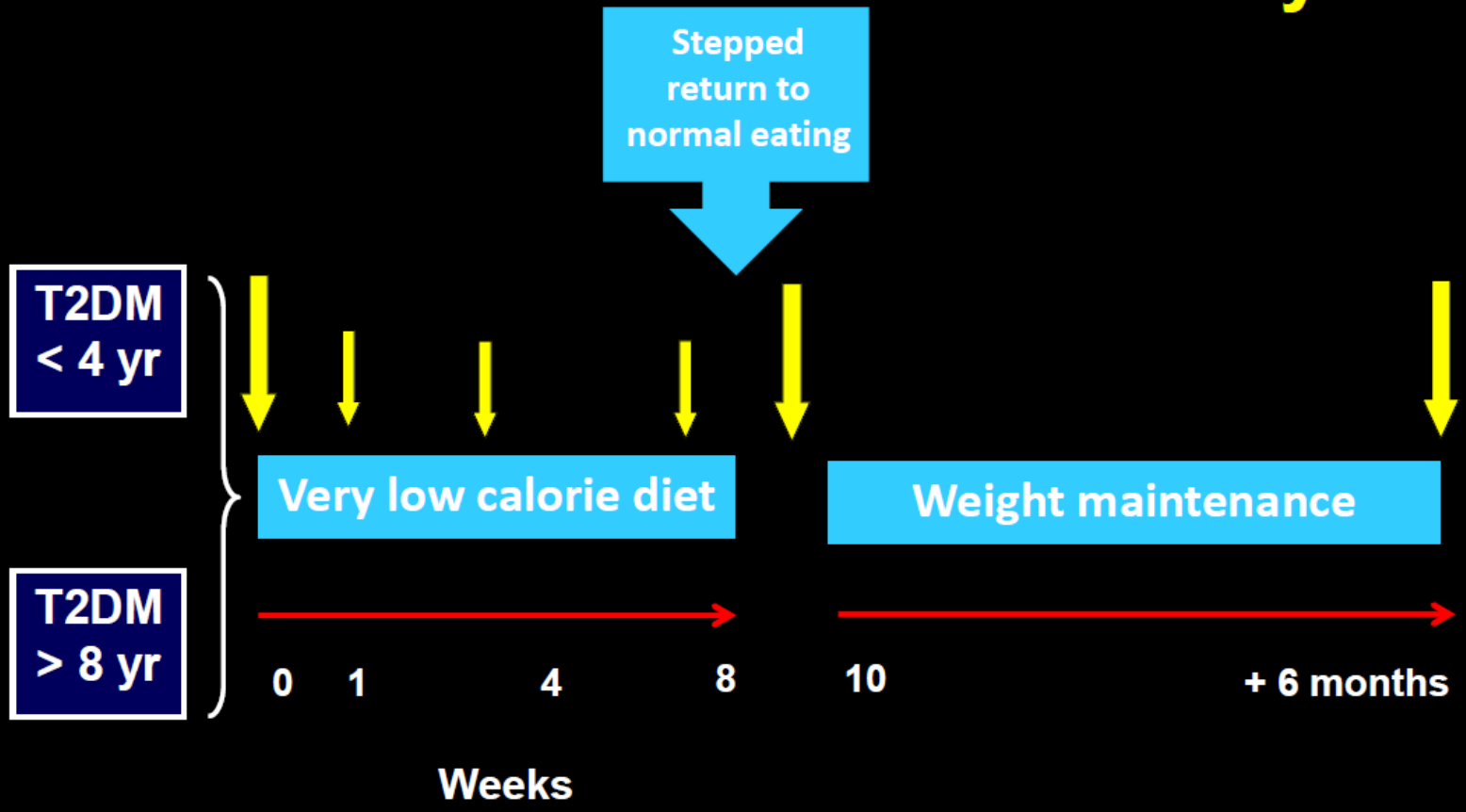
The Pathologic Basis of Reversible β-Cell Dysfunction

Michael G. White et al. Dia Care 2016;39:2080-2088

©2016 by American Diabetes Association

American Diabetes Association

Protocol for CounterBalance study

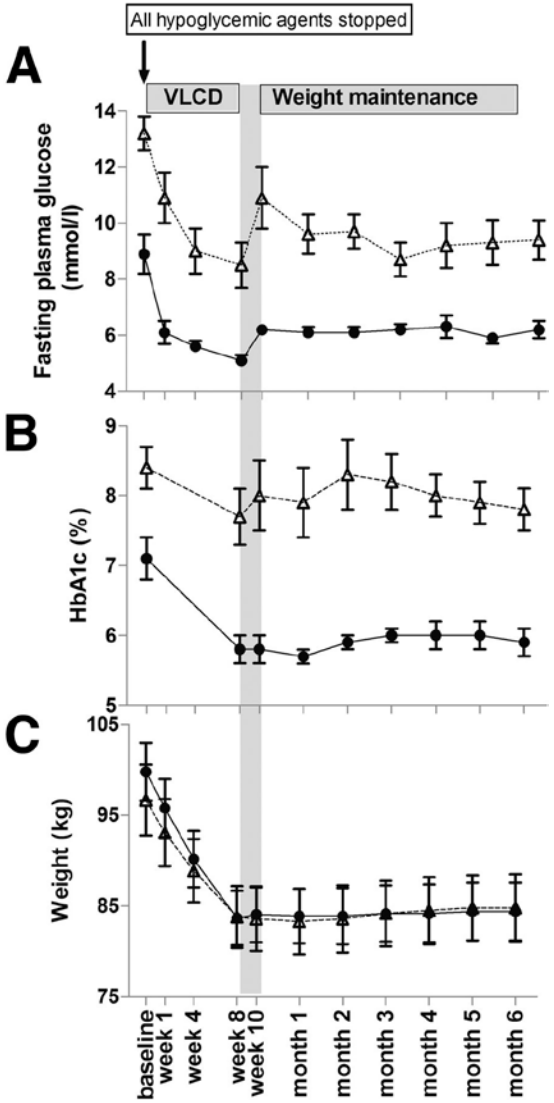


Questions:

Can people with longer duration type 2 diabetes reverse to normal?

Is the reversal of type 2 diabetes durable if body weight remains stable?

Change in fasting plasma glucose (A), HbA1c (B), and weight (C) over the study in responders (●) and nonresponders (△).

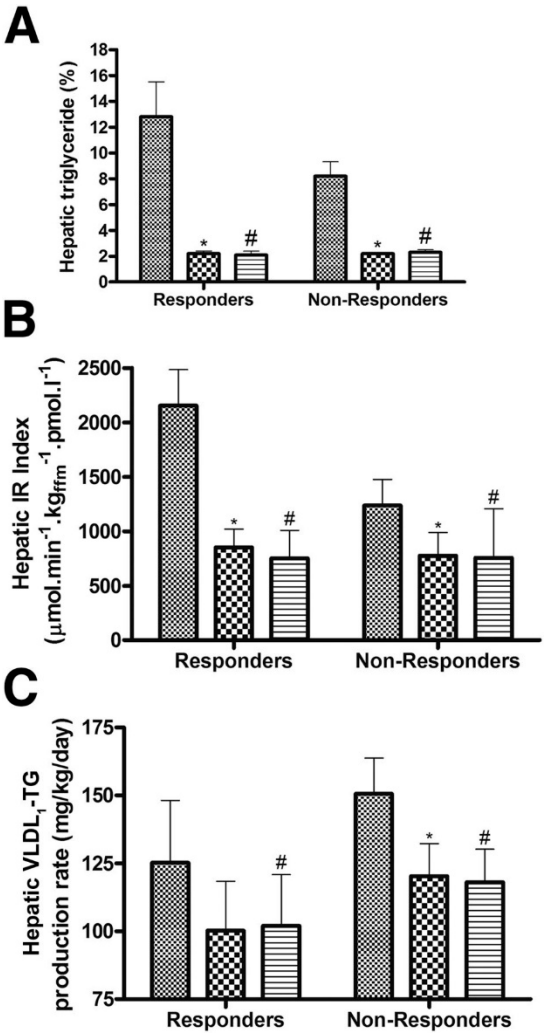


Sarah Steven et al. Dia Care 2016;39:808-815

©2016 by American Diabetes Association

American Diabetes Association

Hepatic triglyceride content (A), hepatic insulin resistance index (B), and hepatic VLDL1-triglyceride production (C) in responders and nonresponders at baseline (hatched bars), after VLCD (checkered bars), and after 6 months of weight maintenance (striped bars). *P < 0.05 for baseline–to–post-VLCD difference; #P < 0.05 for baseline–to–month 6 difference.

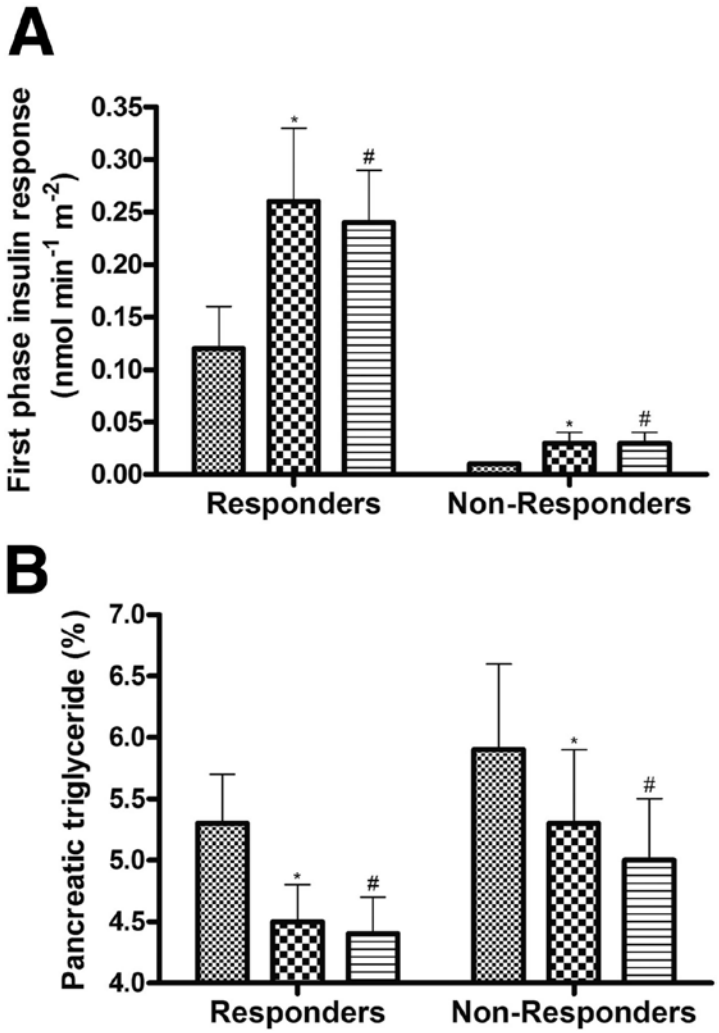


Sarah Steven et al. Dia Care 2016;39:808-815

©2016 by American Diabetes Association

American Diabetes Association

Change in first-phase insulin response (A) and pancreas triglyceride content (B) in responders and nonresponders at baseline (hatched bars), after VLCD (checkered bars), and after 6 months of weight maintenance (striped bars). *P < 0.05 for baseline–to–post-VLCD difference; #P < 0.05 for baseline–to–month 6 difference.



Sarah Steven et al. Dia Care 2016;39:808-815

©2016 by American Diabetes Association

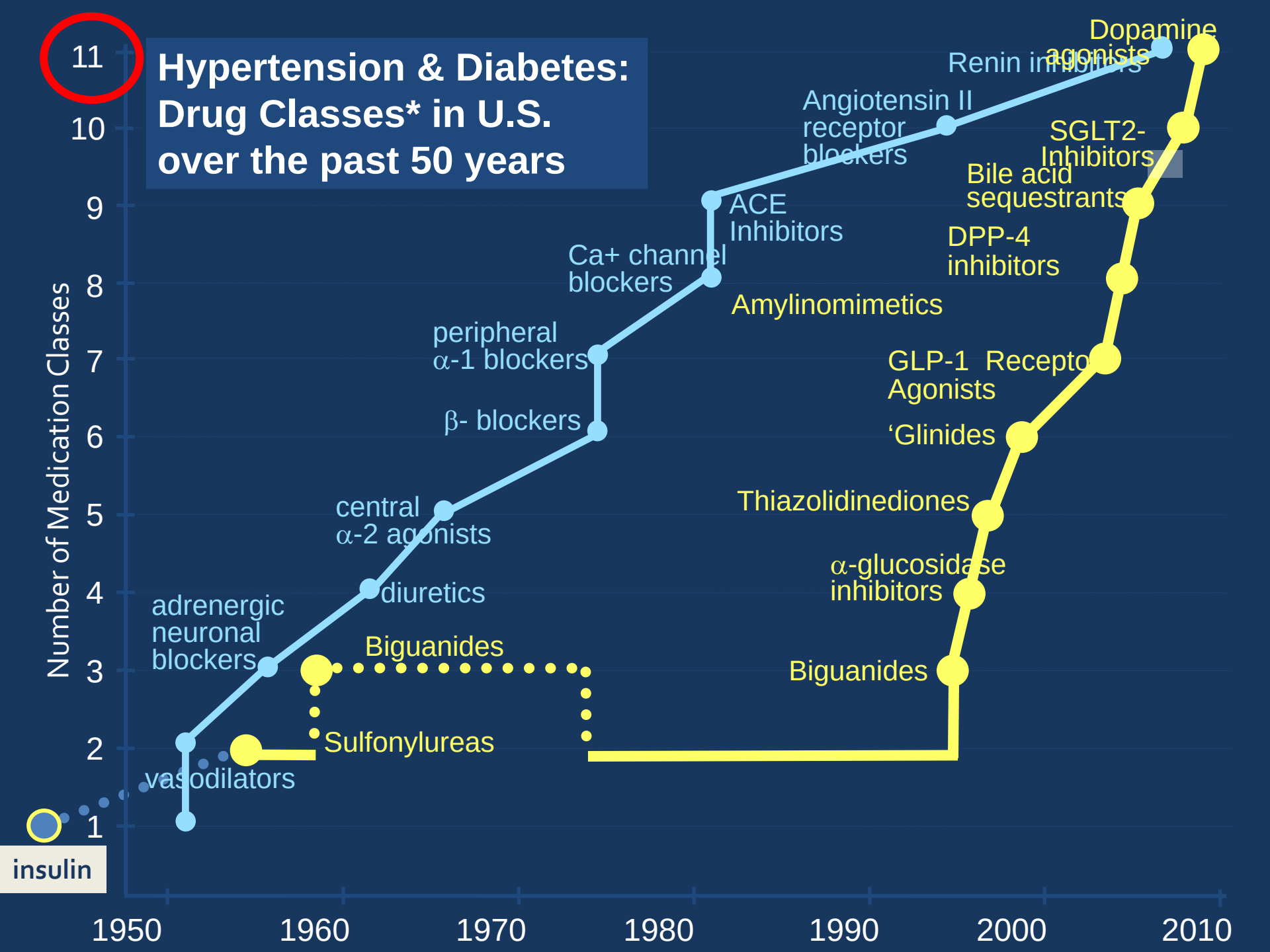
American Diabetes Association

DIABESITA'

- Obesità e diabete condividono fattori di rischio, meccanismi patogenetici e comorbità.
- L'obesità è considerata l'anticamera del diabete mellito tipo 2 che la complica insorgendo nel 50% dei casi.
- Il rapporto tra queste due cronicità non è univoco: nel paziente diabetico di tipo 2, sovrappeso ed obesità insorgono facilmente, favoriti sia dallo stato di insulinoresistenza che dal meccanismo di azione di alcuni farmaci ipoglicemizzanti tradizionalmente utilizzati nella gestione del controllo glicemico.

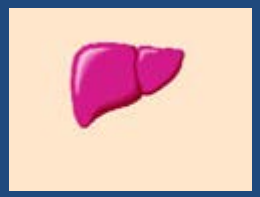
E’ sempre più evidente che i percorsi di cura del paziente ***diabeso*** devono necessariamente tenere conto della sua peculiarità clinica per poter essere efficaci nella gestione e del peso e del controllo glicometabolico.

- Il ruolo di un eccessivo apporto calorico, della inattività fisica e della obesità nella patogenesi del T2DM è pienamente riconosciuto in tutte le linee guida.
- Nonostante ciò, solo in rari casi viene raccomandato l'intervento sullo stile di vita come primo approccio.
- Nel 2008 EASD e ADA raccomandano di iniziare il trattamento con metformina alla diagnosi, in quanto dieta e stile di vita troppo spesso risultano fallimentari nel raggiungimento e mantenimento del peso.
- Negli ultimi anni, l'armamentario terapeutico farmacologico per il diabete si è notevolmente arricchito di molecole con effetto neutro o favorevole sul peso corporeo.
- Recentemente RYGB è stato proposto come *first line therapy* in soggetti diabetici e obesi con BMI >30.


Hypertension & Diabetes: Drug Classes* in U.S. over the past 50 years
Number of Medication Classes
11
10
9
8
7
6
5
4
3
2
1
1950
1960
1970
1980
1990
2000
2010
vasodilators
adrenergic neuronal blockers
Sulfonylureas
Biguanides
diuretics
central α-2 agonists
β- blockers
peripheral α-1 blockers
Ca+ channel blockers
ACE Inhibitors
Angiotensin II receptor blockers
Renin inhibitors
Dopamine agonists
Biguanides
α-glucosidase inhibitors
Thiazolidinediones
'Glinides
GLP-1 Receptor Agonists
Amylinomimetics
DPP-4 inhibitors
Bile acid sequestrants
SGLT2-Inhibitors
insulin

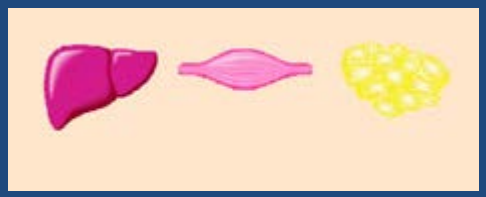
Caratteristiche dei farmaci orali

METFORMINA



SEGRETAGOGHI

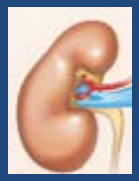
TIAZOLINEDIONI



ACARBOSIO

INCRETINO-MIMETICI

INIBITORI SGLT2

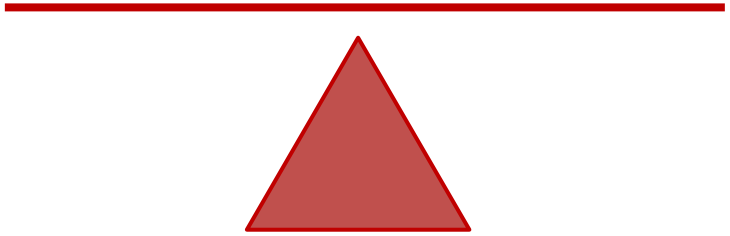


I FARMACI TRADIZIONALI: IL DIFFICILE EQUILIBRIO

- Incremento ponderale
- Ipoglicemie
- Stabile e duraturo controllo glicemico nel tempo

HbA1c

Peso Corporeo
Ipoglicemie



Finally….

- … Finally, is the current medical therapy for T2DM that includes insulin secretagogues and the administration of exogenous insulin an appropiate therapeutic approach, or is causing increased risk of developing other metabolic disorders?
- … Why are we treating a disease associated with hyperinsulinemia with additional insulin?

C.T. Kelly, Surgery 2014: 156: 405-411

Journal of Diabetes and Its Complications 28 (2014) 506–510

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Very-low-energy diet for type 2 diabetes: An underutilized therapy?

Amy E. Rothberg *, Laura N. McEwen, Andrew T. Kraftson, Christine E. Fowler, William H. Herman

University of Michigan, Department of Internal Medicine (AER, LNM, ATK, CEF)
University of Michigan, Departments of Internal Medicine and Epidemiology (WHH)

ARTICLE INFO

Article history:
Received 4 February 2014
Received in revised form 14 March 2014
Accepted 24 March 2014
Available online 29 March 2014

Keywords:
Obesity
Very-low energy diet
Type 2 diabetes mellitus
Weight management

ABSTRACT

Background: Current approaches to the management of type 2 diabetes focus on the early initiation of novel pharmacologic therapies and bariatric surgery.
Objective: The purpose of this study was to revisit the use of intensive, outpatient, behavioral weight management programs for the management of type 2 diabetes.
Design: Prospective observational study of 66 patients with type 2 diabetes and BMI ≥32 kg/m^2 who enrolled in a program designed to produce 15% weight reduction over 12 weeks using total meal replacement and low- to moderate-intensity physical activity.
Results: Patients were 53 ± 7 years of age (mean ± SD) and 53% were men. After 12 weeks, BMI fell from 40.1 ± 6.6 to 35.1 ± 6.5 kg/m^2. HbA1c fell from 7.4% ± 1.3% to 6.5% ± 1.2% (57.4 ± 12.3 to 47.7 ± 12.9 mmol/mol) in patients with established diabetes: 76% of patients with established diabetes and 100% of patients with newly diagnosed diabetes achieved HbA1c <7.0% (53.0 mmol/mol). Improvement in HbA1c over 12 weeks was associated with higher baseline HbA1c and greater reduction in BMI.
Conclusions: An intensive, outpatient, behavioral weight management program significantly improved HbA1c in patients with type 2 diabetes over 12 weeks. The use of such programs should be encouraged among obese patients with type 2 diabetes.

MECCANISMI COINVOLTI NELLA REGOLAZIONE GLICOMETABOLICA IN CORSO DI VLCKD

- Perdita di peso
- Restrizione calorica
- Ridotto contenuto di carboidrati
- Composizione specifica della dieta
- Ruolo specifico dei corpi chetonici
- WP e Inibizione endogena DPP- 4

Nel soggetto diabetico l'effetto ipoglicemizzante della VLCKD è così rapido e rilevante da determinare nella quasi totalità dei pazienti la sospensione o la riduzione della terapia antidiabetica.

Unitamente all'effetto sul peso e sul controllo glicemico, la VLCKD migliora significativamente tutti i parametri della sindrome metabolica.

The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus

EC Westman, Nutrition and Metabolism, 2008

…Additionally, there was no correlation between change in hemoglobin A1c and change in weight

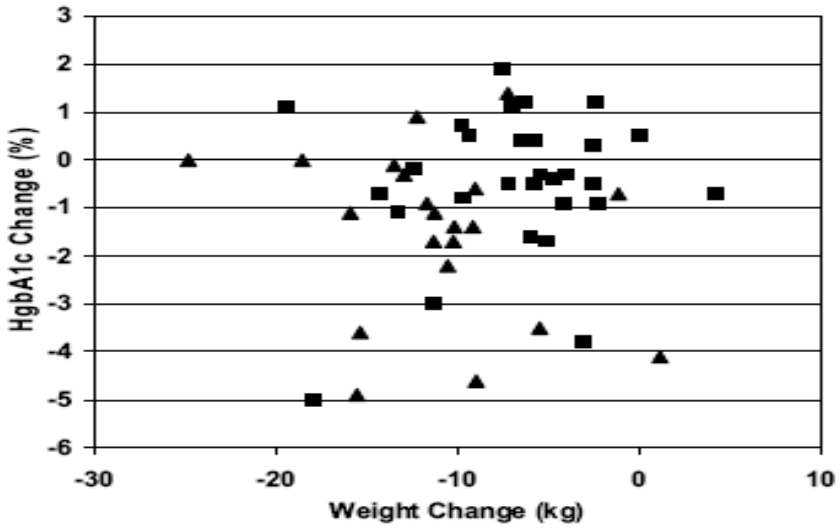


Figure 2
Relationship between change in hemoglobin A1c and change in weight. This figure plots the change in hemoglobin A1c vs. the change in weight from baseline to week 24 for each individual ($r = 0.09425$, $p = 0.5150$). The LCKD group is shown as triangles; the LGID group is shown as squares.

2. Restrizione calorica

Nutrition 28 (2012) 1016–1021

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

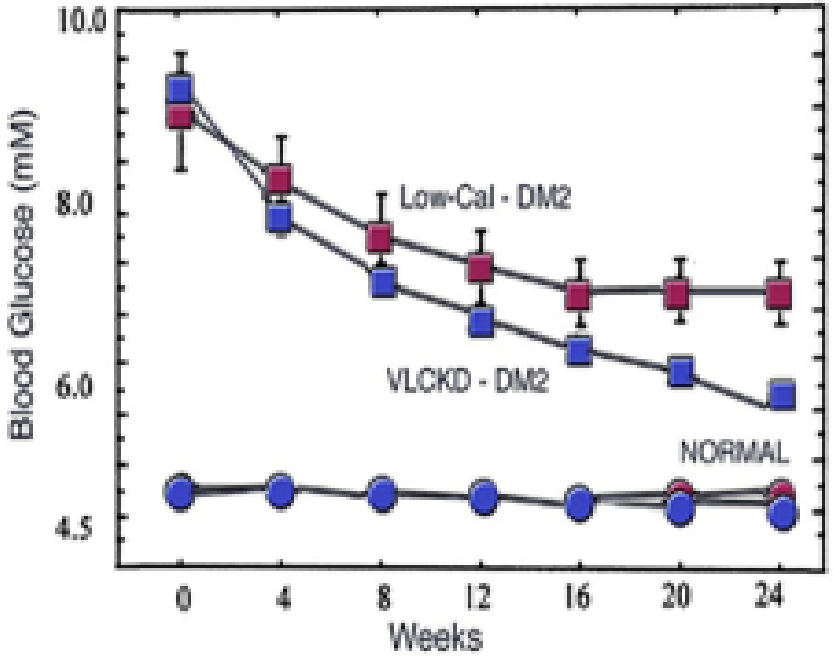
Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes

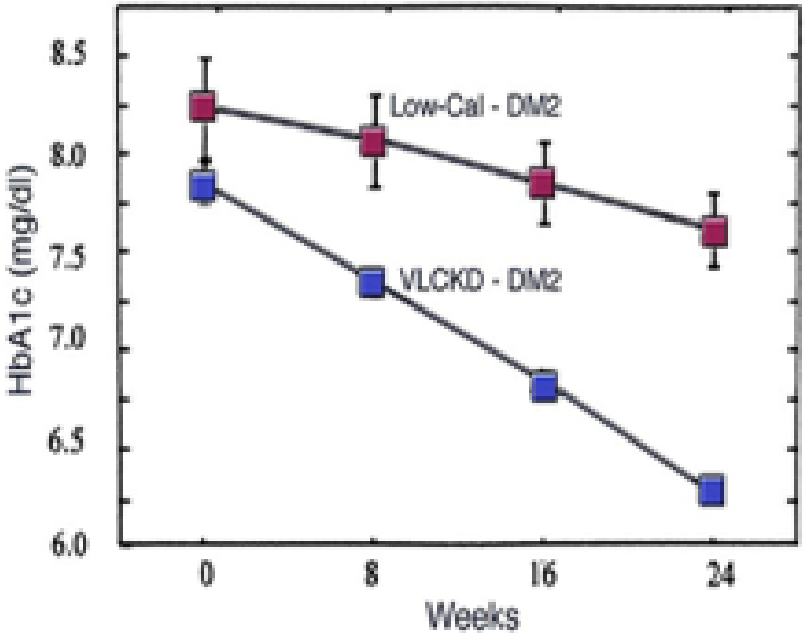
Talib A. Hussain M.B., Ch.B., R.C.G.P. [a], Thazhumpal C. Mathew M.Sc., Ph.D., F.R.C.Path. [b], Ali A. Dashti M.Sc., Ph.D. [b], Sami Asfar M.B., Ch.B., M.D., F.R.C.S., F.A.C.S. [c], Naji Al-Zaid B.Sc., Ph.D. [d], Hussein M. Dashti M.D., Ph.D., F.I.C.S., F.A.C.S. [c,*]

[a] *Al Shaab Family Medicine Medical Center, Ministry of Health, Kuwait*
[b] *Department of MLS, Faculty of Allied Health Sciences, Health Sciences Center, Kuwait University, Kuwait*
[c] *Department of Surgery, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait*
[d] *Department of Physiology, Faculty of Medicine, Health Sciences Center, Kuwait University, Kuwait*

Glicemia e HbA1c durante VLCKD vs LCD

T.A. Hussein, Nutrition 2012, 28: 1016-21





The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus

3. Carico glicemico

EC Westman, Nutrition and Metabolism, 2008

Mean Change Week 0 to 24	LGID	LCKD
HbA1c%	- 0.5	- 1.5
FPG mg/dl	- 16	- 19.9
Fasting Insulin mcU/mL	- 2.2	- 6.0
BMI (kg/m2)	- 2.7	- 3.9
BW (kg)	- 6.9	- 11.1

Il miglioramento del controllo glicemico non correla con l'entità del peso perso.

Inoltre, si mantiene sia nelle fasi di graduale reintroduzione dei carboidrati dopo la fase intensiva della VLCKD, sia alla ripresa di un'alimentazione normocalorica bilanciata.

Si mantiene più a lungo del peso corporeo.

European Journal of Endocrinology (2006) **155** 161–165 ISSN 0804-4643

CLINICAL STUDY

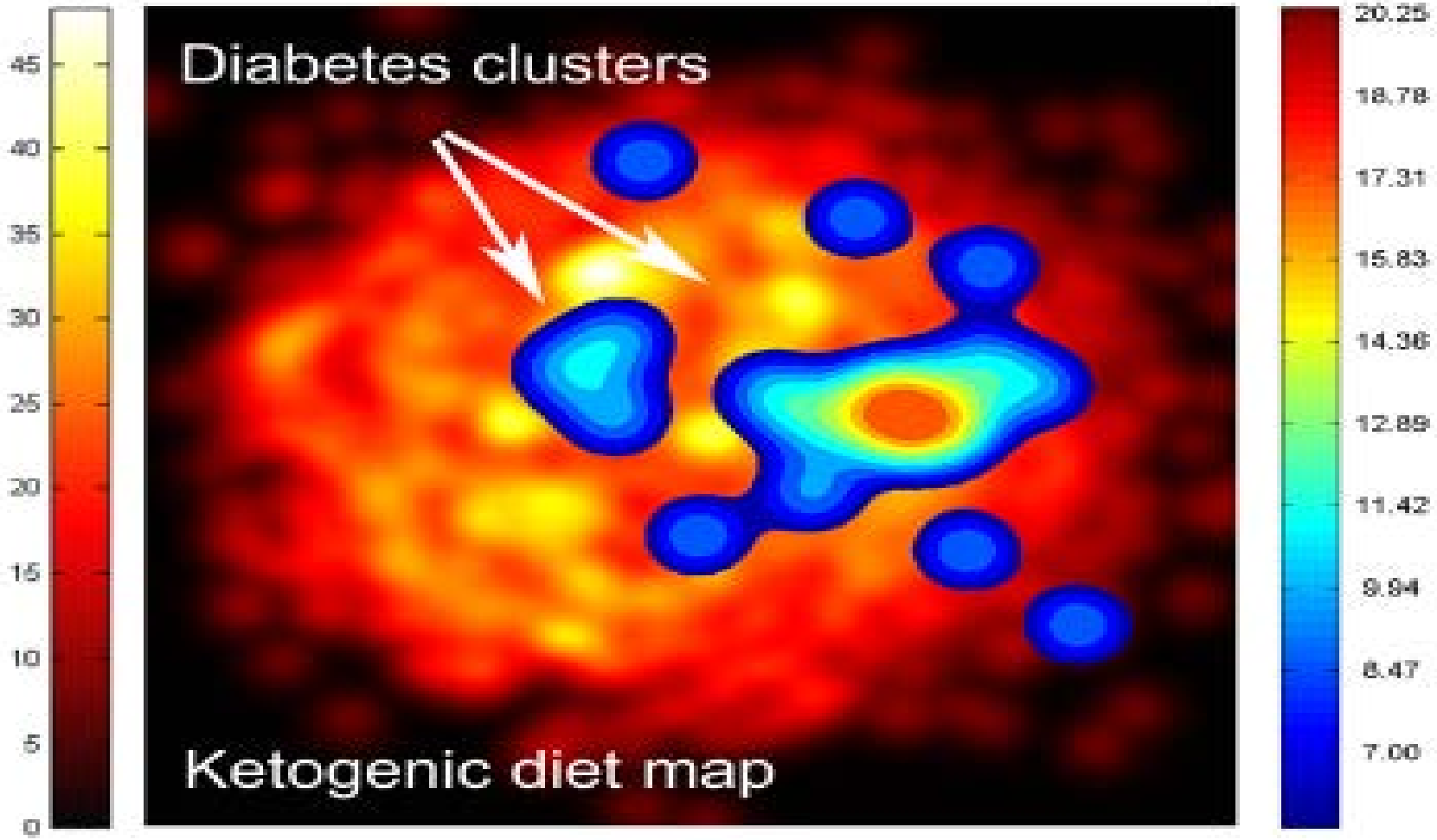
Increased adiponectin receptor-1 expression in adipose tissue of impaired glucose-tolerant obese subjects during weight loss

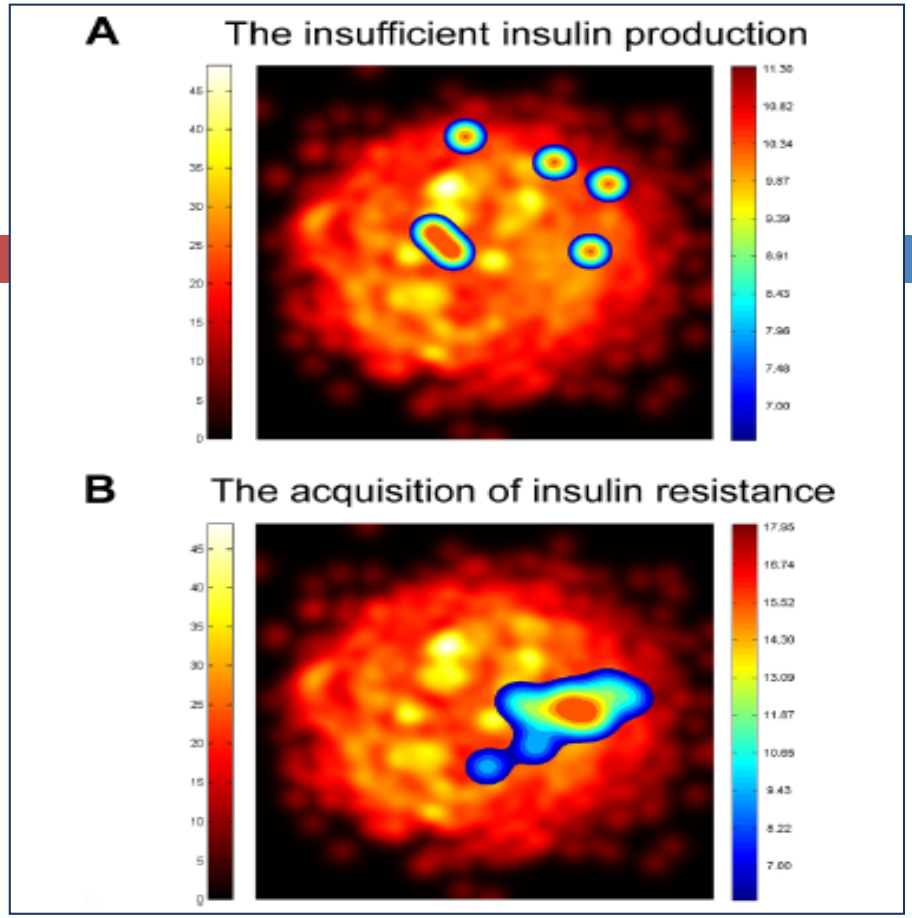
M J Kim[1], M Maachi[1,3], C Debard[4], E Loizon[4], K Clément[2], E Bruckert[5], B Hainque[6,7], J Capeau[1,3], H Vidal[4] and J P Bastard[1,3]

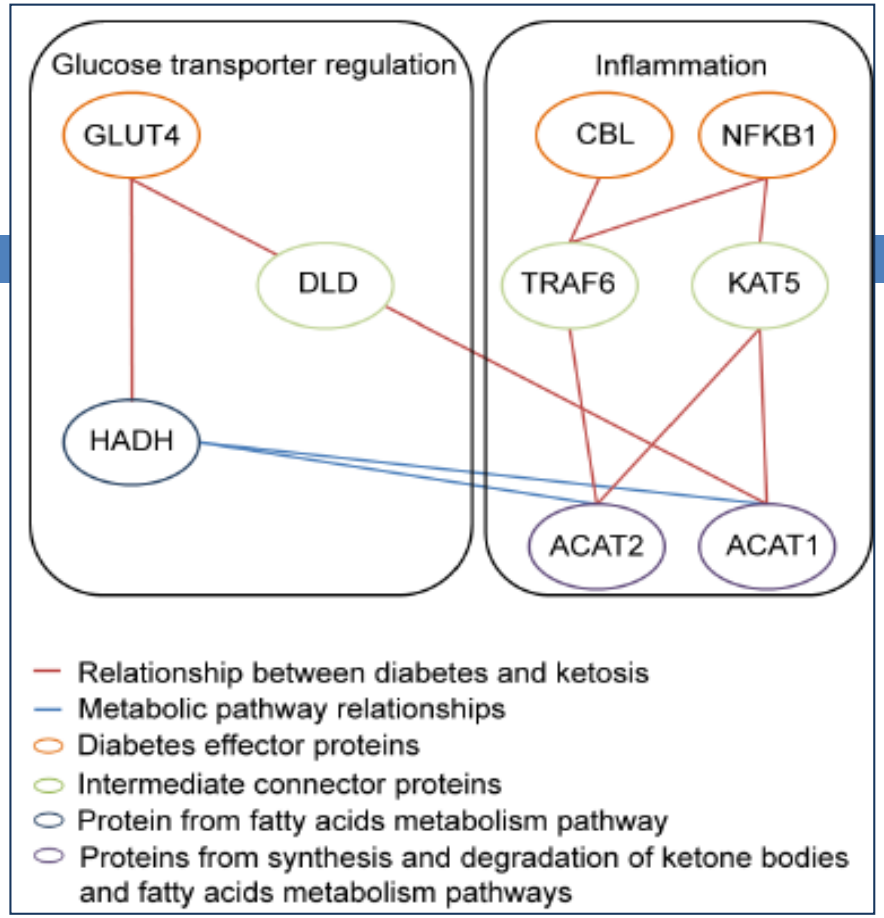
In summary, we show for the first time that the expression of AdipoR1 increased in human s.c.-abdominal adipose tissue of IGT obese subjects during VLCD and confirm that the two adiponectin receptors were differentially regulated under diet manipulation in obese subjects. The coordinate regulation of the adiponectin system in the adipose tissue could be involved in adiponectin action at this level and in increased insulin sensitivity. The factors and the molecular mechanisms involved in adiponectin receptors regulation require further investigations.

Revealing the molecular relationship between type 2 diabetes and the metabolic changes induced by a very-low-carbohydrate low-fat ketogenic diet

Judith Farrés[1], Albert Pujol[1,2], Mireia Coma[1,3], Jose Luis Ruiz[2], Jordi Naval[1], José Manuel Mas[1], Agustí Molins[4], Joan Fondevila[5], Patrick Aloy[2,6*]







1. Elements of lipid metabolism may facilitate proper cellular localization of glucose trasporter and recycling

2. Ketone bodies can alleviate certain infiammatory processes by blocking specific cytokines.

Diabetes Res Clin Pract. 2014 November : 106(2): 173-181.

β-hydroxybutyrate: Much more than a metabolite

John C. Newman[1,2] and **Eric Verdin**[2,*]

- Endogenous inhibitor of histone deacetylase (HDACs): activation of gene expression of glucose metabolism and promotion of resistance to oxidative stress.
- Binds at least 2 G-protein coupled receptors related to glucose control and macrovascular complication of T2D.
- Causes increase levels of other regulatory metabolites (acetyl-CoA, succinyl-CoA, NAD+).

These regulatory functions of βOHB serve to link the outside environment to cell function and gene expression and have important implications for the pathogenesis and treatment of metabolic disease including T2DM

Endocrine. 2017; 58(1): 81–90.

Acid-base safety during the course of a very low-calorie-ketogenic diet

D. Gomez-Arbelaez et al.

	VLCK diet	Diabetic ketoacidosis	*P* value
Number of patients	20	51	
Age (years)	47.2 ± 10.2	39.0 ± 13.5	0.016
Venous blood gases			
pH	7.37 ± 0.02	7.16 ± 0.12	<0.001
Measured bicarbonate (mmol/l)	23.6 ± 2.4	12.3 ± 5.7	<0.001
Base excess (mmol/l)	−1.4 ± 1.7	−18.1 ± 14.8	<0.001
Biochemical parameters			
Sodium (mmol/l)	142.0 ± 2.0	133.8 ± 6.3	<0.001
Potassium (mmol/l)	4.2 ± 0.2	5.0 ± 0.7	<0.001
Chloride (mmol/l)	104.8 ± 1.8	94.9 ± 6.9	<0.001
Anion gap	13.5 ± 2.2	30.3 ± 7.9	<0.001
Glucose (mg/dl)	78.7 ± 9.5	545.5 ± 245.9	<0.001
Ketone bodies			
B-hydroxy-butyrate (mmol/l)	1.0 ± 0.6	5.4 ± 1.2	<0.001

… the VLCK diet is a safe nutritional intervention for the treatment of obesity in terms of acid-base equilibrium. Apart from ketosis both in this clinical trial and in real life situation all the relevant biochemical parameters were not significantly altered by the VLCK dieting.

WHEY PROTEIN

- β-lattoglobulina, α-lattoalbumina, peptone proteosico, immunoglobuline, siero-albumina bovina, lattoferrina, lattoperossidasi, glicomacropeptide

  ⟶ 20% proteine del latte.
- Effetto termogenico maggiore dovuto alla aumentata sintesi proteica
- Alto contenuto in leucina (substrato/regolatore mTOR)
- Rapido assorbimento gastrico senza digestione, elevato e rapido profilo aminoacidico con effetto anabolico

WHEY PROTEIN

- Effetto insulinotropo e normoglicemizzante
- Nel DMT2 l'aggiunta di WP ad un pasto ricco di carboidrati a rapido assorbimento riduce la glicemia postprandiale (- 21%) e aumenta la risposta insulinemica (+57%).
- L'effetto ipoglicemizzante delle WP è paragonabile a quello delle sulfanilnuree e delle glinidi.

WHEY PROTEIN

- Oltre all'effetto insulinotropo e normoglicemizzante, favoriscono un profilo ormonale adatto alla protezione e alla crescita della FFM: GH/IGF-1 e Insulina

- Effetto anoressante centrale (leucina) e aumento della sazietà (secrezione di CCK, PYY, GIP, GLP-1, insulina)

Available online at www.sciencedirect.com

SciVerse ScienceDirect

Journal of Nutritional Biochemistry 24 (2013) 1–5

Journal of Nutritional Biochemistry

REVIEWS: CURRENT TOPICS

Biochemical and metabolic mechanisms by which dietary whey protein may combat obesity and Type 2 diabetes☆

Daniela Jakubowicz[a,*], Oren Froy[b,*]

[a]Diabetes Unit E. Wolfson Medical Center, Tel Aviv University, Holon 58100, Israel
[b]Institute of Biochemistry, Food Science and Nutrition, Robert H. Smith Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot 76100, Israel

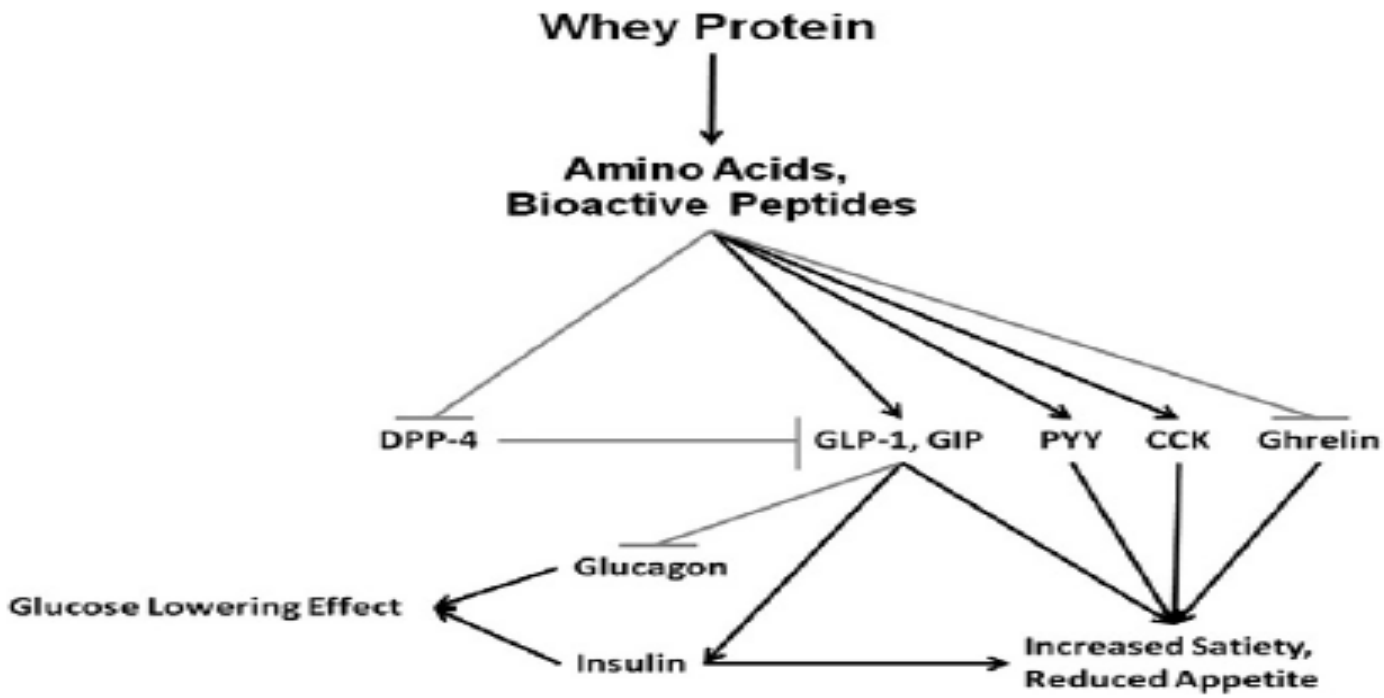


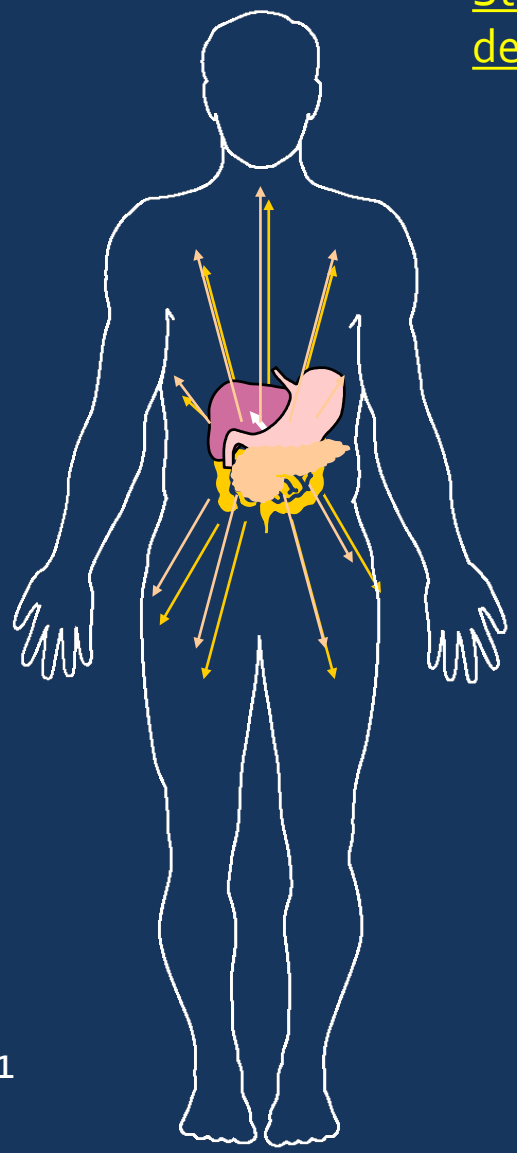
Fig. 1. Metabolic effects of whey protein.

GLP-1: effects in humans

After food ingestion…

GLP-1 is secreted from L-cells of the jejunum and ileum

That in turn…



- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake
- Improves insulin sensitivity

Long-term effects in animal models:

- Increase of β-cell mass and improved β-cell function

Drucker. *Curr Pharm Des.* 2001
Drucker. *Mol Endocrinol.* 2003

ORIGINAL ARTICLE

Short-term safety, tolerability and efficacy of a very low-calorie-ketogenic diet interventional weight loss program versus hypocaloric diet in patients with type 2 diabetes mellitus

A Goday[1,2,3], D Bellido[4], I Sajoux[5], AB Crujeiras[6,7], B Burguera[8,9], PP García-Luna[10], A Oleaga[11], B Moreno[12] and FF Casanueva[6,7]

RESULTS: No significant differences in the laboratory safety parameters were found between the two study groups. Changes in the urine albumin-to-creatinine ratio in VLCK diet were not significant and were comparable to control group. Creatinine and blood urea nitrogen did not change significantly relative to baseline nor between groups. Weight loss and reduction in waist circumference in the VLCK diet group were significantly larger than in control subjects (both $P < 0.001$). The decline in HbA1c and glycemic control was larger in the VLCK diet group ($P < 0.05$). No serious adverse events were reported and mild AE in the VLCK diet group declined at last follow-up.

CONCLUSIONS: The interventional weight loss program based on a VLCK diet is most effective in reducing body weight and improvement of glycemic control than a standard hypocaloric diet with safety and good tolerance for T2DM patients.

Nutrition & Diabetes (2016) **6,** e230; doi:10.1038/nutd.2016.36; published online 19 September 2016

Short-Term Changes after a Weight Reduction Intervention in Advanced Diabetic Nephropathy

Allon N. Friedman, Mary Chambers,* Lisa M. Kamendulis,† and Joan Temmerman‡*

Clin J Am Soc Nephrol 8: 1892–1898, 2013. doi: 10.2215/CJN.04010413

Results There was a 12% reduction in weight (median 118.5 versus 104.3 kg, P=0.03). The intervention was associated with a 36% reduction in albuminuria that did not reach statistical significance (2124 versus 1366 mg/24 h, P=0.08) and significant reductions in the filtration markers serum creatinine (3.54 versus 3.13 mg/dl, $P<0.05$) and cystatin C (2.79 versus 2.46 mg/l, $P<0.05$). Improvements were also noted for the diabetes markers fasting glucose (166 versus 131 mg/dl, $P<0.05$), fasting insulin (26.9 versus 10.4 μU/ml, $P<0.05$), and insulin resistance (9.6 versus 4.2, P=0.03). Physical function, general health, and the number of diabetes medications also showed statistically significant signs of improvement.

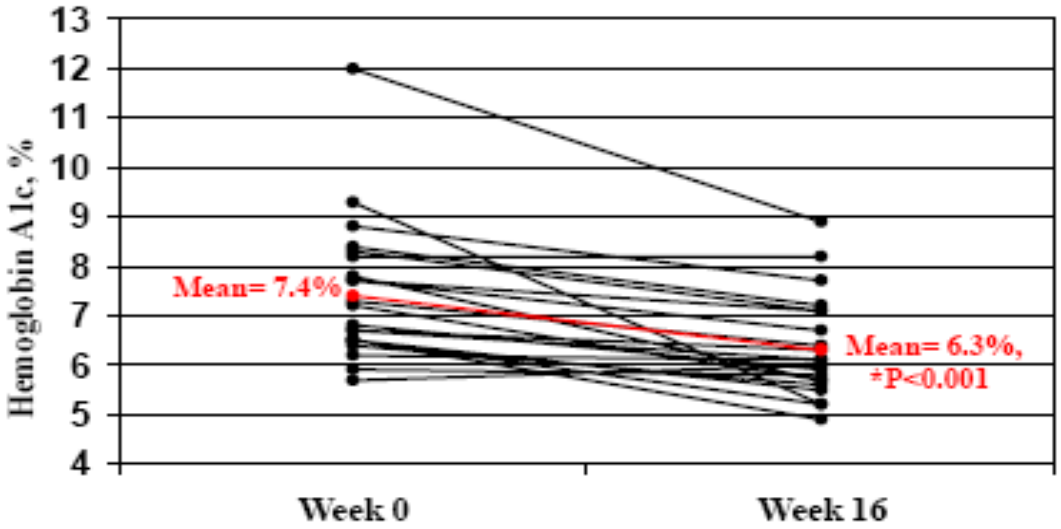
Conclusions After a short-term intensive weight reduction intervention in patients with advanced diabetic nephropathy, improvements were observed in markers of glomerular filtration, diabetes status, and risk factors for kidney disease progression, as well as other general indicators of health and well-being.

Nutrition & Metabolism

Nutrition & Metabolism 2005, 2:34 doi:10.1186/1743-7075-2-34

A low-carbohydrate, ketogenic diet to treat type 2 diabetes

William S Yancy Jr*[1,2], Marjorie Foy[1], Allison M Chalecki[1], Mary C Vernon[3] and Eric C Westman[2]



Conclusion: the LCKD improved glycemic control in patients with type 2 diabetes such that diabetes medications were discontinued or reduced in most partecipants.

Because the LCKD can be very effective at lowering blood glucose, patients on diabetes medication who use this diet shoul be under close medical supervision or capable of adjusting their medication.

At the end of our clinic day, we go home thinking, "The clinical improvements are so large and obvious, why don't other doctors understand?"

Because carbohydrates in the diet raise the blood glucose, and as diabetes is defined by high blood glucose, it makes sense to lower the carbohydrate in the diet. By reducing the carbohydrate in the diet, we have been able to taper patients off as much as 150 units of insulin per day in 8 d, with marked improvement in glycemic control – even normalization of glycemic parameters."

- Eric Westman, MD, MHS

Grazie!

simonaferrero.valeria@gmail.com

Come modificare la terapia farmacologica ipoglicemizzante orale in VLCKD

- La terapia con **metformina** non espone al rischio di ipoglicemie in corso di VLCKD. E' quasi sempre richiesto solo un aggiustamento posologico iniziale e la riduzione della dose giornaliera o il mantenimento della sola dose serale. Sospendere se glicata > 6.5%
- **DPP IV inibitori e analoghi del GLP -1** non aumentano il rischio di ipoglicemie, è comunque frequente la sospensione durante VLCKD, soprattutto quando sono assunti in duplice con metformina.
- Il compenso glicemico all'inizio del trattamento dietetico sarà il parametro decisionale per la sospensione immediata o posticipata.

Come modificare la terapia farmacologica ipoglicemizzante orale in VLCKD

- Sospendere o ridurre (in base al compenso iniziale) **sulfaniluree e tiazolidinedioni** o sostituirli con farmaci neutri sul peso.
- Non dati riguardo **inibitori SGLT2** e VLCKD, ma riterrei opportuno la sospensione o la sostituzione prima dell'inizio del trattamento (glicosuria, uricosuria, perdita di liquidi, calo pressorio).

Come modificare la terapia farmacologica insulinica in VLCKD

1. **IPOGLICEMIZZANTI ORALI + INSULINA BED-TIME**

   Monitorare attentamente glicemia a digiuno e preprandiale e ridurre inizialmente e progreessivamente il dosaggio della insulina basale.

2. **IPOGLICEMIZZANTI ORALI + INSULINE PREMISCELATE**

   Rischio di sovrapposizione di azione delle insuline ad azione lenta e di ipoglicemia.

   Lo schema è sconsigliabile in VLCKD ed è consigliabile modificare la terapia prima di iniziare la VLCKD.

Come modificare la terapia farmacologica insulinica durante VLCKD

- Se unità di insulina totale < 15 al giorno: sospendere
- Se > 15 unità: sospendere analogo rapido e ridurre del 50% il basale.
- Considerare la sostituzione dell'insulina basale con analogo GLP1

Come modificare la terapia farmacologica insulinica durante VLCKD:

Terapia Insulinica Intensiva Basal-Bolus

- Se unità di insulina totale < 15 al giorno: sospendere
- Se > 15 unità: sospendere analogo rapido e ridurre del 50% il basale.
- Considerare la sostituzione dell'insulina basale con analogo GLP1