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The Mysterious Low Carb Diet – Reckon with Oncology

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Abstract

Targeted composition of daily meal and artificial nutrition may influence output of diseases by modification of metabolic pathways. Carbohydrate restriction is one of the dietary interventions that has proved medical impact. Ketogenic diet (KD), the extreme version or low carb diets (LCDs) in epilepsy treatment became a standard treatment modality in drug-resistant forms. Based on the safety of its use over 20 years attempts have been made to influence other diseases, too. Here we review the results in neurology, metabolic diseases (metabolic syndrome), the cardiovascular diseases and others. One of the most controversial is its use in cancer patients therefore we survey the relevant preclinical and clinical research activities. We summarize the recent results and highlight the limitations.

Keywords: Cancer; Diet; Ketogenic; Low Carb; Nutrition

Introduction

Appropriately tailored diet regimens may help maintaining health additionally might be useful in weight reduction and, in many other disease states. Regular western-type food contains ca. 55% carbohydrate, 30% fat and 15-20% protein. Healthy diet recommendation of US Dietary Association is 45-65% carbohydrate + 20-35% fat + 10-35% protein **[1]**. Consensus statement of ADA emphasize the importance of medical nutrition therapy for management (prevention and treatment) of diabetes however does not recommend macronutrient proportions **[2]**. Even the UK Government Dietary Recommendations contain similar data to USDA figures **[3]**. Notwithstanding, therapeutic nutrition with isocaloric low carbohydrate/high fat containing food (eg. modified Atkins diet) or nutrients recently became a popular theme in the nutrition research. In general, low carbohydrate diet (often called as low carb diet; LCD) means all diets and enteral nutrition modalities containing less than 50% carbohydrate (50-150 g/day) and more than 35% fat, including the ketogenic diet (KD)/ ketogenic enteral nutrition (KEN). KD and KEN are used as standard nutritional therapeutic tools in intractable epilepsy since 1921 however they are used in various treatment approaches. Along with calorie restriction low carb diet can be recommended for weight control and the ketogenic diet for certain forms of neurological disorders, inclusive migraine headache. Recently case reports were published about beneficial effect of ketogenic diet in heart failure, and controversial experiences with certain types of cancer, too. Therapeutic results are variable, according to the illness, the macronutrient composition, the adherence and many other factors. Metabolic background and practical use of this nutrition is discussed in the article.

Brief Overview of Physiology and Pathophysiology of Ketogenic Diet

In non-fasting individuals blood ketone concentration is below 0, 3 mmol/L. When patients are fasting or permanently eat food with drastically reduced catbohydrate content, serum

ketone levels rise to 2-8 mmol/L. This is the transient ketosis that is a normal physiological condition, called also „physiological ketosis". As in this instance natural sources of glucose production are missing, glucose reserves are exhausted and the necessary glucose is made from aminoacids (glucogenic AAs) and from glycerol originates from fat decomposition. This is the situation in conditions of ketogenic diet as well. Dominantly the liver produces ketone bodies, mainly acetoacetate that convert to acetone and beta-hydroxybutyrate (BHB). The former one is volatile therefore it is exhaled but BHB can turn back with help of beta-hydroxybutyrate dehidrogenase to acetoacetate and further on to two molecules of acetyl-CoA **(Figure 1)**.

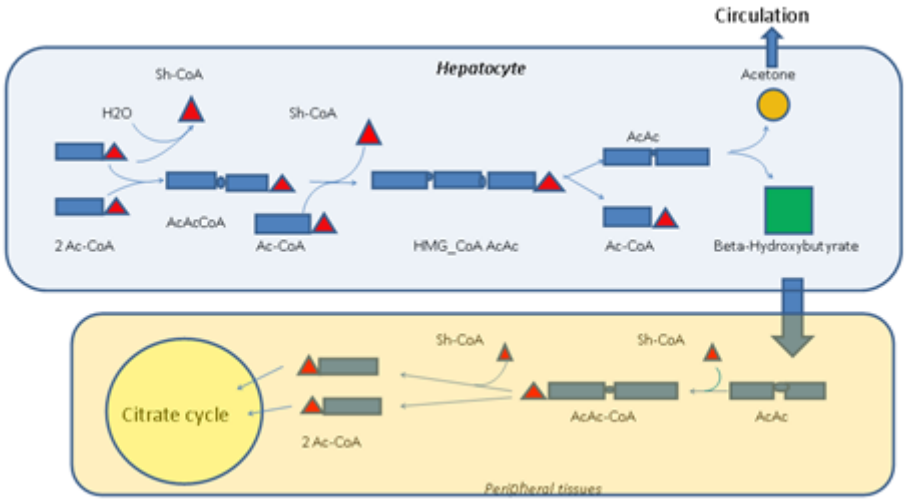

Figure 1: Recirculation of Ac-CoA in ketone body formation pathway.

This compound is precursor for the Krebs-cycle (citric acid cycle) in order to make energy via oxidative phosphorylation. Should this pathway blocked due to lack of carbohydrates or because too much fats are oxidized thus too much acetyl-CoA were produced, the ketogenetic pathway becomes the dominant way and acetoacetate is produced in surplus **(Table 1)**.

100 g of:	glucose	acetoacetate	beta-hydroxybutyrate
generates g ATP	8.7	9.4	10.5
Modified after **[4]**.			

Table 1: Amounts of ATP generated from different sources.

In the group of LCDs classical ketogenic diet plays a specific role. The selective capacity of neurons in utilization of ketone bodies make this type of food and enteral nutrition able to support anti-seizure therapy. KD and KEN usually contains less than 20% (or 20 g/day) carbohydrate and more than 50% fat counted in energy density. During the past 60-80 years this type of aggressive therapeutic intervention regularly became a preferred or dispreferred choice of treatment apart of the representatives of modern pharmacotherapy. General safety of this type of treatment is, however, not questioned and several developed artificial nutrients based on this concept in order to make this nutrient palatable. After therapeutic success of ketogenic diet in epilepsy attempts have been made to cure also patients with several other illnesses incl. forms of cancer disease. Patients with obesity, NAFLD/NASH, heart failure, neurological and neurodegenerative diseases, inborn errors of metabolism and exercise performance were the subjects of clinical trials with LCD **[5]**.

Ketogenic Diet as Treatment Option

Classical ketogenic diet of 4:1 ratio refers to 4g fat to 1g carbohydrate + protein composition. This means 32 kcal fat and 4 kcal (carbohydrate plus protein) where the total daily protein content should be not less than 1 g/kgBW. For a 70 kg body weight outpatient requiring ca. 2.500 kcal energy per day, this recommendation suggests a dose of ca. 70 g protein, 50 g carbohydrate and 225 g fat (triglycerides of long-chain fatty acids) each day. Due to the low adherence with this composition 3:1 and 2:1 macronutrient ratios were also recommended by various authors. Different ketogenic diets **(Table 2)** were tested as non-pharmacological treatment option in several illness in the past.

	Carbohydrate	Protein	Fat/Lipid
Classical Ketogenic Diet	2	8	90
Mild Ketogenic Diet (FedPract)	5	20	75
Modified Atkins Diet	5-10	30-35	55-65
Medium Chain Triglyceride Diet	35	20	45
Western-Type Diet	55	15	30
Standard Diet	50	15	35

Table 2: Some of the therapeutic low carbohydrate diet compositions in calorie %.

Earliest attempts have been registered in the field of neurological disorders, inclusive epilepsy, where low carb diet and the classical KD is still accepted therapeutic modality **[6]**. Some types of epilepsy, especially certain drug-therapy resistant and inborn error induced epilepsies can only be treated by this intervention. Honestly, the mechanism of action is even today poorly understood but it works. There are several suggestions, among others microbiota affected by the ketogenic diet also raised as a possible theory **[7]**. To date, ketogenic diet is used as treatment option of other pathological conditions like cardiovascular diseases, obesity (metabolic syndrome), etc. as well. Main features of this therapies are as follows:

Obesity and Related Disorders

The use of KD in obesity based on the dual metabolic action of KD: the control of hunger (central satiety signaling effect) and on the improvement of fat oxidation **[8]**. Today more and more endocrinological background revealed e.g. that despite the acute changes in orexigenic ghrelin and anorexigenic leptin levels after 12 months of KD ingestion these hormones return to normal, it means the appetite-regulating peripheral hormones are not down regulated by chronic ketosis **[9]**. Animal studies revealed that increased energy expenditure is due to increase in expression of genes involved in fatty acid oxidation and decrease in that of lipid synthesis **[10]**. It is to stress that human studies generally demonstrate a loss of both fat mass and lean mass only during low calorie low carb diet. Some authors suggest that reduced energy intake often accompanied with LCHF diet and this is responsible for weight loss plus related metabolic and functional improvements **[11]**. In trained men, however no decrease in lean body mass was observes beside the positive effects (decrease) in total fat mass and visceral adipose tissue measured with DEXA **[12]**.

Effect of LCD incl. KD in non-alcoholic fatty liver disease (NAFLD), which is present in 90% of obese, is controversial therefore use of low carb diet to improve NAFLD is incorrect. In contrast T2DM patients profit from low carb diet because of the better control of glucose homeostasis and reduction in antidiabetic medication **[13]**. The first mentioning of low carb diet in conjunction with diabetes in the PubMed database goes back to 1825 when AG Mitchell from Cincinatti, USA explained that children with diabetes mellitus should be kept on ketogenic diet consisting of 1g carbohydrate and 2 – 2,5 g fat per pound of body weight beside ample protein intake **[14]**. LCDs seems to be beneficial also to kidney function. Juraschek et al. published an RCT study with 163 overweight/obese patients having diabetes or kidney disease and learned that reducing percentage of carbohydrate by increasing proportion of protein and fat increased GFR of the patients **[15]**.

Cardiovascular Diseases

Low carbohydrate diet in human beings exerts an effective anti-hyperlipidemic effect. Authors report reduction in total cholesterol, triglyceride and LDL-cholesterol levels whereast the HDL-cholesterol improves during and after introduction of low carb diet. de Koning concluded from a prospective cohort of more than 2600 patients that LCD with protein and fat originate from red and processed meat has the best LDL-cholesterine lowering effect **[16]**. With regards to the heart failure, more than 20 years ago it has been revealed that in congestive heart failure serum ketone body levels increased in proportion to the severity of dysfunction **[17]**. Today we know that ketone bodies increase myocardial blood flow and are important cardiac fuels and vasodilatators **[18]**. Moreover ex vivo studies demonstrated that hypertrophied and failure heart shifts to ketone bodies as significant source for oxidative ATP production **[19]**.

Neurology Inclusive Migraine

Ketogenic diet has been found beneficial in various neurologic diseases. The relatively high therapeutic success rate in intractable epilepsy seems to be evidence for more than 20 years. The mechanism of action is however still controversial because the ketone body levels often do not correlate with the anti-seizure effect, moreover with low glycemic index diet similar antiepileptic success can be reached without systemic ketonemia **[20]**. In various neurological diseases, like Alzheimer's disease, stroke, traumatic brain injuries, amyotrophic lateral sclerosis, Huntington's disease, Parkinsons's disease multiple sclerosis were running more or less successful studies **[21]**. Some 10 years ago successful administration of ketogenic agent (MCT oil) was reported in Alzheimer's disease **[22]**. However the therapeutic exploitation has not yet been done **[23]**. In other neurological directions: research groups studied thoroughly the effect of ketogenic diet and ketone-body supplementation in patients with various migraine types and found positive **[24, 25]** or moderately positive effect **[26, 27]**, but in summary LCD is a useful alternative in this difficult-to-treat illness.

Apart from dietary intervention inducing ketogenic sequels administration of exogenic ketones are recently also included in the therapeutic armamentarium **[28]**.

Oncology

Some 100 years ago, Otto H. Warburg invented an idea, later called as „Warburg hypothesis" or „Warburg effect" that firstly intended to explain cancer cell energy metabolism. He stated based on his research activities that cancer cells use a specific glucose-utilization pathway called aerobic glycolysis, in presence of sufficient oxygen, to support their proliferation. This thesis initiated various metabolic research in the field of oncology in order to learn how really the cancerous cells work.

The metabolic pathways behind the curtains, have been studied intensively in the past 100 years but still not fully understood. Recently, Zhang et al **[29]** published a summary of contemporary interpretations of Warburg effect. The point of the hypothesis is that due to the metabolic switch recognized in all tumor cell cultures, glucose and glutamine metabolism changes consistently in these cells and their glucose consumption is many fold higher of that in normal cells. It means carbohydrate restriction can (temporarily?) limit ATP-production as well as the synthesis of building bricks for cancer cell proliferation. From the other side, cancer cells use the aerobic glycolysis that provides much less energy but the production process is quick in contrast to cell respiration thus energy production per time-unit is nearly the same **[30]**.

Unfortunately, some cancer-cell line adapt to the changed circumstances after carbohydrate restriction and remain proliferative even under glucose-poor conditions. This is similar reaction to that of resistance toward classical anticancer interventions. Studies demonstrate that á priori majority of tumors are glycotropic and only a minority of that cell-lines are non-glucotropic, therefore at early phase of the LCD mitigation of tumor cell proliferation is expected. Later on, due tot he pentose-phosphate shunt and the improved lactat utilization the energy deficit can be compensated, moreover acetate originating from the accelerated glutamate consumption, can be utilized by cancer cells for proliferation. Additionally, certain cancer cells are able to let produce energy by adjacent healthy cells. All these cellular alterations explain the diverse results seen in various preclinical studies made with LCDs. The real driver of the switch is not discovered yet.

The Preclinical Studies with Cancer Models

Tumor cell culture experiments as well as animal models were developed for test the effect of LCD to tumor metabolism for decades. To date much more publications were published with use of extreme low carbohydrate content than with the moderate carbohydrate consumption. The results published till the end of 2017 were summarized by Weber et al. They review 13 animal studies with various cancer types and it is demonstrated that some of them respond not at all (e.g. medulloblastoma, melanoma, kidney cc.), some respond partly (eg. glioblastoma, medulloblastoma, protate cancer, pancreas cc.) and others respont well (e.g. colon tumor, neuroblastoma, lung- and breast cancer) on ketogenic nutritional interventions **[31]**. However, in another study glioblastoma responded well to low carb diet in animal studies **[32]**. Other animal studies with neuroblastoma resulted in synergistic effect with chemotherapy (cyclophosphamide) in xenografted mice **[33]**. The peritoneal dissemination of tumor cells was decreased and the KD-fed mice had longer survival time, smaller ascites-production, improved behavior and also blood cell count, hematocrite and hemoglobin improved **[34]**. It seems that not only composition of diet or nutrition and the type of cancer but genetic predisposition plays a key factor as well. In case of melanomas it was demonstrated that different melanoma cell-lines react differently to the same nutritional interventions. Moreover, recent study revealed the signaling basis of high lipid nutrition and the potential pathogenic role of dietary fat related ketone body acetoacetate in certain types of mutant melanoma cells **[35]**. In experimental multiple prostate cancer models 0% – 10% – 20% carbohydrate containing ketogenic diets supported the hypothesis that ketogenic diet slows down the tumor growth **[36]**. Based on the finding maybe precision diet/cancer-dependent dietary therapy could prevent or attenuate cancer risk and/or the cancer progression of patients based on individual genetic background.

The most predictive studies show actually positive (anti-cancer) response in certain cancer types **[37]**. Strong transferable evidences, however are scarce behind the use of ketogenic diet in oncology.

Clinical Experiences

Ketogenic diet exert beneficial effect in various diseases models as described above. More than 10 years ago various industrial manufacturers developed low carb clinical nutrition products to support the ketogenic nutrition **[38]**. After this action several relatives of patients and oncologists started to try this nutritional support in their patients. The tolerability of the classical ketogenic diet is generally poor in contrast to the normal diet but the success in epilepsy flashed a hope. Not groundlessly. A very recent publication reported about a randomized controlled study in ovarian and endometrial cancer patients treated with ketogenic diet (70% fat, 25% protein and 5% carbohydrate **[39]**. Their statement is that adherence of KD and standard diet patients ranged from 57% to 80% respectively after 12 weeks and there were no changes in blood lipid values between the test-meal and control meal groups. In another group of patients (ovarial and endometrial cancer) 67% and 56% were the adherence rate in the same

sequence, it means more KD nourished patients were adherent to the special diet after 12 weeks than in the control group **[40]**. What the effectiveness concerns, recently positive therapeutic effects (overall survival) were reported. In a RCT involving 40 breast cancer patients taking KD and 40 controls under conventional chemotherapy. LCD-fed patients received in this trial MCT-fortified ketogenic diet of 75% fat, 19% protein and 6% carbohydrate. In this homogenous cancer group overall survival was better after 12 week MCT-KD-nutrition therapy than in control group **[41]**. Another study from 2014 also confirmed the good tolerability of the LCD, and displayed a positive interaction with bevacizumab therapy **[42]**. Another recently published clinical trial demonstrated synergic effect of LCD with other conventional cancer-therapeutic modalities. In this metabolically supported chemotherapy treatment (MSCT) KD artificially induced hypoglycemic condition during the chemotheraputic treatment. This was successfully tested in feasibility study (44 patients with metastatic non-small cell lung cancer) with additional ketogenic diet, hyperthermia and hyperbaric oxygen therapy **[43]**.

Gliomas are metabolically active tumors therefore the ketogenic diet is very interesting research target within the neuro-oncologists **[44]**. As early as 1995 there were information about positive oncological results and since that more publications appeared in this regard **[42, 45, 46]**.

The ESPEN Guidelines of 2016 advice: „in weight-losing cancer patients with insulin resistance we recommend to increase the ratio of energy from fat to energy from carbohydrates. This is intended to increase the energy density of the diet and to reduce the glycemic load" **[47]**. This is a careful formulation which comprise the positive result we realized in increasing number of studies at the same time average of the missing evidences. It is clear that more and more experiences preferably ensue from RCTs are needed with various types of cancer. Maybe this is not so far away.

Safety

Safety data of low carb diet and its extreme form the ketogenic diet go back to ca. 100 years ago. During this time periode plenty of experiences were gethered in order to state safety of this therapeutic option. Accumulated information concluded in reliable efficacy and relative safety. There are known contraindications, eg. it is not recommended for patients having uncontrolled diabetes, and pancreatitis, liver failure, dysfunction of fat-metabolism, carnitine deficiency are also among mentioned reasonds to avoid ketogenic diet. And there are side effects, too, they will be discussed below. In the field of KD induced adverse reactions there are several published studies. Earlier there was an obscurity whether KD represents an increased risk for hypoglycemia in patients especially having instable carbohydrate metabolism like diabetes. Recently Loew and coworkes published a study with T1DM patients taking less than 55 g carbohydrate per day for several years (mean 2,6 years). The study resulted in positive outcome from safety point of view as HbA1c levels of the patients decreased and time on euglycemic state increased while a moderate increase in episodes of hypoglycemia was observed **[48]**. In contranst to the fear based on animal studies, in humans KD-induced starvation pseudo-diabetes is a benevolent effect and does not mean low carb diet provoke T2DM but just on the contrary **[49]** Despite the positive effects a lot of patients discontinuate the KD therapy because of the unpalatability of this food. This can be ameliorated with various kitchen-techniques. The unpleasant taste of KD encourage scientist to find alternative ways to produce and maintain ketotic internal conditions. One of these approaches is the use of ketogenic drinks **[50]**. The drinks reported in the publication contain ketogenic salt (Na or K salt of BHB), or ketone ester (3-hydroxybutyl-3-hydroxybutyrate). Both drinks resulted in effective serum ketone body levels. It should be, however, mentioned that effects of ketogenic diet show high inter-individual differences. Therefore in certain cases (eg. epilepsy) the measurement of ketotic state may be necessasry. For this reason several tests were developed, best of all seems to be the measurement of exhaled acetone that is in good correlation with the serum ketone levels **[51]**.

Longer lasting KD therapy usually accompanied with significant and negative changes in arterial morphology and lipid metabolism resulting in dyslipidemia, according to the experience in epileptic children **[52]**. These symptoms are mostly reversible if the diet is stopped after 1-2 years **[53]**. In contrast, obese patients on shorter course of low carb diet present improvement (decrease) in se-cholesterin levels. Interestingly, the lipid profile differs between rodents and humans insomach as KD in rodent models associate with worsening of lipid parameters **[54]**. In a 10 years follow-up of consistently KD-treated patients there were no lipid-alterations and the risk for atherosclerosis did not increased at al **[55]**. KD was considered as increased risk factor for kidney/urinary stone formation especially if carboanhydrase inhibitor is administered simultaneously. Study of Kossoff could not confirm this concerns nevertheless ample hydration is recommended for patients on classical KD therapy **[56]**.

However, KD may be too drastic metabolic intervention in other disorders therefore some scholars suggest to use low carb diet (named also as moderately low carbohydrate diet or modified Atkins diet (MAD) as well) instead. According to Rezaei et al. its efficacy seems to be similar to KD in epileptic children **[57]**.

It should be, however mentioned that long-term low carb high fat diet often leads to vitamin deficiencies due to the limited vitamin intake and the subsequent exhaustion of reserves. For this reasons during the long lasting LCD therapy vitamin supplementation is recommended.

Conclusions

Low carb diet is known therapeutic modality in neurology as well as additive therapy in several other disorders. Here we reviewed most important fields of concerning experiences and trial results. In oncology much attempts have been made in order to improve the knowledge regarding therapeutic feasibility. Unfortunately, preclinical studies are with limited transferability to human beings, further there is no two of the LCD trials are alike therefor no conclusion can be drown. However strong arguments support the safety of this intervention and the individual results are very promising. RCTs are badly needed with patients suffering from same/very similar forms of diseases and treated with same/very similar conventional therapies.

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