REVIEW ARTICLE

JIACM 2021; 22(1-2): 51-56

Ketogenic Diet – Where are we so far?

Avishkar Agrawal, Sunita Aggarwal**, Raghu RV*, Sandeep Garg**, Praveen Bharti***

Abstract

Ketogenic diet is a normo-caloric diet composed of high fat, low carbohydrates and provides adequate calories. It induces a state of nutritional ketosis in which, under shortage of glucose, there is overproduction of ketone bodies which are used as a source of energy, especially in the Central Nervous System (CNS) as it cannot use fat as an alternative source of energy. Ketogenic diets have been of interest since early 1920s, when they were first tried for resistant epilepsy. Since then the benefits of ketogenic diet have been explored in various other conditions. Many active researches are underway to prove their role in other areas as well. As of our current knowledge, ketogenic diet has proven to be beneficial in: Diabetes, Cardiovascular Diseases, Obesity, Epilepsy. Many other areas have shown promising results as well: improving neurocognitive and motor functions in many Central Nervous System disorders, certain cancers, acne, etc. However, the benefits of ketogenic diet come with certain risks like hypoglycaemia, worsening renal functions, renal stones, gut dysbiosis.

Key words: Ketogenic diet, keto diet, cancer, diabetes, neurological diseases, obesity, cardiovascular diseases, weight loss, insulin resistance.

Introduction

Ketogenic diet (KD) is composed of high fat, adequate protein and low carbohydrates (usually less than 50 g/day)[1]. Despite the change in proportion of its contents, it has a normal calorific value. The carbohydrate content provides less than 10% of total daily calorie requirement. It induces a state of nutritional ketosis in body which has a fasting-like effect in the blood with increased levels of ketone bodies.

KD has been of interest since 1920s when it was used as a therapy for epilepsy by Russel Wilde who also coined the term "ketogenic diet". The novel study by Cahill and colleagues in 1960s showed the metabolic benefits of KD and subsequently the benefits of KD in other areas were explored[2]. KD now have shown to be of proven benefits in obesity and weight loss, diabetes, epilepsy, and cardiovascular disease while there is emerging evidence of it benefits in metabolic syndrome, neuro-motor and neurocognitive functions, cancers, etc.

What makes a ketogenic diet?

KD is a very low carbohydrate diet, rich in fat and provides normal calorific requirement. The carbohydrate component provides < 10 per cent of the daily calorie requirement of a 2,000 kcal diet. This is equivalent to 20 - 50 gms of carbohydrate/day[3].

The high content of fat in KD is kept at a ratio of 4:1 (4 gm of fat for every 1 gm of protein and carbohydrate combined).

There have been a few modifications to the classic KD described above; a summary of different types of diets is given in Fig. 1.

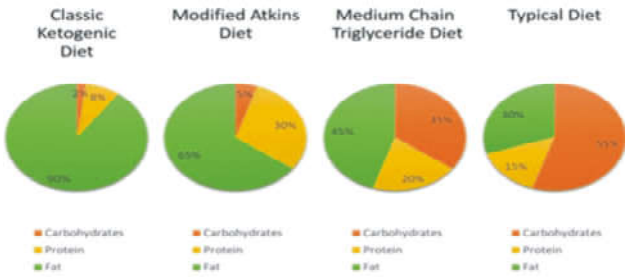

Fig. 1: *Types of very low carbohydrate diet.*

There are a variety of options KD, mostly ones with high fat content. The examples of various food items are:-

1. Nuts and seeds: Almonds, walnuts, cashews, sunflower seeds, chia seeds, pumpkin seeds, flax seeds.
2. Non-starchy vegetables: Green cauliflower, broccoli, tomatoes, mushrooms and peppers.
3. Full-fat dairy: Yogurt, butter and cream.
4. Healthy fats: Coconut oil, olive oil, avocado oil, coconut butter and sesame oil.

Initiation of a ketogenit diet

Initiation of KD involves a careful stepwise approach, with consideration towards pre-existing conditions and

Post-Graduate Resident, **Professor, Department of Medicine, Maulana Azad Medical College, Delhi - 110 002.
Corresponding Author: Dr Sunita Aggarwal, Professor, Department of Medicine, Department of Medicine, Maulana Azad Medical College, Delhi - 110 002. Phone: 9968281414, E-mail: drsunita.mamc@gmail.com.

anticipated nutrient deficiency. Initiation of KD has been explained in Table I.

Table I: Initiation of ketogenic diet.

1. Pre-keto diet counselling and evaluation is required. This is followed by implementation of KD, supplementation, follow-up, monitoring and eventually discontinuing KD.
2. Before starting someone on KD, a detailed history and physical examination, nutritional assessment and laboratory investigations including, renal, thyroid, hepatic, lipids should be checked.
3. Patients who have disorders that are absolute contraindications to KD should be excluded *(Liver failure, pancreatitis, carnitine palmitoyltransferase (CPT)deficiency, carnitine translocase deficiency, pyruvate kinase deficiency and porphyrias*).
4. Risk factors like severe dyslipidemia, renal stones, cardiomyopathy, severe gastroesophageal reflux, and chronic metabolic acidosis can prevent initiation of KD.
5. Patients should be supplemented with essential vitamins and minerals like calcium, magnesium, zinc, selenium, phosphorus, etc.

Metabolic changes in ketosis

After being on KD, there is a drastically reduced carbohydrate consumption, hence the glucose reserves in body becomes insufficient for:-

1. Utilisation by CNS
2. Fat oxidation: This occurs by supply of oxaloacetate from the Kreb's cycle, which is dependent on glucose supply.

After 3 - 4 days without carbohydrate consumption, the CNS derives energy from alternative sources by production of acetyl coenzyme A (CoA)[2].

Acetyl coenzyme A (CoA) is first metabolised to 3-hydroxy-3-methylglutaryl–CoA (HMG CoA) which is normally used for the synthesis of cholesterol. However, during ketosis and relative hypoglycaemia, there are low levels of insulin, which diverts this pathway towards production of ketone bodies (acetoacetate, b-hydroxybutyric acid and acetone). This condition leads to ketonaemia and ketonuria. The pathway has been summarised in a simplified diagram in Fig. 2.

When serum ketone levels reach a concentration of about 4 mmol/l, ketone bodies are then used by tissues as a source

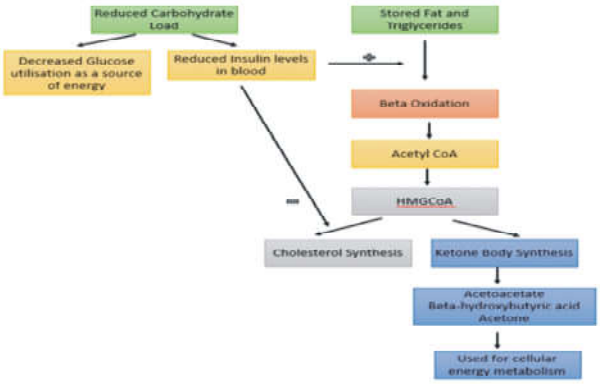

Fig. 2: *Metabolic changes during ketosis.*

of energy.

This state of ketosis can be seen in:-

1. Pathological Ketosis: prolonged fasting, type 1 diabetes mellitus.
2. Physiological Ketosis: while consuming KD.

In physiological ketosis, serum ketone levels reach a maximum of 7 - 8 mmol/l with no change in pH, whereas in uncontrolled diabetic ketoacidosis (i.e., pathological ketosis) it can exceed to more than 20 mmol/l and accompanied lowering of blood pH.

Some unique features to note about this metabolic change are:-

1. Ketone bodies are able to produce more energy than glucose.
2. Although there is a reduction in serum glucose, there is never hypoglycaemia, as glucose is formed from two sources during this time- from glucogenic amino acids and from glycerol liberated via lysis of triglycerides.

Benefits of ketogenic diet

KD has been tried for various conditions in the last century. The first beneficial role of KD was proven in treatment of epilepsy in children in early 1900s. However, it was only after the pioneering work of Cahill and colleagues in 1960s that highlighte the metabolic effects of KD and subsequently the benefits of KD in other area were explored. KD have proven role in certain conditions whereas in others, supportive evidence is there and further studies are being done. These conditions are summarised in Table II.

Table II: Benefits of Ketogenic Diet

Proven Benefit	Emerging Evidence
Epilepsy	Neurological Diseases
Diabetes	Cancer
Weight Reduction	Acne
Cardiovascular Risk	Polycystic Ovarian Syndrome (PCOS)
	Chronic Kidney Disease
	Crohn's Disease
	Respiratory Diseases

1. Weight Loss: There is very strong evidence of the role of KD in weight loss. However, the exact mechanism of weight loss is still not completely understood. There are several proposed mechanisms, the list of which has been ordered below (in order of their supportive evidence):-
   i. Appetite reduction due to satiety effect and also a direct suppressant action on diet[4].
   ii. Reduction in lipogenesis and increased lipolysis[5,6].
   iii. Fat consumption has greater metabolic efficiency by reducing respiratory quotient[7,8].
   iv. Increased metabolic costs of gluconeogenesis and the thermic effect of proteins[9,10]. (Level of evidence, LOE: 3)
2. Cardiovascular benefits: Recent studies have shown clear cardiovascular benefits from KD. The benefit seems to be due to reduction of levels of atherogenic molecules in body. The key metabolic changes that reduce cardiovascular risks are:-
   i. Reduced cholesterol synthesis: Nutritional ketosis decreases the blood Insulin levels, which otherwise on a carbohydrate-rich fed diet, causes cholesterol synthesis (Fig. 2).
   ii. KD increases the levels of high-density lipids[8].
   iii. KD increases the volume of very-low-density- lipid molecules, which reduces the cardiovascular risk, as smaller LDL particles are considered to have more atherogenic potential[11].
   iv. KD also decreases the triglyceride level[12]. (LOE: 3)
3. Insulin Resistance: In conditions with carbohydrate intolerance due to Insulin resistance (e.g., Type-2 Diabetes Mellitus, Metabolic Syndrome, PCOS), the pathophysiology of the disease revolves around hyperinsulinemia. Due to insulin resistance, the skeletal muscles are not able to utilise glucose for their energy needs. High insulin level leads to diversion of this unutilised glucose to liver where it is converted to fatty acids (*de novo* lipogenesis).

   KD, by reducing the carbohydrate load of the body, has shown beneficial effects both in improving biomarkers of risk of disease (i.e., Fasting Plasma Glucose, HbA1c) and also improving insulin sensitivity[13,14]. Several recent studies have confirmed the benefits of KD. In one of the studies, there was reduction of HbA1c levels from pre-treatment 10.5%, to 9.3%, 8.1%, 7.2% and 6.6% over 4 months, solely based on KD without any pharmacological interventions[15]. (LOE: 5)
4. Neurological diseases: KD has shown to be useful in many neurodegenerative and neurocognitive conditions. This is an area of ongoing research and many potential benefits have been proposed from KD. Multiple mechanisms have been proposed which centre around improvement in energy utilisation by cells, and increased mitochondrial biogenesis which then improves synaptic transmission, and improved membrane excitability. Some of the conditions where KD have shown benefits are:-
   i. Epilepsy: KD has been used historically for refractory epilepsies[2]. Based upon the available evidence, a 2018 expert consensus panel recommended that KD therapy should be offered to children with drug-resistant epilepsy after unsuccessful treatment trials of two antiseizure drugs[16]. Several hypotheses have been put forward to explain the mechanism of action of KD: (1) anticonvulsant effect of ketone bodies; (2) a reduced excitability of neurons by ketone bodies[17]; (3) an effect on the mammalian target of rapamycin pathway(mTOR)[18].

      The efficacy of KD was reported in a recent review where studies showed marked reduction (30 - 40%) in seizures, and was also reported that the effects were comparable to modern antiepileptic drugs, atleast in children. (LOE:1)
   ii. Alzheimer's disease: Recent studies have shown that KD has resulted in gain in daily motor activity and also improved cognitive function. It is proposed that KD causes reduction in deposition of amyloid proteins in neurons and improved the neuronal energy utilisation[19]. (LOE: 5)
   iii. Amyotrophic Lateral Sclerosis (ALS): Mitochondrial dysfunction in energy production is the key pathologic mechanism in this disease. KD have shown improvements in energy utilisation and have resulted in longer maintenance of motor function[20]. (LOE:7)

iv. Parkinson's Disease: Although not many studies have been done and benefits remain uncertain early results have shown improvement in motor functions by protection of dopaminergic neurons from degeneration[21,22]. (LOE:7)

v. Others: Apart from the above, KD has also shown benefit in various other conditions, although more data is needed before accepting KD as a treatment alternative. The following diseases where KD have shown potential benefit:-

- Angelman Syndrome
- Mitochondrial myopathy
- Rett Syndrome
- Spinal Cord Injury and Traumatic Brain Injury
- GLUT1 deficiency: Ketogenic diet can be initiated once the diagnosis of GLUT1 deficiency syndrome in paroxysmal exercise-induced dystonia is confirmed[23]. (LOE: 1)

5. Chronic Kidney Disease (CKD): Traditionally, a hypoproteinaemic diet is proposed for CKD. However, recent trials have proved KD are effective in ameliorating metabolic disturbances in CKD, delaying the initiation of dialysis by almost 1 year and slowing down the rate of decline in renal function by 57%[24]. (LOE: 7)

6. Crohn's Disease: Crohn's disease is known to be characterised by a progressive worsening of symptoms. Standard therapies may result in a temporary symptom relief but are accompanied by significant side-effects. In one of the studies, an advanced state of Crohn's disease was treated with KD. It was able to reverse the cluster of symptoms and abnormalities associated with the disease by normalising the intestinal permeability[25]. (LOE:7)

7. Cancers: Preliminary data points towards potential benefits in certain cancers. This is thought to be achieved by inhibition of insulin, which otherwise causes cellular proliferation by Insulin/IGF-1 pathway. KD also results in "glucose starvation" of cancer cells[26].

8. Acne: KD reduces acne by decreasing IGF-1 Levels. This results in reduction in (a) androgen-mediated production of sebum, (b) excessive desquamation of the follicular epithelium, (c) proliferation of basal keratinocytes and (d) *P. acne* colonisation and hence inflammation[27]. (LOE:7)

9. Respiratory functions: KD results in more fat oxidation to meet energy requirements, which leads in turn to reduced respiratory exchange ratio and of metabolic carbon dioxide output, and a decrease in arterial carbon dioxide partial pressure. These effects might be useful in respiratory failure; however, this aspect of KD remains to be investigated.

Risks of ketogenic diet

Much of the risks proposed to be associated with KD have come from the trials on paediatric patients treated for epilepsy. Some of the common problems associated with KD are:-

1. Ketone Flu: The most common short-term side-effects, include nausea, vomiting, dizziness, headache, insomnia, fatigue, referred to as keto flu which resolve in a few days to weeks[28].

2. False-positive breath alcohol test: Due to ketonaemia, acetone in the body can sometimes be reduced by dehydrogenase which can give a false positive alcohol breath test result.

3. Hypoglycaemia: KD can also cause hypoglycaemia in certain patients who have risk factors for the same (older age, previous history, on OHAs)[29].

4. Gastrointestinal system: KD have shown to cause diarrhoea, vomiting, abdominal discomfort in some patients. KD causes gut dysbiosis by reducing the supply of carbohydrate to gut biota, which in turn results in reduced fermentation in the gut leading to decreased butane levels which is thought to decrease inflammation. This may cause many gut inflammatory diseases[30].

5. Bone and calcium metabolism: KD has shown to decrease bone mass and cause frequent fractures. In addition. KD has also shown to increase the incidence of renal stones[31].

6. Cardiovascular: there have been case reports of patients developing cardiomyopathies secondary to nutritional deficiencies (e.g., Selenium and others)[32]. Some reports have even shown development of arrythmias.

7. Haematological: KD has shown to cause bone marrow suppression and anaemia[33].

Conclusion

KD is a low carbohydrate, fat-rich, and adequate calorific value diet. It has proven benefits in weight loss, diabetes, reducing cardiovascular risks, epilepsy. There is emerging evidence of a potential role in – Motor function improvement in ALS; Alzheimer's; Parkinson's Disease, and several other neurological diseases. KD has also shown benefit in cancers, acne, CKD, IBD. However, more study

needs to be done before any conclusive statement. The initiation of KD needs to be supplemented with key essential minerals and vitamins. KD has certain side-effects and should be avoided in at-risk patients.

Annexure 1: Levels of evidence(LOE)

Level of evidence (LOE)	Description
Level I	Evidence from a systematic review or meta-analysis of all relevant RCTs (randomised controlled trial) or evidence-based clinical practice guidelines based on systematic reviews of RCTs or three or more RCTs of good quality that have similar results.
Level II	Evidence obtained from at least one well-designed RCT (e.g., large multi-site RCT).
Level III	Evidence obtained from well-designed controlled trials without randomisation (i.e., quasi-experimental).
Level IV	Evidence from well-designed case-control or cohort studies.
Level V	Evidence from systematic reviews of descriptive and qualitative studies (meta-synthesis).
Level VI	Evidence from a single descriptive or qualitative study.
Level VII	Evidence from the opinion of authorities and/or reports of expert committees.

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