IJBPAS, September, 2022, 11(9): 4112-4126

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

CLINICAL AND NUTRITIONAL EVALUATION OF KETOGENIC DIET IN DIABETES PATIENT: A REVIEW

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Received 16th Oct. 2021; Revised 20th Nov. 2021; Accepted 20th Jan. 2022; Available online 1st Sept. 2022

https://doi.org/10.31032/IJBPAS/2022/11.9.6355

ABSTRACT

A ketogenic diet (KD), an ultimate strategy to prompt metabolic starvation in the body, rigorously restricts the intake of carbohydrates, the significant hotspots for glucose, and increase fat consumption instead. A ketogenic diet was more successful in improving weight control and metabolic parameters related to glycemic and lipid controls in patients with overweight or obesity, particularly those with prior T2DM, when contrasted with low-fat based comparator consumes less calories. In diabetic patient, Low-carbohydrate and ketogenic diets are well known among clinicians and patients, but the appropriateness of reducing carbohydrates intake in obese patients and in patients with diabetes is still debated. So in this review we explored the possible role of ketogenic diets in both clinical and nutritional aspect for management of the both type of diabetes. The ketogenic diets can be powerful choices in patients with

obese and both kind of diabetes, despite the fact that they are not by any means the only accessible dietary methodology for such patients. The use of those diets in patients with type 1 diabetes is still controversial and their long-term safety is still unproven.

Keywords: Ketogenic diet, insulin, glucose, diabetic patient, management, clinical and nutritional

INTRODUCTION

As indicated by Centers for Disease Control and Prevention (CDC), the quantity of individuals with diabetes has nearly significantly increased over the most recent few decades **[1]**. Roughly around 425 million individuals worldwide have diabetes now, which is relied upon to reach to 629 million by 2045 **[2]**. A comparable pattern in diabetes has been seen in Kuwait and other Arab nations **[3]**. Notwithstanding the analyzed cases, a few millions live with undiscovered diabetes and many are at the risk of developing diabetes **[3]**. The direct costs of diagnosed diabetes (about 30.3 million people) and the reduced productivity were $327 billion in the United States alone in 2017 **[1]**. Likewise, the expenses for dealing with the complexities of diabetes add to this economic burden **[4]**. In the last decades, low carbohydrate diets (LCD) and ketogenic diets (KD) have become widely known and popular ways to lose weight, not only within the scientific community, but also among the general public, with best-selling dedicated books or intense discussion on social media networks staying at the top of the diet trend list for years. These dietary methodologies are successful for getting in shape, yet there is developing proof recommending that alert is required, particularly when these weight control plans are followed for extensive stretches of time, or by people of a youthful age or with specific illnesses **[5]**.

Remedial ketosis prompts metabolic variations that may improve cerebrum digestion, reestablish mitochondrial ATP creation, decline receptive oxygen species creation, lessen aggravation, and increment neurotrophic variables' capacity **[9]**. It has been shown that KD impersonates the impacts of fasting and the absence of **[10]** glucose/insulin signal, which advances a metabolic shift towards unsaturated fat use **[11]**. KD can just initiate an unassuming blood ketone level height and requires outrageous dietary starch limitation for keeping up maintained (remedial) levels of ketosis **[12]**. Before the appearance of exogenous insulin for the treatment of diabetes mellitus (type II) in the 1920's, the overall rules for treatment were addressed

simply by dietary adjustments. Previous meta-investigations have demonstrated the adequacy of KD in body weight reduction **[13]**; in any case, fundamental surveys on the impact of KD on weight decrease and glycolipid digestion in patients with DM are as yet restricted. Westman *et al*. **[14]** and Partsalaki *et al*. **[15]** demonstrated that KD improved type 2 diabetes mellitus (T2DM) by lessening the glycemic reaction brought about via starch and improving potential insulin opposition. Leonetti *et al*. **[16]** and Walton *et al*. **[17]** revealed decreased TG and TC with expanded HDL levels after KD utilization for a lipid profile. In any case, discussions are as yet existing; considers uncovered that a low-carb, high-fat eating routine may intensify the lipid profile in patients with diabetes, in spite of the fact that glycemic control improved with hypoglycemic medications **[12]**. Accordingly, the reason for the current survey was to lead on the impacts of a KD in patients with diabetes.

Clinical evaluation of ketogenic diet in diabetes

The possible mechanism for the medical advantage of KD on patients with T2DM is that the extreme restriction of carbohydrate reduces the intestinal absorption of monosaccharide, which prompts lower blood glucose level and lessens the change of blood glucose, and its adequacy on controlling glucose digestion was affirmed by a huge group of evidence **[18, 19]**. Higher decrease amplitudes were reported by Dashti **[20]** and Leonetti *et al*. **[16]** of 5.61 mmol/L (weight random 3.0%) and 3.87 mmol/L (weight random 1.2%), respectively; other reductions in blood glucose were all lower than 1.8 mmol/L. The conceivable justification the higher decrease found in these two examinations could be the higher blood glucose level remembered for the investigations, and furthermore that the normal blood glucose focus was above 10.0 mmol/L, prompting the chance of a bigger decrease; nonetheless, their commitment to the general impact assessments in the meta-investigation was low. The normal changes in fasting blood glucose after the KD uses among the chose considers were −1.29 mmol/L, demonstrating the adequacy of the KD in bringing down fasting blood glucose.

HbA1c viably mirrors the blood glucose control in the past 2−3 months in patients with diabetes. It is accounted for that the risk of cardiovascular dead tissue and miniature vascular complexities decreased by 14% and 37%, individually, when HbA1c diminished by 1%. Consequently, the HbA1c level

showed fundamental clinical importance in assessing the blood glucose control, uncovering the possible issues in the therapy and in this way controlling the remedial schedule **[21]**. Eight of the chose examines showed a decrease of HbA1c after KD utilization, the progressions going from −0.6% to −3.3%; HbA1c diminished <1.5% in most of the examinations remembered for the current investigation other than the examination directed by Walton (−3.3%; weight arbitrary 5.1%). The conceivable clarification for such solid improvement of HbA1c could be that Walton's investigation had enlisted a predetermined number of patients and hence the consistence of patients to KD treatment can be ensured. Also, the considered subjects were recently analyzed diabetic patients who were under dietary administration without taking glucose-bringing down meds; recently analyzed subjects continue well in the examination. Considering the causal factors thoroughly, the above examination showed an ideal decrease in HbA1c. The normal decrease of HbA1c was 1.07 in the current investigation of the chose eight examinations, showing that dietary administration may likewise accomplish the ideal restorative impacts of prescription.

HOMA-IR is considered as a indicator to assess the status of insulin resistance. Insulin opposition as a clinical trait of T2DM is firmly identified with weight. Improving insulin opposition is one of the significant focuses in diabetes treatment **[22]**. Be that as it may, contemplates zeroing in on the job of KD in the improvement of insulin obstruction in patients with diabetes are exceptionally restricted; a large portion of the examinations zeroed in on the impact in fat subjects **[23]**. For example, a controlled clinical preliminary focusing on the impacts of KD utilization in stout individuals without diabetes uncovered that HOMA-IR diminished by about 2.0 after KD utilization for about a month and a half. The current examination showed steady changes in the investigations that included HOMA-IR assessment, with decrease going from −0.4 to −3.4; the justification the huge decrease of 3.4 in the investigation by Tay *et al*. **[24]** is that the populace included was large diabetic patients with BMI higher than 30 kg/m2. Heftiness is firmly identified with insulin opposition; KD utilization is affirmed to be powerful in lessening body weight, and it is normal that KD may improve insulin obstruction in fat diabetic patients. During the ketogenesis, the affectability of the insulin receptor is advanced; along these

lines, KD guarantees the stockpile of essential supplements as well as keeps a negative equilibrium of energy, and lessens the change and decrease of insulin emission brought about by diminished starch consumption too, which in the long run prompts improved insulin sensitivity **[25]**.

Consumption of KD not only improved glucose metabolism, but a large body of evidence has reported that KD improved lipid metabolism as well. Hussain *et al*. **[6]** revealed that KD diminished TG and TC, and expanded HDL level, consequently enhancing the situation with dyslipidemia. In the current examination, eight investigations included showed consequences of lipid digestion in diabetic patients after KD utilization; in any case, just five broke down the TC levels. The current outcomes showed the mean decrease of TG was 0.72 mmol/L, TC was 0.33 mmol/L, and LDL was 0.05 mmol/L, while the increment of HDL was 0.14 mmol/L. The higher abundancy of variety happened in the Dashti *et al*. study **[20]**. This investigation announced that TG decreased by 3.67 mmol/L, TC diminished by 1.88 mmol/L, and LDL decreased by 1.78 mmol/L, while HDL expanded by 0.14 mmol/L. Changes in the sufficiency of the lipid biomarkers were all at the better quality in the above examination. Both glucose and lipid digestion showed extraordinary improvement after KD utilization in such an investigation; the attributes of subjects selected were firmly connected. The examination enlisted 31 corpulent subjects with hyperglycemia, dyslipidemia, and BMI over 30 kg/m2. The benchmark TG, TC, and LDL were higher than those of commonplace patients with T2DM, which may add to the critical changes after the mediation. Utilization of KD showed a huge helpful impact in like manner patients with T2DM, including the Dashti **[20]** study. Problems of lipid digestion are especially solid among patients with insulin obstruction in T2DM. Dyslipidemia is lipotoxic to cells, prompting or potentially exasperating insulin obstruction. Its run of the mill sign is the expansion of TG and free unsaturated fat (FFA) **[26]**. Expanded FFA is a free pathogenic factor for insulin opposition and can build the danger for cardiovascular diseases **[27]**. Accordingly, the improvement of dyslipidemia is useful for directing insulin affectability as well as controlling the event and movement of diabetic complications **[28]**.

Various investigations have affirmed the part of KD utilization in weight decrease in corpulent patients **[29]**; the current meta-examination zeroed in on the impact of KD

on weight decrease in fat diabetic patients. The outcomes showed the normal decrease of body weight was 8.66 kg, midriff periphery was 9.17 cm, and BMI was 3.22 kg/m2, which were reliable with past investigations in nondiabetic patients. We likewise found that KD decreased systolic pulse by 4.30 (95% CI: −7.02 to 1.58) and diastolic circulatory strain by 5.14 (95% CI: −10.18 to 0.10) in patients with T2DM, which potentially advantage from the improvement of body weight **[30]**.

Other than the intercession of glucose and lipid digestion, KD may likewise profit other clinical indications in diabetic patients, including sleep deprivation, chills, blockage, pruritus, deadness of appendages, hypopsia, greasy liver, hypertension, and diminished heart work. The expected symptoms of KD were just referenced in two of the studies **[31]**. remembered for the meta-investigation; along these lines it is difficult to play out an orderly audit as far as the dangers related with KD utilization. In particular, Goday and Leonetti's **[31]** study explored the unfriendly responses of KD. Goday *et al*. **[31]** referenced that weariness, cerebral pain, queasiness and heaving were more normal in the KD diet bunch following a 2-week mediation, while blockage and orthostatic hypotension were more normal following 10 weeks. It was uncovered by Leonetti *et al*. **[16]** that in the beginning phases of applying the KD, patients announced a feeling of appetite, however it very well may be altogether reduced with the advancement of the mediation. Despite the fact that cerebral pain, queasiness, heaving, clogging, looseness of the bowels, and different indications were accounted for during the examination, the manifestations were gentle and gone on for a brief time frame, not identifying with clinical practice.

Nutritional assessment of ketogenic diet in diabetes

Presently it is grounded that the utilization of ketogenic slims down in weight reduction treatment is viable. Over 90% of the diabetic patients are corpulent and here is an immediate connection between type 2 diabetes and heftiness **[32] (Table 1)**. It is shown that an unobtrusive 5% weight reduction can essentially improve the HbA1c levels in fat diabetic subjects. Albeit a few agents recommend that there are no metabolic benefits in low-starch slims down and that weight reduction results from the expanded satiety impact and decreased caloric admission **[33]**, a few different examiners give proves that repudiate the previously mentioned see. Further confirmations propose ketone bodies are

straightforwardly engaged with the adjustment of ghrelin and leptin level that impact hunger **[34]**. As a rule, in light of the current proof the weight reduction impact of LCKD could be because of the decrease in hunger because of higher satiety impact of proteins, consequences for craving control of chemicals like ghrelin and leptin **[34]**, and the immediate craving suppressant activity of the ketone bodies. Additional proof proposes that the weight reduction impact of LCKD could likewise be because of the decrease in lipogenesis and expanded lipolysis, the expanded metabolic prerequisites of gluconeogenesis and the thermic impact of proteins, and diminished resting respiratory remainder because of more noteworthy metabolic productivity in devouring fats **[34]**.

Table 1: Ketogenic diet for diabetes patient

MEAL	MENU
Early morning	**Tea(1 glass) + Biscuits (Nutrichoice -2 pcs)**
Breakfast (9am)	**Oats / Dalia porridge- 1 cup or Oats / Dalia upma- 1 cup /Idli(3pcs)+ Sambar-1 cup / Corn flakes-1cup + Milk (1- glass)**
Mid-morning (11am)	**Apple/ Guava / Orange-(1) without sugar or Tender coconut water-1glass**
Lunch (1pm)	**Parboiled rice-1/2 cup, Soft Roti-2 pcs, Dal-1 cup, Boiled egg curry-2, Mix bhaja -1cup / brinjal bharta/ paneer bharta, Salad- or Mix veg. khichdi- ½ cup, Soft roti- 2 pcs, Soybean curry-1 cup / Paneer curry- 1 cup (4-5 pcs), Salad-1 cup, Bitter gourd/ Ridge gourd**
Snacks (5pm)	**Brown bread sandwich-3 pcs / Non-Veg soup-1 cup**
Dinner (8pm)	**Soft roti- 2 pcs,+ scrambled egg /Santula/ soyabean curry + skimmed milk(1 glass)**

The principle concern in regards to the utilization of ketogenic diet with a high protein and fat substance is that this eating routine will causes unfriendly impacts by adjusting their lipid profile definitely **[35]**. Then again, a few ongoing examinations have shown that a low-carb diet produces critical advantages in the lipid profile **[35]**. Following the organization of a ketogenic diet, there was a decrease in complete cholesterol, expansion in HDL, and diminishing in the degree of blood fatty substances **[36]**. Soaked unsaturated fats that are implied in expanded danger for cardiovascular illnesses and insulin opposition are discovered to be more connected with dietary starch. There is an immediate connection between more significant level of insulin and the enactment of HMG-CoA reductase a vital compound in cholesterol biosynthesis. In this manner, a decrease in dietary starch along with a fitting cholesterol admission will prompt a restraint of cholesterol biosynthesis. Aftereffects of

ongoing investigations have shown that LCKD diminished the degree of triglycerol and LDL cholesterol and expanded the degree of HDL cholesterol **[27]**. Comparable outcomes were acquired when large subjects with elevated cholesterol level and fat subjects with diabetes were treated with LCKD for a more drawn out period. In synopsis, a few examinations on the impact of ketogenic slims down on cardiovascular infection recommend that it is protected to utilize ketogenic diet in diabetic subjects just as in subjects with elevated cholesterol level **[37]**. Notwithstanding the systems of ketogenic activity referenced above, ketogenic slims down are engaged with different other neurotic conditions **[16–20]** like neurodegenerative infections, cerebrum injury, polycystic ovary disorder, malignancy, and osteoporosis.

Ketogenic diet on improving metabolic control

The viability of a ketogenic diet on improving metabolic control in patients with overweight or corpulence, particularly those with basic T2DM, by the by certain constraints should be recognized. Meta-investigation was performed fusing RCTs with various examination plan and control eats less carbs, though generally low-fat based eating regimens. Fluctuating mediation spans were received in included investigations. Some subgroup examination may have been underpowered to identify a contrast between bunches inferable from little example size. Substitute markers were utilized to investigate the metabolic adequacy of a ketogenic diet, for example, serum levels of FG, HbA1c, and lipid segments, rather than assessing more understanding significant endpoints, like cardiovascular and renal occasions, and other weight related dreariness and mortality. Notwithstanding, the discoveries from this meta-investigation as for the effect of a ketogenic diet on those proxy markers can approve and give understanding into the impacts of a ketogenic diet on the more clinically significant endpoints

Obesity has a clear correlation with the incidence of cardiovascular disorders including hypertension, coronary supply route infection, cardiovascular breakdown and unexpected passing, and numerous patients with insulin opposition, the primary etiology of T2DM, will in general have high fatty substance and low HDL levels **[38]**. Thusly, we dissected the effect of a ketogenic diet on lipid controls and cardiovascular danger markers and discovered comparative outcomes to past examinations **[39]** that assessed the impacts of a low-carb diet; our

investigation uncovered that a ketogenic diet diminished fatty substances while expanding all out cholesterol auxiliary to expanded LDL and HDL levels in patients with overweight or corpulence, however no critical changes in other cardiovascular danger markers including pulse, CRP, and SCr were distinguished. Considering low HDL and high fatty substance levels being autonomous danger factors for insulin opposition and cardiovascular problems **[40]**, Analysis recommended that a ketogenic diet has cardioprotective impacts in diabetic patients as the impacts of a ketogenic diet on fatty oil and HDL were considerably huger in diabetic patients. In any case, cardioprotective impacts of a ketogenic diet in patients with stoutness however no T2DM are yet to be resolved because of moderately higher post-mediation levels of LDL and all out cholesterol. Strangely, the investigation directed by Westman *et al*. **[41]** showed that a ketogenic diet changed the sythesis of LDL subclasses, expanding the extent of enormous measured light LDL with cardiovascular defensive impacts while altogether diminishing little estimated thick LDL, which is the essential driver of atherogenesis in the blood vessel intima. In this way, it is imperative to decide if expanded LDL levels saw in patients with heftiness however no T2DM are because of the expansion of huge estimated light LDL, which can possibly add to the cardioprotective impacts by ketogenic consumes less calories. Some forthcoming investigations enrolled on the ClinicalTrials.gov are presently progressing to examine the impacts of ketogenic slims down on the proportion among fatty substance and HDL, and on the piece of LDL subclasses with its drawn out clinical results in cardiovascular diseases.

Side Effects of Ketogenic Diet in diabetic patient

In diabetic patients, because of the adequacy of LCKD, hypoglycemia may happen **[42]** and could bring about a huge decrease in the units of insulin needed to be managed or suspension or decrease in the dosages of oral medications regulated for type 2 diabetes **[43]**. Subsequently, patients the individuals who are on insulin or antidiabetic medications ought to be observed cautiously. Adverse occasions of ketogenic diet incorporate lack of hydration, dyselectrolytemia, and hypovitaminosis **[44]**. Also, short-term LCKD impairs bone mass density and mechanical properties of bone. Therefore, to limit the previously mentioned results, day by day enhancements of electrolytes, multivitamins, potassium citrate and calcium, nutrient D, and minerals ought

to be given during the time of ketogenic diet management. Another side effect of LCKD is the the development of kidney stones and increased production and the decreased excretion of uric acid. This is because of restricted liquid admission and the concealment of thirst by ketone bodies. Likewise, ketone bodies are additionally engaged with the concealment of food admission. Hyperuricemia prompts urate stone formation.

To correct this issue, consideration of 5% carbohydrate composition in the diet is suggested **[45]**. Another concern regarding the ketogenic diet is that the subjects who are on this diet have a reduction in the intake of healthy foods such as products of the soil that contain polyphenols and cancer prevention agents that battle against the free extremists. Type 2 diabetes is related with oxidative pressure and restricting the supply of polyphenols and antioxidants may increase the imbalance of antioxidant-oxidation system in our body. To conquer the present circumstance, it is proposed to enhance the ketogenic diet with concentrates of polyphenols and cancer prevention agents, particularly in patients with type 2 diabetes.

Constipation is likewise a prominent as a result of LCKD, which could be because of the diminished fiber substance and dehydration due to the suppression of thirst by ketones **[46]**. The present situation can be prevented by increasing the fiber content in the diet, increasing fluid intake and utilizing intestinal medicines **[47]**. By and large, investigations of different specialists have convincingly shown that these supplementation and alteration can wipe out the unfavorable impacts LCKD.

CONCLUSION

Low carbohydrate shifts the body to another metabolic pathway that balances out insulin resistance, standardizes blood glucose, glycosylated hemoglobin and hepatic, renal and plasma lipid profile in type 2 diabetic patients. Because of the critical impact of LCKD in bringing down blood glucose level and adding to the decrease of insulin and antidiabetic drug, the diabetic patients on LCKD diet ought to be regularly checked to comprehend the ideal changes for insulin, antidiabetic, and diuretic prescriptions to stay away from hypoglycemia and lack of hydration complications. Also, KDs at various proportions (as indicated specific clinical cases and pathology degree) should be taken into serious consideration as a possible standard therapy in the future treatment panorama of diabetes. Further huge scope, long-term, well-designed randomized trials

are needed on this topic to assess the long-term safety, viability and consistence of lessening dietary CHO in patients with diabetes, and especially with type 1 diabetes, of all ages, and to track down the best dietary arrangement concerning glycemic control, weight reduction, and CV risk in all patients with diabetes.

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