

**3<sup>rd</sup> AME Diabete Update**  
**Napoli, 16-17 marzo 2018**


**VLCKD:  
EFFICACIA SUL MIGLIORAMENTO DEL  
COMPENSO GLICOMETABOLICO E SUI FATTORI DI  
RISCHIO CARDIORENALI**

Simona Valeria Ferrero

# DIABESITA'



- Obesità e diabete condividono fattori di rischio, meccanismi patogenetici e comorbidità.
- 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 insulino-resistenza 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 diabetico devono necessariamente tenere conto della sua peculiarità clinica, per poter essere efficaci nella gestione e del peso e del controllo glicometabolico.

L'indicazione alla perdita di peso è assoluta:  
per i soggetti con BMI >35 o >30 con importanti comorbidità come il diabete, è auspicabile la perdita del 15-20% del peso.  
La chirurgia bariatrica permette la normalizzazione o il forte contenimento del peso corporeo, ma è gravata da costi e rischi a breve e lungo termine, che non la rendono uno strumento applicabile a tutti i pazienti.

## 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<sup>1</sup>, R Taylor<sup>2</sup>, L Harris<sup>3</sup> and MEJ Lean<sup>1</sup>

**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<sup>2</sup>), 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).

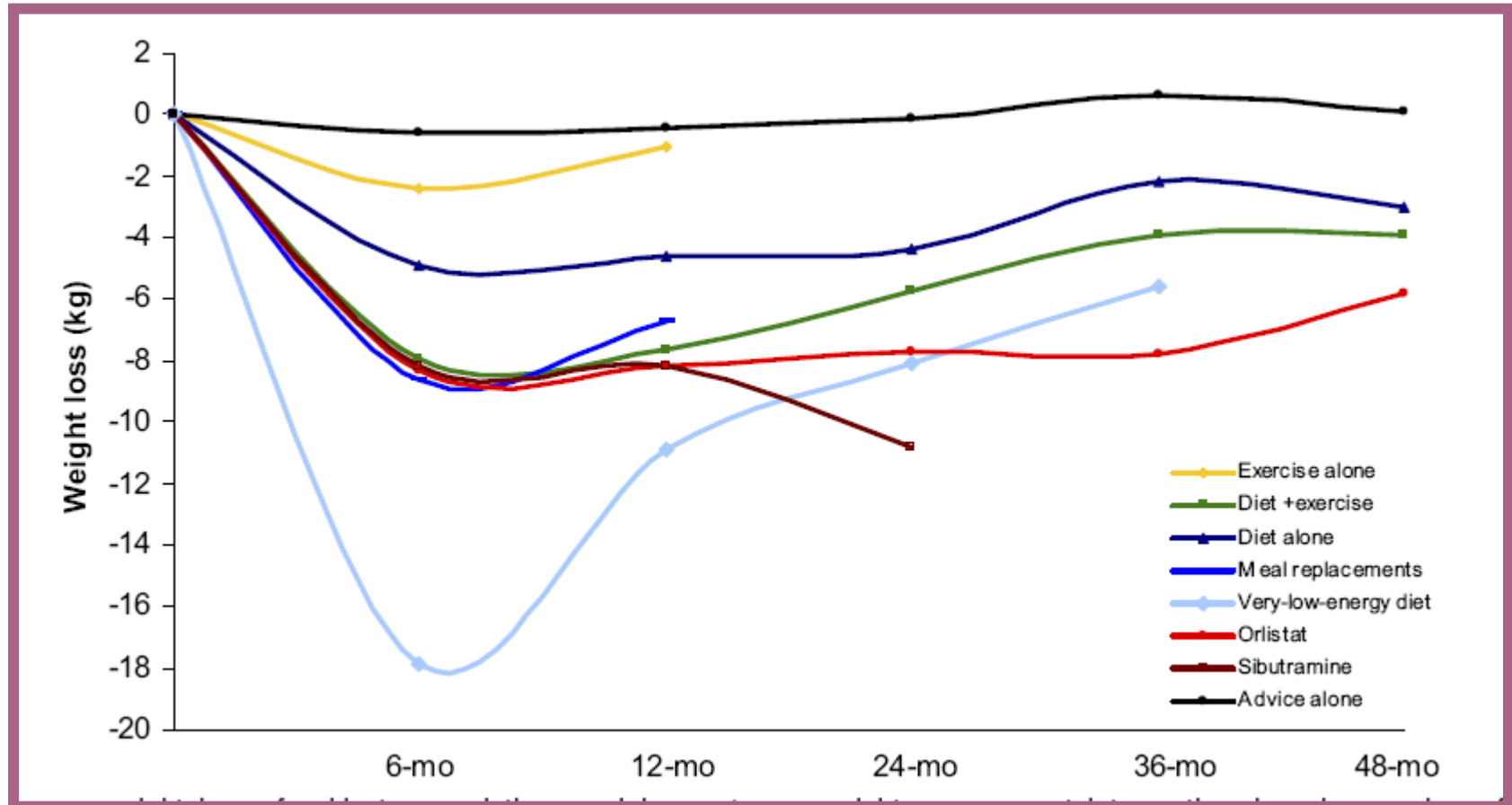
**CONCLUSIONS:** Weight losses with liquid-formula diets are very similar for VLCD and LELD and for obese subjects with or without T2DM. They can potentially achieve new weight loss/ maintenance targets of > 15–20% for people with severe and medically complicated obesity.

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

# LE 3 CARATTERISTICHE CHE DEFINISCONO LA VLCKD

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

# Weight-Loss Outcomes: A Systematic Review and Meta-Analysis of Weight-Loss Clinical Trials with a Minimum 1-Year Follow-Up



Average weight loss of subjects completing a minimum 1-year weight-management intervention; based on review of 80 studies (N26,455; 18,199 completers [69%]).

# Long-term weight loss maintenance and management following a VLCD: a 3-year outcome

C. Rolland,<sup>1,\*</sup> K. L. Johnston,<sup>2</sup> S. Lula,<sup>2</sup> I. Macdonald,<sup>3</sup> J. Broom<sup>1,2</sup>



## SUMMARY

**Background:** Effective weight loss treatment is important as obesity has severe health and socioeconomic repercussions. Emerging evidence suggests that rapid initial weight loss results in better long-term weight loss maintenance. This remains controversial and contradicts current recommendations for slower weight loss. **Aim:** To determine the effect of a very low calorie diet (VLCD) with group-

### What's known

The erroneous belief that rapid weight loss is associated with poorer long-term weight loss outcomes is unsubstantiated, but these cognitive biases are attributable to the repeated exposure of such claims (i.e. through the media) despite no sound scientific evidence base for these. Emerging

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**Conclusion:** ... large amounts of initial weight loss can result in important longer term weight loss maintenance in motivated individuals


while 51% had a BMI > 35 kg/m<sup>2</sup>. The average initial weight of the whole cohort was 99.1 kg (SD 16.6). Initial weight and BMI at entry onto programme, as well as numbers of weeks of weight loss were all significantly associated with weight loss achieved on the first weight loss attempt. Weight lost during the initial weight loss phase was the only factor, which was significantly associated with percentage weight loss maintenance for years 1, 2, and 3. **Conclusion:** The findings of this retrospective analysis suggest that provided a longer term weight loss management programme is adhered to, large amounts of initial weight loss can result in important longer term weight loss maintenance in motivated individuals.

following a VLCD in motivated individuals, but more importantly demonstrate that this can be achieved in a community-based setting where individuals are involved in group support, along with behavioural therapy. Furthermore, this weight loss regime should receive better long-term support from GPs and the scientific community for their value to be optimised.

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### Disclosures

CR has received lecture honoraria and has attended national/international meetings as a guest of LighterLife Ltd, UK. CR, JB have been involved with other companies with an interest in obesity. JB, KLJ, SL are employed by LighterLife Ltd, UK. IM has done consultancy



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.

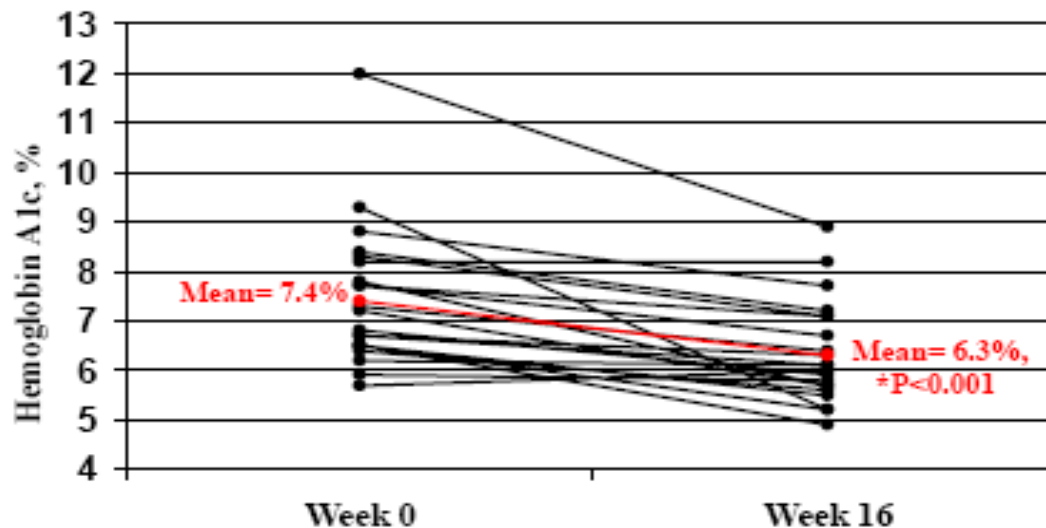


# Nutrition & Metabolism

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<sup>\*1,2</sup>, Marjorie Foy<sup>1</sup>, Allison M Chalecki<sup>1</sup>, Mary C Vernon<sup>3</sup>  
and Eric C Westman<sup>2</sup>



**Conclusion:** the LCKD improved glycemic control in patients with type 2 diabetes such that diabetes medications were discontinued or reduced in most participants. Because the LCKD can be very effective at lowering blood glucose, patients on diabetes medication who use this diet should be under close medical supervision or capable of adjusting their medication.



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# Journal of Diabetes and Its Complications

journal homepage: [WWW.JDCJOURNAL.COM](http://WWW.JDCJOURNAL.COM)



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



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### 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  $\geq 32$  kg/m<sup>2</sup> 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  $53 \pm 7$  years of age (mean  $\pm$  SD) and 53% were men. After 12 weeks, BMI fell from  $40.1 \pm 6.6$  to  $35.1 \pm 6.5$  kg/m<sup>2</sup>. HbA1c fell from  $7.4\% \pm 1.3\%$  to  $6.5\% \pm 1.2\%$  ( $57.4 \pm 12.3$  to  $47.7 \pm 12.9$  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.



## Original article

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

Marieke Snel <sup>a,\*</sup>, Maria A. Sleddering <sup>a</sup>, Inge D. vd Peijl <sup>b</sup>, Johannes A. Romijn <sup>a</sup>, Hanno Pijl <sup>a</sup>,  
A. Edo Meinders <sup>a</sup>, Ingrid M. Jazet <sup>a</sup>

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<sup>b</sup> Department of Physiotherapy, Leiden University Medical Center, Leiden, The Netherlands

Table 2

Overview of medication used at baseline, directly after and 18 months after a 16-week VLCD only or VLCD with exercise in obese insulin-dependent T2DM patients.

	VLCD + exercise			VLCD only			Controls	
	Baseline	16 weeks	18 months	Baseline	16 weeks	18 months	Obese	Lean
Insulin (number of pts)	13	0	0	14	0	6	0	0
Insulin (U/kg)	0.69	0	0	0.76	0	0.34	0	0
Metformin (number of pts)	10	13	12	9	14	12	0	0
SU derivative (number of pts)	3	0	4	1	0	4	0	0
Exercise (min/week)	34	180	192	24	0	45	82	167

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

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

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

- Unitamente all'effetto sul peso e sul controllo glicemico, la VLCKD migliora significativamente tutti i parametri della sindrome metabolica.
- Il miglioramento del controllo glicemico è evidente fin dalle primissime fasi della dieta e precede il calo di peso, 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.

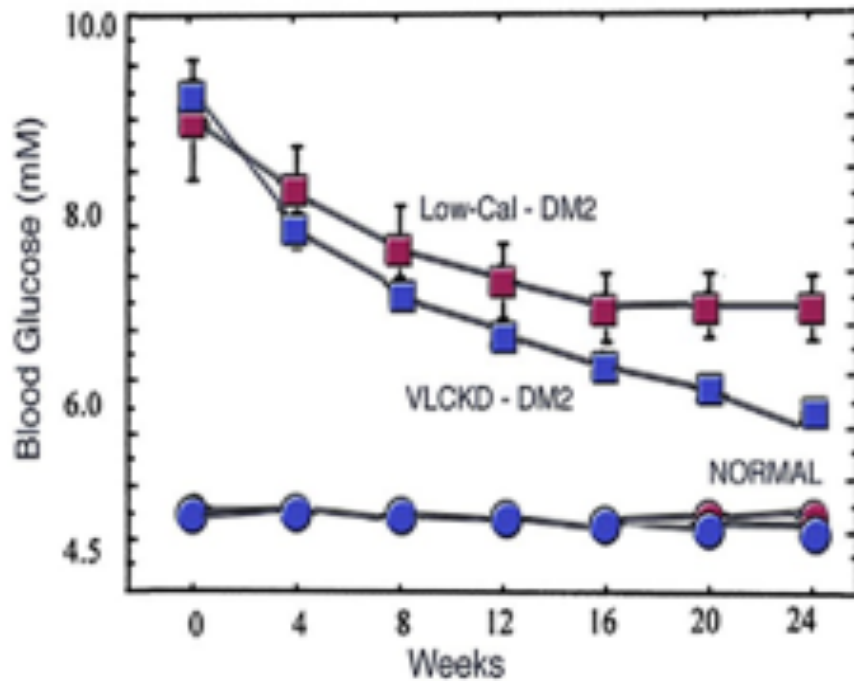
# MECCANISMI COINVOLTI NELLA REGOLAZIONE GLICOMETABOLICA IN CORSO DI VLCKD

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

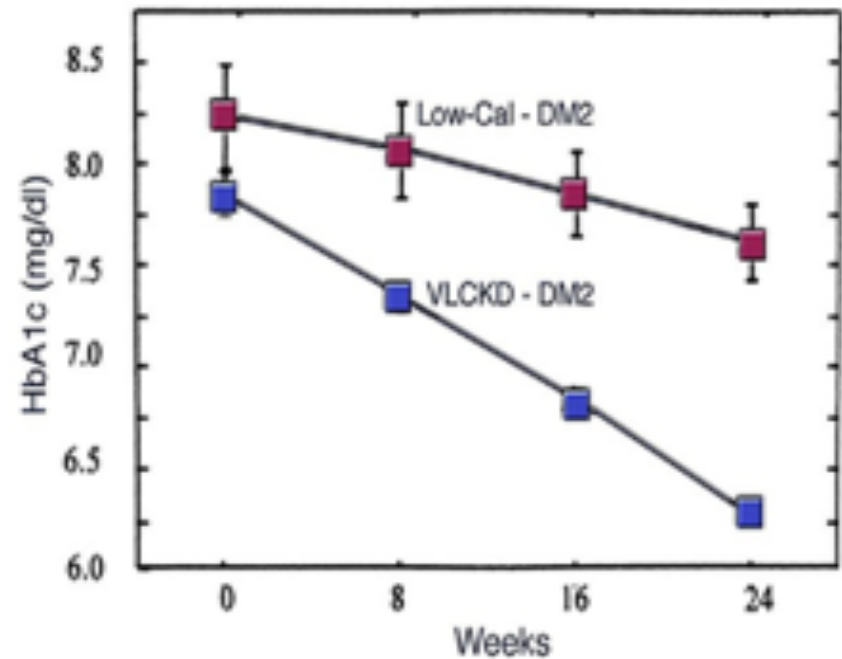
# Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes

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

### Blood Glucose



### HbA1c



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

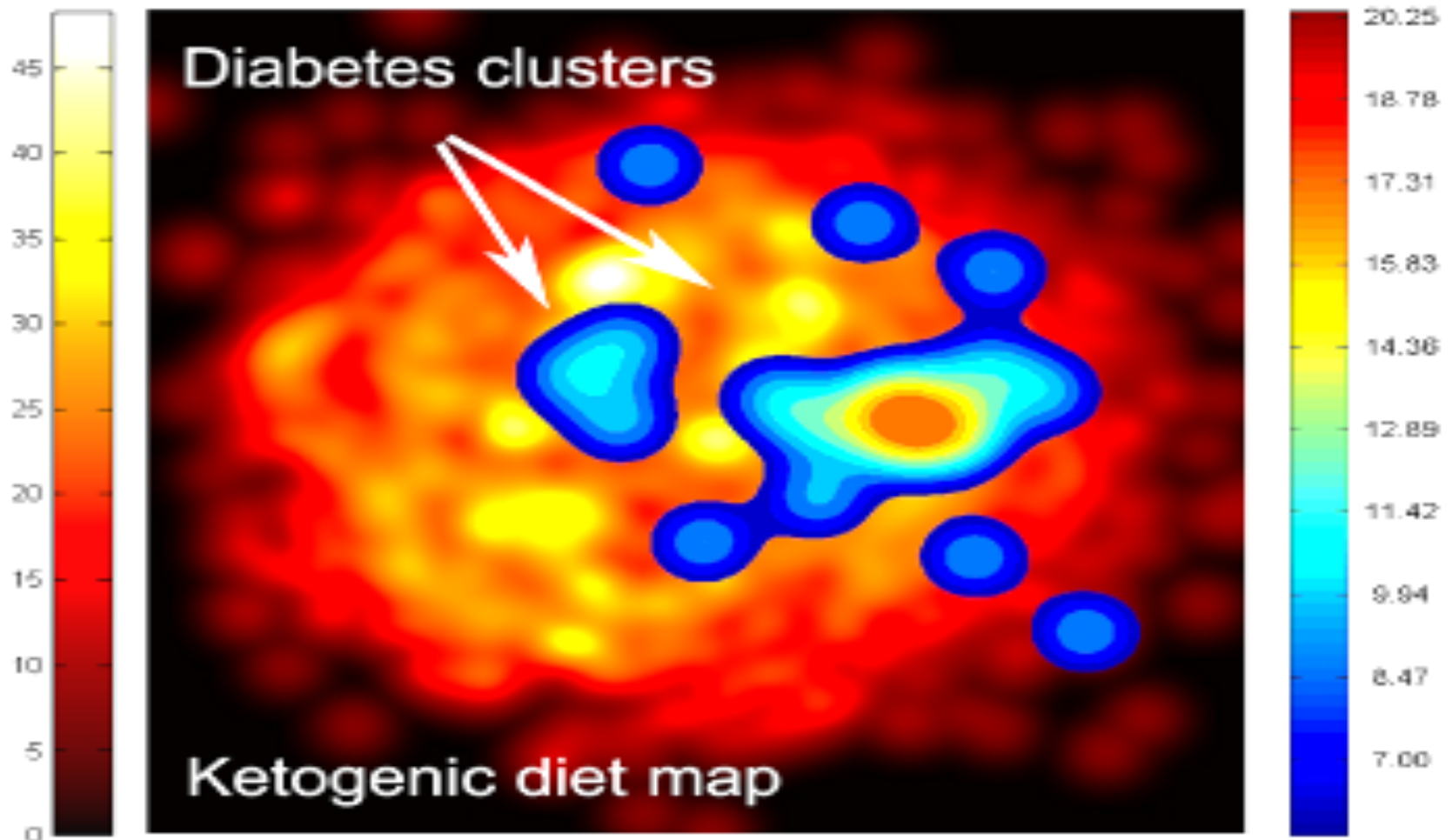
EC Westman, Nutrition and Metabolism, 2008

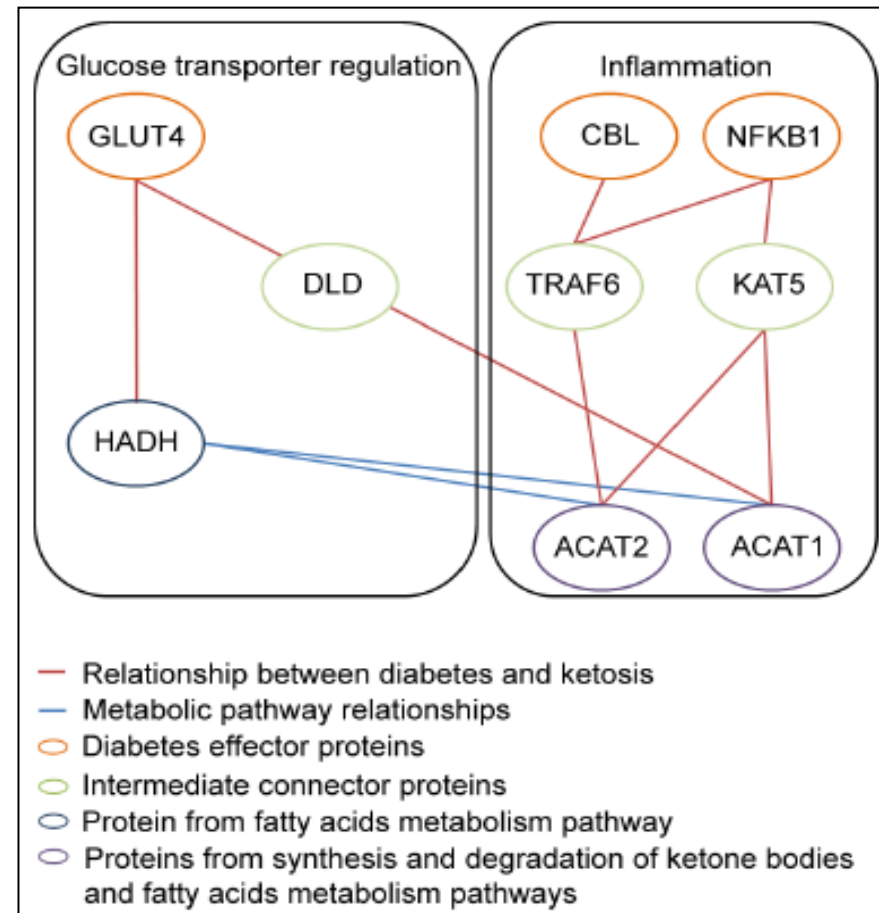
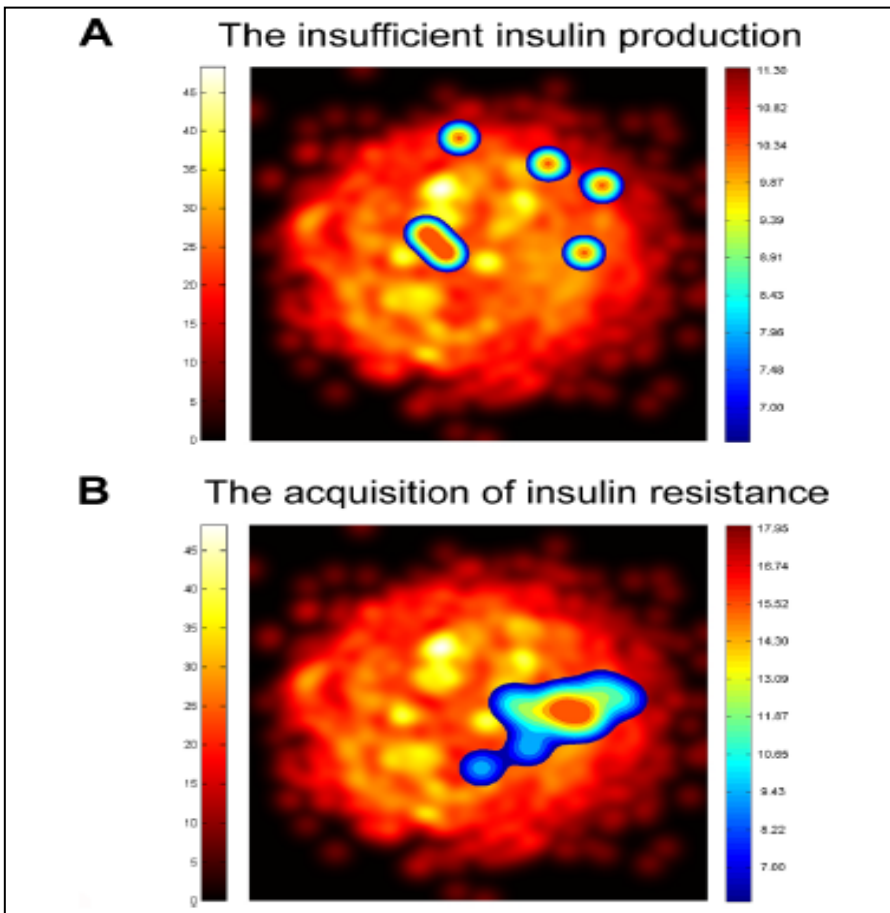
Mean Change Week 0 to 24	LGID	LCKD
HbA1c%	- 0.5	- 1.5
FPG mg/dl	- 16	- 19.9
Fasting Insulin mcU/mL	- 2.2	- 6.0
BMI (kg/m <sup>2</sup> )	- 2.7	- 3.9
BW (kg)	- 6.9	- 11.1



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

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





1. Elements of lipid metabolism may facilitate proper cellular localization of glucose transporter and recycling
2. Ketone bodies can alleviate certain inflammatory processes by blocking specific cytokines.

## **$\beta$ -hydroxybutyrate: Much more than a metabolite**

**John C. Newman**<sup>1,2</sup> and **Eric Verdin**<sup>2,\*</sup>

- 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  $\beta$ OHB 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

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

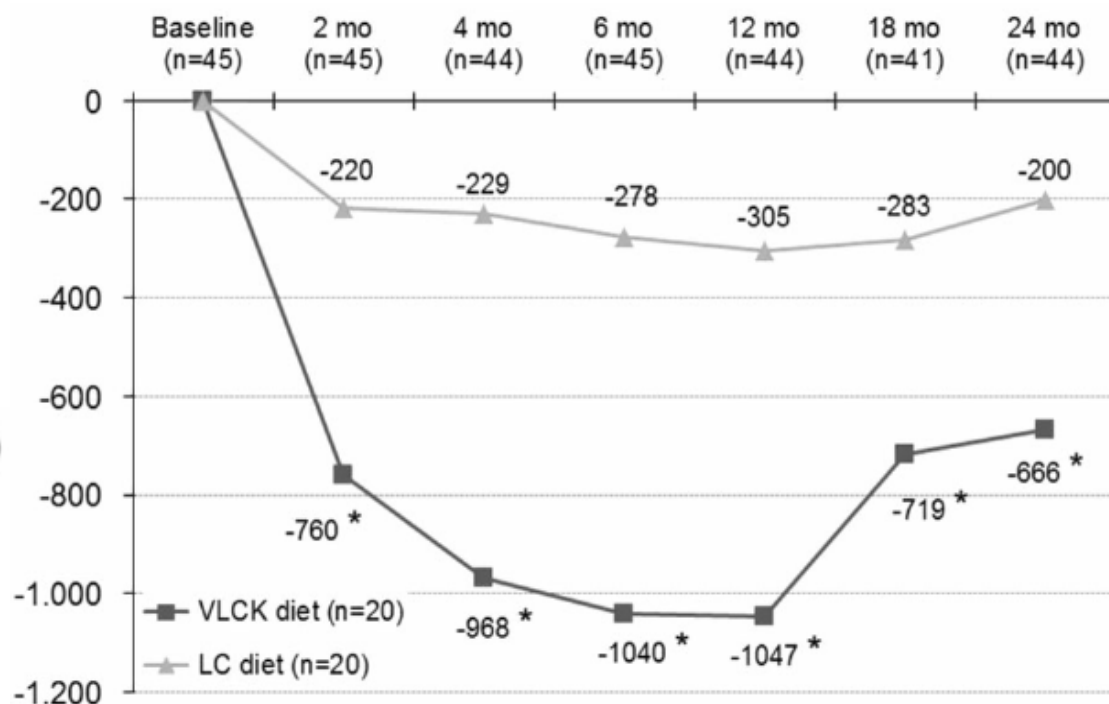


- Visceral adipose tissue is lost preferentially with modest weight loss.
- Acute caloric restriction, using VLCD, produces early preferential loss of VAT.
- Very-low-calorie diets (VLCDs) provided exceptional short-term (<4 weeks) preferential VAT loss, but this effect was lost by 12-14 weeks.

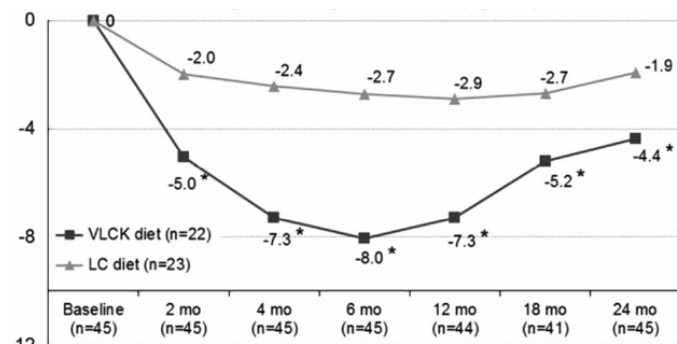
# Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease

Basilio Moreno<sup>1</sup> · Ana B Crujeiras<sup>2,3</sup> · Diego Bellido<sup>4</sup> · Ignacio Sajoux<sup>5</sup> · Felipe F Casanueva<sup>3,6</sup>

### Changes in visceral fat mass (g)



### Changes in body mass index (kg/m<sup>2</sup>)



# 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  $\beta$ -cell dysfunction. **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.**

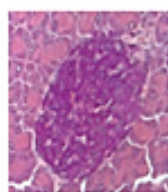
Whether these observations can help develop **better cost-effective and sustainable lifestyle/medical interventions** in patients with T2DM requires further study

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

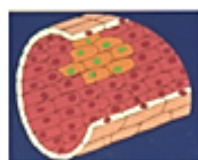
Subcutaneous stores  
overwhelmed  
(genes, ethnicity, ageing)



FAT  
'Spill over'



pancreatic  
beta cell



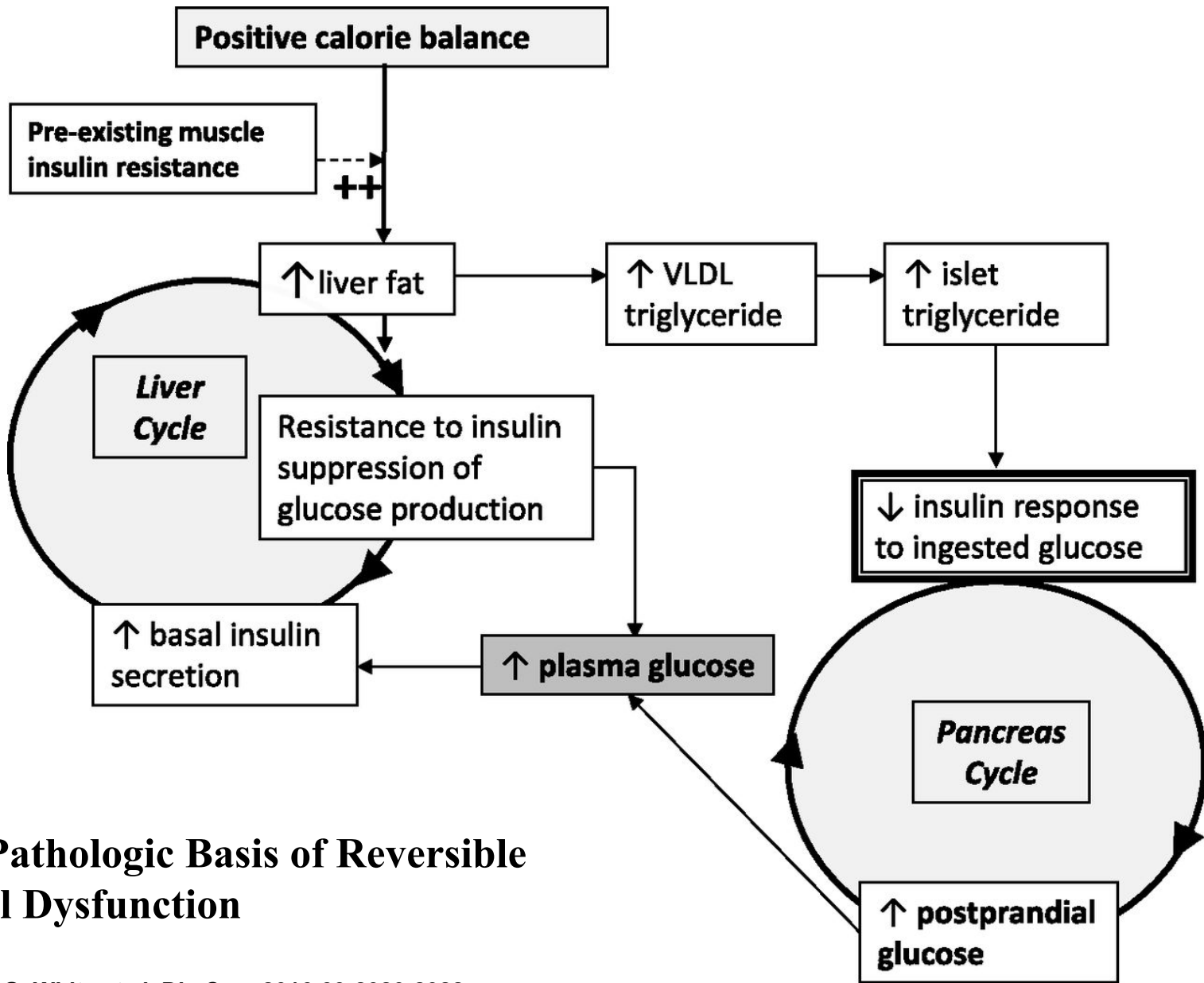
Perivascular fat =>  
Endothelial dysfunction (altered blood flow)

Insulin resistance

$\beta$  cell dysfunction?

Hyperglycaemia



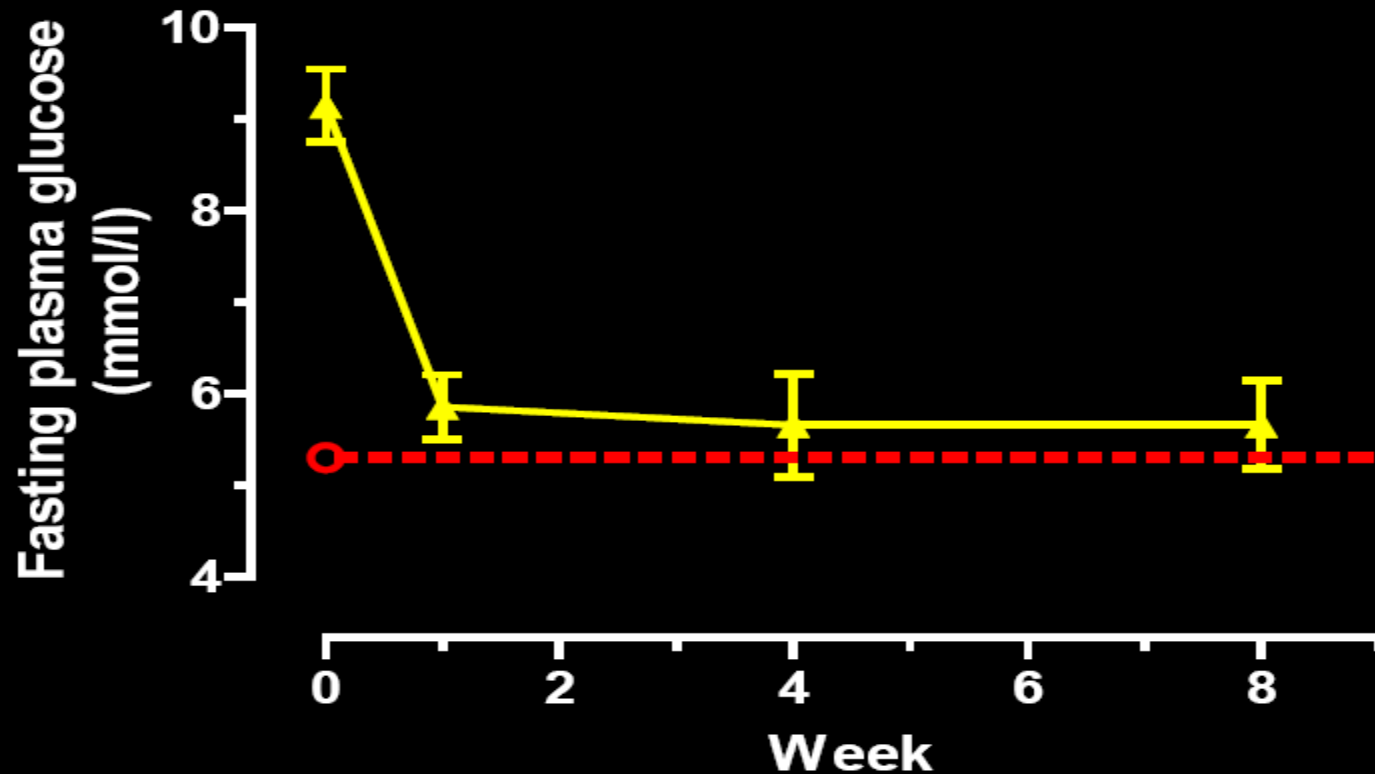


## The Pathologic Basis of Reversible $\beta$ -Cell Dysfunction

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

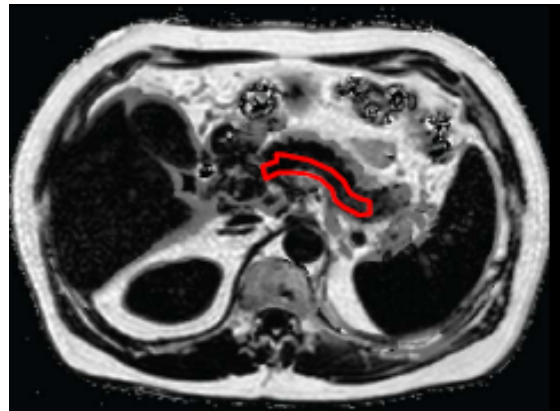
# Plasma glucose

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

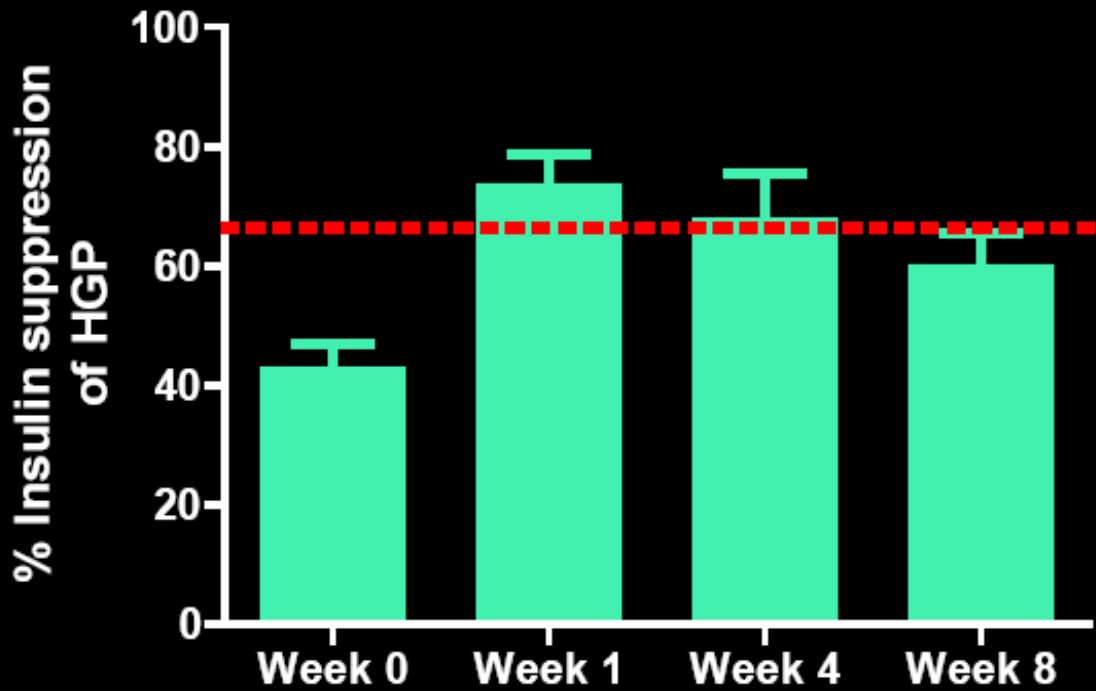


# Reversal of type 2 diabetes: normalisation of beta cell function in association with decreased pancreas and liver triacylglycerol

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

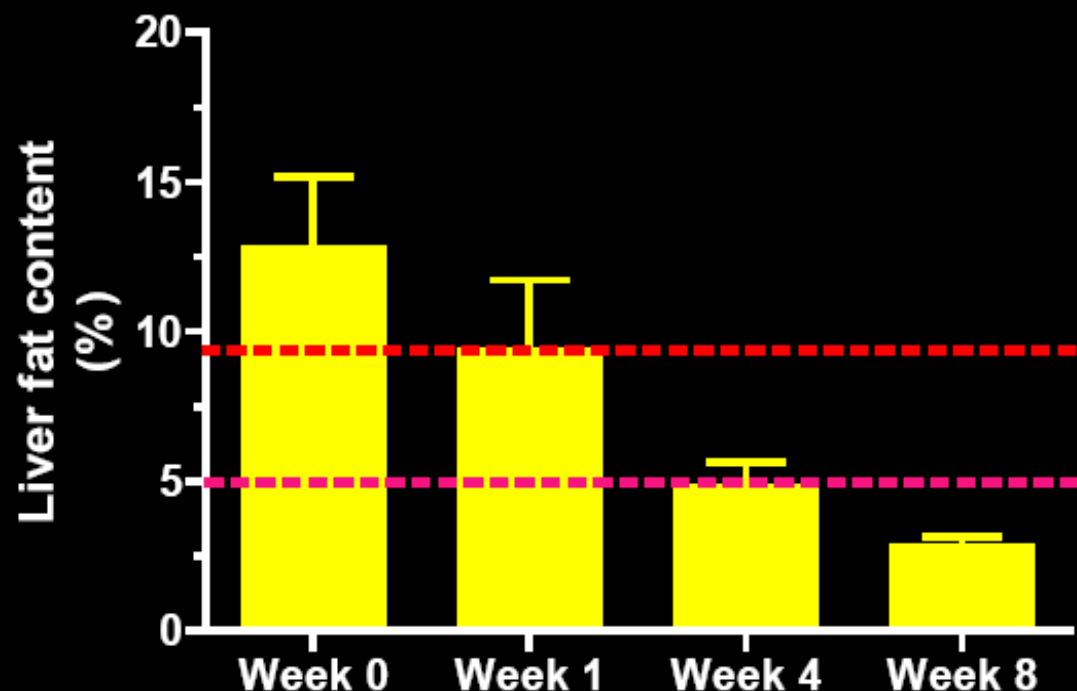


- a) Pancreas: beta cell function using an incremental insulin secretion test
- b) Liver: insulin sensitivity by isoglycaemic hyperinsulinaemic clamp
- c) Liver and pancreatic fat levels: 3 point Dixon MR method



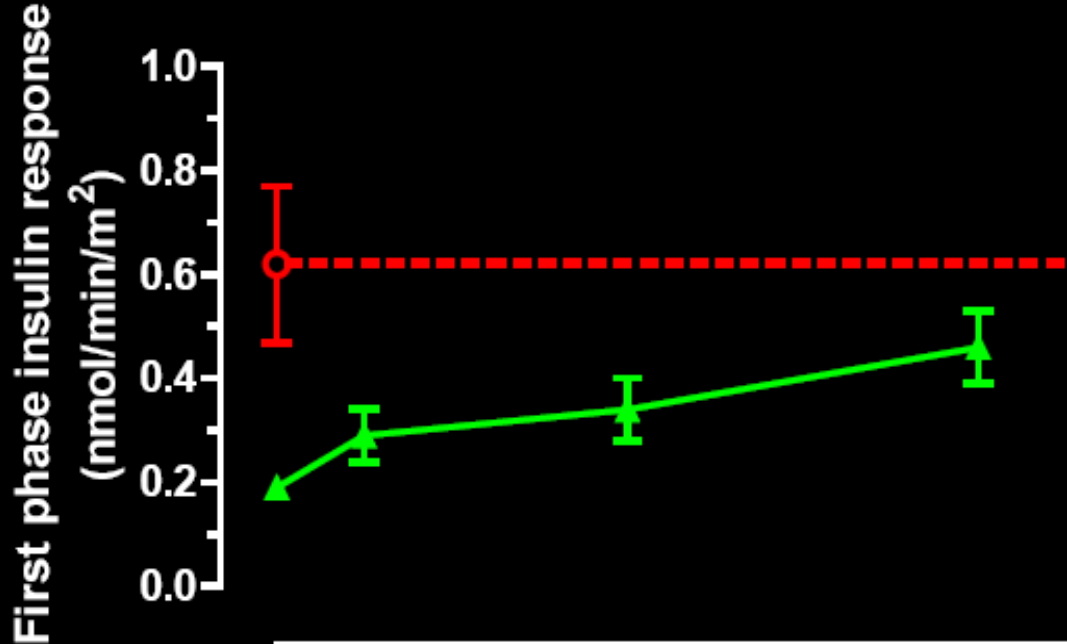
- **CON: 68 ± 5%**  
**DM: 43 ± 4%**  
**(p = 0.001)**

- **Marked ↑ after 1 week of diet (74 ± 5%, p = 0.003)**

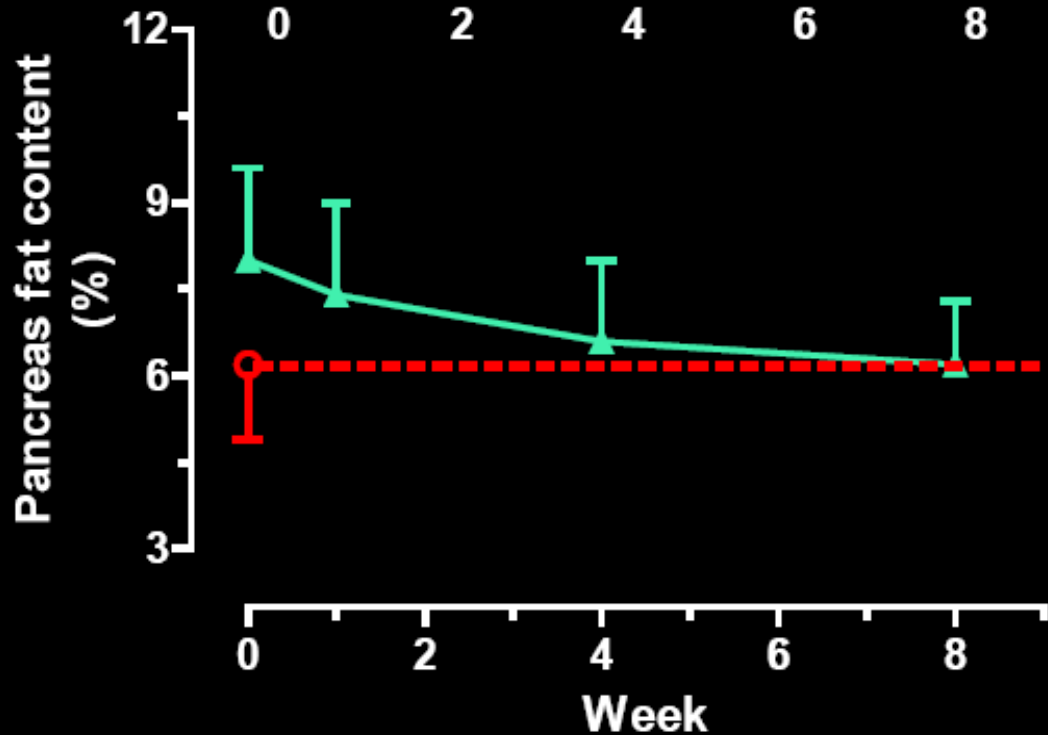


- **CON: 8.5 ± 1.9%**  
**DM: 12.8 ± 2.4%**

- **Reduced by 30% during 1<sup>st</sup> week; 70% by 8 weeks**

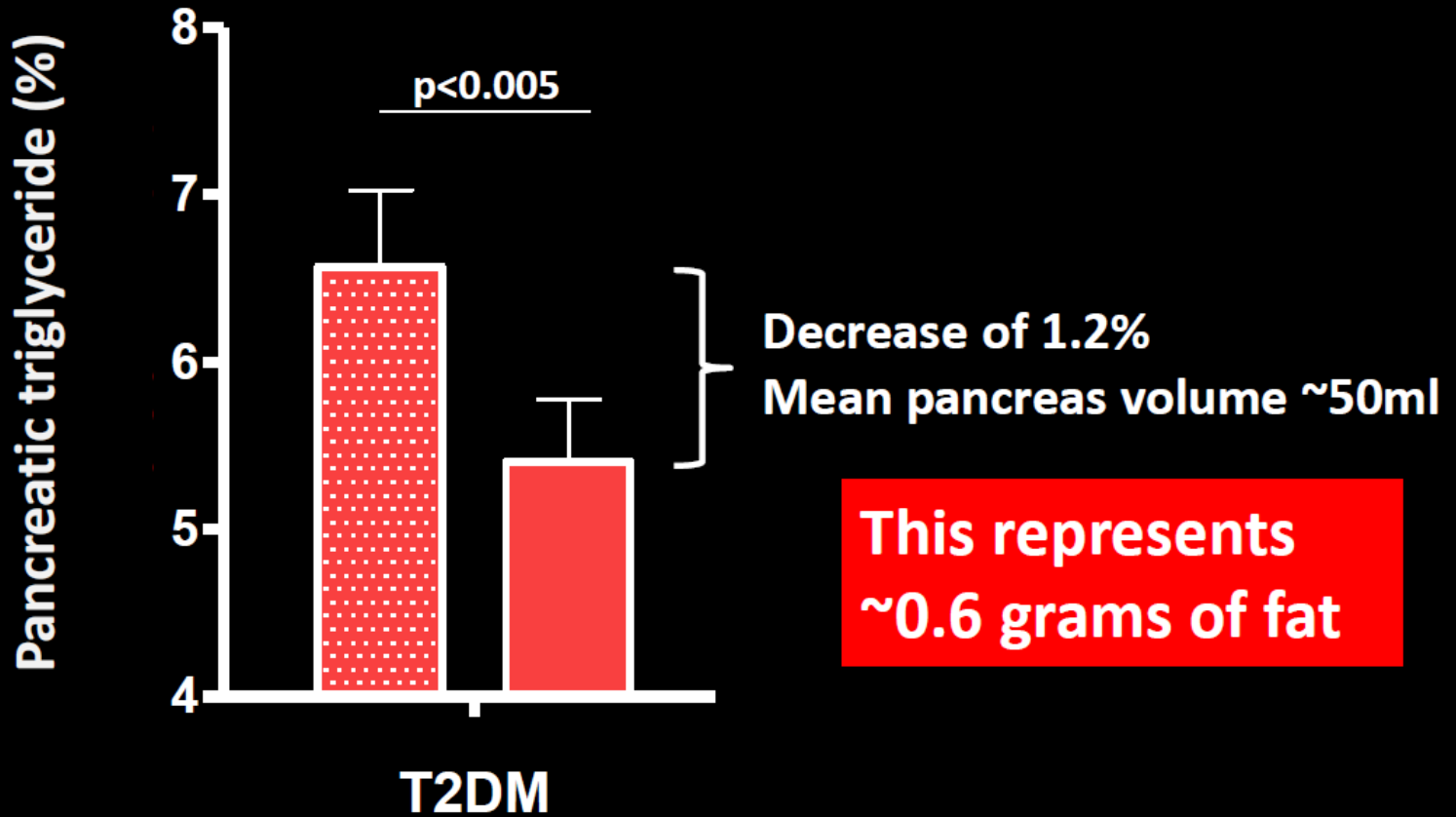


- Insulin secretion ↑ steadily
- At 8 weeks, similar to control values



- Pancreatic fat content fell gradually over 8 weeks

## Pancreatic triglyceride in T2DM before and after weight loss



# *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-Mrabeih, 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*

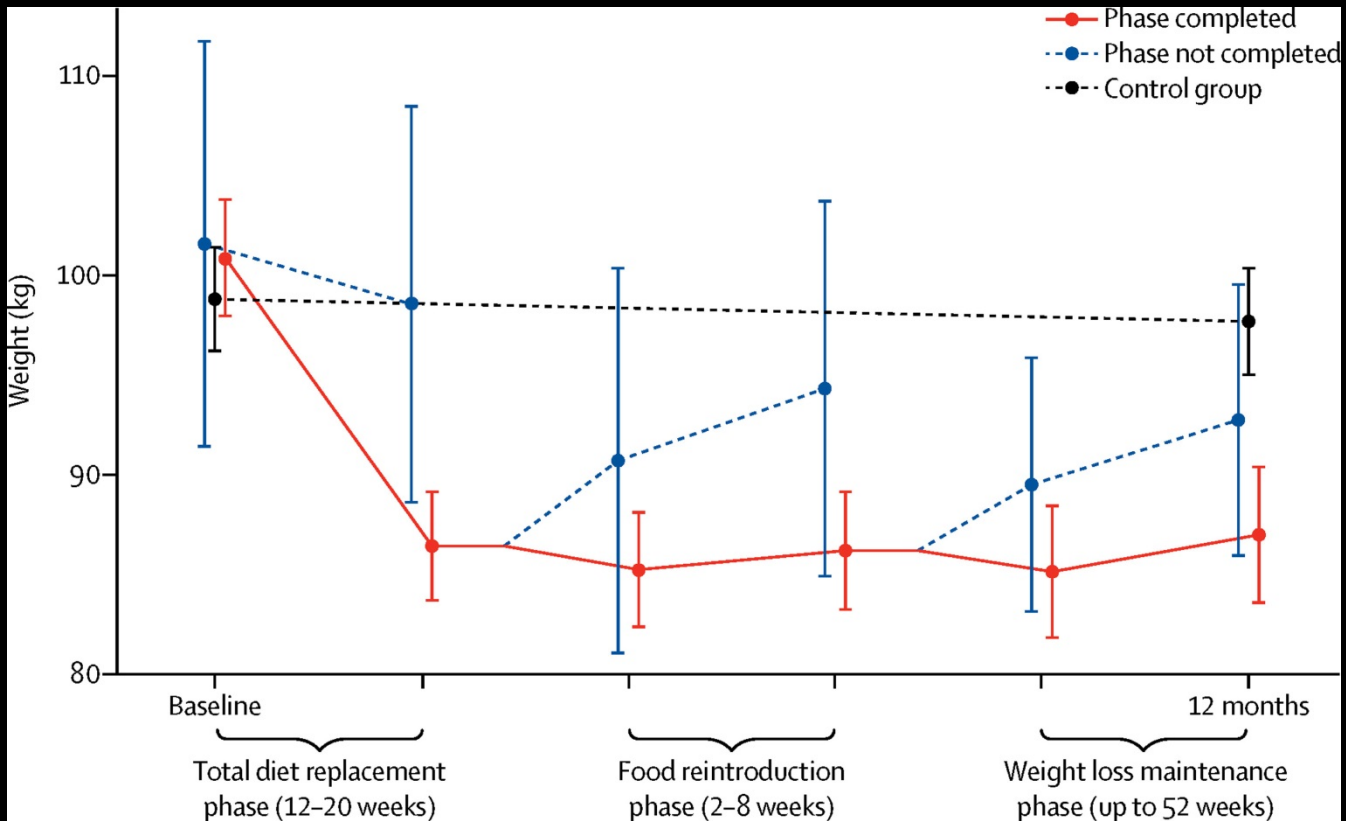
Volume 391, Issue 10120, Pages 541-551 (February 2018)

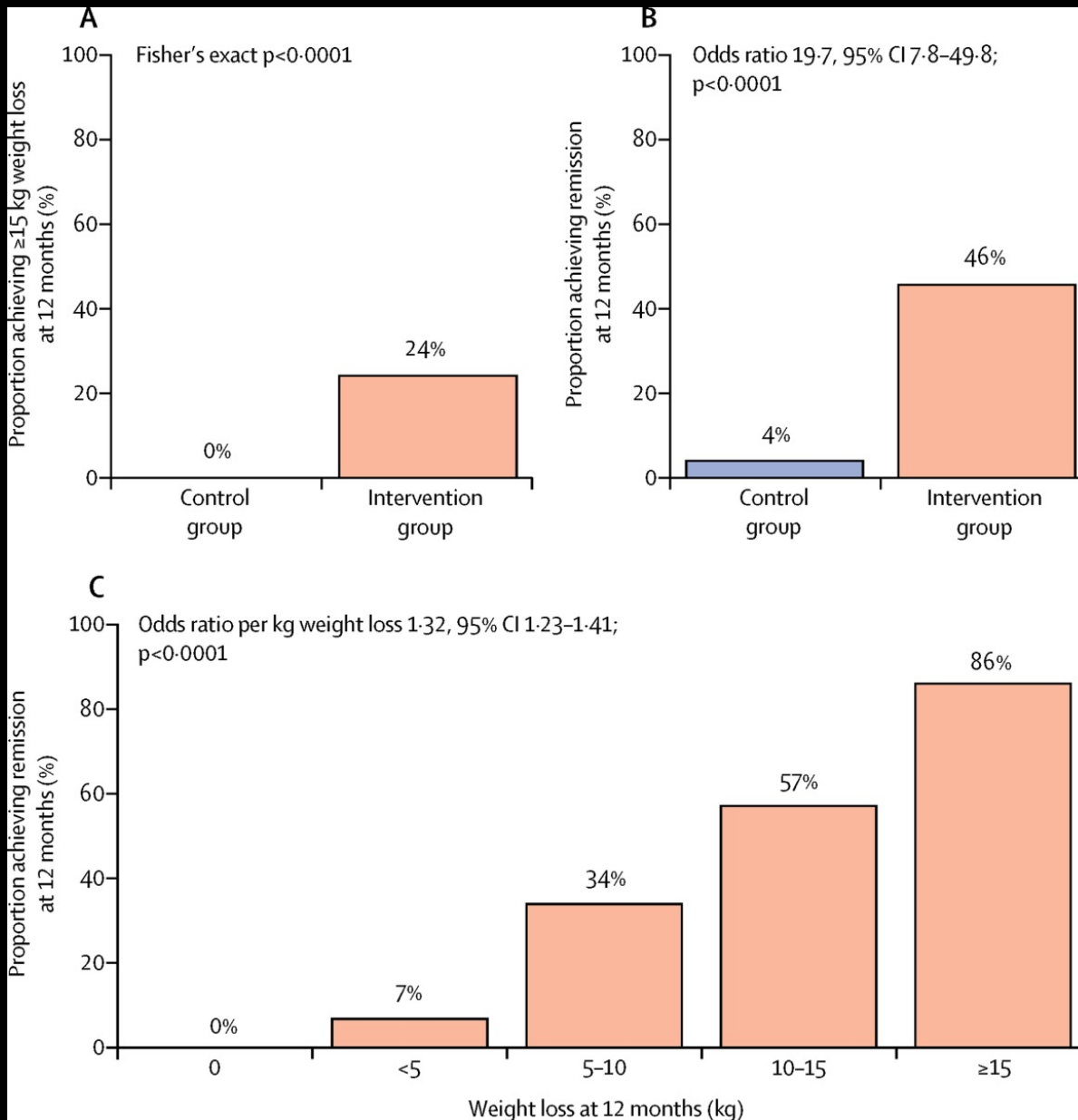
DOI: 10.1016/S0140-6736(17)33102-1



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).







## La VLCKD

È 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!