VII CONGRESSO NAZIONALE B&M 2018

IV SESSIONE

Dott. Pietro Putignano

Medico Dietologo

Responsabile ambulatori di endocrinologia e diabetologia i presidi territoriali dell'Azienda sociosanitaria di Monza – ASST Monza.

BRAIN AND MALNUTRITION
Chronic Diseases Association ONLUS

VII CONGRESSO NAZIONALE B&M

NUTRIZIONE E NEURODEGENERAZIONE

VENERDÌ 11 MAGGIO 2018

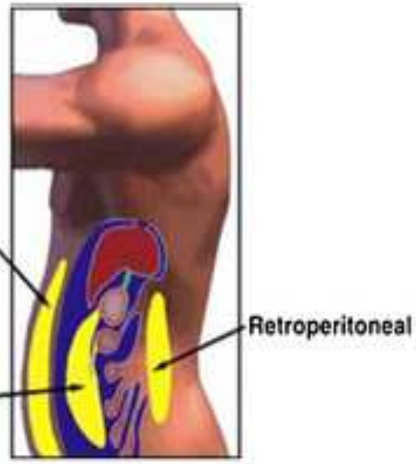
La dieta chetogenica nel paziente diabetico e obeso

Pietro Putignano

Ambulatorio di Endocrinologia e Diabetologia,

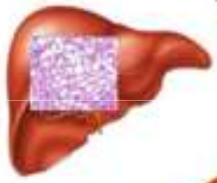
Presidio territoriale ASST Monza

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

VLCD chetogenica (VLCKD) e diabete mellito tipo 2

Indicazioni VLCKD

- **Obesità BMI > 30**

  Sovrappeso 25 > BMI < 30 associato a:

  ◊ **Sindrome metabolica** *Dhindsa P. Diabet Med 2003 – CC Case. Diabetes Obes Metab 2002;*

  ◊ **Diabete tipo 2** . *Bjorntorp P. "Obesity". Lancet 1997;350:423-6*

  ◊ **Apnee del sonno** *Tuomilehto HP . Am J Respir Crit Care Med. 2009* - PM Suratt, American Journal of Clinical Nutrition, 2007

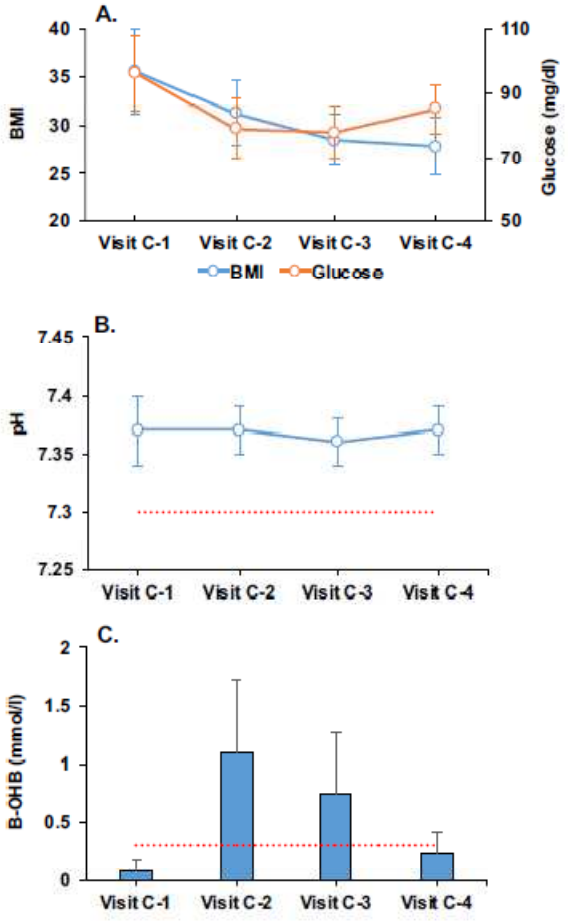
Controindicazioni assolute:

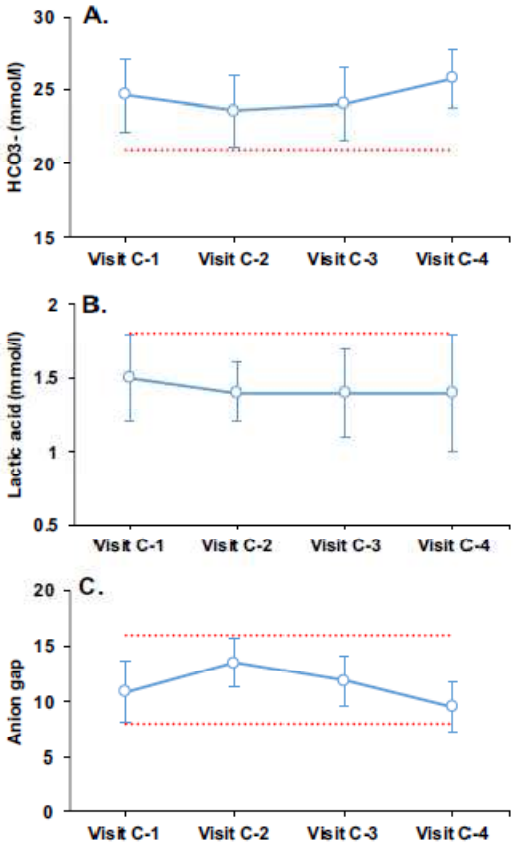
Diabete mellito tipo 1
IRC con GFR stimato < 45 ml/min
Età>75 anni
Recente evento cardiovascolare (<6 mesi)
Cirrosi epatica
Psicosi croniche
Porfirie
Terapia steroidea concomitante
Presenza di infezioni acute/croniche
Incapacità di avvertire i segni dell'ipoglicemia ("hypoglycemia unwareness")
Incapacità di eseguire correttamente l'autocontrollo glicemico domiciliare
Scarsa compliance nell'assunzione del corretto apporto idroelettrolitico e micronutrizionale
Colelitiasi nota
Nefrolitiasi recidivante e nefrolitiasi complicata da idronefrosi

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

Diego Gomez-Arbelaez[1] · Ana B. Crujeiras[1,2] · Ana I. Castro[1,2] · Albert Goday[2,3] · Antonio Mas-Lorenzo[2,3] · Ana Bellon[4] · Cristina Tejera[5] · Diego Bellido[5] · Cristobal Galban[6] · Ignacio Sajoux[7] · Patricio Lopez-Jaramillo[8] · Felipe F. Casanueva[1,2]

Endocrine (2017) 58:81–90





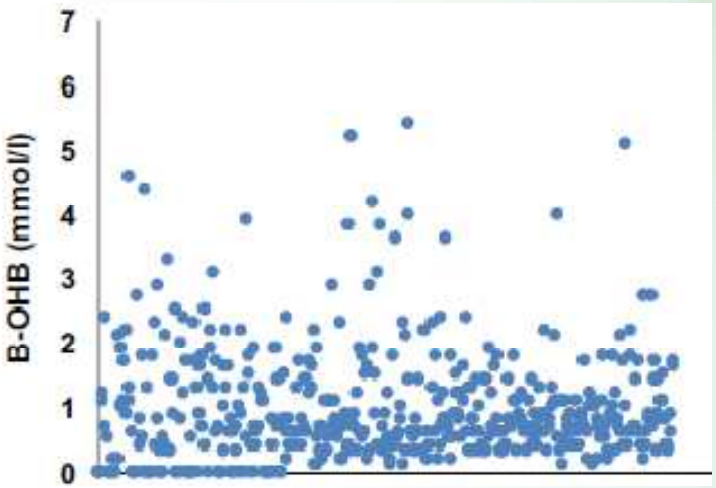
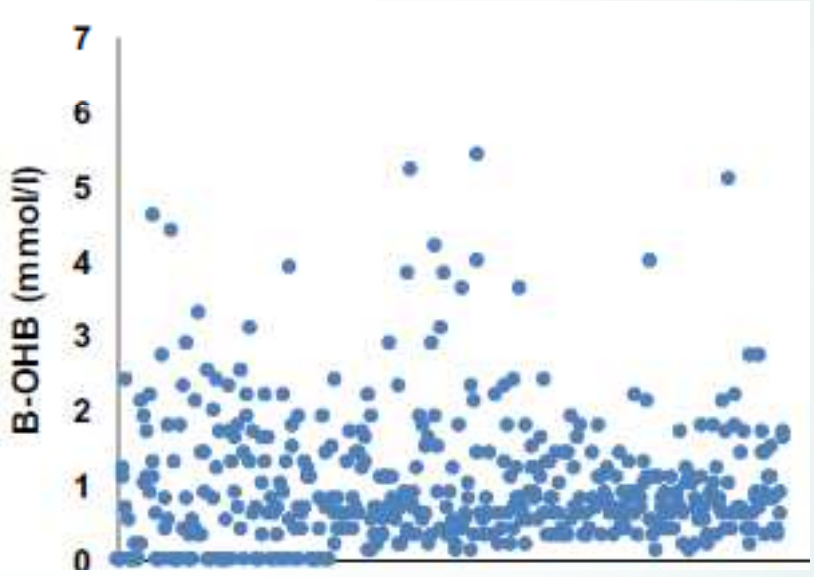


Fig. 2 Changes in venous blood gases parameters during the study. Data are presented as mean ± standard deviation. HCO3, measured

Equilibrio acido-base

Table 2 Comparison of the biochemical parameters between our study population (very low-calorie-ketogenic diet) and a cohort of patients with diabetic ketoacidosis

	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



Differenze tra VLCKD e chetoacidosi diabetica

Livelli ematici	LCD	VLCKD	KD
Glucosio* (mg/dl)	80–120	70–110	>300
Insulina (µU/l)	6–23	6.6–9.4	0
Corpi chetonici(mM/l)	0.1	0,5-5	>5
Corpi chetonici (mM/l) (dopo introduzione di CHO)	0.1	<1	>5
pH	7.4	7.4	<7.3

* La glicemia media nel paziente diabetico aderente ad una LCD o VLCKD è variabile ma solitamente inferiore a 200 mg/dl. Modificato da Paoli et al. Eur J Clin Nutr. 2013 Aug; 67(8): 789–796. 2013 e da Goday et al. Nutr & Diabetes 6 e230, 2016

RESEARCH Open Access

Resting metabolic rate of obese patients under very low calorie ketogenic diet

Diego Gomez-Arbelaez[1†], Ana B. Crujeiras[1,5†], Ana I. Castro[1,5], Miguel A. Martinez-Olmos[1,5], Ana Canton[1,5], Lucia Ordoñez-Mayan[1], Ignacio Sajoux[2], Cristobal Galban[3], Diego Bellido[4] and Felipe F. Casanueva[1,5*]

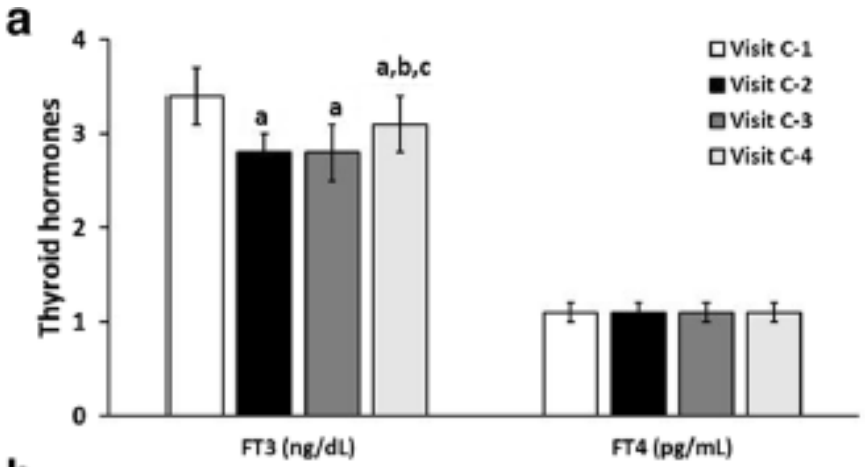
Gomez-Arbelaez et al. Nutrition & Metabolism (2018) 15:18

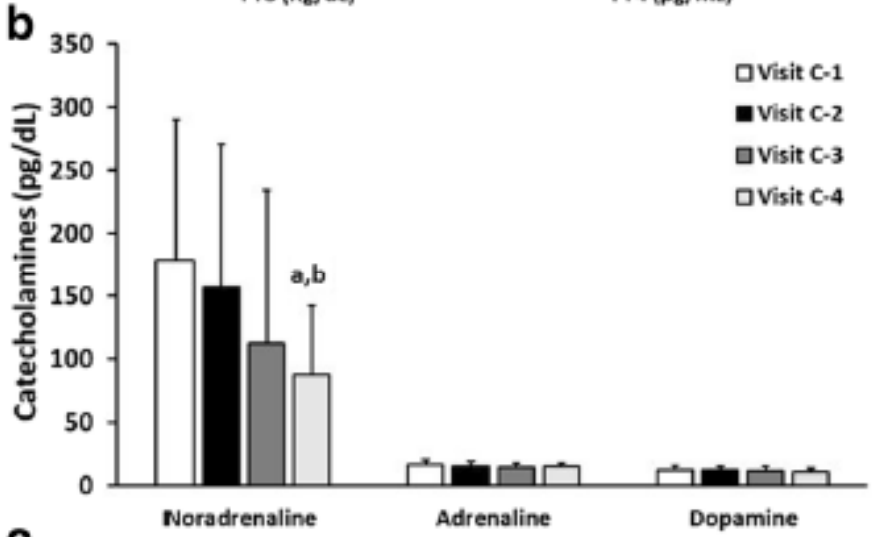
Background: The resting metabolic rate (RMR) decrease, observed after an obesity reduction therapy is a determinant of a short-time weight regain. Thus, the objective of this study was to evaluate changes in RMR, and the associated hormonal alterations in obese patients with a very low-calorie ketogenic (VLCK)-diet induced severe body weight (BW) loss.

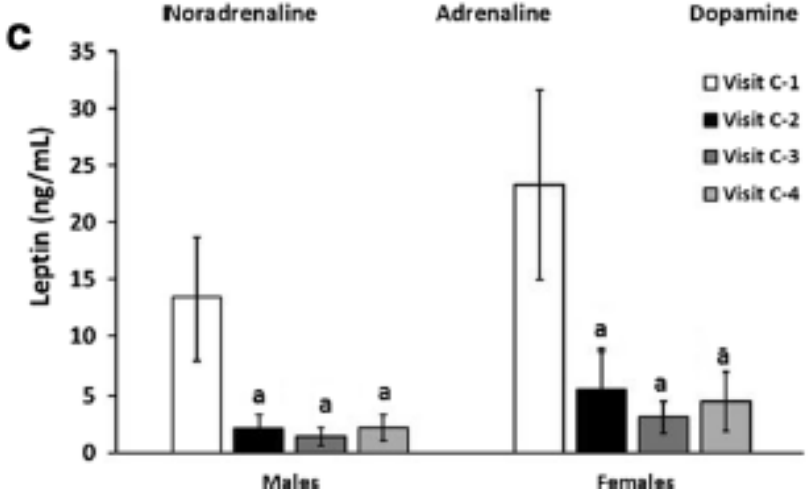
Method: From 20 obese patients who lost 20.2 kg of BW after a 4-months VLCK-diet, blood samples and body composition analysis, determined by DXA and MF-Bioimpedance, and RMR by indirect calorimetry, were obtained on four subsequent visits: visit C-1, basal, initial fat mass (FM) and free fat mass (FFM); visit C-2, − 7.2 kg in FM, − 4.3 kg in FFM, maximal ketosis; visit C-3, − 14.4 kg FM, − 4.5 kg FFM, low ketosis; visit C-4, − 16.5 kg FM, − 3.8 kg FFM, no ketosis. Each subject acted as his own control.

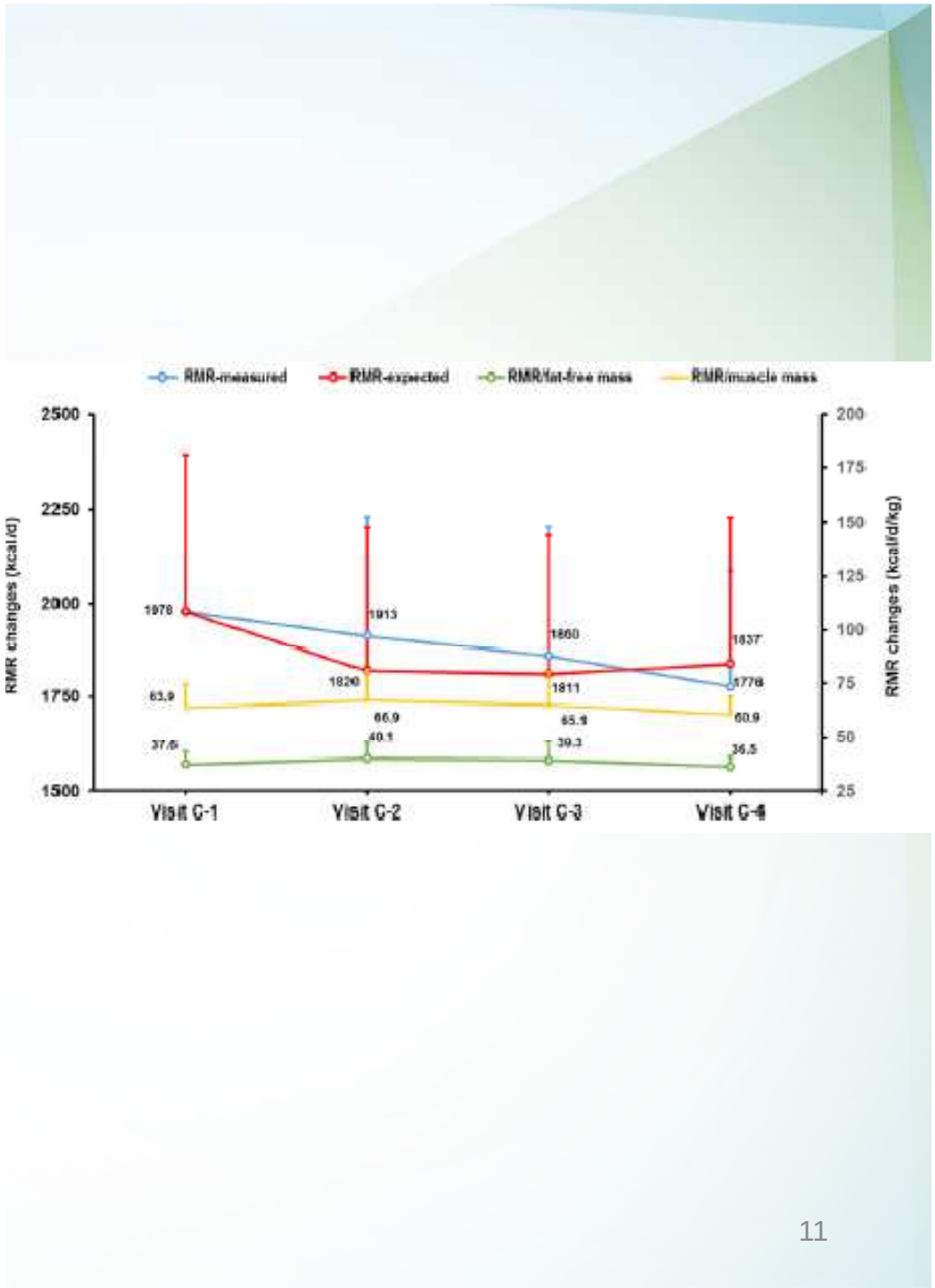
Results: Despite the large BW reduction, measured RMR varied from basal visit C-1 to visit C-2, − 1.0%; visit C-3, − 2.4% and visit C-4, − 8.0%, without statistical significance. No metabolic adaptation was observed. The absent reduction in RMR was not due to increased sympathetic tone, as thyroid hormones, catecholamines, and leptin were reduced at any visit from baseline. Under regression analysis FFM, adjusted by levels of ketonic bodies, was the only predictor of the RMR changes ($R^2 = 0.36$; $p < 0.001$).

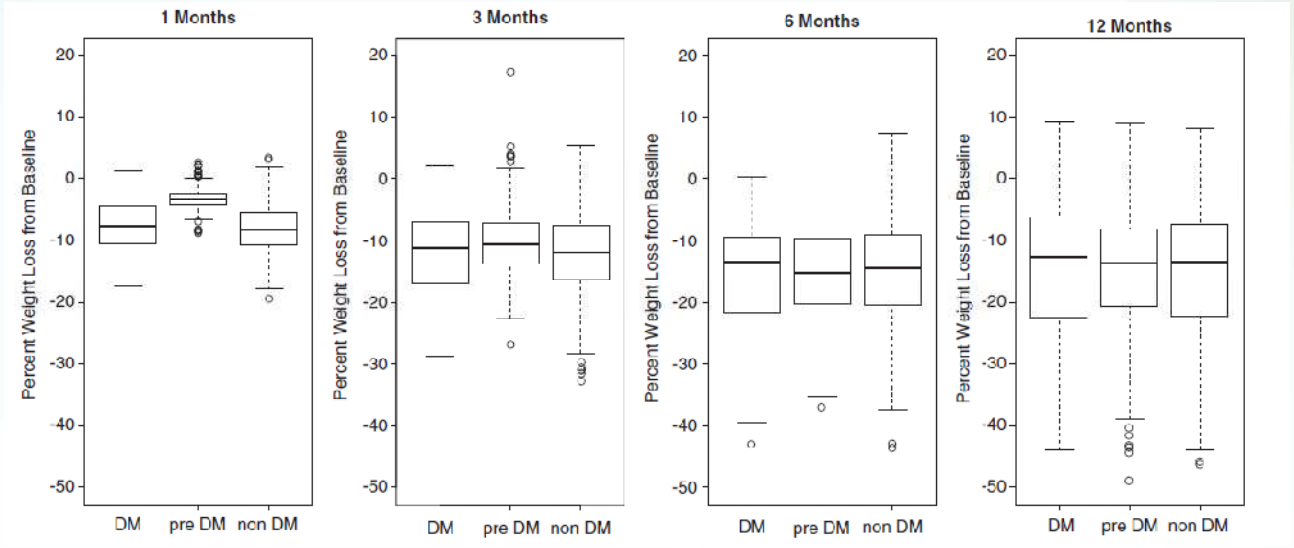
Conclusion: The rapid and sustained weight and FM loss induced by VLCK-diet in obese subjects did not induce the expected reduction in RMR, probably due to the preservation of lean mass.


a
Thyroid hormones
Visit C-1
Visit C-2
Visit C-3
Visit C-4
a
a
a,b,c
FT3 (ng/dL)
FT4 (pg/mL)


b
Catecholamines (pg/dL)
Visit C-1
Visit C-2
Visit C-3
Visit C-4
a,b
Noradrenaline
Adrenaline
Dopamine


c
Leptin (ng/mL)
Visit C-1
Visit C-2
Visit C-3
Visit C-4
Males
Females


RMR-measured
RMR-expected
RMR/fat-free mass
RMR/muscle mass
RMR changes (kcal/d)
RMR changes (kcal/d/kg)
Visit C-1
Visit C-2
Visit C-3
Visit C-4



Perdita di peso (espressa in valori percentuali rispetto al basale) in una popolazione di pazienti obesi normoglicemici (non DM), con alterata tolleranza al glucosio (pre DM) e diabetici (DM). (Tratto da Li Z et al, Nutr Diabetes. 2014 10)

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy

Dovepress

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ORIGINAL RESEARCH

Weight loss for women with and without polycystic ovary syndrome following a very low-calorie diet in a community-based setting with trained facilitators for 12 weeks

Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 2015:8 495–503

Efsevia A Nikokavoura[1]
Kelly L Johnston[2]
John Broom[1]
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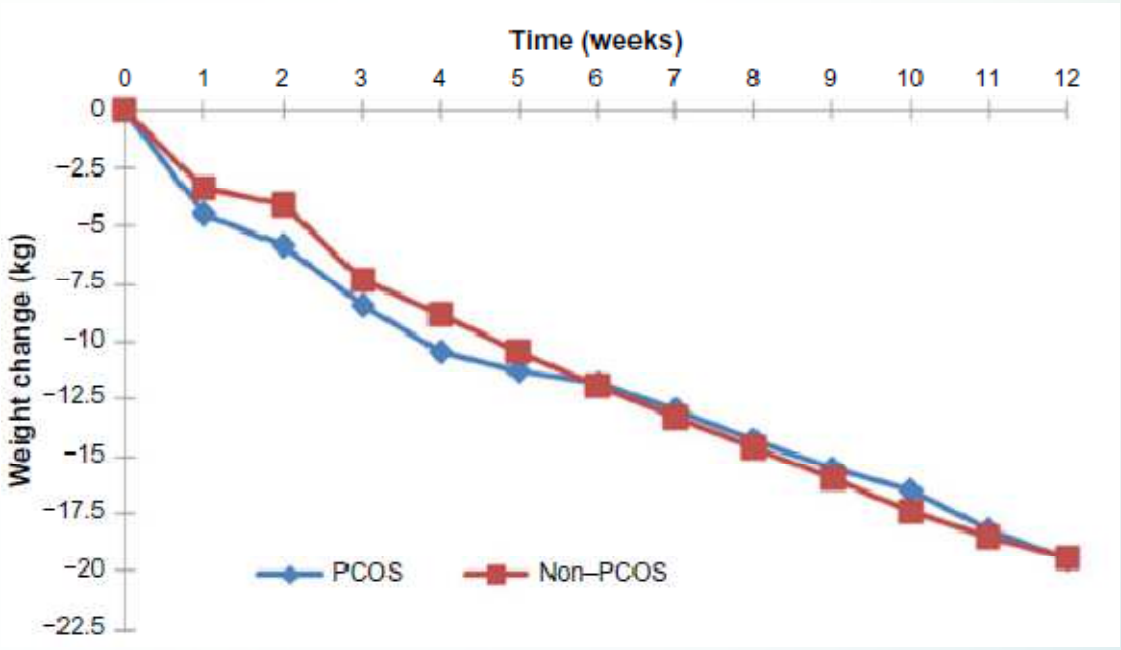

Variazione del microbiota indotto dalle VLCKD

Beneficial Effects of a Dietary Weight Loss Intervention on Human Gut Microbiome Diversity and Metabolism Are Not Sustained during Weight Maintenance

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Dominik M. Schulte[b] Malte C. Rühlemann[a] Kathrin Türk[b] Ute Settgast[b]
Wolfgang Lieb[c] John F. Baines[d] Stefan Schreiber[a, b] Andre Franke[a]
Matthias Laudes[b]

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Obes Facts 2016;9:379–391

Aumento della biodiversità e dell'Acinetobacter

Abstract

Objective: In the present study, we examined the effect of a very low-calorie diet(VLCD)-based obesity program on human gut microbiome diversity and metabolism during weight loss and weight maintenance. ***Methods:*** Obese subjects underwent 3 months of VLCD followed by 3 months of weight maintenance. A lean and an obese control group were included. The microbiome was characterized by performing high-throughput dual-indexed 16S rDNA amplicon sequencing. ***Results:*** At baseline, a significant difference in the Firmicutes/Bacteroidetes ratio between the lean and obese individuals was observed ($p = 0.047$). The VLCD resulted in significant alterations in gut microbiome diversity from baseline to 3 months ($p = 0.0053$). *Acinetobacter* represented an indicator species for the observed effect (indicator value $= 0.998$, $p = 0.006$). Metabolic analyses revealed alterations of the bacterial riboflavin pathway from baseline to 3 months ($p_{nom} = 0.0078$). These changes in diversity and bacterial metabolism induced by VLCD diminished during the weight maintenance phase, despite sustained reductions in body weight and sustained improvements of insulin sensitivity. ***Conclusion:*** The present data show that a VLCD is able to beneficially alter both gut microbiome diversity and metabolism in obese humans, but that these changes are not sustained during weight maintenance. This finding might suggest that the microbiome should be targeted during obesity programs.

ARTICLE

doi:10.1038/nature13793

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez[1], Tal Korem[2]*, David Zeevi[2]*, Gili Zilberman-Schapira[1]*, Christoph A. Thaiss[1], Ori Maza[1], David Israeli[3], Niv Zmora[4,5,6], Shlomit Gilad[7], Adina Weinberger[2], Yael Kuperman[8], Alon Harmelin[8], Ilana Kolodkin-Gal[9], Hagit Shapiro[1], Zamir Halpern[5,6], Eran Segal[2] & Eran Elinav[1]

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]

BRACKGROUND: The safety and tolerability of very low-calorie-ketogenic (VLCK) diets are a current concern in the treatment of obese type 2 diabetes mellitus (T2DM) patients.

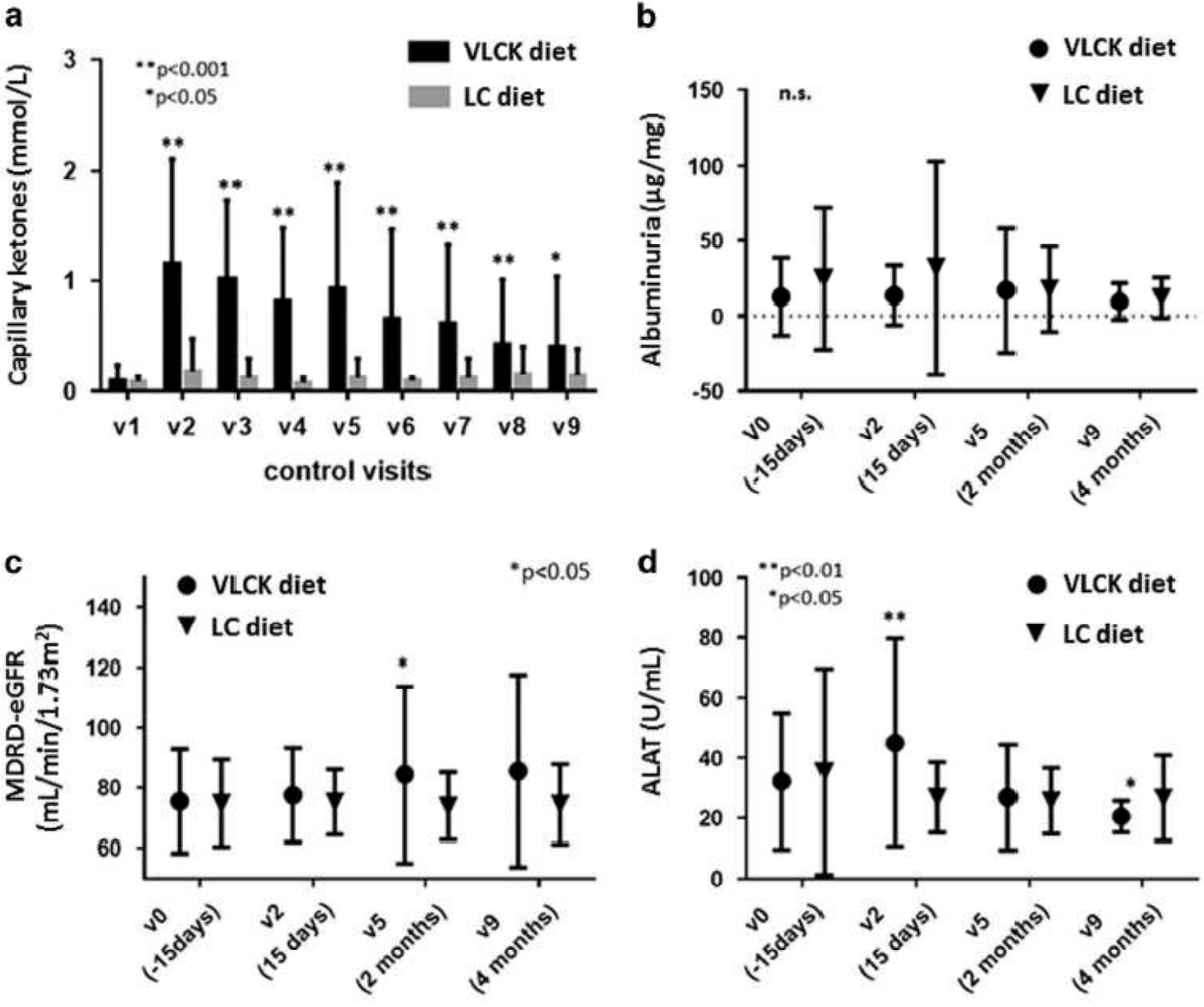
OBJECTIVE: Evaluating the short-term safety and tolerability of a VLCK diet (< 50 g of carbohydrate daily) in an interventional weight loss program including lifestyle and behavioral modification support (Diaprokal Method) in subjects with T2DM.

METHODS: Eighty-nine men and women, aged between 30 and 65 years, with T2DM and body mass index between 30 and 35 kg m^{-2} participated in this prospective, open-label, multi-centric randomized clinical trial with a duration of 4 months. Forty-five subjects were randomly assigned to the interventional weight loss (VLCK diet), and 44 to the standard low-calorie diet.

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


a
**p<0.001
*p<0.05
VLCK diet
LC diet
Capillary ketones (mmol/L)
control visits
v1
v2
v3
v4
v5
v6
v7
v8
v9
b
n.s.
VLCK diet
LC diet
Albuminuria (µg/mg)
V0 (-15days)
v2 (15 days)
v5 (2 months)
v9 (4 months)
c
*p<0.05
VLCK diet
LC diet
MDRD-eGFR (mL/min/1.73m²)
d
**p<0.01
*p<0.05
VLCK diet
LC diet
ALAT (U/mL)

Indicatori di efficacia

Table 3. Efficacy outcomes

	VLCK diet group (n = 45)			*LC diet group (n = 40)*		
	Baseline	*4 months*	*P-value*[a]	*Baseline*	*4 months*	*P-value*[a]
Body weight						
Body weight (kg)	91.5 (11.4)	76.8 (9.1)	< **0.0001**	90.0 (11.3)	84.95 (13.6)	0.5960
Weight lost > 5% of weight	–	40 (97.6%)	–	–	18 (50.0%)[†]	–
Weight lost > 10% of weight	–	35 (85.4%)	–	–	6 (16.7%)[†]	–
BMI (kg m^{-2})	33.3 (1.5)	27.9 (1.8)	< **0.0001**	32.9 (1.6)	31.0 (2.2)	< **0.0001**
Waist (cm)	108.1 (8.6)	96.1 (7.6)	< **0.0001**	105.8 (8.5)	100.4 (9.2)	**0.0481**
Glycemic control						
Fasting glycemia (mg dl^{-1})	136.9 (34.4)	108.9 (20.4)	< **0.0001**	140.5 (43.1)	123.3 (24.3)	0.1821
HbA1c (%)	6.9 (1.1)	6.0 (0.7)	< **0.0001**	6.8 (1.0)	6.4 (0.8)	0.1453
Patients with HbA1c ⩾ 7%	21 (46.7%)	5 (12.8%)	**0.0008**	15 (34.9%)	9 (25.7%)	0.3828
HOMA Index	6.9 (4.4)	3.5 (1.9)	< **0.0001**	5.8 (2.9)	4.6 (2.5)[†]	**0.0010**
Patients treated with oral antidiabetic drugs	33 (73.3%)	20 (50.0%)	**0.0267**	38 (86.4%)	30 (83.3%)	0.7057
Lipid profile						
Total cholesterol (mg dl^{-1})	200.1 (36.0)	187.5 (46.3)	0.1615	199.4 (51.0)	191.7 (34.1)	0.4489
Triglycerides (mg dl^{-1})	150.5 (54.4)	114.6 (57.2)	**0.0040**	176.1 (92.0)	158.3 (61.0)	0.3308
LDL-c (mg dl^{-1})	112.7 (33.6)	110.6 (38.4)	0.7892	109.8 (45.5)	107.1 (29.9)	0.7629
HDL-c (mg dl^{-1})	55.9 (11.1)	54.5 (11.3)	0.5728	55.1 (11.7)	52.4 (10.0)	0.3017

Effetti collaterali

Table 2. Adverse effects in both groups

Symptoms[a]	*V2 (15 days)*			*V9 (4 months)*		
	VLCK diet group (n = 45)	*LC diet group (n = 44)*	*P-value*	*VLCK diet group (n = 45)*	*LC diet group (n = 44)*	*P-value*
Asthenia	7	0	0.0092	1	0	0.3396
Headache	9	1	0.0124	2	0	0.1739
Nausea	9	0	0.0028	3	0	0.0936
Vomiting	7	0	0.0092	1	0	0.3396
Constipation	2	0	0.1772	8	0	0.0046
Cramps	1	0	0.3429	0	0	–
Myalgia	1	0	0.3429	1	0	0.3396
Muscular weakness	1	1	0.9328	0	0	–
Heaviness and tiredness of legs	1	1	0.9328	0	0	–
Hair loss	1	0	0.3429	2	0	0.1739
Orthostatic hypotension	0	0	–	6	0	0.0155
Edema	0	0	–	1	0	0.3396
Others[b,c]	20	4	0.0004	5	8	0.0731
Patients lost						
Due to side-effects	0	0		1	0	
Voluntary dropout	0	4		4	4	
Total dropout	–	–		5	8	

VLCKD e remissione del DMT2

Research Design and Methods: People with T2DM duration 0.5-23 years (n=30) followed a VLCD for 8 weeks. All oral agents or insulins were stopped at baseline. Following stepped return to isocaloric diet, a structured, individualized program of weight maintenance was provided. Glucose control, insulin sensitivity, insulin secretion, hepatic and pancreas fat content were quantified at baseline, after return to isocaloric diet and after 6 months to permit the primary comparison of change between post-weight loss and 6 months in responders. Responders were defined as achieving fasting blood glucose <7mmol/l after return to isocaloric diet.

Results: Weight fell (98.0±2.6 to 83.8±2.4 kg) and remained stable over 6 months (84.7±2.5 kg). 12/30 achieved fasting plasma glucose <7mmol/l following return to isocaloric diet (responders), and 13/30 after 6 months. Responders had shorter duration diabetes and higher initial fasting plasma insulin level. HbA1c fell from 7.1±0.3 to 5.8±0.2% (55±4 to 40±2mmol/mol) in responders ($p<0.001$), and from 8.4±0.3 to 8.0±0.5% (68±3 to 64±5mmol/mol) in non-responders, remaining constant at 6 months (5.9±0.2 and 7.8±0.3%; 41±2 and 62±3 mmol/mol respectively). The responders were characterized by return of first phase insulin response.

Conclusions: A robust and sustainable weight loss program achieved continuing remission of diabetes for at least 6 months in the 40% who responded to a VLCD by achieving fasting plasma glucose of <7mmol/l. T2DM is a potentially reversible condition.

Very low calorie diet and 6 months of weight stability in type 2 diabetes: Pathophysiologic changes in responders and non-responders

Sarah Steven MB ChB[1], Kieren G Hollingsworth PhD[1], Ahmad Al-Mrabeh PhD[1], Leah Avery PhD[2], Benjamin Aribisala PhD[3], Muriel Caslake PhD[4], Roy Taylor MD[1]

Diabetes Care. 2016 May;39(5):808-15

Responders vs. non responders

Table 1. Fasting anthropometric and metabolic data in responders and non-responders at baseline, after the VLCD and return to isocaloric eating, and then after a 6 month weight maintenance period (= p<0.05 for baseline to after VLCD difference; # = p<0.05 for baseline to month 6 difference and ° = p<0.05 for baseline difference between groups). HGP=hepatic glucose production; IR= insulin resistance; IS = insulin sensitivity; VAT=visceral adipose tissue; SAT=subcutaneous adipose tissue; BP= blood pressure.*

	Responders (n=12)			Non-Responders (n=17)		
	Baseline	*After VLCD*	*After 6 months*	*Baseline*	*After VLCD*	*After 6 months*
Weight (kg)	99.8±3.2	84.1±3.1	84.4±3.2	96.7±3.9	83.6±3.5	84.8±3.7
BMI (kg/m^2)	34.0±0.8	28.6±0.8 *	28.7±0.7 #	34.4±1.1	29.8±1.1 *	30.2±1.1 #
Waist:hip ratio	0.97±0.02	0.93±0.02 *	0.93±0.02 #	0.96±0.02	0.91±0.01 *	0.92±0.01 #
Fat mass (%)	36.2±1.9	30.1±2.0 *	31.5±1.9 #	42.6±2.2 °	37.2±2.0 *	40.8±2.5
Serum insulin (mU/l)	20.4 (5.7-48.1)	7.9 (3.4-16.6) *	7.6 (3.1-31.6) #	9.3 (3.9-48.9) °	5.5 (1.4-22.9) *	5.9 (1.2-14.9) #
Serum ALT (U/l)	43 (11-151)	26 (18-42) *	21 (7-27) #	22 (12-61) °	19 (13-47)	18 (9-33) #
Triglycerides (mmol/l)	1.97±0.32	1.25±0.16 *	1.15±0.12 #	1.30 (0.50-8.10)	1.00 (0.60-2.00) *	1.20 (0.50-3.10) #
Non-HDL cholesterol (mmol/l)	3.6±0.3	2.8±0.3 *	2.8±0.3 #	3.3±0.3	2.7±0.3 *	2.7±0.2 #
HDL cholesterol (mmol/l)	1.1±0.1	1.1±0.1	1.4±0.1 #	1.3±0.1 °	1.3±0.1	1.5±0.1
Basal HGP (mg/kg$_{ffm}$/min)	2.6 (2.2-4.0)	2.4 (2.1-3.5)	2.7 (2.4-3.1)	3.3 (2.6-8.1)	3.0 (2.4-4.5) *	3.2 (2.2-8.6)
Hepatic IR index (µmol.min^{-1}.kg$_{ffm}^{-1}$.pmol.l^{-1})	2153 (822-5947)	851 (305-1798)	750 (310-3723)	1237 (425-6602)	773 (156-2201)	755 (166-2397)
Muscle IS (mg/kg$_{ffm}$/min)	5.9±0.4	7.0±0.6	7.2±0.8	8.9±1.3	9.0±0.9	10.4±1.2 #
VAT area (cm^2)	287.0±23.1	191.9±18.9 *	179.5 ±22.3 #	289.6±23.7	209.5±22.1 *	198.9±4.8 #
SAT area (cm^2)	319.6±31.0	232.0±23.1 *	238.6±20.3 #	285.4±24.7	223.3±23.5 *	219.3±22.8 #
Systolic BP (mmHg)	142±5	129±7 *	128±5 #	159±6	139±5 *	143±6 #
Diastolic BP (mmHg)	91±2	84±4 *	82±2 #	90±2	84±2 *	85±2 #

Lancet. 2017 Dec 4. **Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial.** Lean ME et al.

Open-label, cluster-randomised trial (DiRECT) at 49 primary care practices in Scotland and the Tyneside region of England. Practices were randomly assigned (1:1), via a computer-generated list, to provide either a weight management programme (intervention) or best-practice care by guidelines (control), We recruited individuals aged 20-65 years who had been diagnosed with type 2 diabetes within the past 6 years, had a body-mass index of 27-45 kg/m^2, and were not receiving insulin. The intervention comprised withdrawal of antidiabetic and antihypertensive drugs, total diet replacement **(825-853 kcal/day f**ormula diet for 3-5 months), stepped food reintroduction (2-8 weeks), and structured support for long-term weight loss maintenance. Co-primary outcomes were weight loss of 15 kg or more, and remission of diabetes, defined as glycated haemoglobin (HbA_{1c}) of less than 6·5% after at least 2 months off all antidiabetic medications, from baseline to 12 months. We recruited **306 individuals**. At 12 months, we recorded weight loss of 15 kg or more in 36 (24%) participants in the intervention group and no participants in the control group p<0·0001). **Diabetes remission** was achieved in 68 (**46%**) participants in the intervention group and six (**4%**) participants in the control group Remission varied with weight loss in the whole study population, with achievement in none of 76 participants who gained weight, six (7%) of 89 participants who maintained 0-5 kg weight loss, 19 (34%) of 56 participants with 5-10 kg loss, 16 (57%) of 28 participants with 10-15 kg loss, and 31 (86%) of 36 participants who lost 15 kg or more. Mean bodyweight fell by 10·0 kg (SD 8·0) in the intervention group and 1·0 kg (3·7) in the control group (adjusted difference -8·8 kg, 95% CI -10·3 to -7·3; p<0·0001). Quality of life, as measured by the EuroQol 5 Dimensions visual analogue scale, improved by 7·2 points (SD 21·3) in the intervention group, and decreased by 2·9 points (15·5) in the control group (adjusted difference 6·4 points, 95% CI 2·5-10·3; p=0·0012). Nine serious adverse events were reported by seven (4%) of 157 participants in the intervention group and two were reported by two (1%) participants in the control group. Two serious adverse events (biliary colic and abdominal pain), occurring in the same participant, were deemed potentially related to the intervention. No serious adverse events led to withdrawal from the study. At 12 months, almost half of participants achieved remission to a non-diabetic state and off antidiabetic drugs. Remission of type 2 diabetes is a practical target for primary care

Meccanismi ipoglicemizzanti delle VLCKD

Effetti acuti:

1)riduzione drastica apporto di carboidrati (**effetto preponderante)**

2)ripristino precoce funzione beta cellulare

3)incremento secrezione endogena incretinica in risposta al pasto

4)modulazione della secrezione di leptina/adiponectina e altre adipochine

Effetti nel medio e lungo termine:

1)riduzione insulinoresistenza nei tessuti bersaglio per tessuto adiposo nel fegato, nel muscolo scheletrico e del VAT)

2) appetito per modulazione GLP-1, leptina, insulina

3) stile di vita più attivo con incremento attività fisica

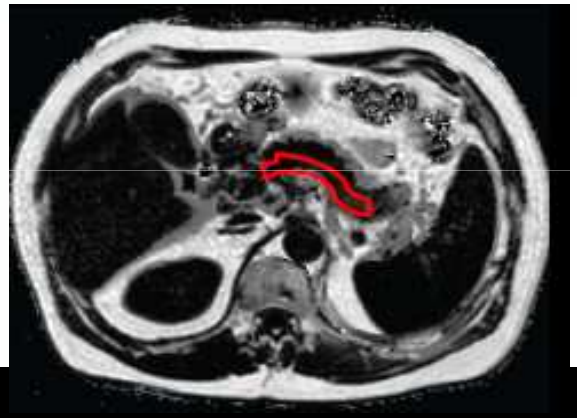
Riduzione tessuto adiposo ectopico epatopancreatico con ripristino precoce funzione beta cellulare

ARTICLE

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

Diabetologia (2011) 54:2506–2514

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

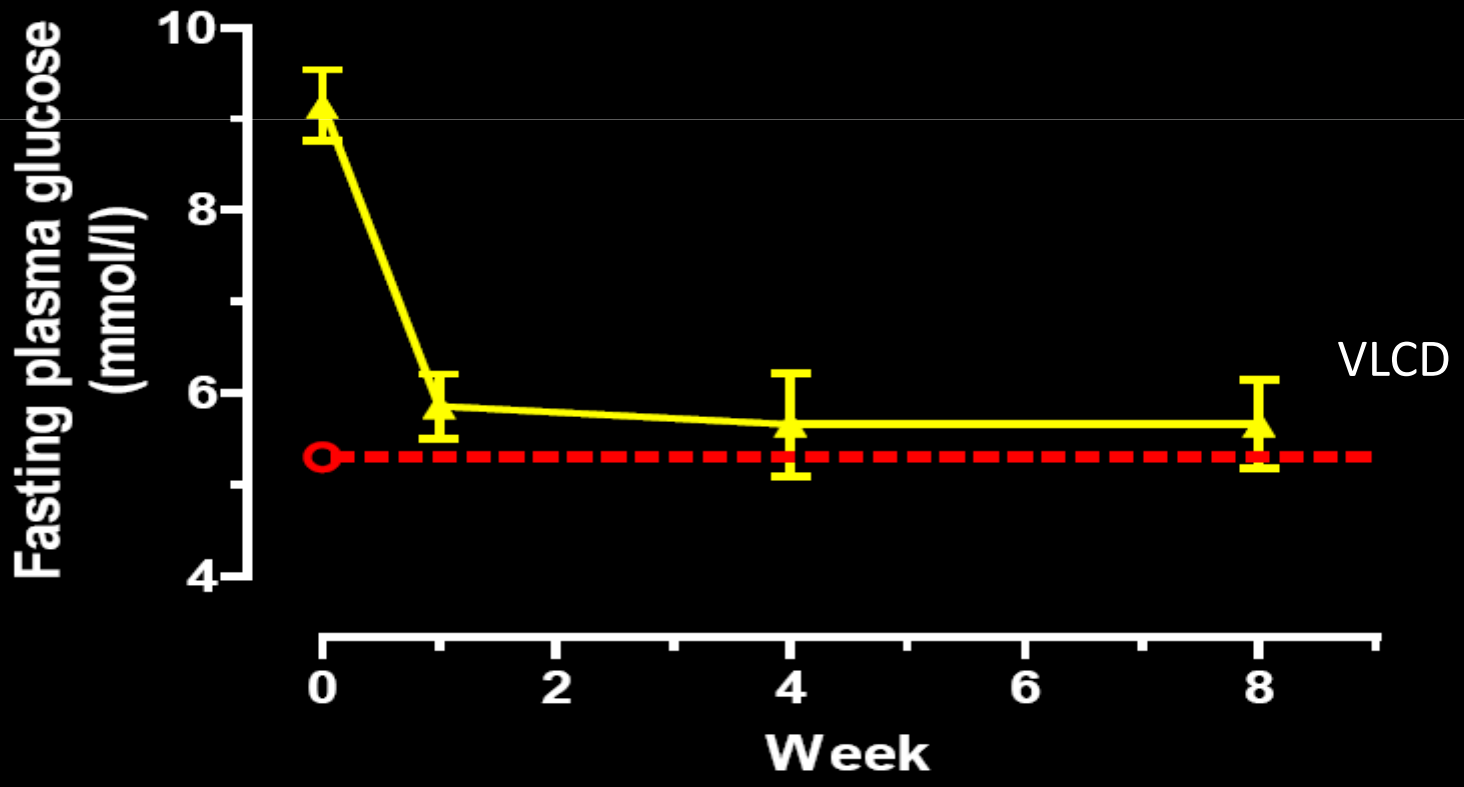
c) Liver and pancreatic fat levels: 3 point Dixon MR method

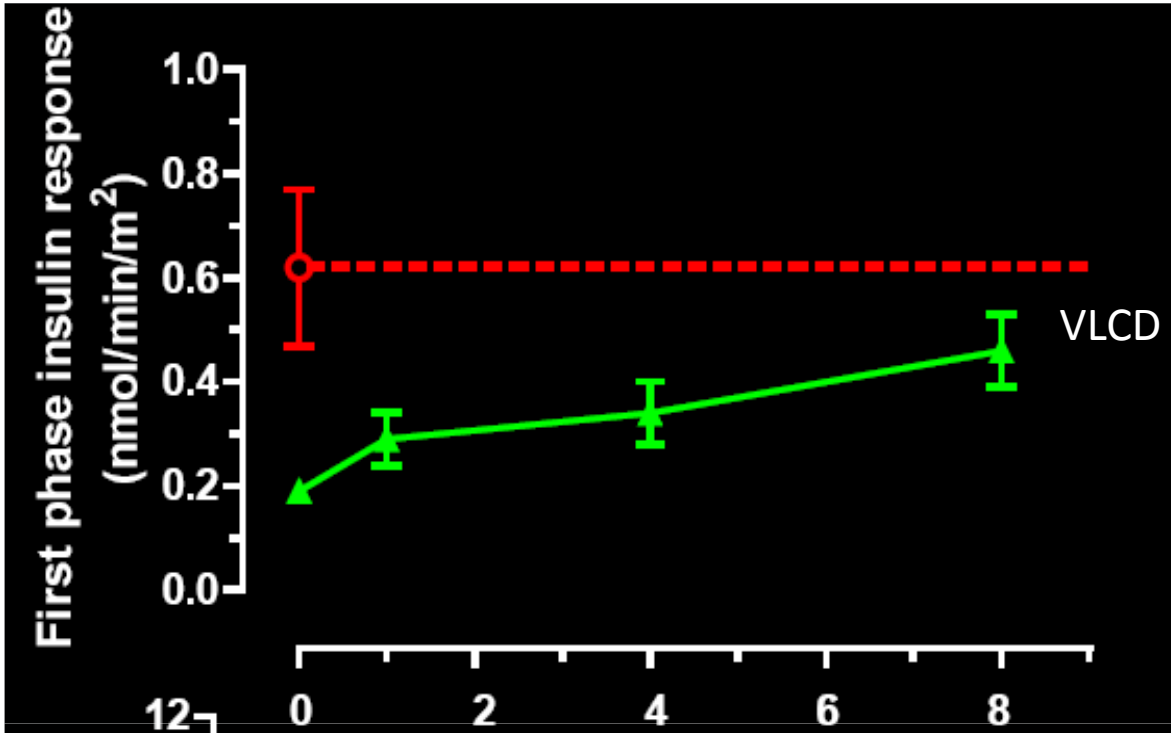
Counterpoint Study

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

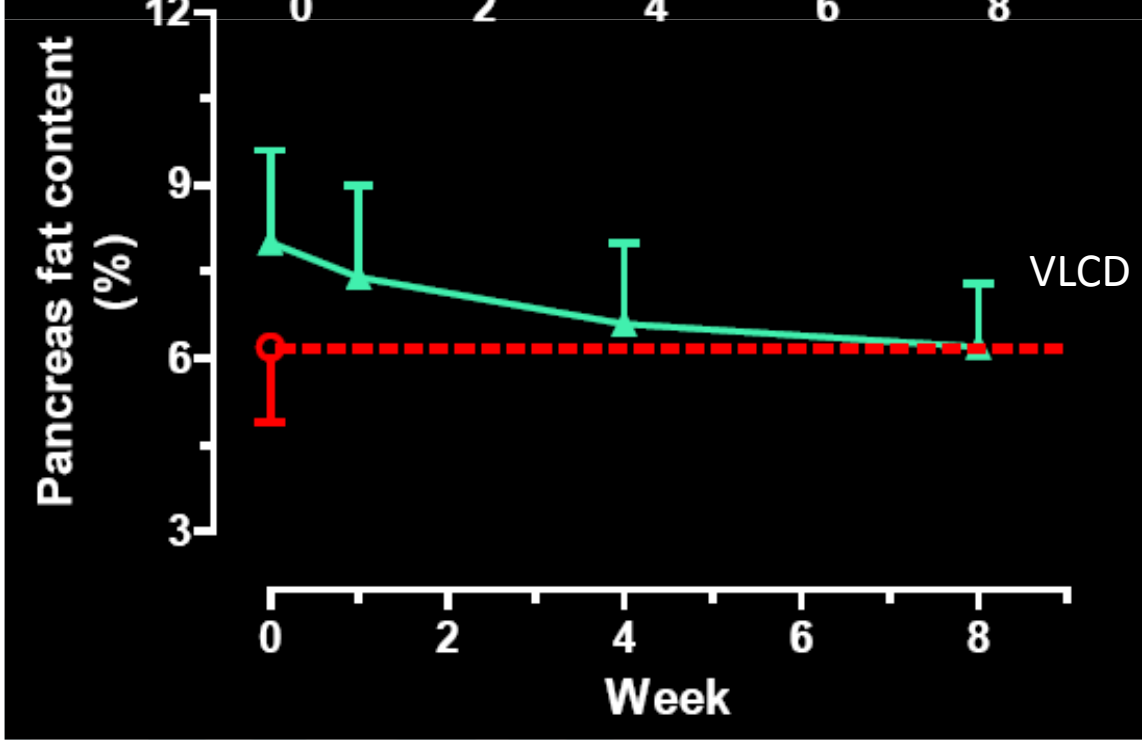
Plasma glucose

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





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



- Pancreatic fat content fell gradually over 8 weeks

Very-low-calorie diet: a quick therapeutic tool to improve β cell function in morbidly obese patients with type 2 diabetes[1–3]

Ilaria Malandrucco, Patrizio Pasqualetti, Ilaria Giordani, Dario Manfellotto, Federica De Marco, Filippo Alegiani, Anna Maria Sidoti, Fabiana Picconi, Alessandra Di Flaviani, Gaetano Frajese, Riccardo C Bonadonna, and Simona Frontoni

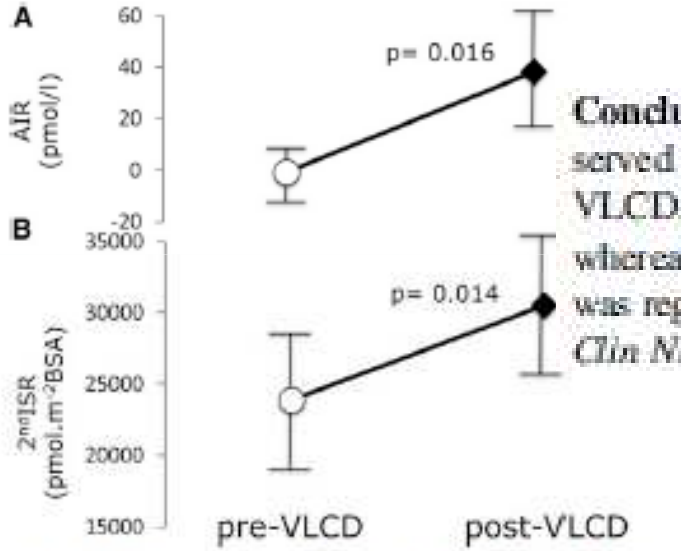
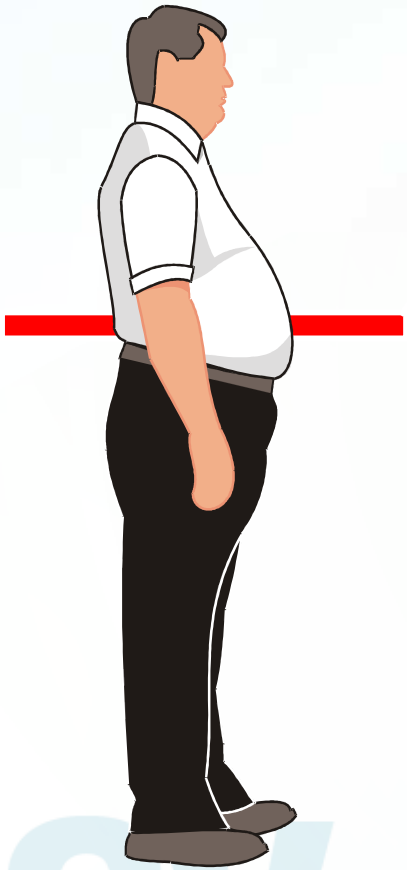


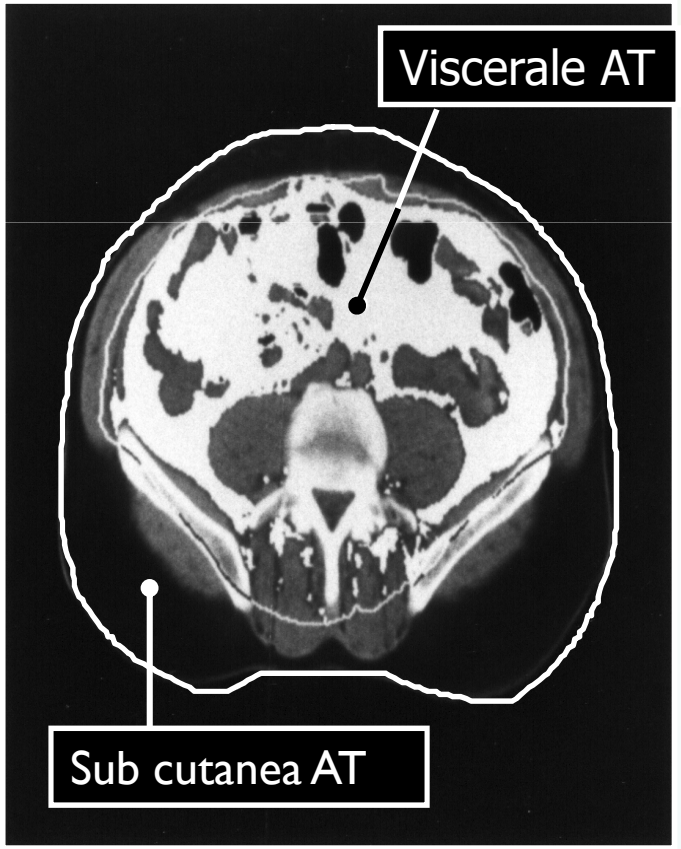
FIGURE 2. Mean (±SEM) AIR (A) and 2ndISR (B) in response to a VLCD. n = 14 in each panel. AIR, acute insulin response; VLCD, very-low-calorie diet; 2ndISR, second-phase insulin secretion rate, ie, total amount of insulin released during second-phase secretion.

Conclusion: The marked improvement in metabolic profile, observed in severely obese patients with type 2 diabetes after a 7-d VLCD, was primarily due to the amelioration of β cell function, whereas no contribution of insulin sensitivity was shown. This trial was registered at www.clinicaltrials.gov as NCT01447524. *Am J Clin Nutr* 2012;95:609–13.

Effetti su tessuto adiposo viscerale e steatosi epatica

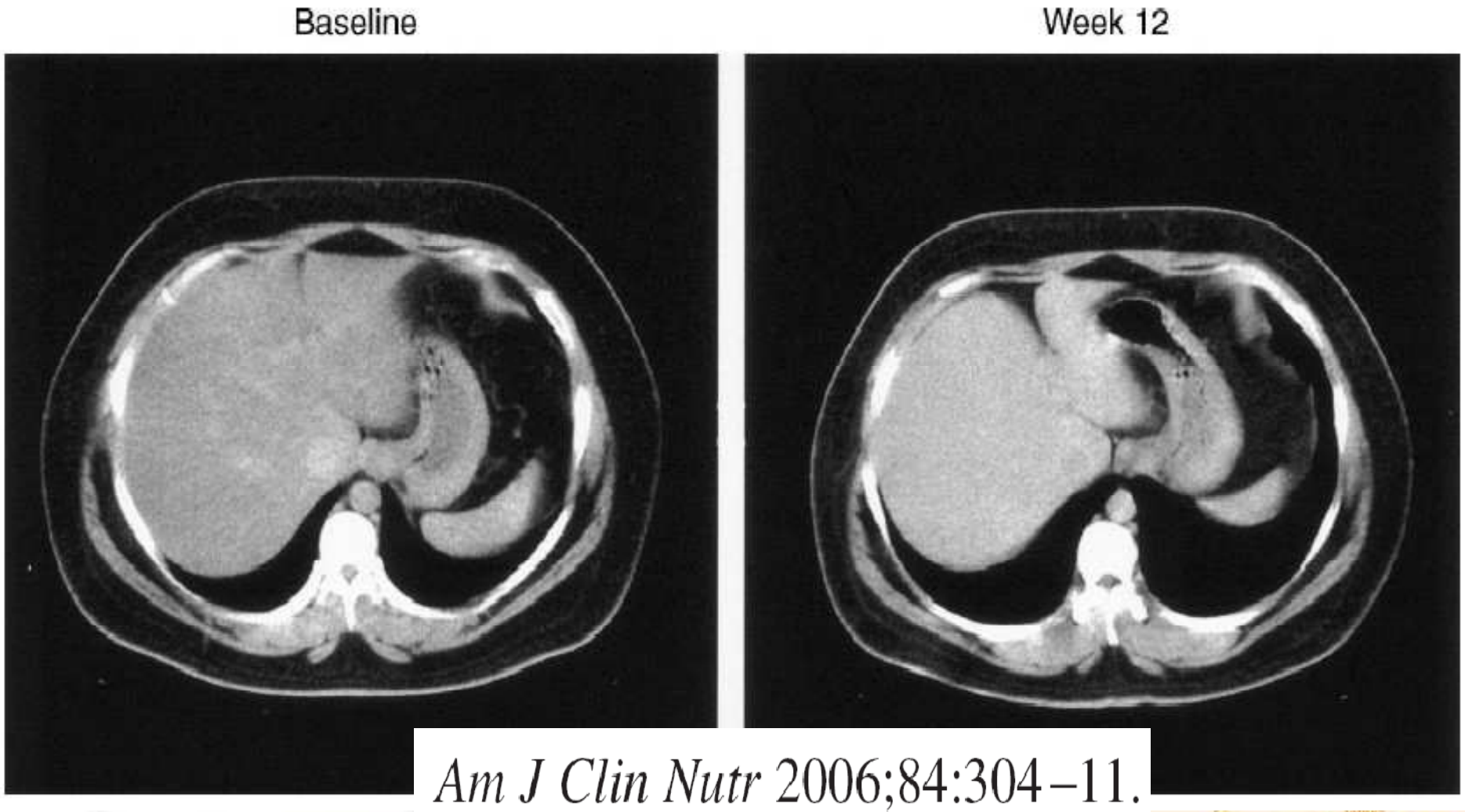


Frontal



Dorsal

Fegato



Am J Clin Nutr 2006;84:304–11.

- Gli effetti antidiabetici delle VLCKD (riduzione dei livelli glicemici con ripristino della funzione beta cellulare) sono **correlati alla riduzione dei livelli di trigliceridi in sede epatica e pancreatica**
- A differenza dei farmaci antidiabetici anche innovativi, la dieta proteica rappresenta uno strumento altamente efficace per arrestare il declino beta cellulare (**REMISSIONE DEL DIABETE)** analogamente a quanto indotto dalla chirurgia bariatrica

Effetti su russamento notturno e OSAS

La riduzione dell'edema dei tessuti molli dell'orofaringe, del grasso cervicale e delle resistenze all'espansione diaframmatica riduce numero e gravità delle apnee notturne

- **Effetto riscontrabile già dopo pochi giorni di dieta**
- **Effetto più marcato nei soggetti con ridotta lunghezza mandibolare**

Preparazione preoperatoria alla chirurgia bariatrica

La **perdita di peso preoperatoria** del paziente (**riduzione della massa grassa viscerale e del volume epatico**):

- **migliora le procedure dell'intervento**
- **ottimizza il timing chirurgico**
- **riduce il rischio anestesiologico**
- **aumenta la compliance del paziente al regime dietetico postoperatorio**
- **rappresenta un utile strumento predittivo del successo dell'intervento nel lungo periodo**

La terapia farmacologica ipoglicemizzante orale e insulinica durante la dieta proteica

È opportuno concordare preventivamente le variazioni del dosaggio con il diabetologo o il medico curante

Autocontrollo: come documentarlo?

Sul diario vanno scritti con relativa **data e ora** anche:

- le **dosi di insulina** assunte
- la **quantità di cibo** ingerita
- l'**attività fisica** svolta
- **tutti gli avvenimenti "imprevisti"**della giornata (per es. febbre, mancata assunzione della terapia, ecc.)

VLCKD e farmaci antidiabetici

1)Sospendere prima dell'inizio della dieta gli SGLT2 inibitori (rischio di chetoacidosi), i secretagoghi (rischio di ipoglicemia) e acarbose (inutilità clinica e meteorismo)
2)Subito dopo i glitazonici (edema e aumento peso)
3)Subito dopo i DPP-4 inibitori/GLP-1 agonisti (per inibizione glucagone e moderata stimolazione insulinica)
4)Infine la metformina

VLCKD e terapia insulinica

Se glicemia media al risveglio (FPG) compresa tra 80 e 110 mg/dl: dimezzare analogo lento serale;

Se FPG tra 110 e 150 mg/dl ridurre dose del 30%

Se FPG tra 150 e 200 mg/dl: lasciare dose invariata

Se FPG>250 mg/dl: iniziare dieta ipocalorica standard fino ad avere FPG<250 mg/dl

Dimezzare dose analoghi insulinici rapidi da subito fino a eventuale progressiva e graduale sospensione

Nel primo mese è opportuno adeguare settimanalmente la dose insulinica via email

Attenzione:

enfatizzare importanza della prevenzione dell'ipoglicemia e del corretto trattamento nel paziente diabetico in corso di VLCKD chetogenica!

Rischi:

il paziente può non correggere l'ipoglicemia per paura di uscire dalla chetosi e di un eventuale incremento ponderale CHO-indotto (non è sufficiente introdurre un integratore proteico)

Sospendere immediatamente la VLCD in presenza di febbre, vomito, dolori addominali, traumi, infezioni

TERAPIA FARMACOLOGICA CARDIOVASCOLARE

TERAPIA ANTIPERTENSIVA

1.Garantire un buon apporto di sodio con la dieta anche in presenza di ipertensione arteriosa
2.Monitorare i valori pressori domiciliari che si riducono già dopo 24-48 ore di dieta
3.In caso di PA non ben controllata prima dell'inizio dieta lasciare la terapia inalterata
4.Se PA a target al basale ridurre/sospendere (se PA<120/80) nell'ordine:
Alfa litici periferici (doxazosin) per ipotensione ortostatica
Diuretici tiazidici/dell'ansa (idroclorotiazide/furosemide) per ipotassiemia
Calcioantagonisti per rischio ipotensione
Beta bloccanti (titolando la dose in modo che FC a riposo sia 60-70 bpm)
ACE inibitori/antagonisti angiotensina II (preferire losartan)

TERAPIA IPOURICEMIZZANTE

Controllo farmacologico con allopurinolo e/o febuxostat predieta; idratazione adeguata

TERAPIA IPOLIPEMIZZANTE

Statine invariate o riduzione subordinata al raggiungimento specifico del target di LDL
Ezetimibe riduzione o sospensione subordinata al raggiungimento specifico del target di LDL
Fibrati riduzione o sospensione in base ai valori di trigliceridi o di colesterolo HDL
Omega 3 riduzione (garantire un apporto fisiologico-sostitutivo con olio di krill)

TERAPIA ANTIAGGREGANTE invariata

TERAPIA ANTICOGULANTE invariata (preferire i NAO; monitorare verdure a foglia larga per dicumarolici con controllo INR dopo 2 settimane di dieta)

REGIME DIETETICO
E TERAPIA FARMACOLOGICA

Data	Peso	Terapia farmacologica
inizio	115,8	Olmesartan 40; Furosemide 25; Atenololo 50; Glimepiride 4; Metformina 1000 x 2; Insulina lispro 10+25+25U; Insulina glargine 35U; ASA 100; Simvastatina 40; Omeprazolo 20.
1 settim	110,2	Olmesartan 40; Furosemide 25; Atenololo 50; Metforal 1000 x 2; Lantus 16 U; ASA 100; Simvastatina 40; Omeprazolo 20.
16 settim	92,8	Olmesartan 20; Furosemide 12,5; Metforal 500 X 2; ASA 100; Simvastatina 20; Omeprazolo 20 mg. a dì alterni.

TERAPIA FARMACOLOGICA:
PRIMA DEL REGIME DIETETICO

TERAPIA FARMACOLOGICA: DOPO 16 SETTIMANE

Grazie per l’attenzione!