

## KETOGENIC DIET'S EFFECT ON GLYCEMIC BALANCE IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: A REVIEW

Lamberti Clelia<sup>1</sup>, Pagano Imma<sup>1,2</sup>

<sup>1</sup>Post Graduate University Course in “Diete e Terapie Nutrizionali Chetogeniche: Integratori e Nutraceutici (NutriKeto)” - Dipartimento di Farmacia, University of Salerno, Via Giovanni Paolo II – Fisciano (SA), Italy

<sup>2</sup>Nutriketo Lab, A.O.R.N. ‘San Giuseppe Moscati’, Contrada Amoretta, Avellino, Italy

Email address: [cleo.lamberti@libero.it](mailto:cleo.lamberti@libero.it); [nutriketo@unisa.it](mailto:nutriketo@unisa.it)

### Abstract

Diabetes mellitus is a serious and diffuse health disease, a metabolic disorder characterized by high blood sugar levels (hyperglycemia). Nutrition has always had a main role in the prevention and in therapy of Type 2 Diabetes Mellitus (DMT<sub>2</sub>). The Ketogenic Diet (KD) is a diet that generally provides less than 50 gr of carbohydrates (CHO) per day, and has been also tested as an adjuvant in the treatment of DMT<sub>2</sub>. In this review were identified relevant studies, clinical trial and clinical study regarding the KD's effects on glycemc balance in patients with DMT<sub>2</sub>. It can be concluded that although useful for inducing rapid weight reduction, more clinical studies are necessary to demonstrate the KD beneficial long-term effects in diabetic patients.

**Keywords:** *Ketogenic Diet (KD), Type 2 Diabetes Mellitus (DMT<sub>2</sub>), Hyperglycemia, Very low calorie Ketogenic Diet (VLCKD).*

## Introduction

Diabetes mellitus is a metabolic disorder mainly characterized by impaired insulin (resistance) coupled with the inability of the pancreatic B-cells to produce adequate amount insulin depending on the increased demand of high blood sugar levels (Hyperglycemia) (1).

Chronic hyperglycemia is linked to an organ damage, with dysfunction and insufficiency of different organs (heart and vessels, kidneys, autonomic and peripheral nervous system).

Currently, diabetic disease is a serious universal health problem, in fact, the International Diabetes Federation reports 382 millions of people who suffer of this metabolic disorder, and 352 millions are at risk of falling ill.

In Italy there are actually 4 millions of people suffering from this disease, and the prevalence is around 6%.

This drastic diffusion, especially of Type 2 Diabetes Mellitus, is due to the continuous and systematic deterioration of the lifestyle and, above all, to the bad diet and to the excessive daily caloric intake. Moreover there aren't enough vivid educational food programs regarding life style change devoted to the population (2).

Nutrition has always had a main role in the prevention and in the therapy of Type 2 Diabetes Mellitus. Its primary aim is not only the improvement of glycemic and other cardio-metabolic risk factors (1, 2) control, but also the reduction of linked cardiovascular diseases (MCV), responsible for about 70% of the total mortality in these patients (3).

Hypocaloric Mediterranean diet has always been considered the gold standard of the diabetic patient's nutritional approach, due to its documented effectiveness not only on weight loss, but also on metabolic control and reduction of cardiovascular risk. However, alternative diets have been recently proposed to the Mediterranean one, for a presumed better ability to reduce body weight and reduce risk factors associated to diabetes. The features of these diets are the low carbohydrate content (CHO), which means a daily amount less

than 50gr / day (correspondent to 5% of the daily caloric requirement), the high fat content which is more than 60% of the daily caloric requirement, and the balanced amounts of protein. This diet induces a metabolic condition called "physiological ketosis", that hasn't to be confused with the ketoacidosis present in glycometabolic decompensation, from which it differs in maintaining physiological pH and in producing lower levels of ketonemia.

The ketogenic diet (KD) is a diet that generally provides less than 50 grams of CHO per day.

The 80-90% of calories derive from fats and proteins. KD has been studied and used for many years in some forms of epilepsy not controlled by drugs and lately, it has been proposed in the treatment of severe and complicated obesity, and also tested as an adjuvant in the treatment of type 2 Diabetes Mellitus (DMT2).

The effects of a CHO's low intake are lower levels of insulin and an increased concentration of glucagon, with an induction of lipolysis and an increased availability of circulating free fatty acids (FFA) (4). FFAs are metabolised and transformed in the liver into Ketone Bodies (KB) which are hydrosoluble acetoacetate and beta-hydroxybutyrate. From acetacetic acid, thanks to enzymatic decarboxylation, derives acetone, which can be eliminated through the respiratory system. An overproduction of acetacetic acid causes the conversion of this into the other KB, and the appearance of ketonemia and ketonuria. So the Ketone Bodies are used as an energy source by the tissues through the pathway that leads to the formation, from Beta-hydroxybutyrate to two acetyl CoA molecules, which enter the Krebs cycle.

There is no doubt about the fact that Ketogenic diet leads to a reduction of body weight, but the operating principle is still a subject of debate. In fact, the weight loss could be explained by:

- 1) The effect of appetite reduction, induced by ketones;
- 2) The reduction of lipogenesis;
- 3) The reduction of the Respiratory Exchange Ratio (RER) at rest, which is a signal of a more efficient metabolic consumption of fats (5);

4) Induction of gluconeogenesis which determines an energy cost of about 400-600 kcal / day;

5) Proteins thermal effect.

Other important points are the improvement of insulin resistance and glycometabolic parameters in diabetic people who, many times, are allowed to interrupt hypoglycemic therapy.

## Methods

Relevant studies were identified by computerized searches on Pub Med, and review of bibliographies of selected article. It has been used Ketogenic Diet, DMT2, Low-calorie diet, Very low-calorie diet as keywords.

It has been included in the search reviews, clinical trial, clinical studies and practice guidelines.

## Results and Discussion

In Orio et al. study (6), have been examined 18 obese patients who suffered DMT2 from less than 10 years, subjected by VLCKD (very low calory KD) for a short period. The study has been organized into two parts: 6 weeks of VLCKD and 6 weeks of transition with gradual reintroduction of CHO. After 12 weeks, the parameters body weight, BMI, HBA1c, and HOMA index, aims of the study, were reduced and moreover Orio et al. could highlight an improvement of the glycometabolic compensation. Therefore the study concluded that, as suggested by the 2018 ADA care standards, the short-term use of VLCKD in selected obese patients with DMT2 is able to improve glycometabolic compensation and weight.

On the other hand, the study by Bolla et al. (7) confirmed that reducing CHO intake reduces body weight and improves glycemic control in patients with DMT2, but also that there are too few available data regarding sustainability, safety and long-term effectiveness of KD.

In DMT2 patients, in fact is essential the balance between the potential increase of cardiovascular risk due to the unfavorable lipid profile observed in the case of KD, and the benefits from the weight loss and an improved glycemic control (7). For this reason, as Nielsen et al. study claims (8), it's clear the need to carry out further large-scale

randomized, long-term studies in order to pinpoint the safety, the efficacy and the compliance of these diets in patients with DMT2.

Gunbiner's study (9) analyzed obese people with DMT2 who were on two types of diets for three weeks, characterized by a very low caloric content. These diets were similar in protein content, but once presented a lower CHO content than the other (24 vs 94 gr / day).

As expected, the diet with a lower CHO content, resulted in higher circulating KB levels (approximately 3 mmol / L) and in a lower hepatic glucose production. This would demonstrate an inverse correlation between circulating ketones and hepatic glucose production, which would means more favorable effects on glycemic control in diabetic patients.

In another study were analyzed diabetic patients with a LC diet (20 g / day) for two weeks, and it was observed a glycemia's decrease, in particular from 7.5 to 6.3 mmol / L, a HBA1c's decrease, from 7.3% to 6.8%, and a noticeable improvement in insulin sensitivity (10).

In a further study carried out on diabetic patients who were on a KD for 56 weeks, were observed significant improvements in weight loss and in the metabolic parameters at 12 weeks, then continued for 56 weeks, as evidenced by fasting level improvements of circulating glucose (51%), total cholesterol (29%), HDL (63%) and triglycerides (41%) (11).

Other studies support the efficacy of a KD in the long-term management of DMT2 complications. Through the CHO's reduced consumption, there is in fact a significant reduction in fat mass, an improvement in glycemic control, in HBA1c, and consequently a reduction in the use of oral hypoglycemic agents (OHA) and insulin. In summary, individuals with DMT2 can feel symptomatic improvements, and also objective improvements related to disease risk biomarkers, if they were on a well formulated low CHO diet. Glycemic control improves not only because there is less incoming glucose, but also because it's increased the sensitivity to systemic insulin (4). Similarly, a study by Stevens et al. (12), based on 30 patients which have been on a VLCD for 8 weeks,

and on an isocaloric diet and weight maintenance program for the next six months, showed a long-lasting remission of DMT2 for at least 6 months in 40% of patients. DMT2 would therefore be a potentially reversible condition and clearly the study reaffirms the importance of excessive caloric intake, in the pathogenesis of DMT2. The normalization of glycemia's level is due to the improvement of the acute phase of insulin secretion and also to the weight loss which normalize the fat content in the liver and takes to an improvement of insulin sensitivity.

Furthermore, the DiRECT study (13) shows the remission of DMT2 after a VLCKD for 12 weeks. During the study patients have been educated to a reintegration of balanced and controlled meals in order to reach a correct lifestyle and to prevent weight recovery.

However a systematic review (14) in order to evaluate the efficacy and safety of low-CHO diets, has showed, that the studies reported in the literature are non-homogeneous regarding the structure, the participants' characteristics, the duration of the observation period and the content of CHO. From the data reported in the literature it is possible to deduce that the KD, in short-medium term is effective in reducing hunger.

As regards lipids, KD's effects are discordant, in fact analyzed data show both developments of atherosclerotic profiles and a reduction in the levels of total cholesterol and triglycerides. For these reasons a definitive judgment about the role of KD is not possible.

If we consider the KD as "therapeutic", the rules on which a balanced diet is based, following the Mediterranean model, are not valid. In KD fats represent 70-80% of calories and sugars less than 5%, so the content is reduced below 50g / day of CHO. The minimum daily level recommended by the American Diabetes Association is 130 g / day, so an intake of around 20-50 g / day of CHO are "threshold" levels to induce ketogenic's metabolic pathway.

The ADI Position Paper 2014, concluded that: "in a world where overweight and obesity are in continuous increase and so DMT2 too is in a worrying increase, KD represents an interesting alternative to other therapeutic pathways. It is not

possible, at present, to foresee KD routine use as a first choice in all forms of overweight and obesity, but it can be surely considered as a treatment especially when it's required a rapid weight loss in order to contain the overall health risk" (15).

The study published on JAMA, in 2019 (16), concludes clarifying that the widespread enthusiasm for ketogenic diets in treating obesity and diabetes overcomes the evidence available to us. The authors have doubts regarding whether these diets are easy to support (easily respected by patients) and whether they can promote long-term health. Currently there are no studies that have evaluated the effects on cardiovascular mortality and for all other causes.

Some recent studies suggest VLCKDs to be a good tool in the management of type 2 diabetes.

Therefore, VLCKDs should be considered as an initial step in properly selected and motivated patients with obesity or type 2 diabetes. VLCKDs have been shown to be beneficial in patients with type 2 diabetes. Relevant reductions in glycemic levels were observed in several studies, together with a reduction in the exogenous insulin needs (18).

A ketogenic diet was more effective in improving weight control and metabolic parameters related to glycemic and lipid controls in patients with overweight, obesity, DMT2, as compared to low-fat based diets (19).

## Conclusion

In conclusion, VLCKD brings benefits in terms of rapid weight reduction, but further studies are needed also to prove beneficial long-term effects in diabetic patients in terms of reducing cardiovascular risk. Based on available studies, a controlled ketogenic diet could be considered a first-line approach for obesity and diabetes. But high-quality clinical trials will be needed to confirm their long-term effects and full potential in clinical nutrition.

## References

1. Franz, M. J., Powers, M. A., Leontos, C., Holzmeister, L. A., Kulkarni, K., Monk, A., ... & Gradwell, E. (2010). The evidence for medical nutrition therapy for type 1 and type

- 2 diabetes in adults. *Journal of the American Dietetic Association*, 110(12), 1852-1889.
2. Lindström, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J. G., Hemiö, K., ... & Louheranta, A. (2006). Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *The Lancet*, 368(9548), 1673-1679.
  3. Laakso, M. (1999). Hyperglycemia and cardiovascular disease in type 2 diabetes. *Diabetes*, 48(5), 937-942.
  4. Paoli, A., Rubini, A., Volek, J. S., & Grimaldi, K. A. (2013). Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *European journal of clinical nutrition*, 67(8), 789-796.
  5. Nylen, K., Likhodii, S., & Burnham, W. M. (2009). The ketogenic diet: proposed mechanisms of action. *Neurotherapeutics*, 6(2), 402-405.
  6. Dyson, P. (2020). Very low carbohydrate ketogenic diets and diabetes. *Practical Diabetes*, 37(4), 121-126.
  7. Bolla, A. M., Caretto, A., Laurenzi, A., Scavini, M., & Piemonti, L. (2019). Low-carb and ketogenic diets in type 1 and type 2 diabetes. *Nutrients*, 11(5), 962.
  8. Nielsen, J. V., & Joensson, E. A. (2008). Low-carbohydrate diet in type 2 diabetes: stable improvement of bodyweight and glycemic control during 44 months follow-up. *Nutrition & metabolism*, 5(1), 1-6.
  9. Gumbiner, B., Wendel, J. A., & McDermott, M. P. (1996). Effects of diet composition and ketosis on glycemia during very-low-energy-diet therapy in obese patients with non-insulin-dependent diabetes mellitus. *The American journal of clinical nutrition*, 63(1), 110-115.
  10. Boden, G., Sargrad, K., Homko, C., Mozzoli, M., & Stein, T. P. (2005). Effect of a low-carbohydrate diet on appetite, blood glucose levels, and insulin resistance in obese patients with type 2 diabetes. *Annals of internal medicine*, 142(6), 403-411.
  11. Yancy, W. S., Foy, M., Chalecki, A. M., Vernon, M. C., & Westman, E. C. (2005). A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutrition & metabolism*, 2(1), 34.
  12. Steven, S., Hollingsworth, K. G., Al-Mrabeh, A., Avery, L., Aribisala, B., Caslake, M., & Taylor, R. (2016). Very low-calorie diet and 6 months of weight stability in type 2 diabetes: pathophysiological changes in responders and nonresponders. *Diabetes care*, 39(5), 808-815.
  13. Lean, M. E., Leslie, W. S., Barnes, A. C., Brosnahan, N., Thom, G., McCombie, L., ... & Rodrigues, A. M. (2018). Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *The Lancet*, 391(10120), 541-551.
  14. Bravata, D. M., Sanders, L., Huang, J., Krumholz, H. M., Olkin, I., Gardner, C. D., & Bravata, D. M. (2003). Efficacy and safety of low-carbohydrate diets: a systematic review. *Jama*, 289(14), 1837-1850.
  15. Moriconi, E., Infante, M., Gorini, S., Fabbri, A., & Caprio, M. (2019). Come avviare il paziente obeso alla terapia chetogenica. *L'Endocrinologo*, 20(4), 196-201.
  16. Joshi, S., Ostfeld, R. J., & McMacken, M. (2019). The ketogenic diet for obesity and diabetes—Enthusiasm outpaces evidence. *JAMA internal medicine*, 179(9), 1163-1164.
  17. Giacco, R., Frontoni, S., Bruttomesso D., De Simone. G. Orsi. R. (2017). Diete alternative: una guida per il paziente con diabete. SID.
  18. Casanueva, F. F., Castellana, M., Bellido, D., Trimboli, P., Castro, A. I., Sajoux, I., ... & Martinez-Olmos, M. A. (2020). Ketogenic diets as treatment of obesity and type 2 diabetes mellitus. *Reviews in Endocrine and Metabolic Disorders*, 21(3), 381-397.
  19. Choi, Y. J., Jeon, S. M., & Shin, S. (2020). Impact of a Ketogenic Diet on Metabolic Parameters in Patients with Obesity or Overweight and with or without Type Diabetes: A Meta-Analysis of Randomized Controlled Trials. *Nutrients*, 12(7), 2005.