SI PUO' DEBELLARE IL DIABETE SFRUTTANDO LA CHETOSI?

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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.

Obesità e diabete condividono anche la possibilità di remissione in seguito a un bilancio energetico negativo e sufficientemente prolungato da causare una rilevante perdita di peso corporeo.

Le attuali indicazioni propongono nel trattamento dell'obesità una perdita del 5-10% di peso corporeo, ma è evidente che nel

paziente diabeso

sono necessarie richieste più incisive per ottenere un rilevante calo ponderale e la risoluzione delle anomalie metaboliche.

La chirurgia bariatrica è decisamente efficace nella riduzione sostanziale del peso e nella remissione del diabete, ma comporta rischi nell’immediato e nel lungo termine, non è accettata da molti pazienti ed è poco sostenibile in termini economici.

REVIEW

Weight losses with low-energy formula diets in obese patients with and without type 2 diabetes: systematic review and meta-analysis

Updated online 14 March 2017: This article was originally published under a standard license, but has now been made available under a CC BY-NC-ND 4.0 license. The pdf and html versions of the paper have been modified accordingly.

WS Leslie[1], R Taylor[2], L Harris[3] and MEJ Lean[1]

AIM: To provide a systematic review, of published data, to compare weight losses following very low calorie (<800 kcal per day VLCD) or low-energy liquid-formula (>800 kcal per day LELD) diets, in people with and without type 2 diabetes mellitus (T2DM).
METHODS: Systematic electronic searches of Medline (1946–2015) and Embase (1947–2015) to identify published studies using formula total diet replacement diets (VLCD/LELD). Random effects meta-analysis using weighted mean difference (WMD) in body weight between groups (with and without diabetes) as the summary estimate.
RESULTS: Final weight loss, in the five included studies, weighted for study sizes, (n=569, mean BMI=35.5–42.6 kg/m^2), was not significantly different between participants with and without T2DM: −1.2 kg; 95% CI: −4.1 to 1.6 kg). Rates of weight loss were also similar in the two groups −0.6 kg per week (T2DM) and 0.5 kg per week (no diabetes), and for VLCD (<800 kcal per day) and LELD (>800 kcal per day).
CONCLUSIONS: Weight losses with liquid-formula diets are very similar for VLCD and LELD and for obese subjects with or without T2DM. They can potentially achieve new weight loss/ maintenance targets of >15–20% for people with severe and medically complicated obesity.

International Journal of Obesity (2017) **41,** 96–101; doi:10.1038/ijo.2016.175

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)

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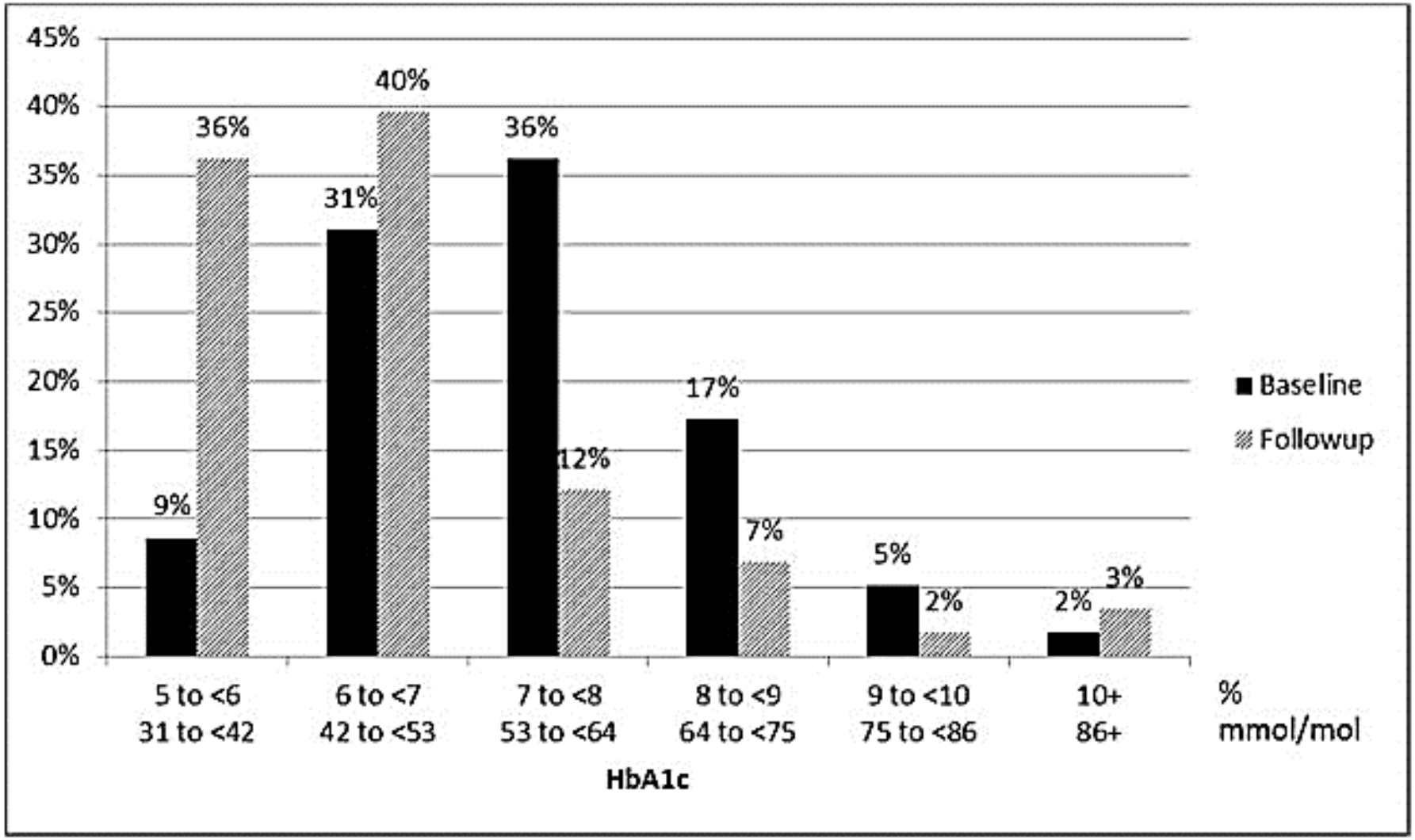
Weight management

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.

Percent distribution of HbA1c levels at baseline and follow-up for patients with established diabetes



J Diabetes Complications, 2014

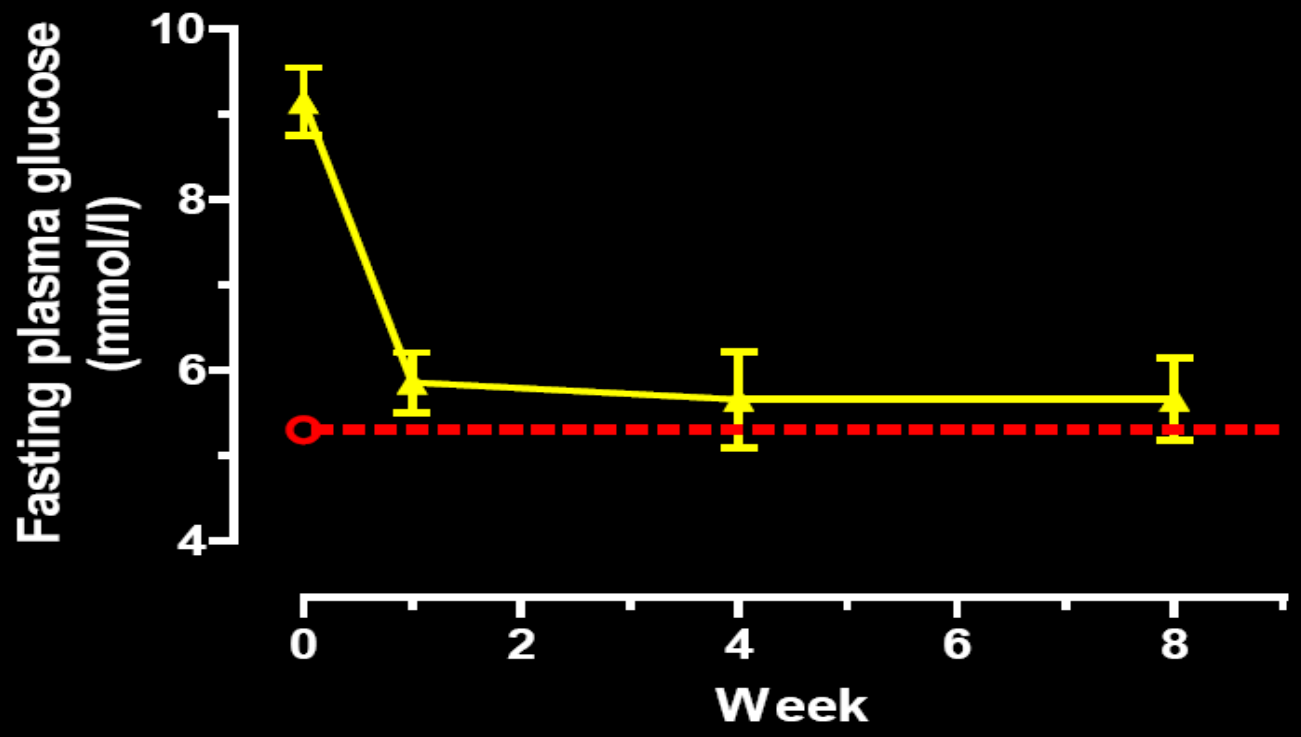
Nel soggetto diabetico l’effetto ipoglicemizzante della VLCKD è così rapido e rilevante da determinare nella quasi totalità dei pazienti la sospensione o la riduzione della terapia antidiabetica.

Counterpoint Study

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

Plasma glucose

$9.2 \pm 0.4 \rightarrow 5.9 \pm 0.4$ mmol/l; $p = 0.003$

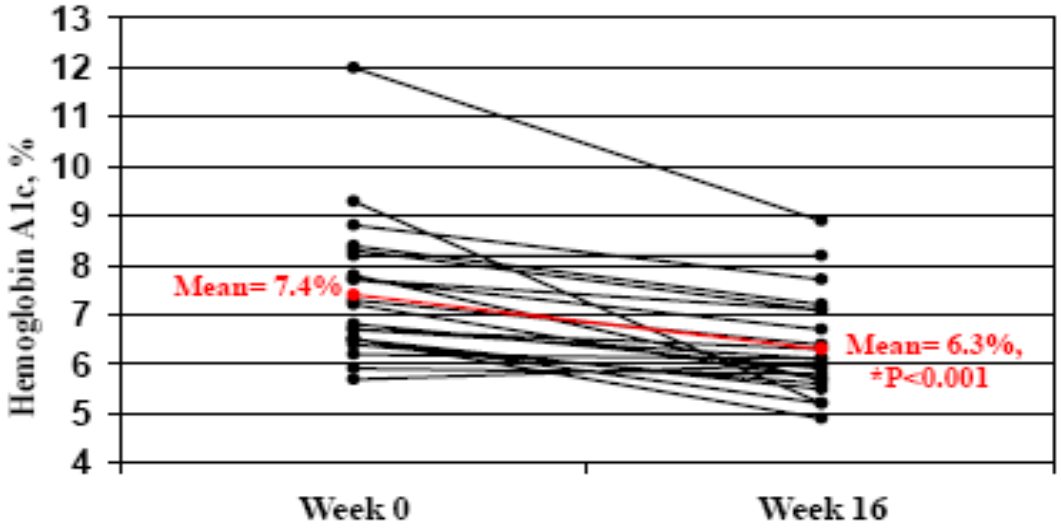


Nutrition & Metabolism

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.

European Journal of Internal Medicine 23 (2012) 143–149

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

Quality of life in type 2 diabetes mellitus after a very low calorie diet and exercise

Marieke Snel [a,*], Maria A. Sleddering [a], Inge D. vd Peijl [b], Johannes A. Romijn [a], Hanno Pijl [a], A. Edo Meinders [a], Ingrid M. Jazet [a]

[a] Department of Endocrinology and Metabolism/General Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands
[b] Department of Physiotherapy, Leiden University Medical Center, Leiden, The Netherlands

Table 2
Overview

	Lean
Insulin (	0
Insulin (	0
Metform	0
SU deriv	0
Exercise	167

Learning points:

- ✓ A 16-week very low calorie diet with exercise does have sustained effects even 18 months after start of the intervention on weight and Quality of life.
- ✓ Diet induced weight reduction in addition to its beneficial effects on glycemic control, insulin resistance and cardiovascular risk factors can improve Quality of life up to the level of healthy controls.

- Il miglioramento del controllo glicemico precede il calo ponderale.
- Si mantiene sia nelle fasi di graduale reintroduzione dei carboidrati dopo la fase intensiva della VLCKD, sia alla ripresa di un’alimentazione normocalorica bilanciata, perdurando anche in caso di recupero ponderale.
- Unitamente all’effetto sul peso e sul controllo glicemico, la VLCKD migliora significativamente tutti i parametri della sindrome metabolica.

MECCANISMI COINVOLTI NELLA REGOLAZIONE GLICOMETABOLICA IN CORSO DI VLCKD

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

VARIAZIONE DEI PARAMETRI DI RISCHIO CV PER OGNI CHILOGRAMMO DI PESO PERSO

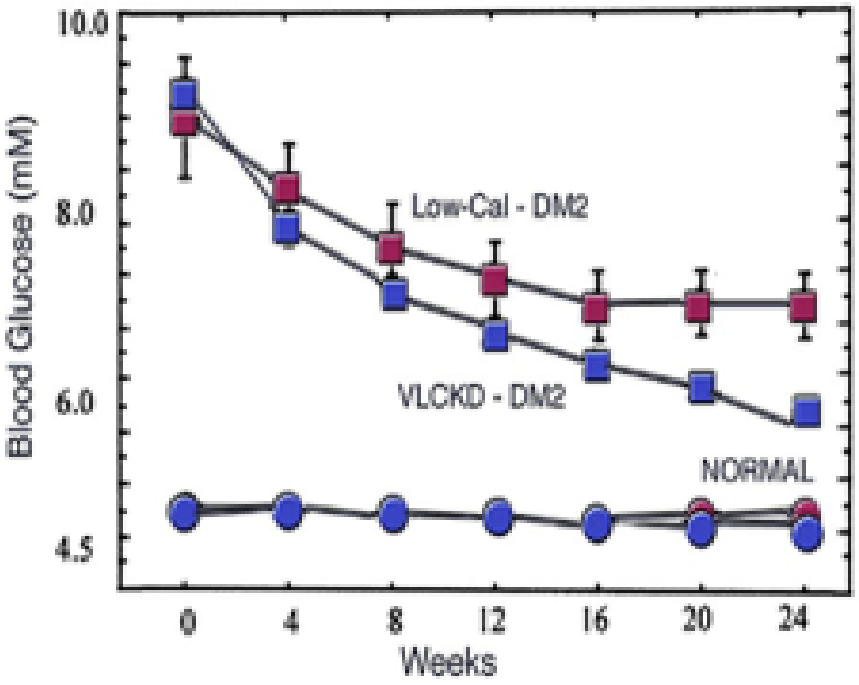
Cholesterol	%	- 0.99
	mg/dL	- 2.28
LDL	%	- 0.68
	mg/dL	- 0.91
HDL	%	+ 0.15
	mg/dL	+ 0.07
Triglycerides	%	- 1.93
	mg/dL	- 1.54

Sistolic BP	%	- 0.49
	mmHg	- 0.68
Diastolic BP	%	- 0.38
	mmHg	-0.34
Fasting Plasma Glucose	mMol **mg/dl**	- 0.2 **- 4.0**

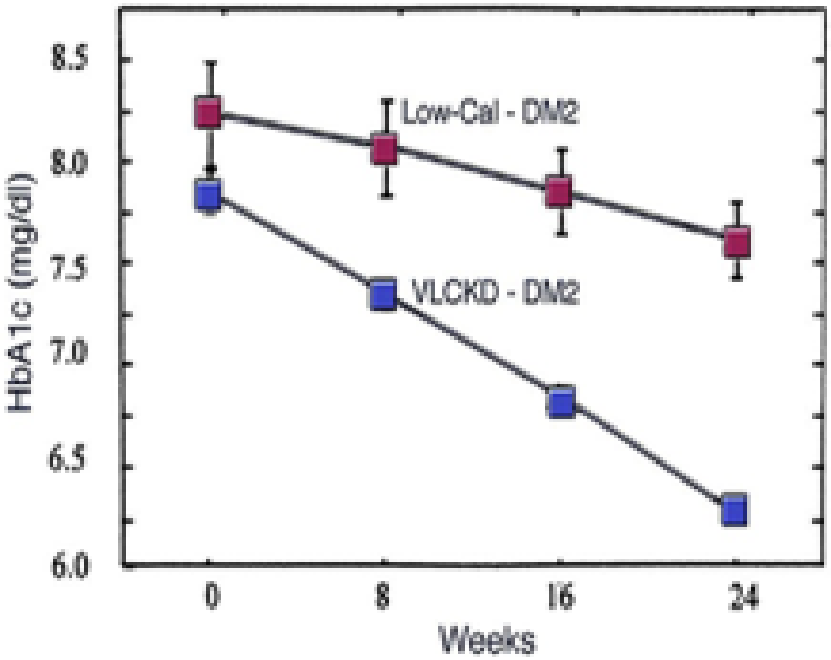
Anderson JW, Ob Res, 2001

Effect of Low-Calorie versus Low-Carbohydrate Ketogenic Diet in Type 2 Diabetes

Blood Glucose



HbA1c



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

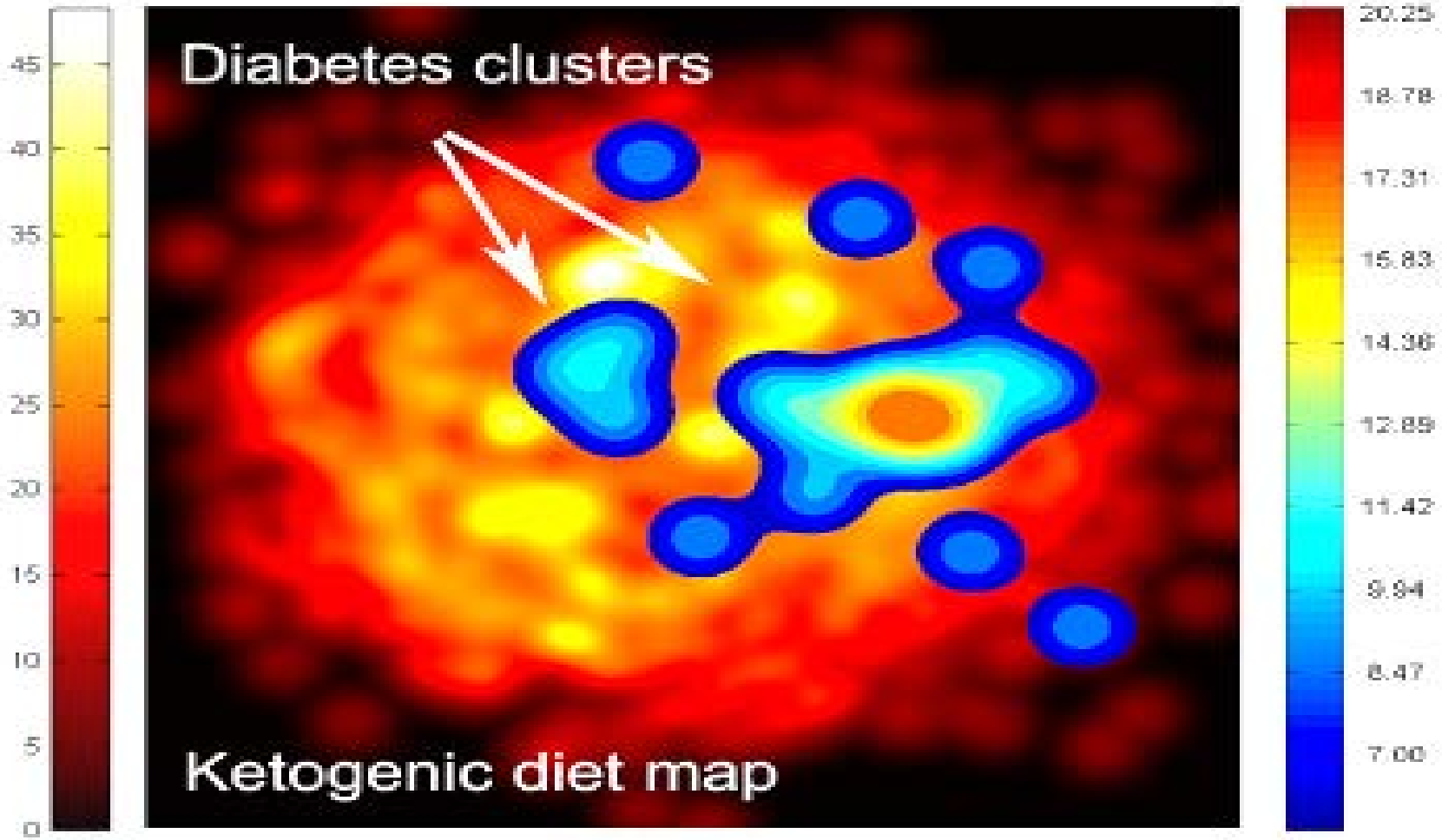
The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus

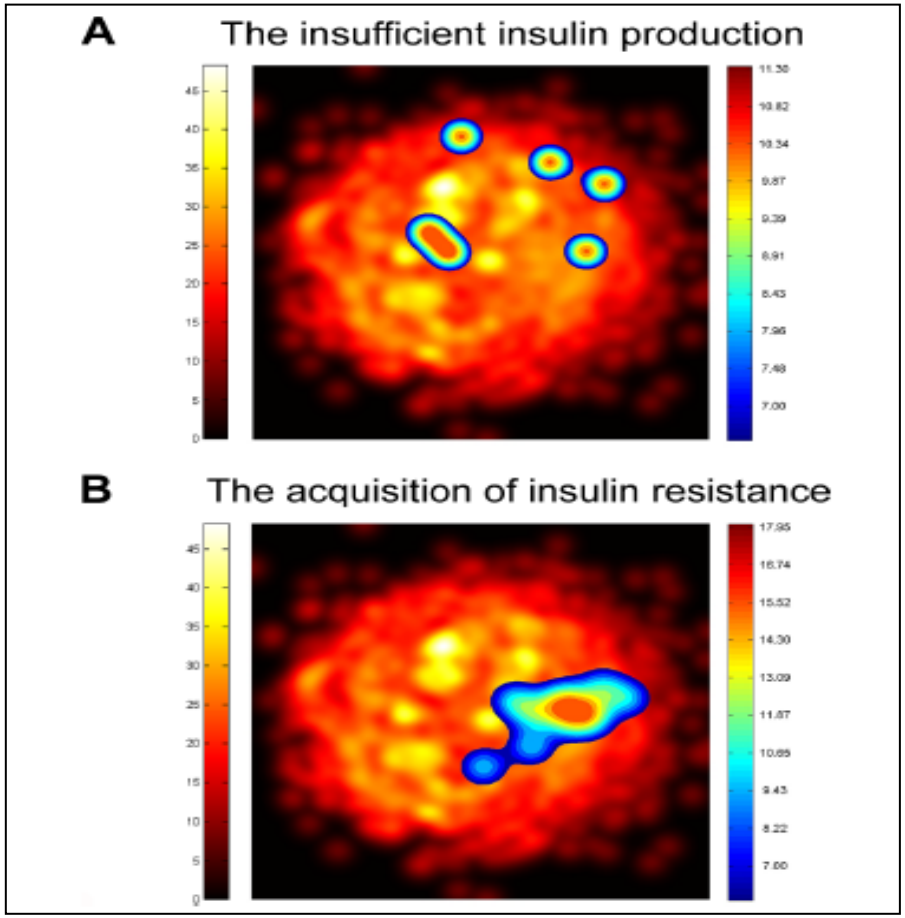
EC Westman, Nutrition and Metabolism, 2008

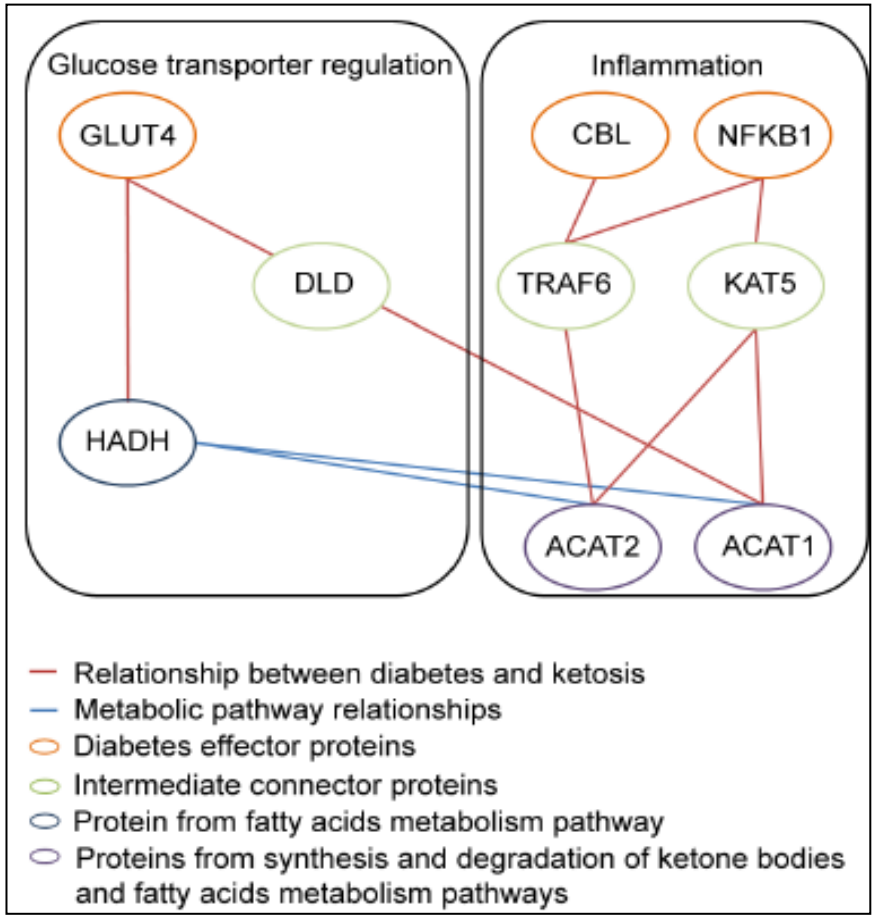
Mean Change Week 0 to 24	LGID	LCKD
HbA1c%	- 0.5	- 1.5
FPG mg/dl	- 16	- 19.9
Fasting Insulin mcU/mL	- 2.2	- 6.0
BMI (kg/m2)	- 2.7	- 3.9
BW (kg)	- 6.9	- 11.1

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.

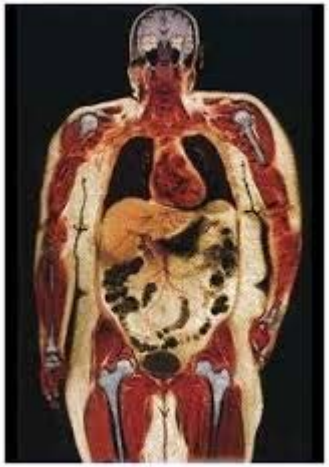
Diabetes Res Clin Pract. 2014 November : 106(2): 173-181.

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



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

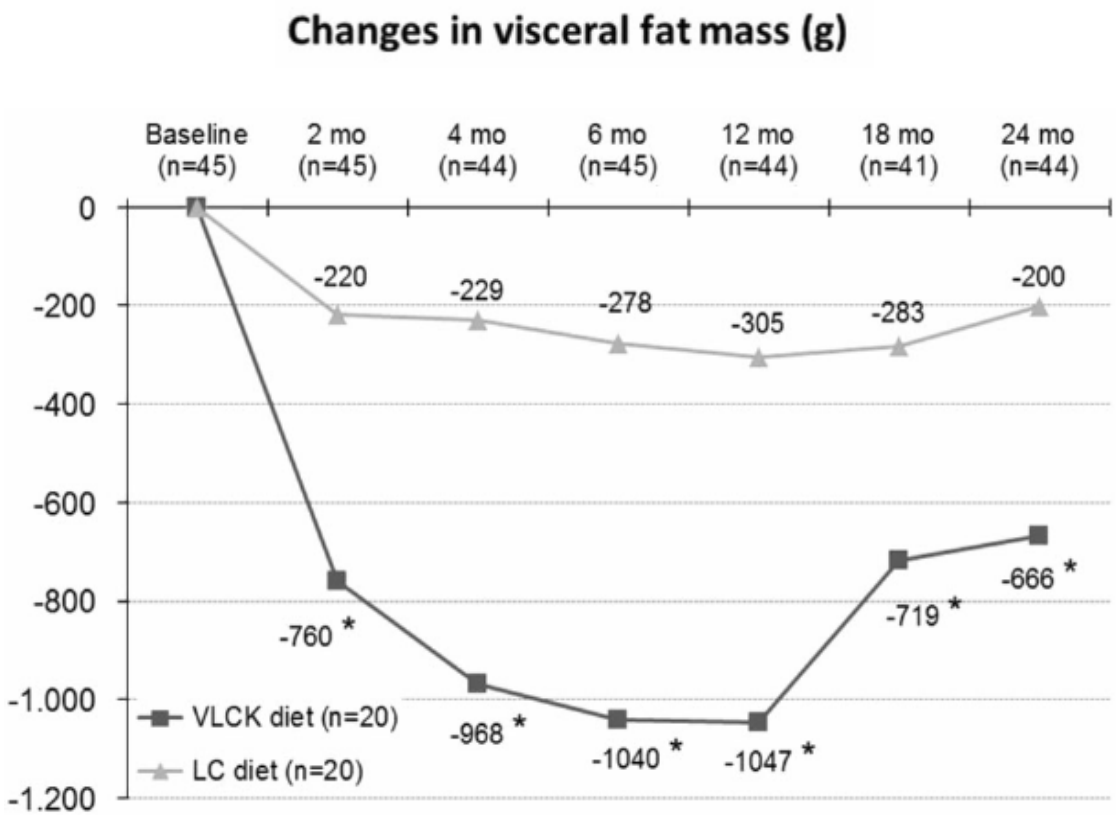
TB Chaston, JB Dixon
Int J Obesity 2008

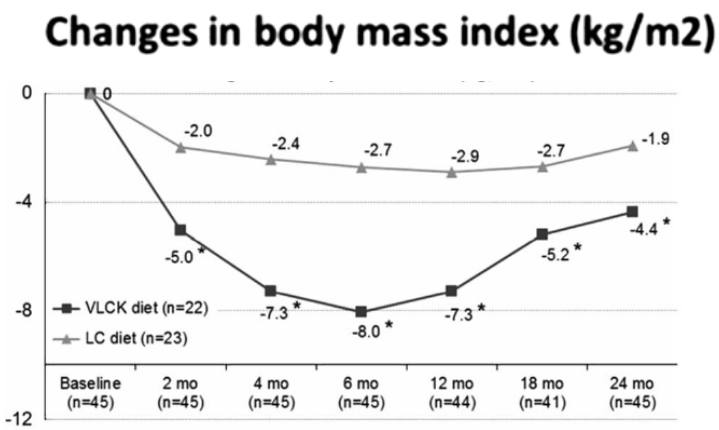
- Visceral adipose tissue is lost preferentially with modest weight loss.
- Acute caloric restriction, using VLCD, produces early preferential loss of VAT.
- Very-low-calorie diets (VLCDs) provided exceptional short-term (<4 weeks) preferential VAT loss, but this effect was lost by 12-14 weeks.

Endocrine, 2016

Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease

Basilio Moreno[1] · Ana B Crujeiras[2,3] · Diego Bellido[4] · Ignacio Sajoux[5] · Felipe F Casanueva[3,6]

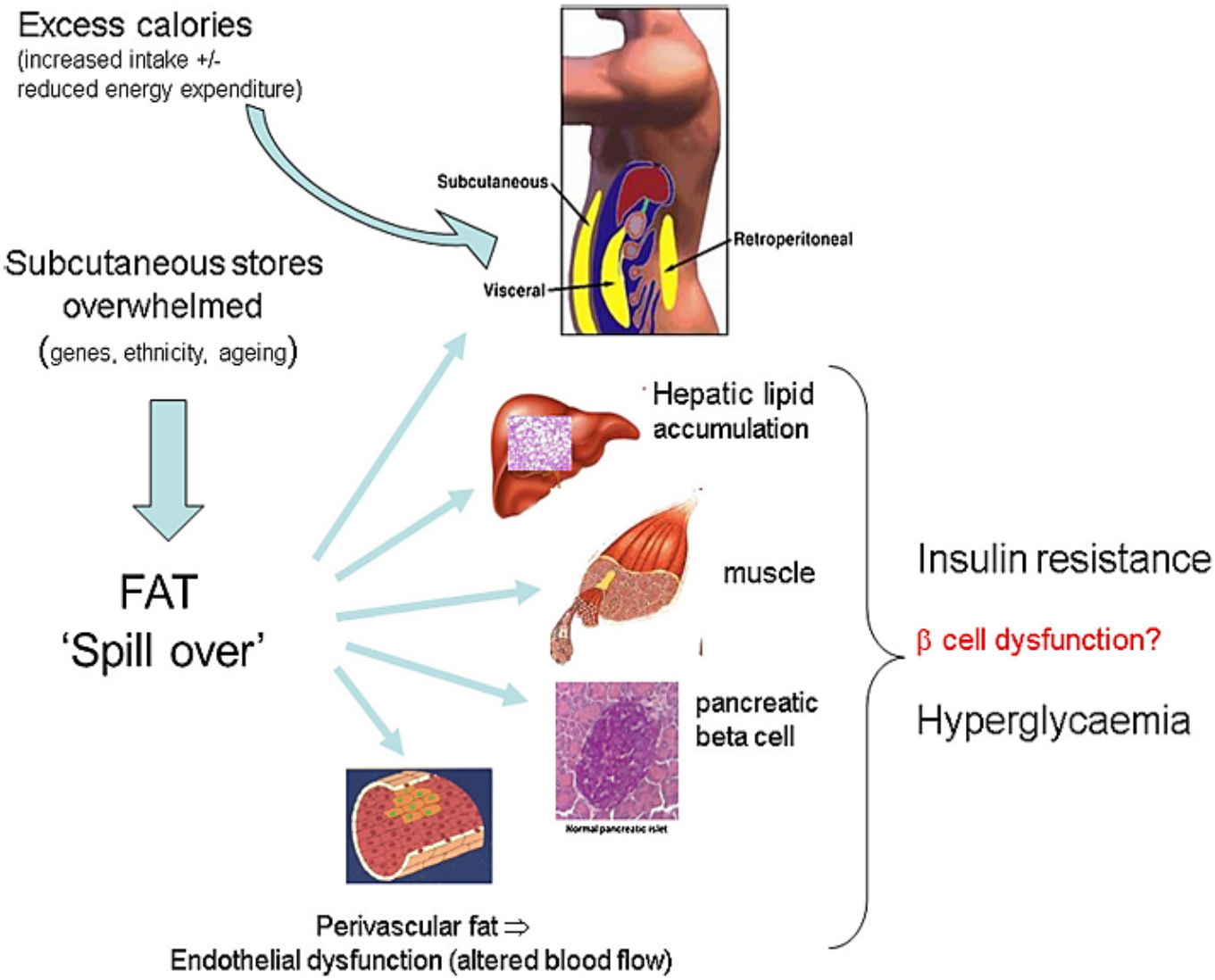




Type 2 diabetes as a disease of ectopic fat?

Naveed Sattar* and Jason MR Gill

BMC Medicine 2014, **12**:123

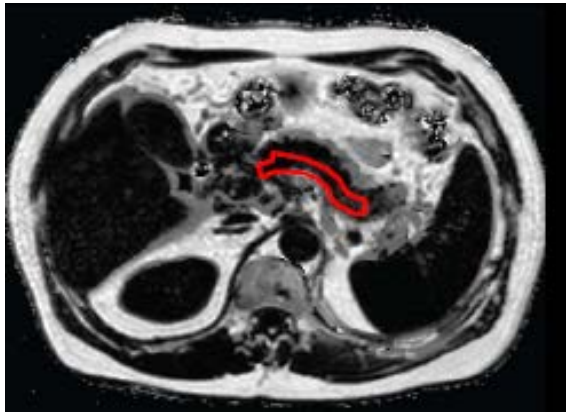


ARTICLE

Diabetologia (2011) 54:2506-2514

Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

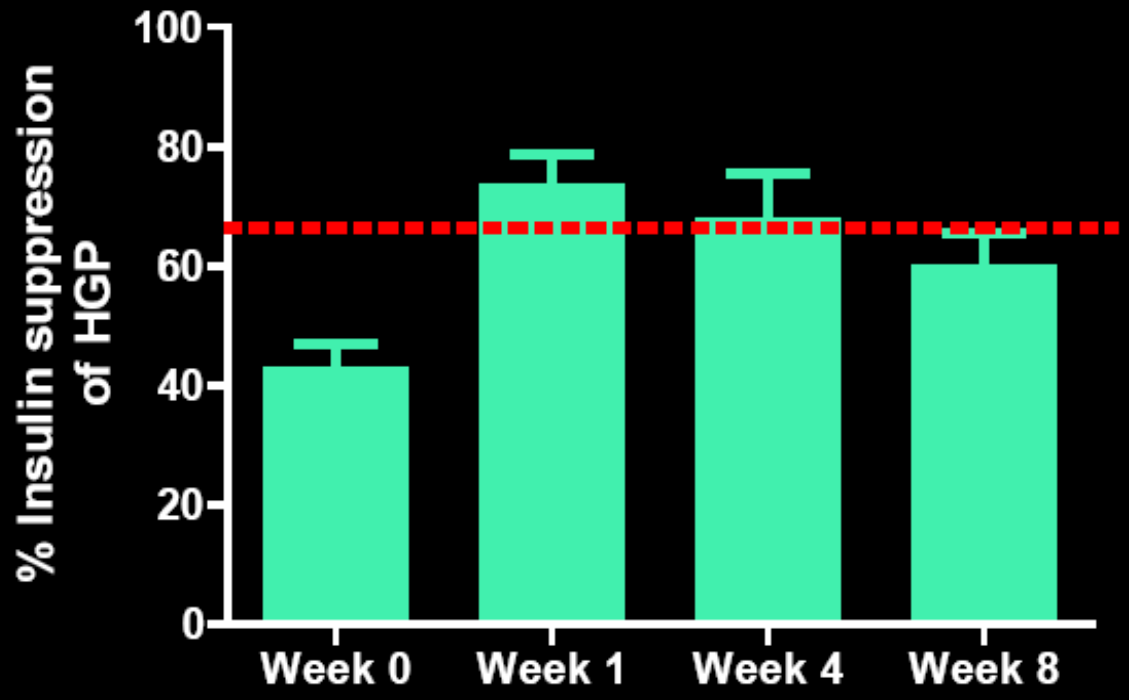
E. L. Lim • K. G. Hollingsworth • B. S. Aribisala • M. J. Chen • J. C. Mathers • R. Taylor



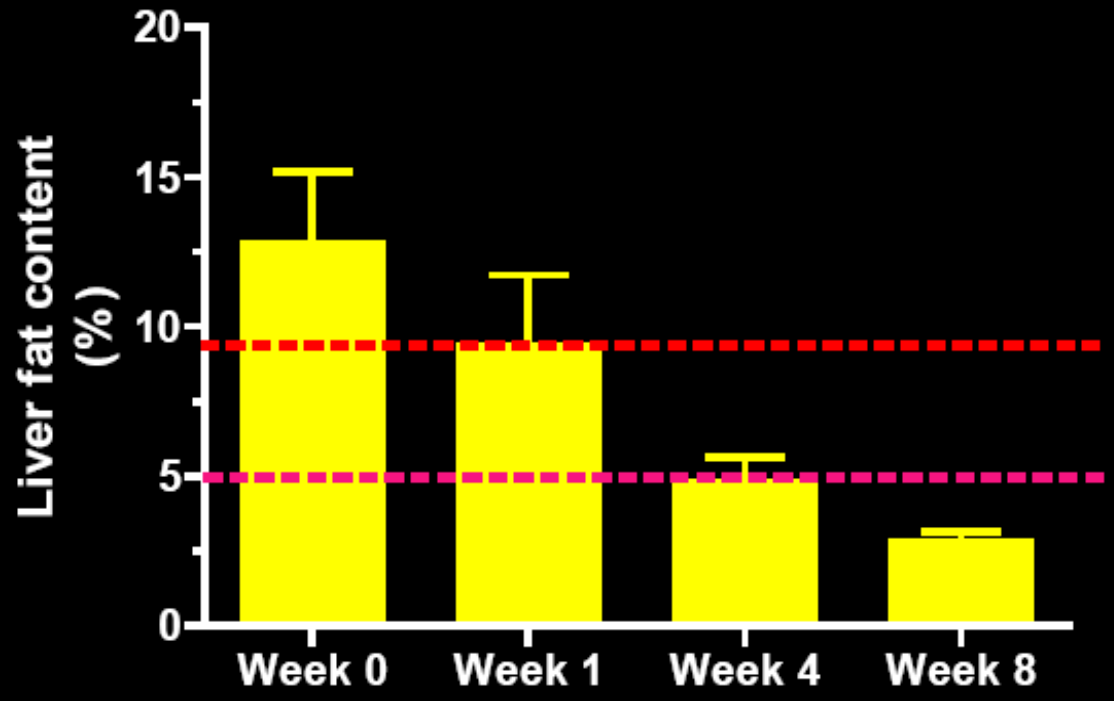
a) Pancreas: beta cell function using an incremental insulin secretion test

b) Liver: insulin sensitivity by isoglycaemic hyperinsulinaemic clamp

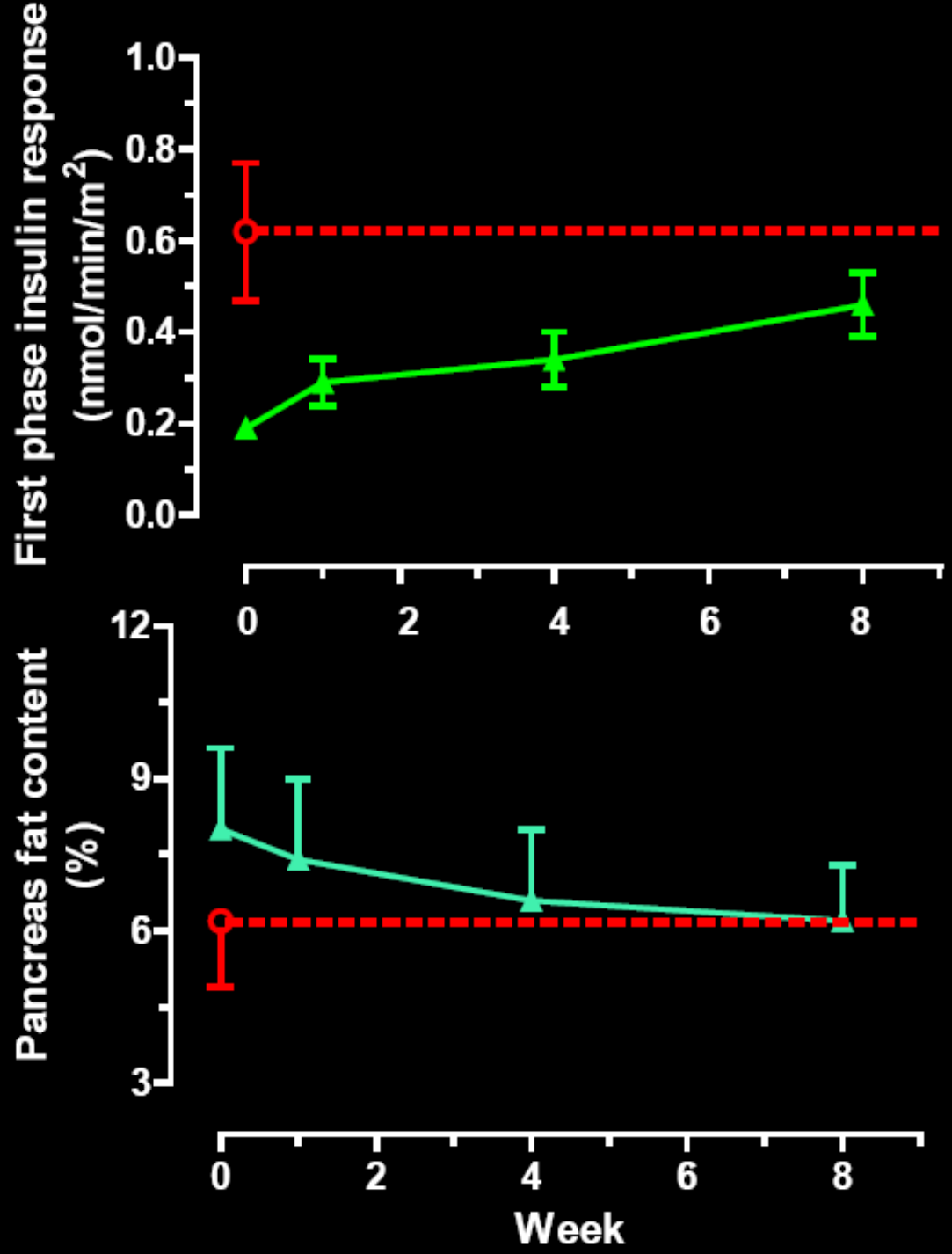
c) Liver and pancreatic fat levels: 3 point Dixon MR method



- 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

Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial

Prof Michael EJ Lean, MD, Wilma S Leslie, PhD, Alison C Barnes, PGDip, Naomi Brosnahan, PGDip, George Thom, MSc, Louise McCombie, BSc, Carl Peters, MB, Sviatlana Zhyzhneuskaya, MD, Ahmad Al-Mrabeh, PhD, Kieren G Hollingsworth, PhD, Angela M Rodrigues, PhD, Lucia Rehackova, PhD, Prof Ashley J Adamson, PhD, Prof Falko F Sniehotta, PhD, Prof John C Mathers, PhD, Hazel M Ross, BSc, Yvonne McIlvenna, MSc, Renae Stefanetti, PhD, Prof Michael Trenell, PhD, Paul Welsh, PhD, Sharon Kean, Prof Ian Ford, PhD, Alex McConnachie, PhD, Prof Naveed Sattar, FMedSci, Prof Roy Taylor, MD

The Lancet
Volume 391, Issue 10120, Pages 541-551 (February 2018)
DOI: 10.1016/S0140-6736(17)33102-1

ELSEVIER
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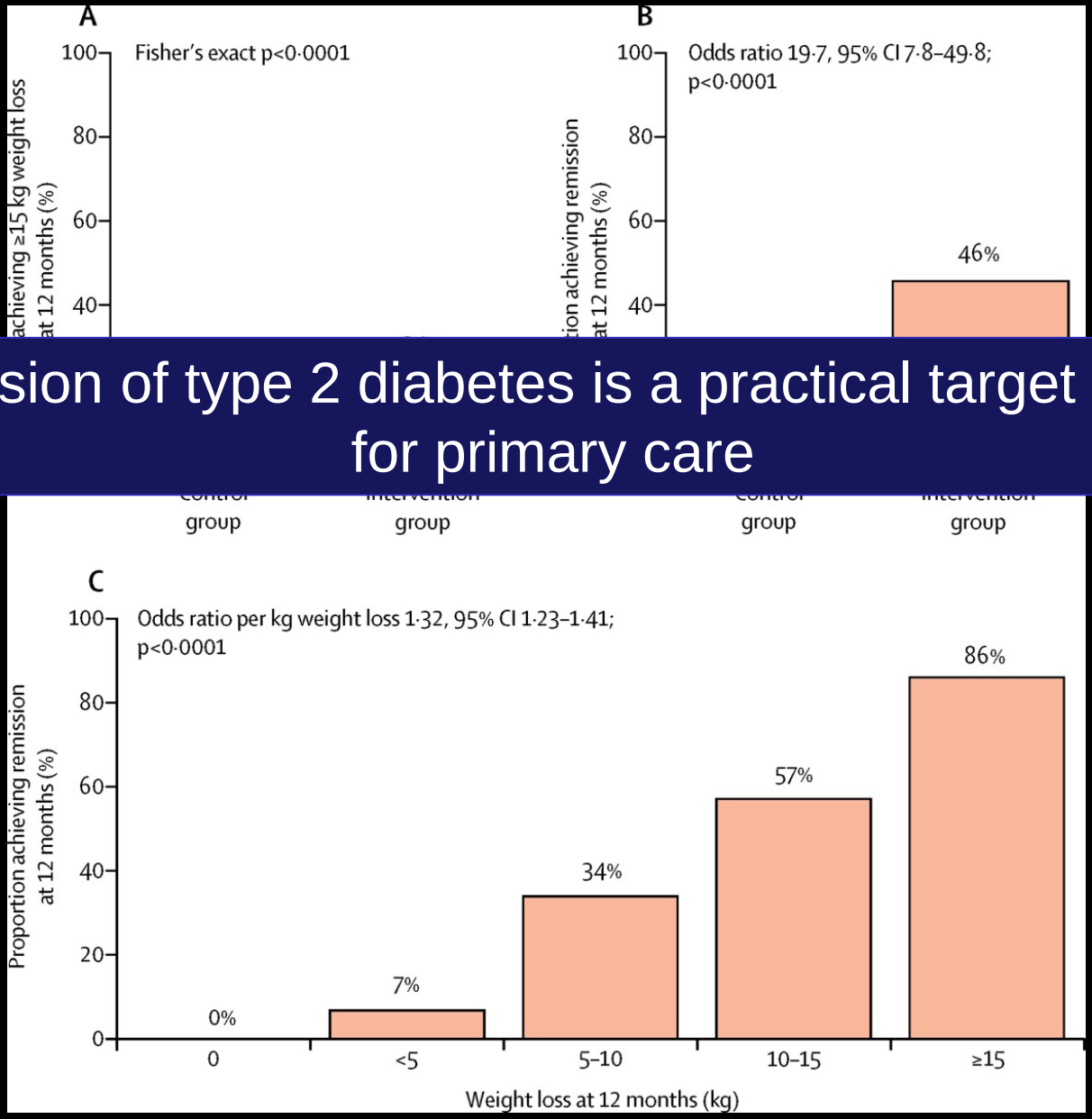
1. First co-primary outcome: achievement of at least 15 kg weight loss at 12 months.
2. Second co-primary outcome: remission of diabetes (glycated haemoglobin <6·5% [48mmol/mol], off antidiabetic medication for 2 months).

Remission of type 2 diabetes is a practical target for primary care



The Lancet 2018 391, 541-551DOI: (10.1016/S0140-6736(17)33102-1)
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Bhanpuri *et al. Cardiovasc Diabetol (2018) 17:56*
https://doi.org/10.1186/s12933-018-0698-8

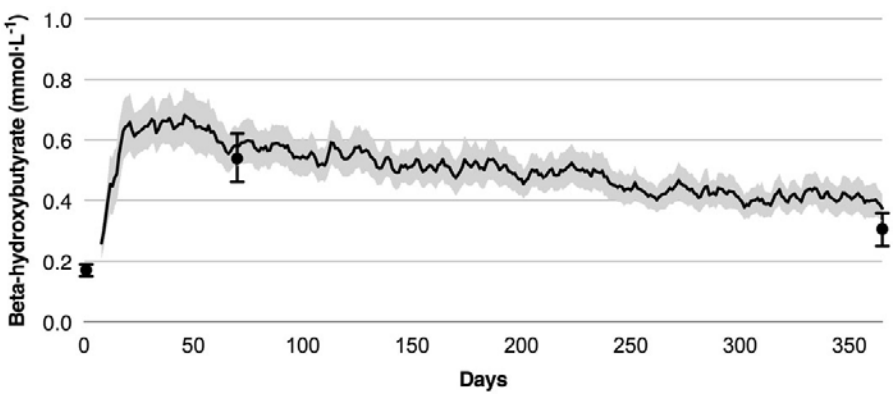
Cardiovascular Diabetology

ORIGINAL INVESTIGATION

Open Access

Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: an open label, non-randomized, controlled study

Nasir H. Bhanpuri[1*], Sarah J. Hallberg[1,2], Paul T. Williams[3], Amy L. McKenzie[1], Kevin D. Ballard[4], Wayne W. Campbell[5], James P. McCarter[1,6], Stephen D. Phinney[1] and Jeff S. Volek[1,7]



Diabetes Ther (2018) 9:583–612
https://doi.org/10.1007/s13300-018-0373-9

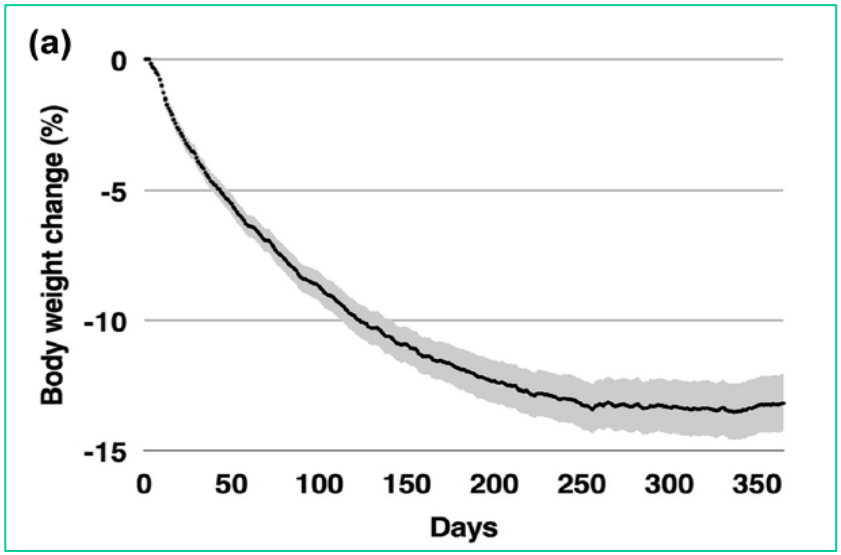
ORIGINAL RESEARCH

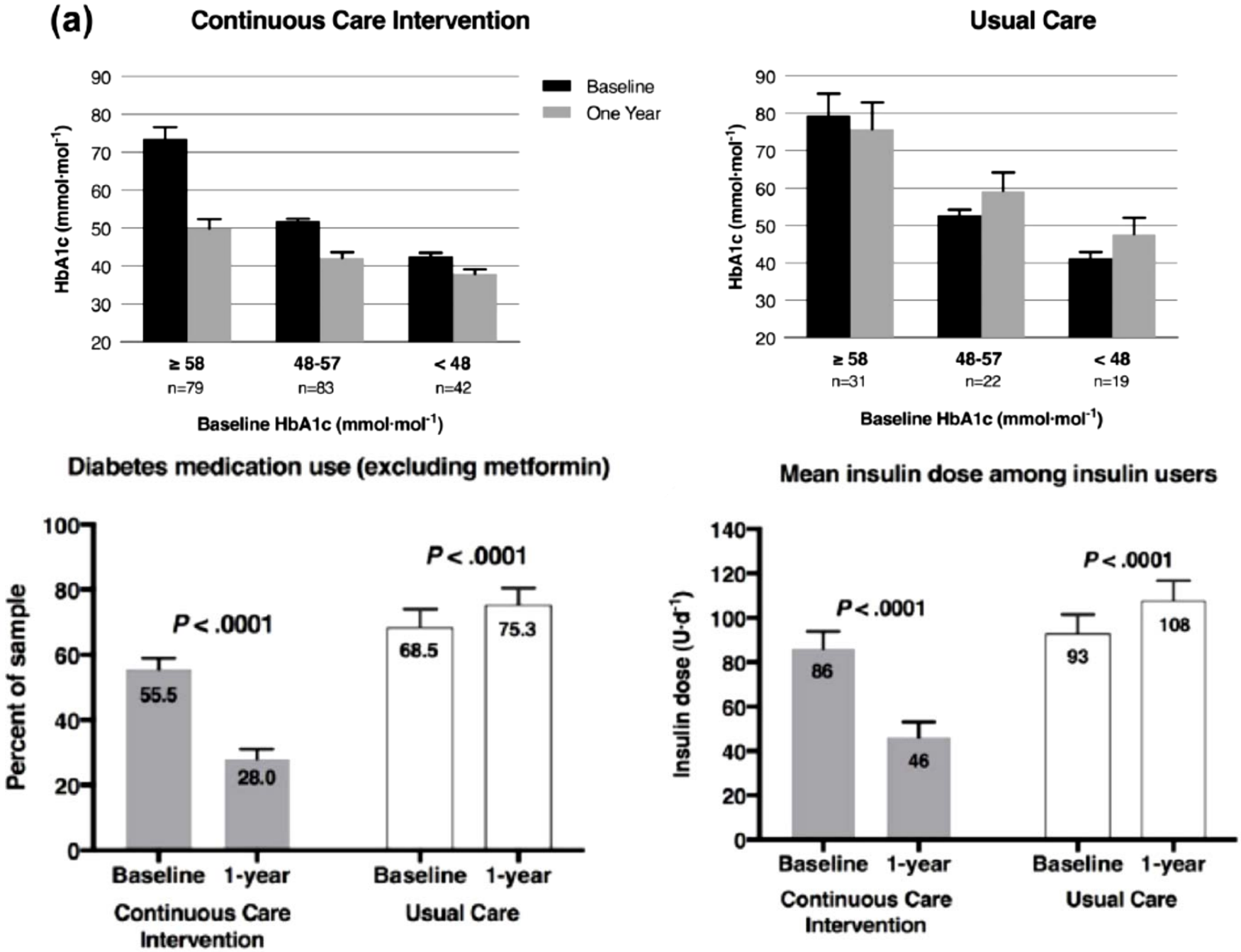
Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study

Sarah J. Hallberg · Amy L. McKenzie · Paul T. Williams ·
Nasir H. Bhanpuri · Anne L. Peters · Wayne W. Campbell · Tamara L. Hazbun ·
Brittanie M. Volk · James P. McCarter · Stephen D. Phinney ·

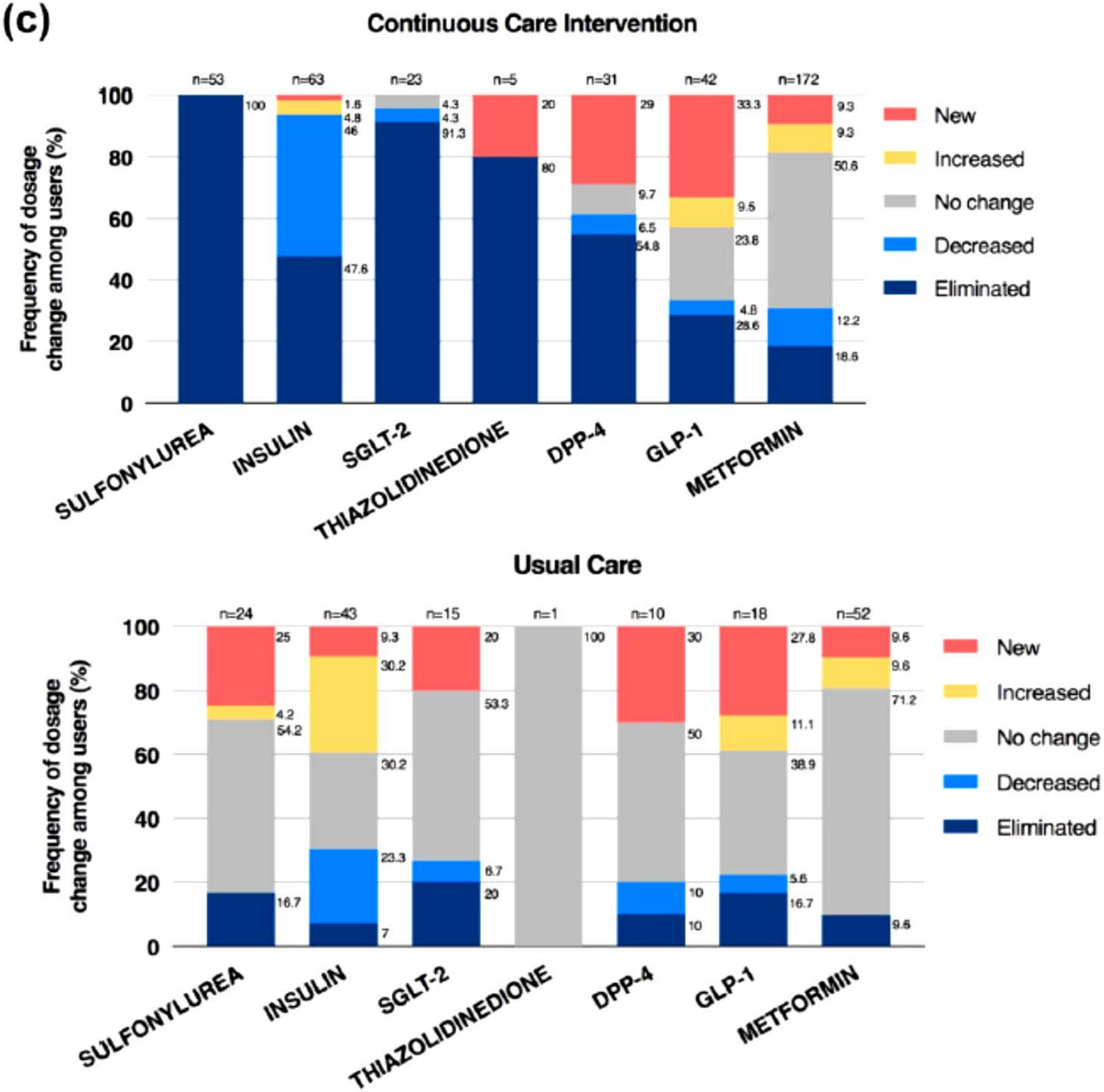
Follow up 12 mesi:

- HbA1c da 7,6 a 6,3%
- Perdita peso corporeo 12%
- Riduzione terapia farmacologica: 94% stop o riduzione insulina, 100% stop SU
- Miglioramento quadro lipidico, markers infiammazione e parametri di funzione epatica




(a)
Continuous Care Intervention
Usual Care
Baseline
One Year
HbA1c (mmol·mol-1)
90
80
70
60
50
40
30
20
≥ 58
n=79
48-57
n=83
< 48
n=42
Baseline HbA1c (mmol·mol-1)
≥ 58
n=31
48-57
n=22
< 48
n=19
Diabetes medication use (excluding metformin)
Percent of sample
100
80
60
40
20
0
P < .0001
55.5
28.0
P < .0001
68.5
75.3
Baseline
1-year
Continuous Care Intervention
Baseline
1-year
Usual Care
Mean insulin dose among insulin users
Insulin dose (U·d-1)
140
120
100
80
60
40
20
0
P < .0001
86
46
P < .0001
93
108
Baseline
1-year
Continuous Care Intervention
Baseline
1-year
Usual Care

(c)


Continuous Care Intervention
n=53
n=63
n=23
n=5
n=31
n=42
n=172
Frequency of dosage change among users (%)
100
80
60
40
20
0
100
1.6
4.8
46
47.6
4.3
4.3
91.3
20
80
29
9.7
6.5
54.8
33.3
9.5
23.8
4.8
28.6
9.3
9.3
50.6
12.2
18.6
New
Increased
No change
Decreased
Eliminated
SULFONYLUREA
INSULIN
SGLT-2
THIAZOLIDINEDIONE
DPP-4
GLP-1
METFORMIN
Usual Care
n=24
n=43
n=15
n=1
n=10
n=18
n=52
Frequency of dosage change among users (%)
100
80
60
40
20
0
25
4.2
54.2
16.7
9.3
30.2
30.2
23.3
7
20
53.3
6.7
20
100
30
50
10
10
27.8
11.1
38.9
5.6
16.7
9.6
9.6
71.2
9.6
New
Increased
No change
Decreased
Eliminated
SULFONYLUREA
INSULIN
SGLT-2
THIAZOLIDINEDIONE
DPP-4
GLP-1
METFORMIN

La VLCKD

E’ un trattamento sicuro ed efficace nella riduzione ponderale del paziente diabetico e nel controllo glicometabolico della malattia.

Rappresenta l’unica alternativa medica alla chirurgia metabolica per quanto riguarda la remissione del diabete e deve essere considerata come opzione terapeutica da proporre al paziente motivato al cambiamento.

...Grazie!