

Severe type 2 diabetes (T2D) remission using a very low-calorie ketogenic diet (VLCKD)

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Summary

There is a close association between obesity and type 2 diabetes (T2D). The value of weight loss in the management of patients with T2D has long been known. Loss of 15% or more of body weight can have a disease-modifying effect in people with diabetes inducing remission in a large proportion of patients. Very low-carbohydrate ketogenic diets (VLCKDs) have been proposed as an appealing nutritional strategy for obesity management. The diet was shown to result in significant weight loss in the short, intermediate, and long terms and improvement in body composition parameters as well as glycemic and lipid profiles. The reported case is a 35-year-old man with obesity, dyslipidemia, and T2D for 5 years. Despite the use of five antidiabetic medications, including insulin, HbA1c was 10.1%. A VLCKD through a commercial multidisciplinary weight loss program (PnK method) was prescribed and all medications were discontinued. The method is based on high-biological-value protein preparations and has 5 steps, the first 3 steps (active stage) consist of a VLCKD (600–800 kcal/d) that is low in carbohydrates (<50 g daily from vegetables) and lipids. The amount of proteins ranged between 0.8 and 1.2 g/kg of ideal body weight. After only 3 months, the patient lost 20 kg with weight normalization and diabetes remission, and after 2 years of follow-up, the patient remained without the pathologies. Due to the rapid and significant weight loss, VLCKD emerges as a useful tool in T2D remission in patients with obesity.

Learning points:

- Obesity and type 2 diabetes (T2D) are conditions that share key pathophysiological mechanisms.
- Loss of 15% or more of body weight can have a disease-modifying effect in people with T2D inducing remission in a large proportion of patients.
- Diabetes remission should be defined as a return of HbA1c to <6.5% and which persists for at least 3 months in the absence of usual glucose-lowering pharmacotherapy.
- The very low-carbohydrate ketogenic diet (VLCKD) is a nutritional approach that has significant beneficial effects on anthropometric and metabolic parameters.
- Due to the rapid and significant weight loss, VLCKD emerges as a useful tool in T2D remission in patients with obesity.

Background

The International Diabetes Federation estimates that 1 in 10 people aged 20–79 years have diabetes, which equates to 537 million people in the world. By 2045, this number will

increase to 784 million (idf.org in 2022). There is a close association between obesity and type 2 diabetes (T2D). The likelihood and severity of T2D are closely linked with



body mass index (BMI). There is a seven times greater risk of diabetes in people with obesity compared to those of healthy weight.

Significant behavioral changes, mainly related to nutrition and weight management, can lead to a return from overt hyperglycemia to nearly normal glucose levels for extended periods of time (1, 2). Diabetes remission is most likely early in the course of the disease and can involve partial recovery of both insulin secretion and insulin action (3).

Very low-carbohydrate ketogenic diets (VLCKD) have been proposed as an appealing nutritional strategy for obesity management. Recently, the European Association for the Study of Obesity published a guideline for obesity management in adults with a VLCKD. The diet was shown to result in significant weight loss in the short, intermediate, and long terms and improvement in body composition parameters as well as glycemic and lipid profiles (4).

Based on this evidence, we report the case of a patient with obesity and a diagnosis of T2D for 5 years. Despite the use of 5 antidiabetic medications, including insulin, HbA1c was 10.1%. It was decided to initiate a VLCKD through a commercial method (PnK). During the diet, all medications were discontinued. After only 3 months, the patient lost 20 kg with weight normalization and diabetes remission, and after 2 years of follow-up, the patient remained without the pathologies.

Case presentation

This is a male, 35-year-old patient, with obesity, dyslipidemia, and T2D for 5 years. He was using gliclazide 60 mg/day, linagliptin 5 mg/day, metformin 2 g/day, canagliflozin 300 mg/day, and rosuvastatin 20 mg/day. Degludec insulin was started 3 years after diabetes diagnosis with a progressive increase in dose up to 30 units/day. He had a history of using liraglutide 1.8 mg in a previous treatment with undesirable side effects. Despite the regular use of medications, HbA1c was 10.1%.

Anthropometric measurements showed weight: 98 kg, height: 180 cm, BMI 30.2 kg/m², and waist circumference: 112 cm. A physical examination was performed with no significant alterations. The patient was not studied for changes in his body composition.

The patient had never undergone any treatment for obesity and had the heaviest weight of adult life.

It was decided to initiate a VLCKD through a commercial multidisciplinary weight loss program (PnK® method). During the diet, all medications were

discontinued, except for rosuvastatin, and he used a continuous glucose monitoring system.

Investigation

The patient had the following biochemical parameters before starting de PnK method: HbA1c: 10.1%, fasting glucose (FG): 132 mg/dL, creatinine: 0.8 G/dL, uric acid: 6.2 mg/dL (reference value (RV): 2.4–5.7 mg/dL), serum glutamic oxaloacetic transaminase (AST): 55 U/L (RV: until 32 U/L), gamma-glutamyl transferase (GGT): 90 U/L (RV: until 40 U/L), total cholesterol (TC): 132 mg/dL, triglycerides (TG): 81 mg/dL, HDL: 43 mg/dL, LDL: 73 mg/dL, thyroid-stimulating hormone (TSH): 1.11 mIU/L, and C-peptide: 4.83 ng/mL. The C-peptide dosage was performed with the objective of analyzing the pancreatic insulin reserve. The patient also had positive microalbuminuria: 89.6 mg/24 h and moderate hepatic steatosis diagnosed by ultrasound. Unfortunately, no tool was used for the screening of fibrosis.

Treatment

The nutritional intervention that the patient underwent was based on a commercial multidisciplinary weight-loss program (PnK® method). Briefly, the intervention included an evaluation by a specialist physician, an assessment by an expert dietician, and exercise recommendations. The method is based on high-biological-value protein preparations obtained from cow's milk, soy, avian eggs, green peas, and cereals. Each protein preparation contained 15 g protein, 4 g carbohydrates, 3 g fat, and provided 90–100 kcal. The weight-loss program has 5 steps, the first 3 steps (active stage) consist of a VLCKD (600–800 kcal/d) that is low in carbohydrates (<50 g daily from vegetables) and lipids (only 10 g of olive oil per day). The amount of high-biological-value proteins ranged between 0.8 and 1.2 g/kg of ideal body weight, to ensure meeting the minimal body requirements and to prevent the loss of lean mass. In step 1, the patients ate high-biological-value protein preparations five times a day, and vegetables with low glycemic indices. In step 2, one of the protein servings was substituted with a natural protein (egg, meat, or fish) either at lunch or at dinner. In step 3, a second serving of low-fat natural protein was substituted for the second serving of biological protein preparation. Throughout these ketogenic phases, supplements of vitamins and minerals were provided in accordance with international recommendations. The active stage usually lasts 8–12 weeks, until the subjects lose most of the weight loss target (about 80%).



In either steps 4 or 5, ketosis was ended by the physician and the patient began a low-calorie diet (LCD) (800–1500 kcal/day). At this point, the patients underwent progressive incorporation of different food groups and participated in a program of alimentary re-education to guarantee the long-term maintenance of the weight loss. Carbohydrates are gradually reintroduced according to the following order: foods with the lowest glycemic index (fruit and dairy products (step 4)), followed by foods with moderate (legumes) and a high glycemic index (bread, pasta, and cereals), step 5. Finally, the maintenance diet consisted of an eating plan balanced in carbohydrates, protein, and fat. Depending on the individual, calories consumed ranged between 1500 and 2000 kcal/day, with the goal of maintaining the weight lost and promoting a healthy lifestyle.

Outcome and follow-up

The patient did the PnK method for 90 days. During the first 2 months, he did the first 3 steps (active stage) of the method that consist of a VLCKD. In the first month, steps 1 and 2 and in the second month, step 3. In the last month, ketosis was ended, and he began an LCD (last two steps). At the end of the PnK® method, the eating plan balanced in carbohydrates, protein and fat, the maintenance diet, was prescribed.

After only 3 months, the patient lost 20 kg (20.4% of body weight) with weight normalization and diabetes remission. The biochemical parameters showed no change in renal function, improvement in hepatic function, and microalbuminuria normalization. After 2 years of follow-up, the patient remained without the pathologies, including remission of steatosis.

The evolution of the anthropometric measures and biochemical parameters are presented in [Table 1](#).

Discussion

Recently, an international expert group was convened by the American Diabetes Association (ADA) to propose nomenclature and principles for data collection and analysis, with the goal of establishing a base of information to support future clinical guidance. This group proposed diabetes remission as a return of HbA1c to <6.5% and that persists for at least 3 months in the absence of usual glucose-lowering therapy (3).

The value of weight loss in the management of patients with T2D has long been known. Studies of comprehensive lifestyle interventions have generated impressive data regarding glycemic control and even remission of diabetes. The Look AHEAD randomly assigned 5145 adults with T2D to intensive lifestyle modification aimed at 7% weight loss or to usual care. After 4 years of follow-up, participants in the intensive lifestyle group had lost a mean of 4.7% of body weight vs 0.8% in the control group, but few (7% in the intervention group vs 2% in the control group) people had an HbA1c of less than 6.5% suggesting that greater weight loss is required for a meaningful effect on the disease course of T2D (1).

The DiRECT randomized controlled trial evaluated an intensive dietary intervention in 306 adults with BMI of 27–45 kg/m² and T2D with a duration of less than 6 years. After 2 years of follow-up, 11% of people on the dietary intervention lost at least 15 kg, compared with 2% of people in the routine care control group. In a *post-hoc* analysis of 272 participants for whom 24-month data were available, 70% of people who lost at least 15 kg had diabetes remission. They established strong correlation between the magnitude of weight loss and the likelihood of remission from T2D and showed that a loss of 15% of body weight can result in remission in most patients with diabetes (2).

Table 1 Evolution of the anthropometric measures and biochemical parameters.

	Basal	30 days	60 days	90 days	1 year	2 years
Weight	98	90	82	78	79	80
BMI	30.2	27.8	25.3	24.1	24.4	24.7
FG	132	126	92	77	91	86
HbA1c	10.1	8.1	6.8	5.3	5.4	5.2
Uric acid	6.2	5.4	4.4	4.3	4.4	4.9
Creatinine	0.8	0.9	0.7	0.7	0.9	1.0
AST	55	37	37	32	27	34
GGT	90	43	45	24	19	12
TC	132	145		153	145	142
TG	81	114		90	130	80
HDL	43	51		51	44	44
LDL	73	71		84	75	82
Microalbuminuria	89.6			28.0	25.2	22.3



Lingway and coworkers (5) reviewed the clinical evidence supporting weight loss as a fundamental target, proposed a novel therapeutic framework, and explored challenges for the widespread implementation of this approach for people with T2D. They concluded that the time is right to consider the addition of substantial (i.e. double-digit) weight loss as a principal target for the treatment of many patients with diabetes.

In this scenario, the VLCKD is a nutritional approach that has significant beneficial effects on anthropometric and metabolic parameters. VLCKDs are characterized by a low carbohydrate content (< 50 g/day), 1–1.5 g of protein/kg of ideal body weight, 15–30 g of fat/day, and about 500–800 kcal/day. The reduction of carbohydrate intake under the above-reported threshold leads to ketone synthesis. Ketone bodies are then utilized as fuel by several extrahepatic tissues such as the CNS, skeletal muscle, and the heart (4).

Among the beneficial effects, when compared with other weight loss interventions with the same duration, the VLCKD showed a major effect on reduction of body weight, fat mass, waist circumference, total cholesterol, and triglyceridemia as well as improved insulin resistance. VLCKDs have been reported to induce more weight loss than a standard LCD after 1 and 2 years of follow-up to preserve muscle mass, muscle strength, and resting metabolic rate (4, 6, 7, 8). The VLCKD can also be considered a safe nutritional approach under a health professional's supervision since the most common side effects are usually clinically mild and easy to manage and recovery is often spontaneous (4).

The main indications for the use of VLCKD in obesity are severe obesity, treatment of obesity with bariatric indications in the preoperative period before the bariatric procedure, sarcopenic obesity, and obesity associated with hypertriglyceridemia and/or hypertension and/or T2D and/or metabolic syndrome. Some absolute contraindications are type 1 diabetes mellitus, latent autoimmune diabetes in adults, β -cell failure in T2D, use of sodium/glucose cotransporter 2 inhibitors (risk of euglycemic diabetic ketoacidosis), pregnancy, and breastfeeding. To favor the patients' compliance, VLCKDs are often delivered through meal replacements mimicking a natural diet (4).

In 2016, a study evaluated the short-term safety and tolerability of a VLCKD as part of an interventional weight loss program including lifestyle and behavioral modification support in subjects with T2D. This medical nutritional therapy intervention resulted in significant weight loss in most study participants, along with marked amelioration of glycemic control as compared with a

standard of care nutritional intervention based on the ADA guidelines (9).

Finally, due to the rapid and significant weight loss, VLCKD emerges as a useful tool in T2D remission in patients with obesity.

Patient's perspective

I had been diagnosed with diabetes for 5 years until the day of the appointment with the endocrinologist. Two years after the diagnosis, even with the use of several medications, I had to start using insulin. My weight was increasing day after day and yet my blood sugar did not go down. That's when the doctor proposed a dietary treatment option with great power to reduce blood glucose and also with greater effectiveness in weight loss. In a few days, I saw my blood sugar return to normal levels without the use of medication. I returned to the desired weight and my blood glucose never went up again.

Declaration of interest

L L Correa, S Senhorini, P Alves, L Dinis, L B Carloto, M Nuñez-García, and I Sajoux declare that they have no conflict of interest. The Pronokal personnel (M Nuñez-García and Ignacio Sajoux) were involved in revising the final version of the manuscript, without intervention in the results of this case.

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Patient consent

Written informed consent for publication of their clinical details was obtained from the patient after full explanation of the purpose and nature of all procedures used.

Author contribution statement

All authors participated equally in the case report.

References

- 1 Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, Pownall HJ, Johnson KC, Safford MM, Kitabchi AE, *et al.* Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012 **308** 2489–2496. (<https://doi.org/10.1001/jama.2012.67929>)
- 2 Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, *et al.* Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *Lancet* 2018 **391** 541–551. ([https://doi.org/10.1016/S0140-6736\(17\)33102-1](https://doi.org/10.1016/S0140-6736(17)33102-1))
- 3 Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, Rothberg AE, le Roux CW, Rubino F, Schauer P, *et al.* Consensus report: definition and interpretation of remission in type 2 diabetes. *Diabetes Care* 2021 **44** 2438–2444. (<https://doi.org/10.2337/dci21-0034>)



- 4 Muscogiuri G, El Ghoch M, Colao A, Hassapidou M, Yumuk V, Busetto L & Obesity Management Task Force (OMTF) of the European Association for the Study of Obesity (EASO). European guidelines for obesity management in adults with a very low-calorie ketogenic diet: a systematic review and meta-analysis. *Obesity Facts* 2021 **14** 222–245. (<https://doi.org/10.1159/000515381>)
- 5 Lingvay I, Sumithran P, Cohen RV & le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022 **399** 394–405. ([https://doi.org/10.1016/S0140-6736\(21\)01919-X](https://doi.org/10.1016/S0140-6736(21)01919-X))
- 6 Gomez-Arbelaez D, Bellido D, Castro AI, Ordoñez-Mayan L, Carreira J, Galban C, Martinez-Olmos MA, Crujeiras AB, Sajoux I & Casanueva FF. Body composition changes after very-low-calorie ketogenic diet in obesity evaluated by 3 standardized methods. *Journal of Clinical Endocrinology and Metabolism* 2017 **102** 488–498. (<https://doi.org/10.1210/jc.2016-2385>)
- 7 Moreno B, Crujeiras AB, Bellido D, Sajoux I & Casanueva FF. Obesity treatment by very low-calorie-ketogenic diet at two years: reduction in visceral fat and on the burden of disease. *Endocrine* 2016 **54** 681–690. (<https://doi.org/10.1007/s12020-016-1050-2>)
- 8 Gomez-Arbelaez D, Crujeiras AB, Castro AI, Martinez-Olmos MA, Canton A, Ordoñez-Mayan L, Sajoux I, Galban C, Bellido D & Casanueva FF. Resting metabolic rate of obese patients under very low calorie ketogenic diet. *Nutrition and Metabolism* 2018 **15** 18. (<https://doi.org/10.1186/s12986-018-0249-z>)
- 9 Goday A, Bellido D, Sajoux I, Crujeiras AB, Burguera B, García-Luna PP, Oleaga A, Moreno B & Casanueva FF. 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. *Nutrition and Diabetes* 2016 **6** e230. (<https://doi.org/10.1038/nutd.2016.36>)

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