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Mini Review

# Sarcopenia: New Perspectives of Use of Ketogenic Diet in Endocrine Dysfunctions - How to Use with Indications and Contraindications

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## Abstract

Ketogenic diet (KD) consists of a diet which is rich in high fat, has enough protein and low carbohydrates, which effectively causes nutritional ketosis. This has been accepted for long that it has antiepileptic efficacy for which therapeutic use is employed for treatment of refractory epilepsy. This minireview is basically done for the use of KD in some endocrine disorders like diabetes mellitus (DM), obesity, polyvcystic ovary syncrome (PCOS)and metabolic syndrome. Although KD is mainly animal protein based, here we have considered the Indian version of KD in view of food habits of Indians. KD is effective in cardiac preconditioning for ischaemia, give better oxygenation in patients having respiratory failure. Also glycaemic control gets better in DM, which is accompanied by marked weight loss and similarly weight loss is seen in obesity in lieu of improved satiety explained by multiple mechanisms, along with weight loss, improved hormonal parameters in PCOS. Although one contraindication is use of SGLT inhibitors along with KD in DM patients in view of inherent ketogenic action of same, one recommends mineral supplementation along with KD. Ketones have been proposed as super metabolic fuel because of which KD is thought of as a dietary therapy in DM and obesity.

**Keywords:** KD; Epilepsy; DM; Obesity; PCOS; Metabolic Syndrome; SGLT Inhibitors

## Introduction

Ketogenic diet (KD) comprises of a high -fat, enough protein, and low carbohydrate diet. Since availability of carbohydrates is low, body burns fat instead of carbohydrates for providing energy. Liver converts fats into fatty acids, and as a result produces ketone bodies (KB), that replace glucose as a primary energy source. Accumulation of ketones in blood as a result of dietary changes is also called nutritional ketosis (NK) [1].

Since its inception in 1920, further work has been done regarding mechanism of action of KD and usefulness in different clinical scenario. Having multiple actions on the central nervous system, its cellular metabolism along with metabolic pathways, KD has been found to be efficacious in different neurological disorders like traumatic brain injury, acne, cancers and metabolic disorders [2-7]. Some think ketones can be used as super metabolic fuels, in view of its effects on cellular metabolism in different tissues.

## Methods

For this review we included data and relevant information obtained through a PUBMED database search for articles published in English from 1978-2017, which included the MeSH terms ketogenic diet (KD), obesity, type 2 diabetes mellitus (T2DM), Metabolic syndrome, poly cystic ovary syndrome (PCOS), effect on heart, central nervous system (CNS), respiratory system, kidney to update our knowledge regarding the effect of KD on heart, CNS, respiratory system and how to use KD in different endocrine disorders.

## Results

The electronic search included a total of 578 articles, of which 284 pertained to KD in T2DM, 165 to obesity, 121 to metabolic syndrome, and 50 to PCOS. After excluding repeated articles and doing counter search for references we selected a total of 69 articles for this review. No meta-analysis was done.

The aim of this review is to consider the role of KD in different endocrine disorders, that include obesity, diabetes, PCOS etc. Its use clinically along with its contraindications along with where complete caution needs to be exerted is considered. Both glucose and fatty acids get metabolized into acetyl coenzyme A(CoA), that is produced by incomplete metabolism of free fatty acids (FFA's) in the liver where they get entry into the citric acid cycle or tri-

carboxylic acid cycle by condensing with oxaloacetate, that is coming from pyruvate. Since glycolysis decreases considerably after intake of KD in lieu of low carbohydrates there is non availability of oxaloacetate, that can condense with acetyl Co A, that is produced from fatty acid metabolism. Thus acetyl Co A gets shunted towards ketogenesis=>formation of ketones [8], which are beta hydroxyl butyric acid (β OHB), acetoacetate and acetate, that can cross the BBB for giving brain an alternate source of energy. KB's can get easily used by heart, muscle and renal cortex, but brain uses it only following prolonged starvation. Since red blood cells (R. B. C's) do not have mitochondria they can't use them. Similarly, liver can't use it in view of absence of enzyme thiophorase [9].

Degree of increase in KB in a person varies with different physiological factors like body fat percentage, body mass index (BMI), along with resting metabolic rate [1]. Normally KD is safe as concentrations of ketones, seen is much less than the amounts, one encountered in patients of diabetic ketoacidosis and hence there is no change in blood pH seen with a KD. One fact is that right from birth human babies receive colostrums which is ketogenic, meeting all requirements of the baby [10].

Possibly this diet helps in greater loss of fat, preserving lean body mass. The change is brought about by decrease in plasma insulin levels [11,12]. By supplementation with aminoacids and whey proteins one can decrease the risk of loss of lean body mass and sarcopenia [13,14]. Induction of fibroblast growth factor 1(FGF1) gene by KD have been shown by different studies. This FGF1 regulates lipolysis, serum phosphate, active vitamin D along with triglyceride clearance in the liver [15,16].

## Effects of KB on various systems

KB, develops more adenosine triphosphate (ATP) energy, as compared to glucose or fatty acids by causing a reduction of the mitochondrial nicotinamide adenine dinucleotide couple along with oxidation of the coenzyme Q Couple. It is seen that 100g of acetoacetate produces 9. 4kg of ATP, while 100g of 3 hydroxy butyric acid gives 10. 5kg ATP, and in contrast 100g glucose produces only 8. 7kg ATP. Thus body can develop enough fuel development, while calories are lost [10]. Further KB reduces free radical damage and increases antioxidant capacity by activating NF E2-related factor2, that upregulates transcription of genes, which are involved in prevention of oxidation damage.

## Effect on the central nervous system

Evidence has been seen regarding KB's having a therapeutic role in a lot of neurological problems. This could bring about the neuroprotective effect by affecting the cellular energy usage. NK improves both physical along with cognitive performance, besides improving cerebral function along with improving survival in rats and mice that are anoxic. In humans it improves posttraumatic metabolism. In treating epilepsy KD has become an important aspect with drug therapy in allover world. Also, the move from glucose to KB in terms of bioenergy can influence brain tumors by an integration of ant inflammatory pathways. There is increased phagocytic activities of macrophages, antiangiogenic, along with proapoptotic mechanisms which decrease tumor energy metabolism along with glycolytic energy which is needed for the growth of a tumor [18].

## Effect on heart

The heart muscle utilizes energy from various substrates in the form of fuel, having preference for FFA's which is before glucose, KB, lactate, pyruvate. glycogen, and amino acids. NK's leads to a shift of cardiac fuel metabolism from fat/glucose oxidation to fuel from KB that is more efficient in energy along with improving the work efficiency of the myocardium along with its function [10]. In view of the decreased ability for oxidation of fatty acids in the failing heart there is shift to KB over the normal FA, for oxidative ATP production. This prevents free radicals causing injury, increases energy reserves of heart, along with increasing Acetyl CoA amount of the myocardium and further increases the utilization of oxygen consumption to work efficiency at the mitochondrial level in the myocardium that is in danger along with increasing myocardial metabolism [19, 20]. In animals it has been demonstrated that the ischaemic tissue damage following myocardial infarction or stroke is prevented =>much smaller ischaemic, necrotic lesion area [21,22]. An increase in mitochondrial numbers, with better toleration of ischemia with a faster recovery of heart function has been demonstrated on electron microscopy studies in cases where reperfusion is done in rats that are fed KB, and hence might be cardioprotective [23].

## Effect on respiratory system

With KD glucose synthesis requirement in liver is reduced, which further spares its precursor, i. e muscle derived amino acid and reduces apoptosis in lung cells in rodents in shock. Death of lung cells in response to haemorrhagic shock is reduced. Also, it

helps in respiratory problems in a scenario where oxygen supply or substrate utilization is not enough [17]. Respiratory exchange ratio, carbon dioxide output and carbon dioxide end tidal partial pressure is reduced that helps in patients having increased arterial carbon dioxide partial pressure because of respiratory insufficiency or failure [24].

## How to use KD

### Selection of patient and assessment before KD

A detailed history and general physical examination, some important laboratory tests, nutritional assessment is needed besides counseling. It's both the patient as well as family members who need this counselling. There are absolute contraindications in patients having specific metabolic disorders for KD. Also certain factors that might complicate like renal stones, patients with severe dyslipidemia, marked liver disease, failure to thrive, marked gastroesophageal reflux, decreased oral intake, chronic metabolic acidosis, cardiomyopathy might be relative contraindications [25]. Therapeutic drugs like many anticonvulsants might have increased carbohydrate content which should be changed to preparations that have lower carbohydrate content if it is possible. Multivitamins need tobe added that have enough doses of essential minerals along with calcium supplements before starting KD [26].

### How to Initiate KD

Certain dietary instructions are needed that is decrease intake of carbohydrate to < 20g/day, in addition to increasing fats/oils besides supplementing nutrition, that ensures adequate calorie intake that is enough for the individual. Total number of calories to be given depends on the body measures, previous dietary patterns of food intake, along with physical activity done. One example of how menu should be planned for vegetarians is at breakfast -cheese/paneer pakora, coffee/tea that is mixed with coconut oil, cream and butter or coffee with cream/coconut oil, grilled mushrooms with buttered vegetable, scrambled tofu, coconut milk or almond oil.

In mid-morning mushroom and onion frittata, cabbage rolls with coconut, apple crumbpie with walnut crush cream of tomato soup with stir fried broccoli and cheese crackers.

Lunch -spinach pancakes made of flaxseed flour having lots of cheese, cauliflower curry in coconut milk and coconut oil, soya nugget curry, chilli beans with sour cream, cheese and salsa, tofu puddings having full fat yoghurt, simple salad stir fried in butter topped with lots of cheese, red channa salad having olive oil dressing.

Evening-vegetable spring rolls wrapped in lettuce having peanut sauce, pumpkin smoothie with coconut oil, carrot and cucumber sticks having peanut butter, cheesy muffins topped with strawberries and blueberries.

Basically, the diet is planned so that it gives 80-90%of energy from fat in a ratio of grams of fat to gram of protein +carbohydrate as 4:1, meaning 4 g of fat to1g of protein +carbohydrate like a 1500 kcal diet can contain 133. 5g fat with 55g protein + 20g carbohydrate.

This diet needs modification in patients having poor diet toleration, along with frequent gastrointestinal (GIT) symptoms [25-32].

There is flexibility of using long chain triglycerides (LCT) or medium chain triglycerides (MCT) in use of KD. Adding omega -3 fatty acids to same has additional benefits [33]. Fat rich diet is given along with low carbohydrate fruits along with vegetables in each meal. Diets that are homemade having liquid fat added, supplemented with micronutrients or commercial formulas like Ketocal, Ross carbohydrate free soy Formula base with iron might be used [25,26].

No fluid restriction is needed, and routine exercises can be continued. Multivitamins and multimineral preparations which are carbohydrate free or contain minimal carbohydrate should be given for prevention of nutritional deficiencies. Important nutrients needed with KD are calcium along with vitamin D, selenium, zinc, magnesium and phosphorus [29]. One should keep monitoring the diet for examining the benefits along with any risks.

That the management of diet is correct one needs to monitor urinary ketones. Also, patients on KD need to monitor their serum glucose, total protein, albumin, total triglycerides, total cholesterol and serum creatinine every 3 months along with yearly bone density, renal ultrasound, carnitine, selenium levels along with ECG for prevention of long term effects like nephrolithiasis, hyperlipidemia, osteoporosis, carnitine deficiency along with cardiomyopathy.

Though very low carbohydrate KD in morbidly obese patients kept for laparoscopic bariatric surgery has been found to be safe and effective, enough data is still not available on its use before BS for managing morbid obesity. Mostly use of restricted energy diets to get preoperative weight loss is recommended for decreasing the risk of postoperative complications, decrease liver volume and fat content in obese patients for improving patient outcome.

The KD can be stopped abruptly in case of an emergency but better is to gradually taper over 2-3 months decreasing the ketogenic ratio from 4:1-3:1-2:1. Calories and liquids can be increased at will, and larger amounts of carbohydrate foods and nutritional supplements are readded once urinary ketones are lost [25].

## Use in Endocrine Conditions

In view of the effects of this KD on caloric intake, body weight, lipid changes, glucose level changes along with insulin sensitivity, it calls for its use in treating obesity, metabolic syndrome along with type2 diabetes mellitus (T2DM). Further there is influence of different hormones on ketone metabolism like insulin glucagon, cortisol, growth hormone and catecholamines [34].

## Role in T2DM

Different types of dietary changes have been demonstrated to make the glycaemic control better e. g low calorie diet, low fat diet, low protein diet, high protein diet along with low glycaemic load diet [35]. With the carbohydrate being the important macronutrient of diet that increases blood glucose levels, has been aimed by many that decreasing carbohydrate content in the diet might help in improving glycaemic load, improve therapeutic antidiabetic treatment, help in reducing dosage of various drugs for treating DM. It has been observed that decreasing carbohydrates in diet decreases high blood glucose that doesn't need weight loss and sometimes not only decreases number of drugs needed but might obviate the need for the same [28,36].

On studying the influence of KD effects in T2DM it has been seen that a big link is there between the insulin resistance path and KD. Importance of lipid metabolism parameters helping in cellular localization of glucose transporters, there recycling might be helped by KD besides improving inflammatory development by blockage of some cytokines [28,36]. Increase in plasma ketones is associated with reduction in plasma glucose, reduction in cerebral metabolic rate of glucose (CMRglc) along with an increase in cerebral metabolic rate of acetoacetate [37]. Obese type2 diabetics have an influence of high ketogenic VLED therapy in lowering fasting, OGTT glycaemia, besides improving glycaemic control [38,39]. There is decrease in hunger by the low carbohydrate, high protein KD along with decrease in food intake [40]. Markedly better glycaemic control as observed by glycated hemoglobin change, reduction or complete stoppage of antidiabetic medicines along with an increase in high density lipoprotein-cholesterol (HDL-C) occurs with use of KD. Also it causes weight reduction in overweight/obese people having T2DM over a24week span in contrast to that seen with low glycaemic index diet [41,42]. Further a reduction in both carbohydrates and proteins improves diabetic nephropathy [43]. Yet no improvement is shown in prevention of beta cell function decrease and it might not improve the insulin secretory function or show a change in beta cell mass [44].

A class of antidiabetics-the sodium glucose cotransporter 2 (SGLT2) inhibitors, mainly emphagliflozin and canagliflozin has been seen to be effective in cardiovascular (CVS) defects in T2DM patients. The proketogenic effects is brought about by a shift from glucose to lipid utilization. They increase the synthesis of KB from the liver, by an increase in glucagon levels and decreases the insulin: glucagon ratio. One of the possible reasons in why they are so effective in preventing CVS and kidney disorders in T2DM patients is probably because of mild ketosis produced by these drugs which =>an improved peripheral insulin sensitivity, decreasing hyperinsulinemic stress along with increasing natural insulin secretion and thus decreasing the need for supplementing any insulin from outside. Further mild ketosis is also effective in improving the metabolism of a heart that is on the verge of collapse in T2DM patients. But one important thing to be noted is that patients who are already on SGLT2 inhibitors are markedly at risk of development of euglycaemic diabetic ketoacidosis if they receive supplementation with low carbohydrate KD, therefore one should not prescribe this diet in T2DM patients on SGLT2 inhibitors [10].

There might be an increase in risk of development of hypoglycaemia, with a carbohydrate decrease mainly patients getting therapy with insulin along with insulin secretagogues like sulphonylurias, incretin based therapies. Hence dosage of any antidiabetic drug needs to be adjusted prior to starting any diet that is based on glycaemic control and different class of antidiabetic drugs [45].

## Obesity

Greater weight loss is observed with KD therapy in comparison to other balanced diets. Thus this might be an alternative method of treating obesity [46-48]. Possibly cause of this>loss is control in hunger in view of high satiety effect produced by proteins or a direct suppression of appetite by KB, along with changes in circulating amount of various hormones like ghrelin and leptin that control appetite by themselves [49,50]. The other possible mechanisms are a decrease in lipogenesis, an increase in lipolysis, decrease in resting respiratory quotient, an increase in metabolic cost of neoglucogenesis, along with the thermic effect caused by proteins [51,52].

Castaldo., *et al.* demonstrated that short term ketogenic EN which is followed by an almost carbohydrate free oral diet might have weight loss effectively, a decrease in waist circumference, BP, along with insulin resistance in morbidly obese adults having a BMI > 45 kg/$m^2$ [53]. Marked reduction in cholesterol, blood glucose, body weight, BMI is seen with this diet and hence a reduction in risk factors for various chronic diseases in obese hypercholesterolemic patients having a BMI > 35 kg/$m^2$ without any side effects in longterm [54].

## Role in Metabolic Syndrome (MetS)

As a result of insulin resistance in peripheral tissues, hyperglycemia, hyperinsulinemia with abnormal fatty acid metabolism along with atherogenic dyslipidemia occur in MetS, along with CVS diseases. Lipolysis is controlled by carbohydrate in diet, along with processing of lipoprotein [45,55]. Long term KD over a12mth or greater span causes a decrease in body weight, triglycerides and diastolic BP, while it increases HDL-C and low density lipoprotein in contrast to low fat diet [51,56].

The increased plasma βHydroxy butyric acid that correlates with reduced plasma cholesterol, mevalonate, a marker of liver cholesterol synthesis, along with reduced mevalonate precursors, like acetoacetyl CoA and 3hydroxy -3 methyl glutaryl CoA in liver. An increase in β Hydroxy butyric acid helps in a nonatherogenic lipid profile, improves CVS risk factors, besides lowering BP, decreasing insulin resistance without causing bad effects on liver and kidney function [57,58].

## Role in Poly cystic ovary Syndrome (PCOS)

As is well known there is an association of PCOS with obesity, hyperinsulinemia, insulin resistance along with metabolic and reproductive problems. Low carbohydrate KD has the following metabolic and endocrine effects like, better body weight, free testosterone percentage, LH/FSH ratio and fasting insulin levels. There is a reduction In androgen secretion along with increase in sex hormone binding globulin, an increase in insulin sensitivity and hence normalization of endocrine functions. Thus, this diet combined with lifestyle intervention has good effects in PCOS patient's treatment who are affected by obesity and T2DM [59-61]. Further there is an improvement of depressive symptoms, psychological disturbances and health related quality of life in these patients.

## Side Effects

These can be either mild, moderate or severe or short term and long-term [62,63]. Commonest being mild which are headache, constipation, diarrhea, insomnia and backache. MCT's present in high levels in KD might result in GIT discomfort associated with abdominal cramps, diarrhea and vomiting [25]. In moderate side effects dyslipidemia, mineral deficiency, metabolic acidosis along with increased susceptibility for development of renal stones. Further an increased triglyceride might be seen within 6mth of intake of this diet [63,64]. Similarly, there may be hypoproteinemia occurring secondary to decreased protein intake [65]. Severe effects are in relation to increased ketone levels, which cause any complications by an increase in redox imbalance and henceincrease risk of morbidity and mortality in diabetic patients [66]. Although as far as possible acidosis during KD is concerned the levels of KB's never rise above 8mmol/L, a risk which is practically never present in people with normal insulin function.

Long term glucose intolerance that is related to insufficient insulin secretion, insulin resistance along with decreased both beta and alpha cell in mice getting KD [67]. Risk of more visceral and bone marrow fat associated with increased leptin, a reduction in insulin like growth factor, decrease in bone mineral density, reduced transcription factors which promote osteoblastogenesis and thus decreased bone formation [68]. Cholesterol, triglycerides, monocyte chemotactic protein -1, leptin, interleukin (IL]-1 and IL6, that are plasma markers associated with dyslipidemia and inflammation were found to be raised, along with mice fed a KD demonstrated signs of hepatic steatosis following a 22week period of KD [67].

One can prevent and treat symptoms like dehydration, hypoglycemia and mild acidosis very easily. By decreasing the amount of MCT in combination with LCT along with an increase in meal frequency may cause a better tolerance of diet [25]. One needs to prescribe calcium, selenium, zinc, vitamin D along with oral alkalis for decreasing nutritional deficiencies along with incidence of kidney stones [69]. Proton pump inhibitors or H2-blockers can be added for prevention of GIT dysmotility along with gastroesophageal reflux [25]. Besides that, one recommends high fiber vegetable, adequate fluids, along with carbohydrate free laxatives to take care of constipation.

## Contraindications

Since adaptation to KD metabolically needs a switch from use of carbohydrates to lipids as a main energy source, patients having disorder of fat metabolism may develop severe catabolic crisis like coma or even death in a setting if patient is fasting or on KD. Hence before starting KD one must screen for any disorders of fatty acid transport along with oxidation, mainly in children having seizure disorders along with developmental abnormalities. Further KD is contraindicated in porphyria, a disorder of heme biosynthesis, where deficient porpohobilinogen deaminase exists along with patients having deficiency of the enzyme pyruvate carboxylase [25]. Thus, a detailed history, physical examination, assessment of growth in children along with routine monitoring of laboratory investigations is a must before starting KD along with on follow up visits. One should not advise KD in T2DM patients who are already on SGLT2 inhibitors.

## Conclusions

Hence it has been highlighted that KD is effective in the treatment of T2DM, obesity along with endocrine disorders, although one needs to use them under strict medical supervision of both physicians and nutritionists and thus needs a hospital setting for starting them. To increase the acceptability, tolerability along with palatability, one needs to modify the diet protocols slowly when starting the diet with or without fasting, have regular follow ups for prevention of or have minimal side effects, change in ratio of fat versus nonfat components of fatty acid composition. Thus, these diets might have a positive effect on hormonal balance and endocrinological disorders. Still one needs more studies to see the long-term effects on health and reversing complications in T2DM in man. One is not sure of the clinical effects following discontinuation of this diet which warrants further studies for understanding disease specific mechanisms.

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