
# Dieta e remissione del diabete mellito tipo 2

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# Nutritional basis of type 2 diabetes remission

**Roy Taylor and colleagues** explain how type 2 diabetes can be reversed by weight loss and avoidance of weight regain

Type 2 diabetes mellitus was once thought to be irreversible and progressive.

Processes that cause type 2 diabetes can be returned to normal functioning by restriction of food energy to achieve weight loss of around 15 kg. Around half of people who are within the first 10 years of diagnosis and manage to follow food energy restriction can stop all diabetes medication and return to non-diabetic glucose control.

**Box 1: Definition of remission***

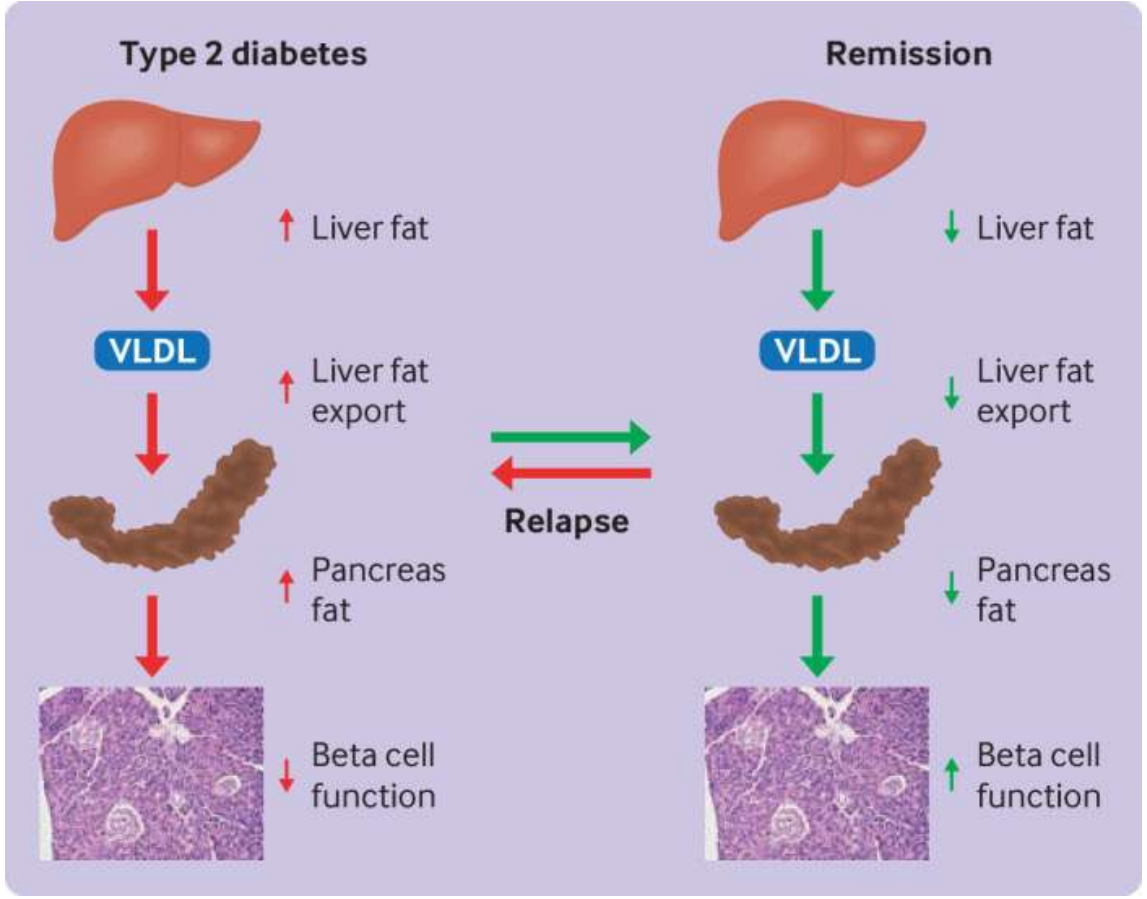
The consensus guideline from UK Primary Care Diabetes Society and Association of British Clinical Diabetologists lays out three criteria for remission of type 2 diabetes[4]:

- Weight loss
- Fasting plasma glucose <7 mmol/L or $HbA_{1c}$ <48 mmol/mol (WHO diagnostic thresholds) on two occasions separated by at least six months
- Attainment of these glycaemic parameters after complete cessation of all glucose lowering therapies

# Nutritional basis of type 2 diabetes remission

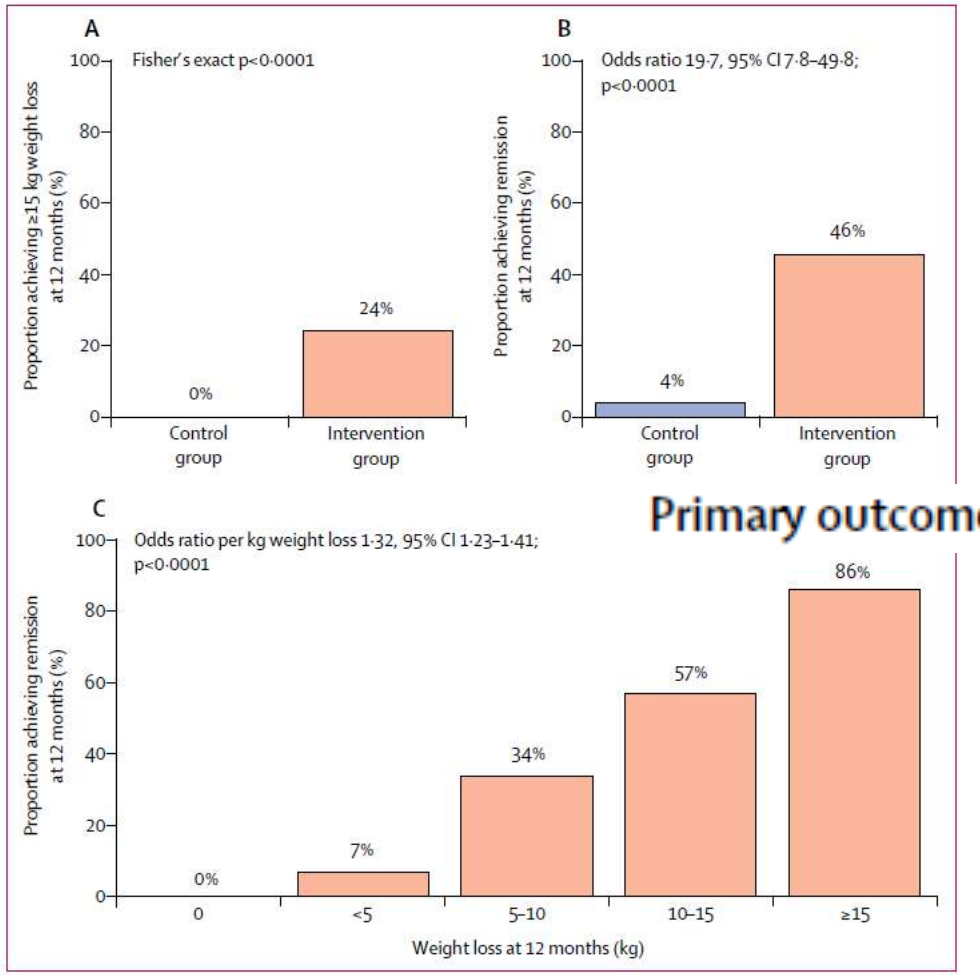
**Roy Taylor and colleagues** explain how type 2 diabetes can be reversed by weight loss and avoidance of weight regain

Type 2 diabetes develops as **long term intake of excess food energy** leads to accumulation of liver fat, driven by a vicious cycle of hepatic insulin resistance and hyperinsulinaemia. The raised liver fat level causes **increased hepatic export of very low density lipoprotein (VLDL) triglycerides**. If the subcutaneous fat depot cannot accommodate this, **ectopic fat will build up, including in the pancreas**. In people with susceptible β cells, the acute insulin response to food becomes diminished and de novo lipogenesis from glucose is enhanced. β Cell function can be restored if liver fat is reduced through weight loss.



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

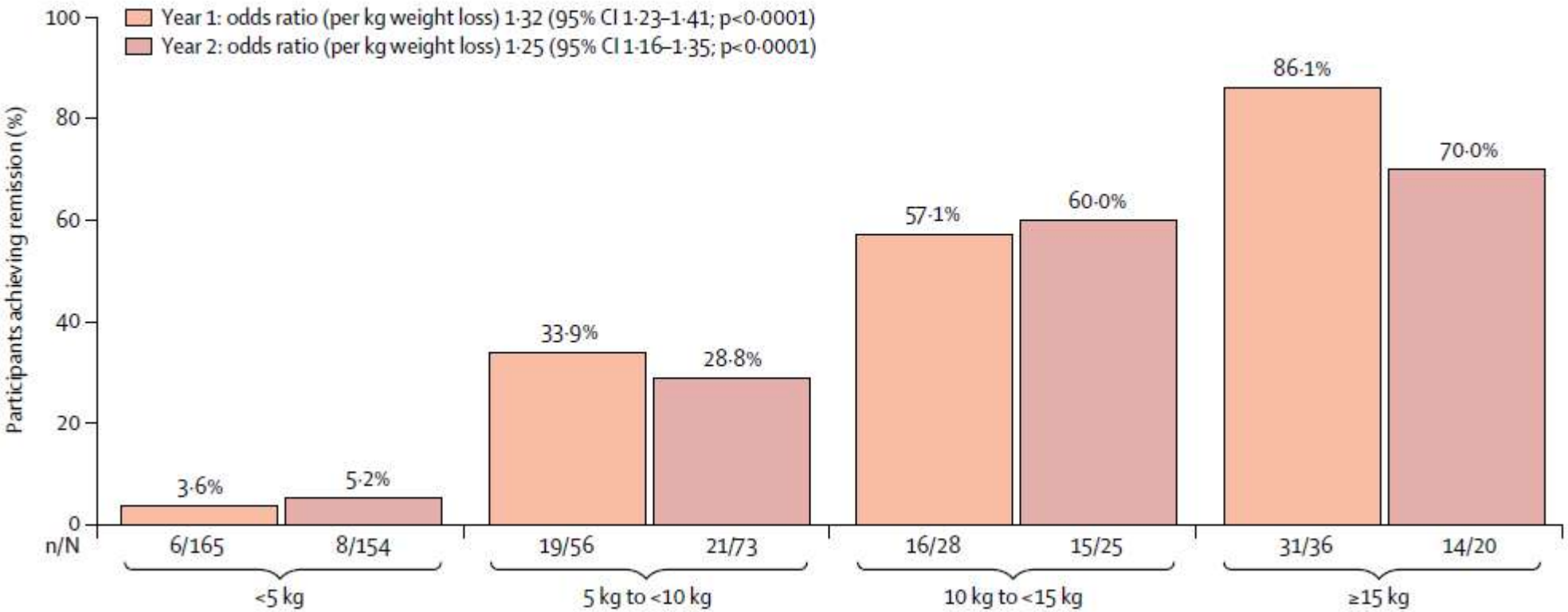
*Michael E J Lean*, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna,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




Primary outcomes and remission of diabetes in relation to weight loss at 12 months

# Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial

*Michael E J Lean*, Wilma S Leslie, Alison C Barnes, Naomi Brosnahan, George Thom, Louise McCombie, Carl Peters, Sviatlana Zhyzhneuskaya, Ahmad Al-Mrabeh, Kieren G Hollingsworth, Angela M Rodrigues, Lucia Rehackova, Ashley J Adamson, Falko F Sniehotta, John C Mathers, Hazel M Ross, Yvonne McIlvenna, Paul Welsh, Sharon Kean, Ian Ford, Alex McConnachie, Claudia-Martina Messow, Naveed Sattar, Roy Taylor**



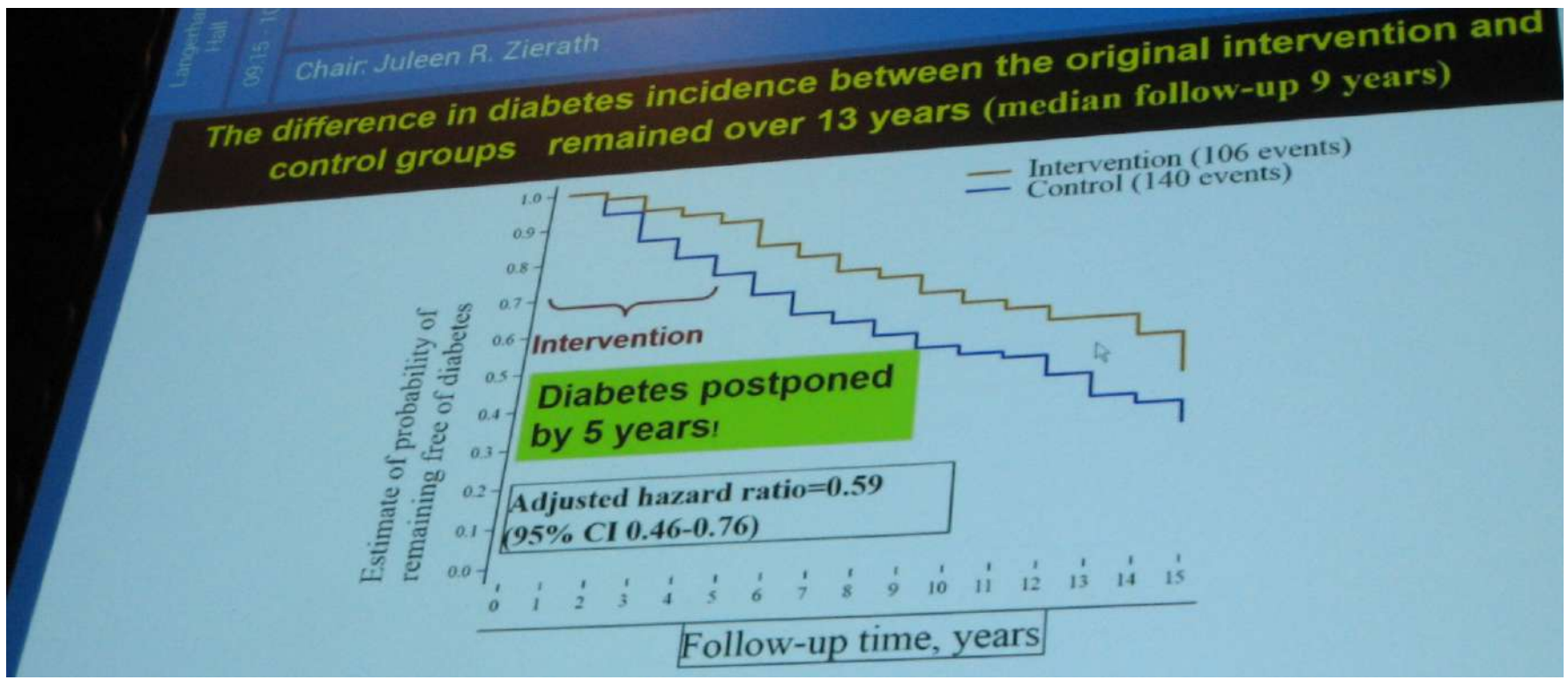

**Primary outcomes and remission of type 2 diabetes in relation to weight loss at 12 and at 24 months**

Diabetologia (2013) 56:284–293
DOI 10.1007/s00125-012-2752-5

ARTICLE

# Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS)

J. Lindström · M. Peltonen · J. G. Eriksson · P. Ilanne-Parikka · S. Aunola · S. Keinänen-Kiukaanniemi · M. Uusitupa · J. Tuomilehto · for the Finnish Diabetes Prevention Study (DPS)



# Very Low-Calorie Diet and 6 Months of Weight Stability in Type 2 Diabetes: Pathophysiological Changes in Responders and Nonresponders

*Sarah Steven,[1] Kieren G. Hollingsworth,[1] Ahmad Al-Mrabeh,[1] Leah Avery,[2] Benjamin Aribisala,[3] Muriel Caslake,[4] and Roy Taylor[1]*

**People with a T2DM duration of 0.5–23 years (n = 30) followed a VLCD for 8 weeks. All oral agents or insulins were stopped at baseline.**
**Responders were defined as achieving fasting blood glucose <7 mmol/L after return to isocaloric diet.**

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 <7 mmol/L. T2DM is a potentially reversible condition.**

**Steven S, Diabetes Care 2016;39:808–815**

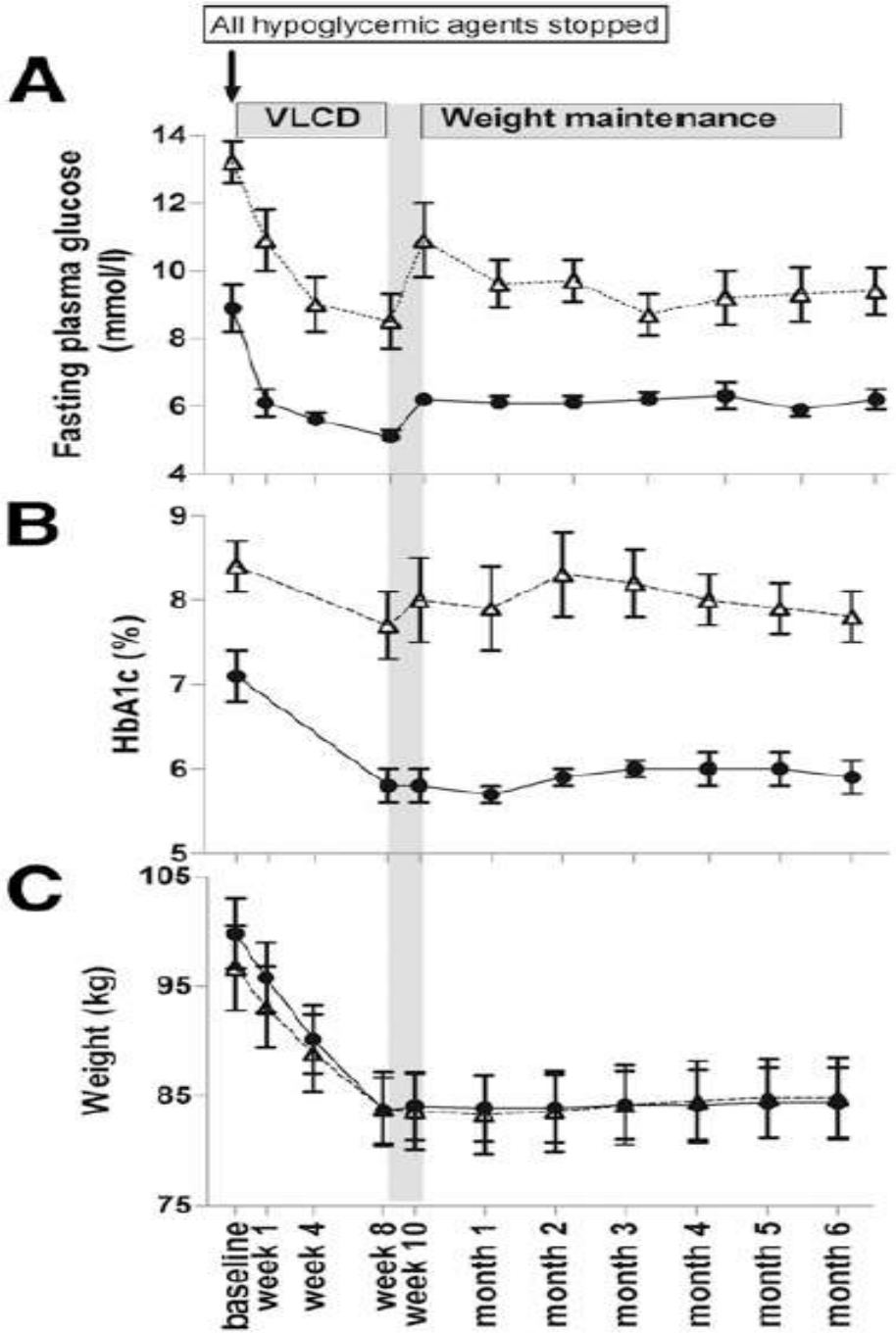
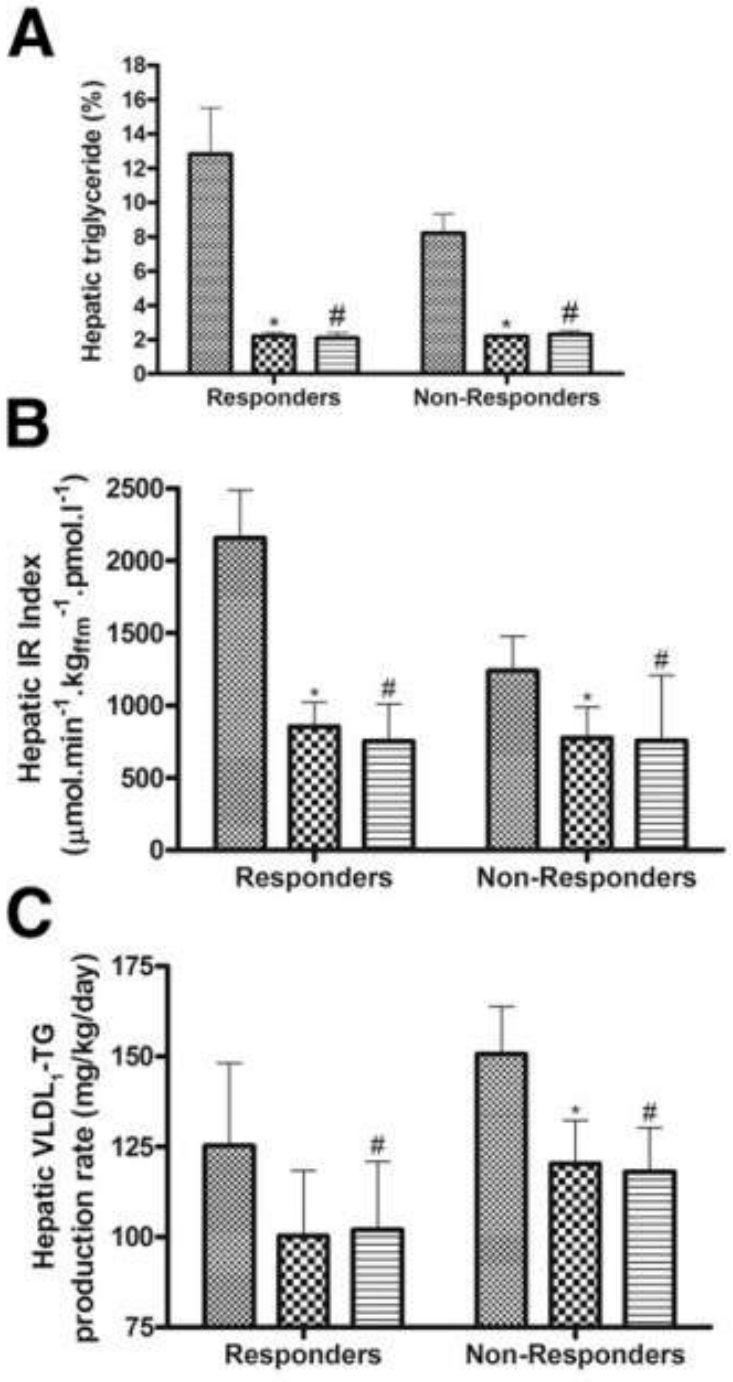


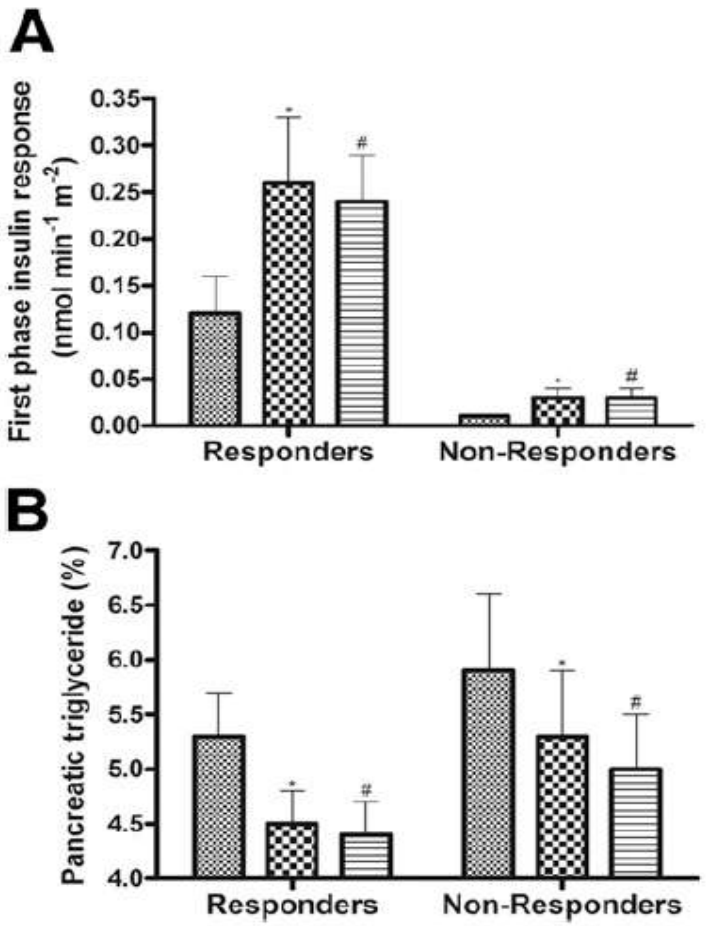

**Figure 1**—Change in fasting plasma glucose (*A*), $HbA_{1c}$ (*B*), and weight (*C*) over the study in responders (●) and nonresponders (△). The gray band represents the stepped transition from VLCD to isocaloric eating of solid foods. Data are mean ± SEM.

**Steven S, Diabetes Care 2016;39:808–815**

**Hepatic triglyceride content, hepatic insulin resistance index, hepatic VLDL triglyceride production, change in first-phase insulin response and pancreas triglyceride content in responders and nonresponders at baseline (hatched bars), after VLCD (checkered bars), and after 6 months of weight maintenance (striped bars)**




**Responders had a shorter duration of diabetes and a higher initial fasting plasma insulin level**




Steven S, Diabetes Care 2016;39:808–815

# Prolonged Caloric Restriction in Obese Patients With Type 2 Diabetes Mellitus Decreases Myocardial Triglyceride Content and Improves Myocardial Function

Sebastiaan Hammer, MSc,*† Marieke Snel, MD,‡ Hildo J. Lamb, MD, PhD,†
Ingrid M. Jazet, MD, PhD,‡ Rutger W. van der Meer, MD,† Hanno Pijl, MD, PhD,*
Edo A. Meinders, MD, PhD,‡ Johannes A. Romijn, MD, PhD,* Albert de Roos, MD, PhD,†
Johannes W. A. Smit, MD, PhD*

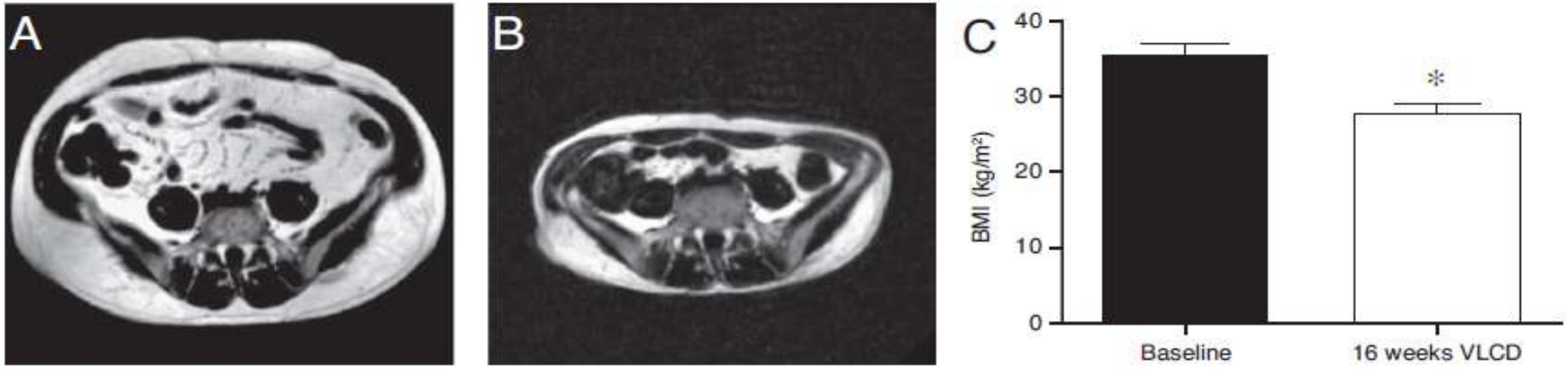



**Figure 1** Fat Stores and Body Mass Index

Example of a transverse slice at the level of the 5th lumbar vertebrae showing visceral and subcutaneous fat depots, illustrating the effects of 16 weeks of caloric restriction in the same patient **(A and B)**. Body mass index (BMI) is decreased after prolonged caloric restriction **(C)**. *$p < 0.001$. VLCD = very-low-calorie diet.

**Hammer S, J Am Coll Cardiol 2008**

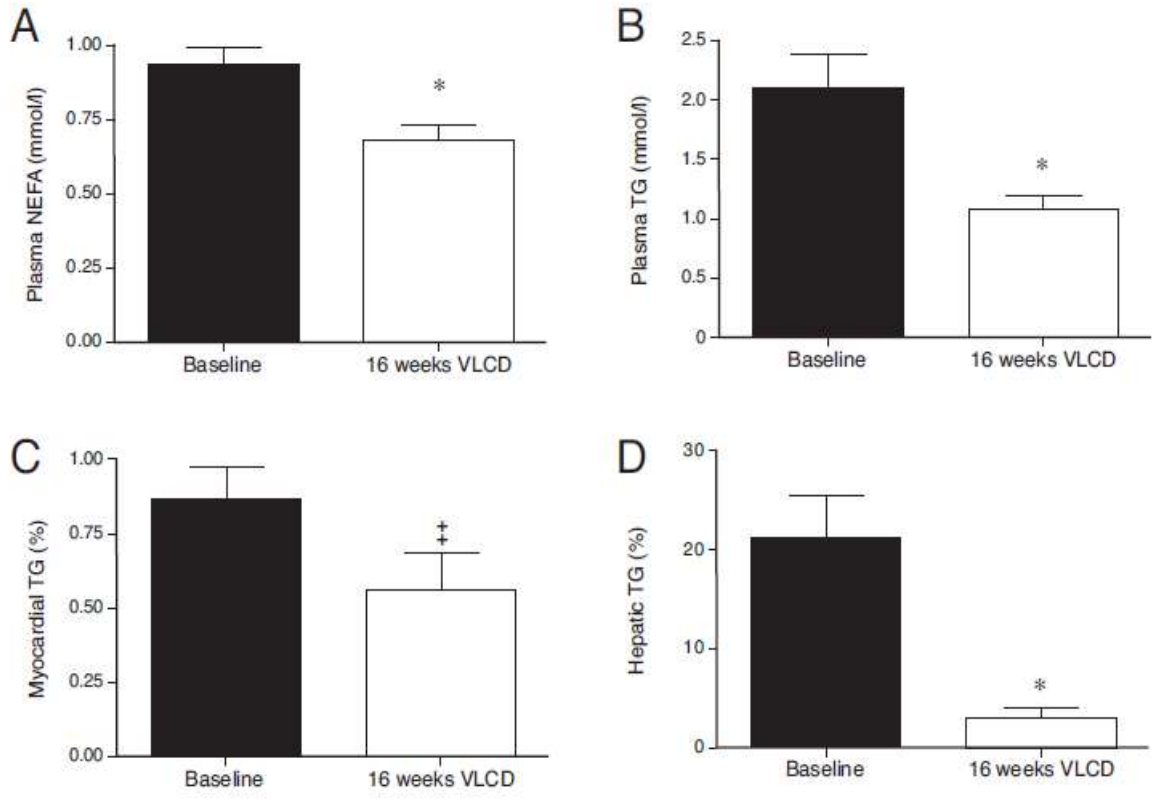



**Figure 2** Metabolic Changes at Baseline and After 16 Weeks of VLCD

Changes in plasma NEFA **(A)**, plasma TG levels **(B)**, and myocardial **(C)**, and hepatic **(D)** TG content on prolonged caloric restriction. *$p < 0.001$; ‡$p < 0.05$. Data are mean ± SEM. NEFA = nonesterified fatty acids; TG = triglyceride; VLCD = very-low-calorie diet.

**Table 2** Intraindividual Effects of 16 Weeks of Caloric Restriction on Systolic and Diastolic Function in Obese Patients With T2DM

| | Baseline | After 16 Weeks of Caloric Restriction |
|---|---|---|
| Systolic blood pressure (mm Hg) | 144 ± 8 | 118 ± 6* |
| Diastolic blood pressure (mm Hg) | 81 ± 2 | 71 ± 2* |
| Heart rate (beats/min) | 78 ± 3 | 61 ± 2* |
| LVEF (%) | 57 ± 2 | 58 ± 2 |
| Stroke volume (ml) | 102 ± 6 | 103 ± 8 |
| Stroke volume index (ml/m$^2$) | 45 ± 2 | 51 ± 3† |
| Cardiac output (ml/min) | 7,971 ± 601 | 6,508 ± 401‡ |
| Cardiac index (l/min/m$^2$) | 3.5 ± 0.2 | 3.2 ± 0.2 |
| LV mass (g) | 118 ± 7 | 99 ± 6* |
| LV mass index (g/m$^2$) | 53 ± 3 | 49 ± 3† |
| ED volume (ml) | 177 ± 8 | 177 ± 11 |
| ED index (ml/m$^2$) | 79 ± 3 | 88 ± 4† |
| ES volume (ml) | 76 ± 4 | 74 ± 5 |
| ES index (ml/m$^2$) | 34 ± 2 | 37 ± 2 |
| E deceleration (ml/s$^2$ × 10$^{-3}$) | 4.04 ± 0.50 | 4.30 ± 0.42 |
| E/A peak ratio | 1.02 ± 0.08 | 1.18 ± 0.06† |
| E/Ea | 11.9 ± 1.2 | 11.4 ± 1.5 |

## Conclusions

Prolonged caloric restriction in obese T2DM patients decreases BMI and improves glucoregulation associated with decreased myocardial TG content and improved diastolic heart function. Therefore, myocardial TG stores in obese patients with T2DM are flexible and amendable to therapeutic intervention by caloric restriction.

**Hammer S, J Am Coll Cardiol 2008**

**Table 1 | The controversy about low carbohydrate or low calorie approaches to remission of type 2 diabetes: Areas of agreement and disagreement**

| | Low or very low carbohydrate diets | Low or very low calorie diets† |
|---|---|---|
| Good for cardiovascular health | Improves indices of cardio-vascular risk for up to 2 years[20 21] | Improves QRISK score up to 2 years[8] |
| Long term outcome data | Not available | Not available |
| Long term weight management | The major problem. Need for continuing support and rescue management of weight regain | The major issue. Need for continuing support and rescue management of weight regain |
| Acceptability | Single centre reports acceptability[22] | RCT data to 2 years shows ongoing compliance in the majority.[8] Psychological study reports good acceptability up to 6 months[23] |
| Weight loss: | | |
| RCT evidence | Significant difference from controls at 6 months only (reduction in the low carb group of 2.6-11.1 kg at 6 months, 3.1-9.8 kg at 1 year, and 2.0-6.8 kg at 2 years[20 21 24] | Significantly different from controls up to 2 years.[8 25 26] Weight loss around 10 kg in the active arm at 12 months in Direct and Droplet and 7.6 kg at 2 year in Direct[26 27] |
| Observational studies | Selected paying participants achieved 10 kg weight loss at 2 years.‡[28]<br>A 1 year study reported 4.3 kg weight loss in a 1% sample completing follow-up (1000/105 950 initially signed up)[29] | Mean weight loss of 13.7 kg at 6 months[2] |
| Improvement in glucose control: | | |
| RCT evidence | Meta-analyses of multiple trials show significant decrease in $HbA_{1c}$ of 0.3-1.5% at 6 months. Decreases of 0.3-1.0% at 1 year and 0-0.6% at 2 years were not significantly different from active controls[20 21] | One multisite trial found clinically important decrease in $HbA_{1c}$ at 6, 12, and 24 months with 36% remission at 2 years[8] |
| Observational studies | Private clinic participants undertaking a very low carb diet while continuing hypoglycaemic agents achieved 0.9% decrease in $HbA_{1c}$[28]<br>A 1 year study reported 0.3% decrease in $HbA_{1c}$ in 1000 people[29] | Observational data with withdrawal of all hypoglycaemic agents achieved a 1.1% fall in short duration diabetes and 0.6% fall in long duration diabetes over 6 months[2] |
| Remission of type 2 diabetes | A primary care series reports 46% of completers on continued metformin were in remission at an average of 2 years[30]<br>Non-randomised cohort reports 17.6% at 2 years[28]<br>RCT evidence of remission following weight management based on low carbohydrate diet in 11% at 1 year‡¶[31] | RCT evidence of remission in 46% by intention to treat off all diabetes drugs at 12 months and 36% at 24 months from Direct.[8] Diadem-1 in a Middle Eastern population achieved 61% remission. Observational studies of remission confirm these effects.[12 32§] |

*Low: 50-130 g/day or between 10-26% total energy; Very low: 20-50 g/day or under 10% total energy
†700-1000 kcal/day (or 35-50% of a 2000 kcal/day intake) for a defined period then weight maintaining diet
‡This study used <30 g/day of carbohydrate initially.
¶Oral hypoglycaemic agents not stopped on commencing the diet.
§All oral hypoglycaemic agents were stopped on commencing the diet in all studies.

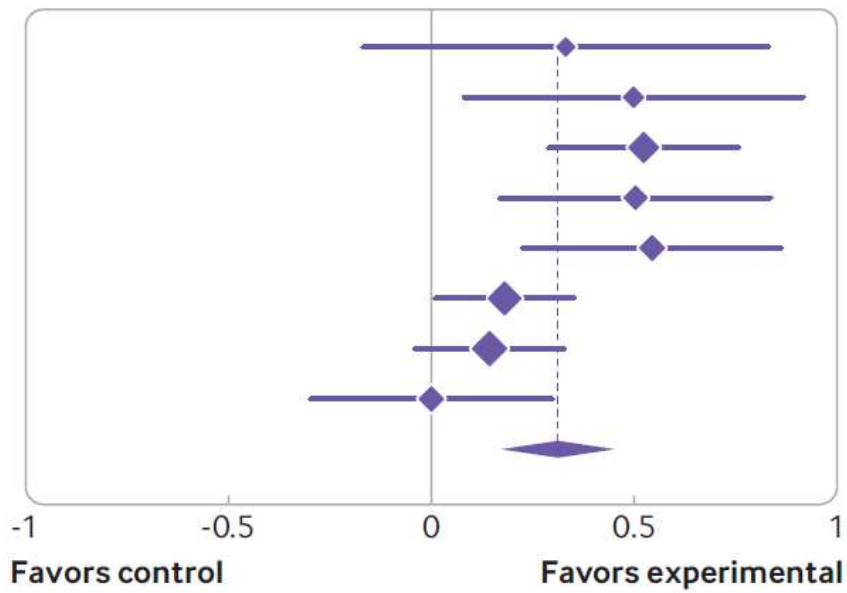
BMJ 2021;373:n1449 | doi: 10.1136/bmj.n1449

# Efficacy and safety of low and very low carbohydrate diets for type 2 diabetes remission: systematic review and meta-analysis of published and unpublished randomized trial data

Joshua Z Goldenberg,[1,2] Andrew Day,[3] Grant D Brinkworth,[4] Junko Sato,[5] Satoru Yamada,[6] Tommy Jönsson,[7] Jennifer Beardsley,[8] Jeffrey A Johnson,[9] Lehana Thabane,[10,11] Bradley C Johnston,[1,10]

**Remission at 6 months**

| Study or subgroup | No of events/total Experimental | Control | Risk difference, IV, random (95% CI) | Weight (%) | Risk difference, IV, random (95% CI) |
|---|---|---|---|---|---|
| Dyson 2010 | 3/6 | 1/6 | | 6.5 | 0.33 (-0.17 to 0.83) |
| Jönsson 2009 | 6/6 | 3/6 | | 8.3 | 0.50 (0.08 to 0.92) |
| Morris 2019 | 11/21 | 0/12 | | 15.0 | 0.52 (0.29 to 0.76) |
| Saslow 2014 | 8/9 | 5/13 | | 10.8 | 0.50 (0.17 to 0.84) |
| Saslow 2017 | 6/11 | 0/8 | | 11.4 | 0.55 (0.23 to 0.86) |
| Sato 2017 | 4/22 | 0/27 | | 18.2 | 0.18 (0.01 to 0.35) |
| Tay 2014 | 36/46 | 30/47 | | 17.5 | 0.14 (-0.04 to 0.33) |
| Yamada 2014 | 2/12 | 2/12 | | 12.2 | 0.00 (-0.30 to 0.30) |
| Total (95% CI) | 76/133 | 41/131 | | 100.0 | 0.32 (0.17 to 0.47) |
| Test for heterogeneity: $\tau^2$=0.02; $\chi^2$=16.50, df=7, P=0.02; $I^2$=58% | | | | | |
| Test for overall effect: Z=4.15, P<0.001 | | | | | |




doi: 10.1136/bmj.m4743 | BMJ 2021;372:m4743

# Nutrition Therapy for Adults With Diabetes or Prediabetes: A Consensus Report

Diabetes Care 2019;42:731–754 | https://doi.org/10.2337/dci19-0014

Alison B. Evert,[1] Michelle Dennison,[2] Christopher D. Gardner,[3] W. Timothy Garvey,[4,5] Ka Hei Karen Lau,[6] Janice MacLeod,[7] Joanna Mitri,[8] Raquel F. Pereira,[9] Kelly Rawlings,[10] Shamera Robinson,[11] Laura Saslow,[12] Sacha Uelmen,[11] Patricia B. Urbanski,[13] and William S. Yancy Jr.[14,15]

Although the recommended dietary allowance for carbohydrate for adults without diabetes (19 years and older) is 130 g/day and is determined in part by the brain's requirement for glucose, **this energy requirement can be fulfilled by the body's metabolic processes, which include glycogenolysis, gluconeogenesis (via metabolism of the glycerol component of fat or gluconeogenic amino acids in protein), and/or ketogenesis in the setting of VLCKD**

**For select adults with type 2 diabetes not meeting glycemic targets or where reducing antiglycemic medications is a priority, reducing overall carbohydrate intake with low- or very low carbohydrate eating plans is a viable approach**

STOP DIABETES℠

American Diabetes Association®

Diabetologia (2023) 66:1752–1753
https://doi.org/10.1007/s00125-023-05961-0

LETTER

# Not all very-low-carbohydrate diets are created equal

Caterina Conte[1,2] · Elisabetta Camajani[1,3] · Alessio Lai[4] · Massimiliano Caprio[1,3]

Received: 12 May 2023 / Accepted: 18 May 2023 / Published online: 5 July 2023


**Keywords** Ketogenic diet · Obesity · Type 2 diabetes · Weight loss

VLCKD represents a nutritional intervention that mimics fasting through a marked restriction of daily carbohydrate intake, usually **lower than 30 g/day** (≃13% of total energy intake), with a relative increase in the proportions of fat (≃44%) and protein (≃43%) and **a total daily energy intake <800 Kcal.**

**VLCKD should not be considered as a high-protein diet**, since its daily protein intake is approximately 1.2-1.5 g/Kg of ideal body weight

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-019-01061-2

CONSENSUS STATEMENT

# Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

2019

M. Caprio[1,2] · M. Infante[3] · E. Moriconi[1,4] · A. Armani[1] · A. Fabbri[3] · G. Mantovani[5] · S. Mariani[4] · C. Lubrano[4] · E. Poggiogalle[4] · S. Migliaccio[6] · L. M. Donini[4] · S. Basciani[4] · A. Cignarelli[7] · E. Conte[7] · G. Ceccarini[8] · F. Bogazzi[9] · L. Cimino[10] · R. A. Condorelli[10] · S. La Vignera[10] · A. E. Calogero[10] · A. Gambineri[11] · L. Vignozzi[12] · F. Prodam[13] · G. Aimaretti[13] · G. Linsalata[14] · S. Buralli[14] · F. Monzani[14] · A. Aversa[15] · R. Vettor[16] · F. Santini[8] · P. Vitti[9] · L. Gnessi[4] · U. Pagotto[11] · F. Giorgino[7] · A. Colao[17] · A. Lenzi[4] on behalf of the Cardiovascular Endocrinology Club of the Italian Society of Endocrinology

**Table 2** Indications for the use of VLCKD in metabolic diseases

| Strong recommendations | Strength of recommendations and quality of evidence according to GRADE system |
|---|---|
| Severe obesity | (1 ØØØO) |
| Management of severe obesity before bariatric surgery | (1 ØØØO) |
| Sarcopenic obesity | (1 ØØØO) |
| Obesity associated with type 2 diabetes (preserved beta cell function) | (1 ØØØO) |
| Obesity associated with hypertriglyceridemia | (1 ØØØO) |
| Obesity associated with hypertension | (1 ØØØO) |
| Pediatric obesity associated with epilepsy and/or with a high level of insulin resistance and/or comorbidities, not responsive to standardized diet | (1 ØØØO) |

Journal of Endocrinological Investigation
https://doi.org/10.1007/s40618-019-01061-2

CONSENSUS STATEMENT

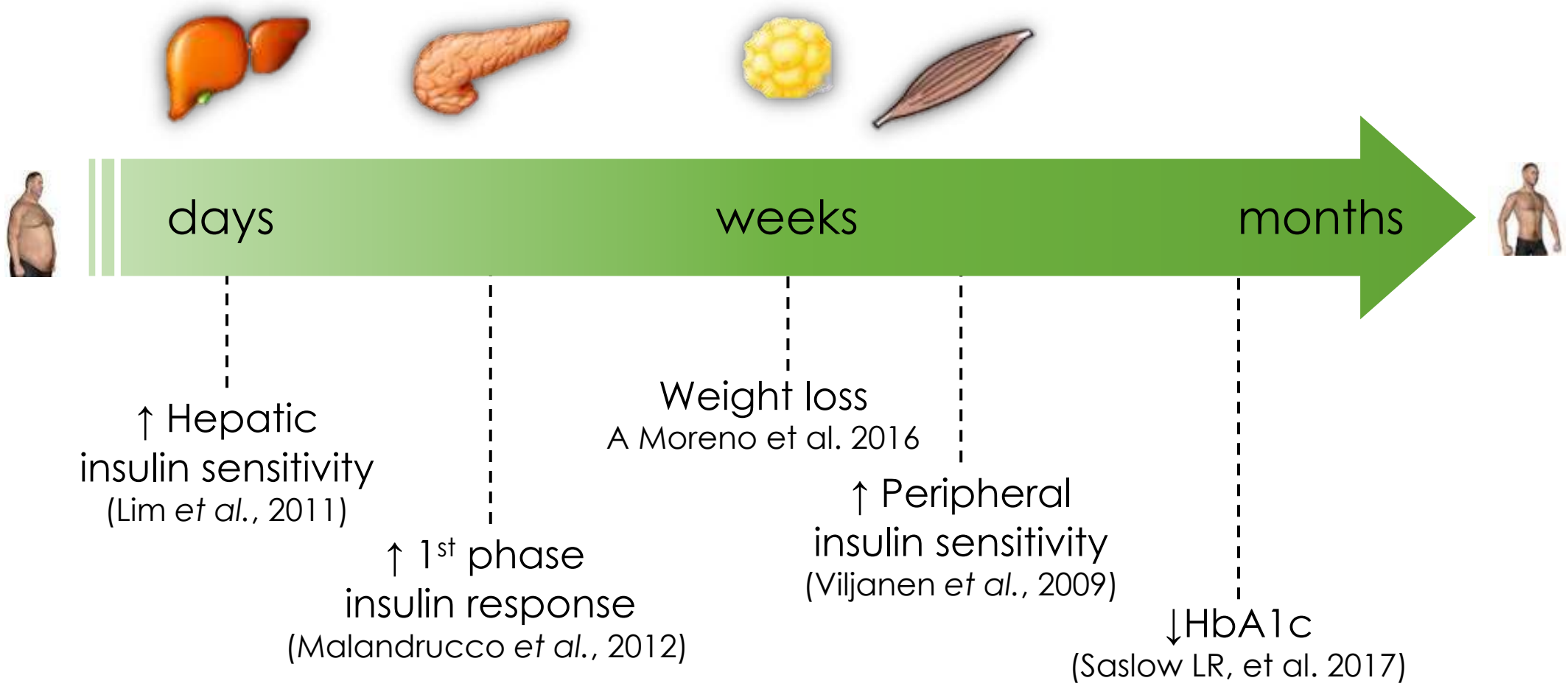
# Very-low-calorie ketogenic diet (VLCKD) in the management of metabolic diseases: systematic review and consensus statement from the Italian Society of Endocrinology (SIE)

## VLCKD, insulin resistance and type 2 diabetes

### Recommendations

- VLCKD should be considered to obtain an early efficacy on glycemic control, particularly in obese patients with short duration of the disease (1 ØØØO).
- VLCKD should be considered to reduce the use of glucose-lowering agents, including insulin (1 ØØØO).

# VLCKD effects on glucose metabolism in obese subjects



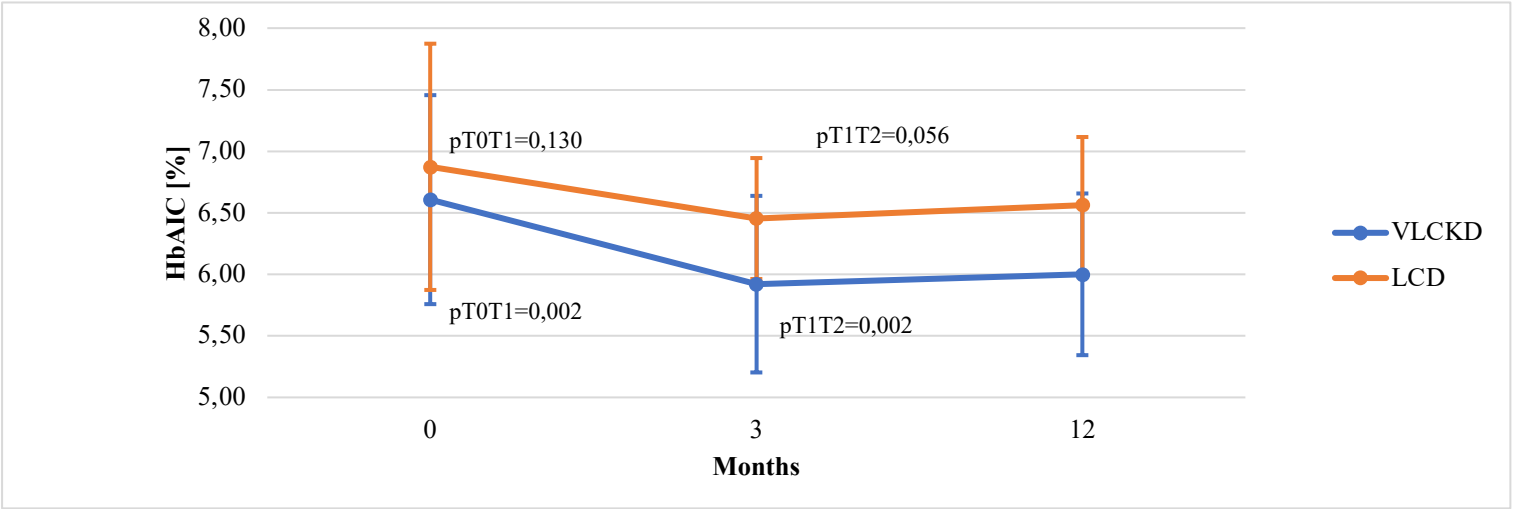

Caprio M, Infante M et al. J Endocrinol Invest 2019

*Article*

# Very-Low-Calorie Ketogenic Diet as a Safe and Valuable Tool for Long-Term Glycemic Management in Patients with Obesity and Type 2 Diabetes

Eleonora Moriconi [1,2], Elisabetta Camajani [2,3], Andrea Fabbri [4], Andrea Lenzi [5] and Massimiliano Caprio [1,3,*]

**Kinetics of HbA1c % in patients following a VLCKD vs a LCD**




| | ΔT0-T1 (mean ± DS) | | P-value | ΔT2-T0 (mean ± DS) | | P-value |
|---|---|---|---|---|---|---|
| | VLCKD | LCD | | VLCKD | LCD | |
| HbA1c% | 0,69 ± 0,65 | 0,42 ± 1,01 | 0,533 | 0,61 ± 0,54 | 0,13 ± 0,76 | 0,070 |

**Moriconi et al. Nutrients 2021**

# Variation of pharmacological therapy at baseline and after 12 months

| | VLCKD group | | LCD group | |
|---|---|---|---|---|
| | Baseline | After 12 months | Baseline | After 12 Months |
| Subjects | 15 | | | |
| Men | 8 | | | |
| Women | 7 | | | |
| Diabetes Duration (years) | | | | |
| Diet | | | | |
| Metformin | | | 15 | 8 |
| Sulphonylurea | | | 0 | 0 |
| Metformin + GLP-1 agonist | | | 0 | 6 |
| Metformin + SGLT2 inhibitor | 3 | 0 | 0 | 1 |
| DD4-inhibitor | 2 | 0 | 0 | 0 |

**26.6%** stopped antidiabetic drugs

**73.3%** were taking Metformin at the end of the study

**46.6%** increased antidiabetic medications

Moriconi et al. Nutrients 2021

frontiers in Endocrinology

CLINICAL TRIAL
published: 14 September 2020
doi: 10.3389/fendo.2020.00607

# Efficacy of a 2-Month Very Low-Calorie Ketogenic Diet (VLCKD) Compared to a Standard Low-Calorie Diet in Reducing Visceral and Liver Fat Accumulation in Patients With Obesity

*Guilherme Moura Cunha[1], German Guzman[2]*, Livia Lugarinho Correa De Mello[3], Barbara Trein[3], Luciana Diniz Carneiro Spina[4], Isabela Bussade[5], Juliana Marques Prata[6], Ignacio Sajoux[2] and Walmir Countinho[3]*

OPEN ACCESS

46 patients

**Conclusion:** Patients undergoing a VLCKD achieved superior weight loss, with significant VAT and liver fat fraction reductions when compared to the standard LC diet. The weight loss and rapid mobilization of liver fat demonstrated with VLCKD could serve as an effective alternative for the treatment of NAFLD.

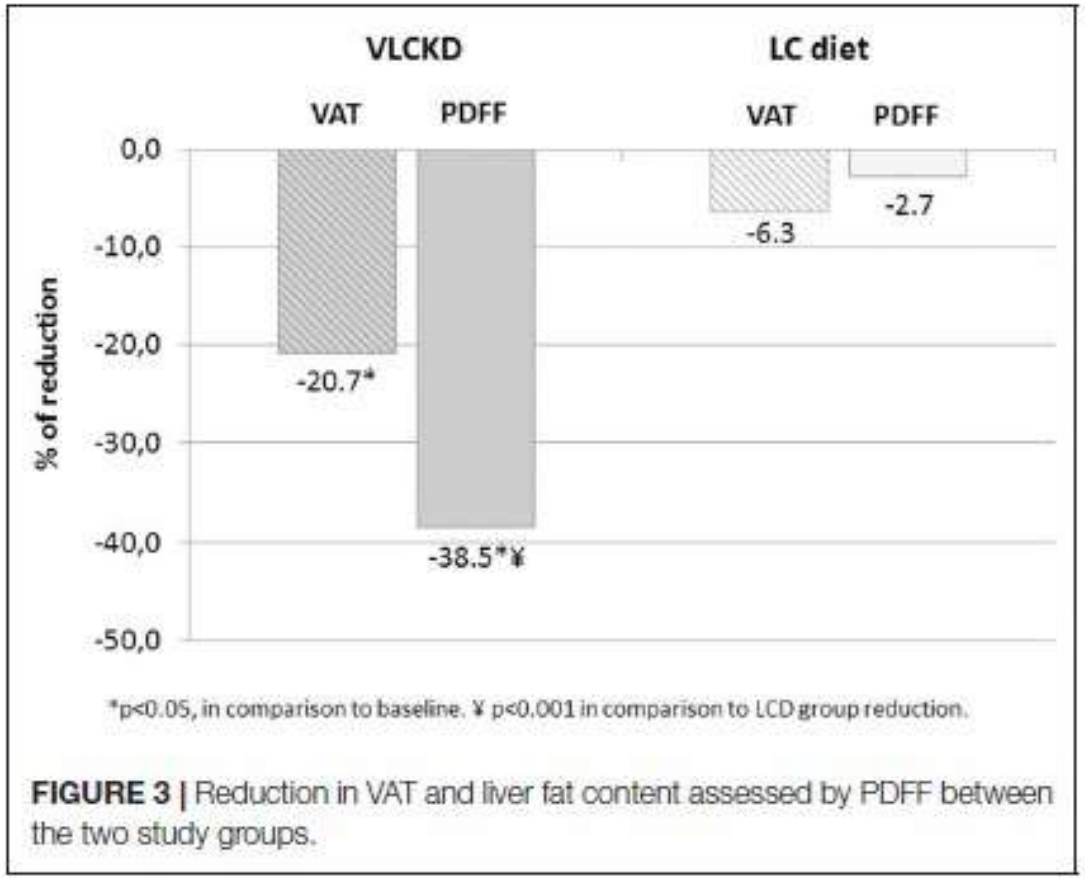
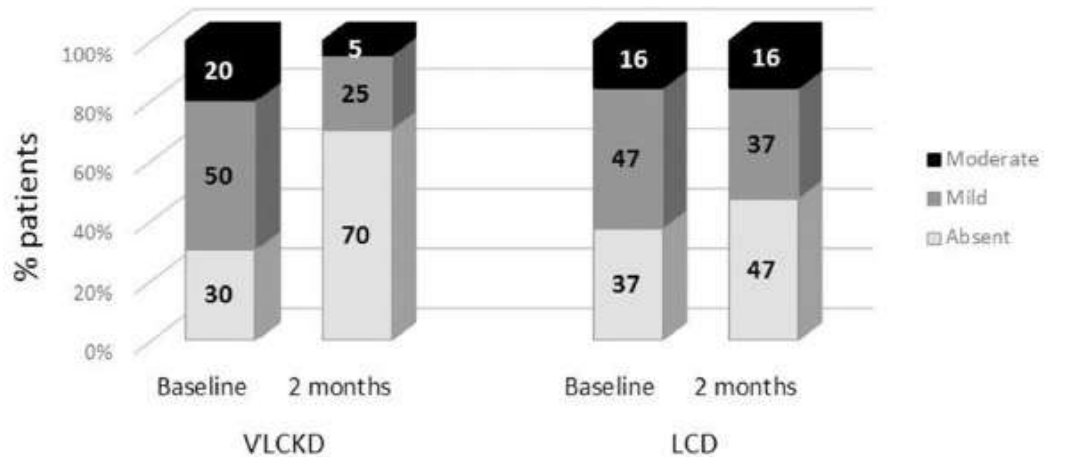


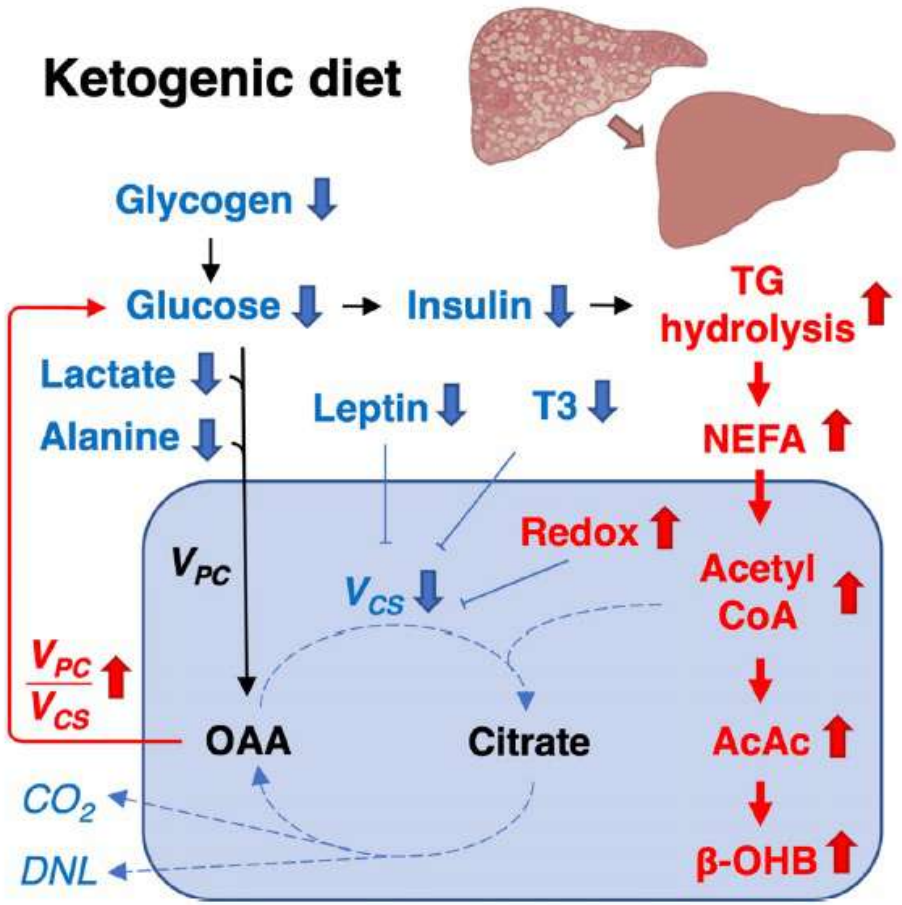

**FIGURE 3 |** Reduction in VAT and liver fat content assessed by PDFF between the two study groups.



# Effect of a ketogenic diet on hepatic steatosis and hepatic mitochondrial metabolism in nonalcoholic fatty liver disease

Panu K. Luukkonen[a,b,c], Sylvie Dufour[a,d], Kun Lyu[e], Xian-Man Zhang[a,d], Antti Hakkarainen[f,g], Tiina E. Lehtimäki[f], Gary W. Cline[a,d], Kitt Falk Petersen[a,d], Gerald I. Shulman[a,d,e,1,2], and Hannele Yki-Järvinen[b,c,1,2]

Ketogenic diet is an effective treatment for nonalcoholic fatty liver disease (NAFLD). Here, we present evidence that hepatic mitochondrial fluxes and redox state are markedly altered during ketogenic diet-induced reversal of NAFLD in humans. Ketogenic diet for 6 d markedly decreased liver fat content and hepatic insulin resistance. These changes were associated with increased net hydrolysis of liver triglycerides and decreased endogenous glucose production and serum insulin concentrations. Partitioning of fatty acids toward ketogenesis increased, which was associated with increased hepatic mitochondrial redox state and decreased hepatic citrate synthase flux. These data demonstrate heretofore undescribed adaptations underlying the reversal of NAFLD by ketogenic diet and highlight hepatic mitochondrial fluxes and redox state as potential treatment targets in NAFLD.



# Take home messages

- **Type 2 diabetes develops when personal tolerance for fat levels in the liver and pancreas are exceeded**
- **Weight loss sufficient to reverse this phenomenon will permit return to non-diabetic conditions in the early years after diagnosis**
- **Remission is durable provided that weight regain is avoided**
- **Avoidance of weight regain can be achieved by various strategies and individuals must find the dietary strategies most suited to them alongside increased physical activity**
- **To enable healthful dietary intakes, policy interventions such as taxation on calorie dense foods and restrictions on portion size are mandatory.**

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