

The Role of Ketogenic Diet in the Management of Diabetes and Overcome it's Effect: A Review

Versha¹, Yashika Jangra¹, Luxita Sharma², Abhishek Meher³, Harshal Tare⁴

¹*Dietetics and Applied Nutrition, Amity University, Gurgaon, Haryana, India*

²*Department of Dietetics and Applied Nutrition, Amity Medical School, Amity University, Gurgaon, Haryana, India*

³*Department of Pharmaceutics, Sharadchandra Pawar College of Pharmacy, Otur, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India*

⁴*Department of Pharmacognosy, Sharadchandra Pawar College of Pharmacy, Otur, Affiliated to Savitribai Phule Pune University, Pune, Maharashtra, India*

Received: 20th January, 2023; Revised: 08th February, 2023; Accepted: 10th March, 2022; Available Online: 25th March, 2023

ABSTRACT

The ketogenic diet, which is low in carbohydrates, may help diabetic people reduce their medication and improve their glycemia. Obesity and diabetes are two of the most well-known metabolic diseases connected with unfortunate dietary patterns and a stationary way of life. In the direst outcome imaginable, metabolic issues are a contributing reason to a wide range of diseases. The ketogenic diet replaces glucose with ketone bodies and is useful in various conditions, including metabolic disorders, epileptic seizures, peripheral neuropathy, kidney cancer, and skeletal muscle atrophy. Obesity is connected to a higher risk of type two diabetes. In obese people with glucose intolerance, it has been discovered that successful weight management and dietary adjustments, particularly in terms of carbohydrate content and glycemic index, have favorable benefits. We've already demonstrated that a ketogenic diet could help you to lose weight.

Furthermore, even in hyperlipidemic obese people, it improves cardiac risk factors. For a period of 56 weeks, the effect of low carbs or ketogenic diet was evaluated in patients having obesity with high glucose levels of blood to those with moderate blood glucose levels in this study. In many circumstances, excess insulin treatment and protein limitation slow the onset of diabetic nephropathy, and very few therapies are known to reverse nephropathy. The Keto diet regulates glucose and insulin levels in the body, making it an efficient diabetes treatment. As a result, the keto diet can be used to demonstrate the gap between diabetes treatment and obesity. Obesity is connected to a higher risk diabetes of type 2. In obese people with glucose intolerance, it has been discovered that successful weight management and dietary adjustments, particularly in carbohydrate content and glycemic index, have favorable effects. Diabetic nephropathy was entirely restored after two months of following a ketogenic diet, as measured by albumin/creatinine ratios and stress-induced gene expression.

On the other hand, histological evidence of nephropathy was only partially reversed. This shows that diabetic nephropathy can be restored with a relatively straightforward dietary change. It's still unclear if the ketogenic diet's beneficial effects are mediated by lower glucose metabolism. Glycemic levels are affected by dietary changes. The low-carb ketogenic diet was found to be quite promising in managing diabetic mellitus in preliminary investigations.

Keywords: Diabetes, Glycemic control, Ketogenic diet, Low carbohydrate diet.

International Journal of Pharmaceutical Quality Assurance (2023); DOI: 10.25258/ijpqa.14.1.38

How to cite this article: Versha, Jangra Y, Sharma L, Meher A, Tare H. The Role of Ketogenic Diet in the Management of Diabetes and Overcome it's Effect: A Review. International Journal of Pharmaceutical Quality Assurance. 2023;14(1):220-225.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

Different types of diets with minimal carbs (50–20 g/day) have shown to be very effective for diabetes mellitus and weight loss in recent years. Whether or not low-carbohydrate diets are effective is a point of contention. Ketogenic diets are low in carbs, moderate in protein, and higher in fats.¹ It's also known as low carbs and higher fats diet. A low-carb diet

alters the overall quality of diets, and long-term use alters body metabolism. Ketosis is a metabolic state that occurs when you eat a ketogenic diet. This is healthy diet is particularly useful for treating epilepsy in children.²

The ketone bodies enter the brain and take the place of glucose (C₆H₁₂O₆) as a source of energy. Ketosis, or the presence of significant amounts of ketone bodies in the blood,

reduces epileptic episodes. The basics of a keto diet are as follows:

- Get 5–10% of your calories from carbs
- 15–25% of appropriate protein
- 65–80% of your calories from high fats. A ketogenic diet includes items such as seafood, coconut oil, avocados, meat and poultry, and eggs.³
- In a low-carb diet, ketone levels blood ketones range from 0.1 to 0.2 millimoles, but on the keto diet, they jump to 0.5 to 5.0 millimoles.

A keto diet is divided into five stages.

- Why body continues to absorb fuel from prior diet meals for the first eight to ten hours after commencing a keto diet.
- One to two days after commencing the keto diet, liver glycogen disappears after twelve to 16 hours.
- Gluconeogenesis has started three to four days after the offset diet began, and protein failure will grow.
- Ketosis begins four to seven days after starting the keto diet. Ketones are used more by the mind. Ketone bulks are produced in greater quantities in the liver. A few responses, such as keto-infirmity, can be seen.
- Weight and nutritional habits have favorable benefits on obesity, with protein mistakes slows unhappiness
- Later, seven days from the era of offset the keto diet – gluconeogenesis and

Obesity is most certainly linked to type 2 diabetes. That authority of carcass glucose narrow-mindedness has been visualized. Ketogenic diets can help people with type 2 diabetes reduce their medication intake while also increasing their glycemia.¹ As per the World Diabetes Federation's eighth Diabetes Guide, around 425 trillion individuals worldwide have diabetes, and by 2045, 629 trillion individuals matured 20 to 79 will have diabetes assuming latest things proceed.³ Notwithstanding proof that lessening sugar admission brings down body weight and further develops glucose control in people having type 2 diabetes, there are not much long-term information on manageability, security, and viability.⁴ Due to lower insulin levels, a diuretic impact, and a diminished craving, individuals on ketogenic eats less get thinner. The “keto-flu,” a transient syndrome characterized by lightheadedness, dizziness, lethargy, and constipation, is the most prevalent unfavorable acute consequence.⁵ Obesity, diabetes, PCOS, metabolic syndrome, congenital hyperinsulinism, depression, glucose transporter type 1 diabetes and other illnesses have all been treated with the ketogenic diet in clinical trials.⁶ This review aims to investigate the conceivable roles of low-carb and ketogenic diets in managing of diabetes disease.

Ketogenic Diet History

In 1921 a researcher named Russel Wilder was quick to embrace the ketogenic diet to treat epilepsy. What's more, he begat the expression “ketogenic diet.” The ketogenic diet had a situation in the clinical world for about 10 years as a helpful eating routine for pediatric epilepsy, and it was broadly used until antiepileptic drugs made it outdated. The ketogenic diet's resurrection, like a quick weight reduction recipe, is generally

a new idea that has shown to become very compelling, basically for the time being.⁷ Control of diabetes comprises therapeutic adaptations designated toward glycemic control and a Hemoglobin A1c position of < 7.4%. As referenced before to patients with PCOS, a similar benefit of a very low carbs keto diet applies to patients with diabetes too.⁸ Prior to the discovery of insulin, ketogenic diets were originally employed to treat diabetes in the 1920s. These diets were also used to treat children with difficult-to-control epilepsy.⁹ A review concentrate on claims that the viability, security and strength of an extremely low-carb ketogenic diet contrasted with a normal low-carb diet on weight reduction, glycemic the board, dietary pattern and people with obesity and type 2 diabetes are personally satisfied.¹⁰

Biochemistry and Physiology

Gluconeogenesis

Gluconeogenesis is the human body's natural process of producing glucose from glycerol, lactic acid, and the amino acid residues and glutamine, which occurs mostly in the liver. As a critical wellspring of energy, ketone bodies play the job of glucose

Ketogenesis

The improvement for insulin discharge is comparably low during ketogenesis, leading to low blood glucose yield, and significantly reducing the upgrade for fat and glucose storage.

Acetoacetate is framed from unsaturated fats. It is converted to $(\text{CH}_3)_2\text{CO}$ and beta-hydroxybutyrate. These were largely the essential $\text{R}_2\text{C}=\text{O}$ particles that gather within body. When a low-carb diet is continued for an extended period of time, this metabolic state is referred to as “healthy ketosis.” The body's metabolism continues in ketosis as long it is deprived of carbohydrates. The heart, solid tissue and kidneys can without much of a stretch use the ketone body created in the human body to produce energy. Acetoacetate can likewise cross the blood-cerebrum hindrance, and provides the mind with a substitute wellspring of energy. Ketones are not used by RBCs or the liver because of an absence of mitochondria and the catalyst diaphorase, separately. Ketone body production is influenced by basal BMI, percentage of body fat, and basal energy expenditure. Acetoacetate make more ATP than glucose, acquiring them the moniker “super fuel 100 gm of $\text{C}_4\text{H}_5\text{O}_3$ makes 9401 gm of adenosine triphosphate, while 100 gm of β -hydroxy β -methylbutyric acid produces 10,501 g; in any case, 100 gm of glucose creates only 8,700 gm of adenosine triphosphate. The body can continue effective fuel production even when there is a caloric deficit. In addition, ketone bodies reduce free radical damage and boost antioxidant capability.^{11,12}

Benefits of Ketogenic Diet for Long Use

Ketogenic dietetic techniques may help improve important metabolic parameters in a short time with the potential for long-term benefit. Still, due to individual capacity to keep up with long-time carb limitation, the response may vary.¹³ In mice, a ketogenic diet that is followed for a lengthy period of time produces intolerance to glucose, and insulin defense, with

a decrease in beta cell mass and alpha cell mass (the long-term effects are beneficial to pancreatic endocrine cell).⁶ Headache, sleeplessness, constipation, diarrhea, and backache are some mild side effects of the ketogenic diet.¹⁴

Ketogenic Diet in Diabetes Mellitus

According to the most recent CDC study, approx 30 billion people had diabetes, with another 85 billion having pre-diabetes. This shows 45% of Americans have pre-diabetic symptoms or diabetes. Diabetes are at an elevated possibility of retinal microvascular pathology, strengthening neuropathy, renal glomerulus, and atherosclerosis grumbling, influencing streets because of diabetes, which is accompanied by a lengthy range of secondary consequences.¹⁵

Weight list, body weight, change in waistline periphery, a glucose level of blood, change in hemoglobin, absolute cholesterol, HDLs cholesterol, LDLs cholesterol, fatty substances and uric corrosive were measured previously and barely some weeks after the low carb diet or low carb keto diet were given.¹⁶ By activating the PPAR technique and its associated uncoupling mitochondrial uncoupling proteins, metabolic failure may result.¹⁷ The mediate weight loss was assigned to 45 subjects randomly, while the usual low-calorie diet was assigned to 44.¹⁸ Glucose-sensitive neurons have been found in various CNS locations, including the hypothalamic metabolic controller capitals.¹⁹ Although satisfactory, anecdotal evidence is still the gold standard when it comes to the appetite-suppressing effects of ketosis. Primary scientific data appear to back up this miracle, and evidence reveals that the Keto diet is very effective at fat loss, at least in short and mediate term.¹⁹ It's worth noting that carbohydrate vacuity can boost long-chain FA-CoA cellular conditions by increasing malonyl-CoA, which limits FA oxidation.

Ketogenic Diet in Type 1 Diabetes

Because of expansion in risk of diabetic ketoacidosis and probable hypoglycemia, type 1 diabetes mellitus is possible the defined disallowance to ketogenic diet. Still, patients afflicted by both Type 1 diabetes and obesity are becoming increasingly widespread, necessitating a shift in dietary habits. The most recent American Diabetic Association guidelines do not recommend one dietary plan over another; however, carbohydrate counting knowledge is strongly recommended.²⁰ In a similar vein, a recent study of 11 people with type 1 diabetes who used an HFKD for nonstop glucose monitoring found glycogenic benefit in the type of lowered variableness, a well-known risk factor for cardiovascular disease.²¹ Nonetheless, it came at the expense of an expanded variable of hypoglycemia in this case.²² It is impossible to say whether ketogenic diets can be used safely in people with type 1 diabetes.

Furthermore, current study has focused on determining if the keto diet can be used to improve glucose control in people with type 1 diabetes rather than researching its safety in people with type 1 diabetes who consume it for other reasons, such as weight loss.²³ Volek *et al.*,²⁰ discovered that

women are more likely sensitive to a ketogenic diet than males because males have a higher level of high-density lipoprotein. Nonetheless, both sexes have lower fasting triglyceride levels after following a keto diet.²⁴ Keto diet actions include maintaining metabolic behavior on glucose sugar level, stifling insulin-like development factor-1 and phosphoinositide 3-kinase or mammalian objective of rapamycin pathways, restoring systemic ketone body homeostasis, contributing to the reduction of diabetic hyperketonemia, and others. The Keto diet lowers blood sugar levels and insulin levels, making it a viable diabetes treatment option. As a result, the keto diet could be used as a bridge between diabetes treatment and obesity.²⁵

Ketogenic Diet in Type 2 Diabetes

Hyperinsulinemia causes type 2 diabetes, and carbohydrate consumption immediately affects insulin levels. Protein eating may cause a minor increase in insulin secretion and blood glucose, whereas consuming fat has no significant impact.²⁶ Lean *et al.* direct's study. It was discovered that weight loss could result in diabetes remission in roughly 46% of cases after 12 months. Furthermore, this ignores the problem of diabetics who aren't overweight.²⁷ Glycemic control should be the first goal for both type 1 diabetes and type 2 diabetes, according to Feinman *et al.* Carbohydrate limitation has been shown to assist diabetes patients' blood indicators even if they don't lose weight. This is significant since many diabetics are not fat but must regulate their blood glucose levels. Because large jumps in blood glucose are less likely, the benefit of carbohydrate limitation in type 1 diabetes lowers the inaccuracy in calculating insulin quantity to meet excessive blood glucose level.²⁸ The use of a low-carbohydrate diet to treat diabetes isn't a new or novel concept. Diets were the principal intervention utilized by diabetic patients prior to the advent of insulin. Westman *et al.* investigated the effect of a low-carb ketogenic diet vs a low-glycemic index diet on blood glucose control in type 2 diabetes mellitus as measured by hemoglobin A1C. They enlist 49 people and assign them to various eating plans at random. Both of the groups adhered to group meetings, dietary advice, and some activity suggestion. Hemoglobin A1c, dieting glucose, dieting insulin, and weight loss were improved after both therapies.²⁹ In spite of the fact that there are not many randomized controlled preliminaries assessing the ketogenic diet's impact on diabetes, there are some new case reports. The good findings in these research could be due to the provocation of these individuals who chose or are now following keto diets.³⁰

Act as a Hypoglycemic Agent

Although this analysis revealed that diabetes-related diseases are reversible with a simple dietetic adjustment, focus should be drawn to the potential drawbacks of this type of diet, particularly when you've been following for a long time. For starters, the low carbohydrate diet may be so intense for long-term use for an adult patient, as it could cause complications. Undesirable iatrogenic impact patients with type 2 diabetes mellitus on oral hypoglycemic drugs kept on a keto diet

were at a higher risk of low blood sugar. Hence lowering the hypoglycemic drug dosage should be recommended.³¹ Because of the way in the perioperative period, there would be an expanded catabolic condition and expanded oxidation stress that might adversely affect the eventual outcome. Those recorded for bariatric medical procedure who were set on a low starch ketogenic diet had a higher metabolic after effect than the individuals than those who weren't set on such a diet.³²

Keto Diet Helps in Weight Loss

Many studies had demonstrated the beneficial effects of a keto diet for type 2 diabetic patients, including weight reduction, diminishing hba1c, correcting nephrology, improving lipid profiles, and possibly reversing diabetic neuropathy and retinopathy.³³ Carbohydrate limitation can also boost energy expenditure, which is a key aspect of obesity research that has traditionally been pursued with medications and exercise. In a 20 week of weight-loss-conservation feeding study involving 163 approx participants, those assigned to a lower-carbohydrate (20%) versus a higher-carbohydrate (60%) diet had higher energy use (200–250 kcal/d), affirming the carb insulin model's forecast of impact alteration by insulin emission.³⁴

Foods in the Ketogenic Diet

Meat, turkey, chicken, shellfish, fish and egg were allowed in unlimited quantities; cheese (2–4 ounces per day), vegetable salad (2 cupfuls per day), and non-starchy veggies were allowed in definite quantities (1 cupful per day). The participants were advised to drink at least 6 glasses of fluids daily. During the first two weeks, drinking water 2–3 times a day was recommended to reduce the risk of side effects.²⁹ Keto diets are much more effective than conventional calorie-restrictive dieting for fat loss and improved blood sugar control in diabetic patients,³⁰⁻³⁴ and in some diabetic instances, they allow for the withdrawal or decrease of medications.⁵ In one study, fat-free keto diets (100 gm of protein per day and no fat or carbohydrates) allowed max patients to stop taking insulin after just one week.³⁴

Glycemic Control by Ketogenic Diet

Learning of the diet would assist you in supporting people around you and avoid treatment miscalculations which can sabotage the diet's remedial effects. The keto diet is higher in fats, acceptable proteins and very lower carbs diet that a child neurologist uses gradually to cure children with delicate-to-control traumatic brain injuries.³⁵ In order to switch from using glucose as an energy source to using ketone bodies derived from fat, a breakdown in nerve function must occur. For the longest time, the diet was used to help kids who had suffered brain damage. Alzheimer's disease, obesity, Parkinson's disease, type 2 diabetes, and cancer³⁶ are just some of the diseases being studied in relation to this diet.

Further research defines determining elements, such as the amount of pancreatic beta-cell reserve and insulin resistance,³⁷ that affect the time it takes to achieve glycaemic control in type 2 diabetes with any of these methods. The length and intensity of carbohydrate restriction for the purpose of maintaining glycemic control must be individualized. Our case study

showed that fasting durations may be shortened once glycemic control was achieved without compromising the patient's ability to maintain stable blood sugar levels.³⁸

Disadvantages of Ketogenic Diet

The short-term effect of the ketogenic diet has been thoroughly explained. thus, due to a deficit of exploration, the long-term health impacts are unknown.³⁹ Major common and moderate short-term bad effects of keto diets are puking, headache, wakefulness, complications with exercise forbearance, constipation, etc. which can also called as "keto flu".⁴⁰ Fatty liver, hypoproteinemia, kidney stone and minerals and vitamin deficit are each long-term side effects. In a study published in Nutrients, researchers discovered that while on a low-carb diet, high-fat, indulging in a high-sugar indulgence (like a large bottle of soda) can actually harm blood vessels.⁴¹

CONCLUSION

This review specifically show that neither calorie limitation nor weight loss is the key working force behind the accomplishment of the ketogenic diet. This review concludes the ketogenic diets have a favourable effect in fat diabetic persons after long-time use. Then, it also reveals that, after adding it's therapeutic effectiveness, low-carb diets are safe to employ in obese diabetic people for a long period of time. The low-calorie keto diet bettered glycemic management in patient having type 2 diabetes, similar that diabetic medicines were stopped or lowered in maximum participants. Because the low-calorie keto diet could be actually efficient at lowering down blood glucose, cases on diabetes drug who so ever use this diet should be under medical supervision or able to adjust their medicine. Dietetic modification used for advancements in glycemic control and medicine reduction with type 2 diabetic patient. A diet lower in carbs used for higher enhancements of glycemic control and medicine reduction or canceling than lower glycemic level diet. Style of living modified by low carbohydrates is very useful for enhancing and treating type 2 diabetic persons. This weight loss method is based on the low carbohydrate keto diet, which is most efficient in lowering body weight and enhancing glycemic control more than a normal hypocaloric diet with safeness and forbearance for type 2 diabetes mellitus. The low carbs keto diet improves glycemic control in type 2 diabetic patients till the point that most of the participant were able to stop or modify their diabetic medicines. Patients on diabetes medication who take the low carbs keto diet should be under very strict medical monitoring or capable of changing their prescription because the low carbs keto diet could be quite effective for decreasing blood glucose. The low carbs keto diet improves glycemic control in people suffering from type 2 diabetes. Patients on diabetic medication who take the low carbs keto diet could be under strict medical monitoring or capability of changing their prescription because the low carbs keto diet can be quite effective for decreasing blood glucose.

REFERENCES

1. Veech RL. The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis,

- ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism. Prostaglandins, leukotrienes and essential fatty acids. 2004 Mar 1;70(3):309-19. <https://doi.org/10.1016/j.plefa.2003.09.007>
2. International Diabetes Federation IDF Diabetes Atlas, 8th ed. Brussels, Belgium: International Diabetes Federation. [(accessed on 31 March 2019)];2017 Available online: <http://www.diabetesatlas.org>
 3. Ellen Davin. The ketogenic diet for type 1 diabetes: Reduce Your HbA1c and Avoid Diabetic Complications. Cheyenne(WY):Gutsy Badger. Copyright © 2017, 2015
 4. Joshi S, Ostfeld RJ, McMacken M. The ketogenic diet for obesity and diabetes—enthusiasm outpaces evidence. *JAMA internal medicine*. 2019 Sep 1;179(9):1163-4. doi:10.1001/jamainternmed.2019.2633
 5. Yancy WS, Foy M, Chalecki AM, Vernon MC, Westman EC. A low-carbohydrate, ketogenic diet to treat type 2 diabetes. *Nutrition & metabolism*. 2005 Dec;2(1):1-7. <https://doi.org/10.1186/1743-7075-2-34>
 6. Paoli A, Moro T, Bosco G, Bianco A, Grimaldi KA, Camporesi E, Mangar D. Effects of n-3 polyunsaturated fatty acids (ω -3) supplementation on some cardiovascular risk factors with a ketogenic Mediterranean diet. *Marine drugs*. 2015 Feb 13;13(2):996-1009. <https://doi.org/10.3390/md13020996>
 7. Masood W, Annamaraju P, Uppaluri KR. Ketogenic diet. *InStatPearls [Internet]* 2021 Nov 26. StatPearls Publishing.
 8. Batch JT, Lamsal SP, Adkins M, Sultan S, Ramirez MN. Advantages and disadvantages of the ketogenic diet: a review article. *Cureus*. 2020 Aug 10;12(8). 10.7759/cureus.9639
 9. Li Z, Heber D. Ketogenic diets. *Jama*. 2020 Jan 28;323(4):386-. doi:10.1001/jama.2019.18408
 10. Moriconi E, Camajani E, Fabbri A, Lenzi A, Caprio M. Very-low-calorie ketogenic diet as a safe and valuable tool for long-term glycemic management in patients with obesity and type 2 diabetes. *Nutrients*. 2021 Feb 26;13(3):758. <https://doi.org/10.3390/nu13030758>
 11. Jagadish S, Payne ET, Wong-Kisiel L, Nickels KC, Eckert S, Wirrell EC. The ketogenic and modified Atkins diet therapy for children with refractory epilepsy of genetic etiology. *Pediatric neurology*. 2019 May 1;94:32-7. <https://doi.org/10.1016/j.pediatrneurol.2018.12.012>
 12. Mohorko N, Černelič-Bizjak M, Poklar-Vatovec T, Grom G, Kenig S, Petelin A, Jenko-Pražnikar Z. Weight loss, improved physical performance, cognitive function, eating behavior, and metabolic profile in a 12-week ketogenic diet in obese adults. *Nutrition research*. 2019 Feb 1;62:64-77. <https://doi.org/10.1016/j.nutres.2018.11.007>
 13. Kuchkuntla AR, Shah M, Velapati S, Gershuni VM, Rajjo T, Nanda S, Hurt RT, Mundi MS. Ketogenic diet: an endocrinologist perspective. *Current nutrition reports*. 2019 Dec;8:402-10. <https://doi.org/10.1007/s13668-019-00297-x>
 14. Gupta L, Khandelwal D, Kalra S, Gupta P, Dutta D, Aggarwal S. Ketogenic diet in endocrine disorders: Current perspectives. *Journal of postgraduate medicine*. 2017 Oct;63(4):242. https://doi.org/10.4103%2Fjpgm.JPGM_16_17
 15. Brownlee M, Hirsch IB. Glycemic variability: a hemoglobin A1c-independent risk factor for diabetic complications. *Jama*. 2006 Apr 12;295(14):1707-8. doi:10.1001/jama.295.14.1707
 16. Hussain TA, Mathew TC, Dashti AA, Asfar S, Al-Zaid N, Dashti HM. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition*. 2012 Oct 1;28(10):1016-21. <https://doi.org/10.1016/j.nut.2012.01.016>
 17. Cotter DG, Schugar RC, Wentz AE, André d'Avignon D, Crawford PA. Successful adaptation to ketosis by mice with tissue-specific deficiency of ketone body oxidation. *American Journal of Physiology-Endocrinology and Metabolism*. 2013 Feb 15;304(4):E363-74. <https://doi.org/10.1152/ajpendo.00547.2012>
 18. 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 & diabetes*. 2016 Sep;6(9):e230-. <https://doi.org/10.1038/nutd.2016.36>
 19. Paoli A, Cenci L, Grimaldi KA. Effect of ketogenic Mediterranean diet with phytoextracts and low carbohydrates/high-protein meals on weight, cardiovascular risk factors, body composition and diet compliance in Italian council employees. *Nutrition journal*. 2011 Dec;10:1-8. <https://doi.org/10.1186/1475-2891-10-112>
 20. American Diabetes Association. 5. Lifestyle management: standards of medical care in diabetes—2019. *Diabetes care*. 2019 Jan 1;42(Supplement 1):S46-60.
 21. Nusca A, Tuccinardi D, Proscia C, Melfi R, Manfrini S, Nicolucci A, Ceriello A, Pozzilli P, Ussia GP, Grigioni F, Di Sciascio G. Incremental role of glycaemic variability over HbA1c in identifying type 2 diabetic patients with high platelet reactivity undergoing percutaneous coronary intervention. *Cardiovascular Diabetology*. 2019 Dec;18:1-9. <https://doi.org/10.1186/s12933-019-0952-8>
 22. Leow ZZ, Guelfi KJ, Davis EA, Jones TW, Fournier PA. The glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults with Type 1 diabetes mellitus may be opposed by increased hypoglycaemia risk and dyslipidaemia. *Diabetic Medicine*. 2018 Sep;35(9):1258-63. <https://doi.org/10.1111/dme.13663>
 23. Watanabe M, Tuccinardi D, Ernesti I, Basciani S, Mariani S, Genco A, Manfrini S, Lubrano C, Gnessi L. Scientific evidence underlying contraindications to the ketogenic diet: An update. *Obesity Reviews*. 2020 Oct;21(10):e13053. <https://doi.org/10.1111/obr.13053>
 24. Volek JS, Phinney SD, Forsythe CE, Quann EE, Wood RJ, Puglisi MJ, Kraemer WJ, Bibus DM, Fernandez ML, Feinman RD. Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet. *Lipids*. 2009 Apr;44:297-309. <https://doi.org/10.1007/s11745-008-3274-2>
 25. Kumar S, Behl T, Sachdeva M, Sehgal A, Kumari S, Kumar A, Kaur G, Yadav HN, Bungau S. Implicating the effect of ketogenic diet as a preventive measure to obesity and diabetes mellitus. *Life sciences*. 2021 Jan 1;264:118661. <https://doi.org/10.1016/j.lfs.2020.118661>
 26. Nuttall FQ, Gannon MC. Plasma glucose and insulin response to macronutrients in nondiabetic and NIDDM subjects. *Diabetes care*. 1991 Sep 1;14(9):824-38. <https://doi.org/10.2337/diacare.14.9.824>
 27. Lean ME, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. *The Lancet*. 2018 Feb 10;391(10120):541-51. [https://doi.org/10.1016/S0140-6736\(17\)33102-1](https://doi.org/10.1016/S0140-6736(17)33102-1)
 28. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, Accurso A, Frassetto L, Gower BA, McFarlane SI, Nielsen JV. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition*. 2015 Jan 1;31(1):1-3. <https://doi.org/10.1016/j.nut.2014.06.011>
 29. Westman EC, Yancy WS, Mavropoulos JC, Marquart M,

- McDuffie JR. The effect of a low-carbohydrate, ketogenic diet versus a low-glycemic index diet on glycemic control in type 2 diabetes mellitus. *Nutrition & metabolism*. 2008 Dec;5(1):1-9. <https://doi.org/10.1186/1743-7075-5-36>
30. Ahmed SR, Bellamkonda S, Zilbermint M, Wang J, Kalyani RR. Effects of the low carbohydrate, high fat diet on glycemic control and body weight in patients with type 2 diabetes: experience from a community-based cohort. *BMJ Open Diabetes Research and Care*. 2020 Mar 1;8(1):e000980. <http://dx.doi.org/10.1136/bmjdr-2019-000980>
 31. Feinman RD, Pogozelski WK, Astrup A, Bernstein RK, Fine EJ, Westman EC, Accurso A, Frassetto L, Gower BA, McFarlane SI, Nielsen JV. Dietary carbohydrate restriction as the first approach in diabetes management: critical review and evidence base. *Nutrition*. 2015 Jan 1;31(1):1-3. <https://doi.org/10.1016/j.nut.2014.06.011>
 32. Leonetti F, Campanile FC, Coccia F, Capoccia D, Alessandrini L, Puzziello A, Coluzzi I, Silecchia G. Very low-carbohydrate ketogenic diet before bariatric surgery: prospective evaluation of a sequential diet. *Obesity surgery*. 2015 Jan;25:64-71. <https://doi.org/10.1007/s11695-014-1348-1>
 33. Azar ST, Beydoun HM, Albadri MR. Benefits of ketogenic diet for management of type two diabetes: a review. *J Obes Eat Disord*. 2016;2(2). doi: 10.4172/2471-8203.100022
 34. Ludwig DS. The ketogenic diet: evidence for optimism but high-quality research needed. *The Journal of Nutrition*. 2020 Jun 1;150(6):1354-9. <https://doi.org/10.1093/jn/nxz308>
 35. Freeman JM, Kossoff EH. Ketosis and the ketogenic diet, 2010: advances in treating epilepsy and other disorders. *Advances in pediatrics*. 2010 Jan 1;57(1):315-29. <https://doi.org/10.1016/j.yapd.2010.08.003>
 36. Alarim RA, Alasmre FA, Alotaibi HA, Alshehri MA, Hussain SA. Effects of the ketogenic diet on glycemic control in diabetic patients: meta-analysis of clinical trials. *Cureus*. 2020 Oct 5;12(10). DOI: 10.7759/cureus.10796
 37. Furmli S, Elmasry R, Ramos M, Fung J. Therapeutic use of intermittent fasting for people with type 2 diabetes as an alternative to insulin. *Case Reports*. 2018 Sep 18;2018:bcr-2017. <http://dx.doi.org/10.1136/bcr-2017-221854>
 38. Lichtash C, Fung J, Ostoich KC, Ramos M. Therapeutic use of intermittent fasting and ketogenic diet as an alternative treatment for type 2 diabetes in a normal weight woman: a 14-month case study. *BMJ Case Reports CP*. 2020 Jul 1;13(7):e234223. <http://dx.doi.org/10.1136/bcr-2019-234223>
 39. Ma S, Suzuki K. Keto-adaptation and endurance exercise capacity, fatigue recovery, and exercise-induced muscle and organ damage prevention: a narrative review. *Sports*. 2019 Feb 13;7(2):40. <https://doi.org/10.3390/sports7020040>
 40. Athanasian CE, Lazarevic B, Kriegel ER, Milanaik RL. Alternative diets among adolescents: facts or fads?. *Current Opinion in Pediatrics*. 2021 Apr 1;33(2):252-9. DOI: 10.1097/MOP.0000000000001005
 41. Broom GM, Shaw IC, Rucklidge JJ. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. *Nutrition*. 2019 Apr 1;60:118-21. <https://doi.org/10.1016/j.nut.2018.10.003>