Promising Perspectives of Low Carbohydrate Diet in Cancer Adjuvant Therapy

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Abstract: Low carbohydrate diet (LCD) and nutrition is a very popular topic in the nutritional scientific literature. Main reason is that it is an old established therapy in intractable epilepsy and there are plenty of positive preclinical and sporadic clinical results in other disorders, including certain cancers. The problem is that a) the metabolic background of this therapy is not elucidated enough, b) animal studies and human experiences are sometimes divergent, c) there are negative human results and d) the clinical studies are not comparable because of the wide variety of study design and conclusion regarding the indication, the composition of diet and duration of treatment can not be drawn. This publication reviews the current situation and gives some hints to the solution.

Key words: Low carb diet; Ketogenic; Cancer; Nutrition

Introduction

Conventional anticancer therapy is accompanied with a lot of adverse effects. Several attempts have been made to alleviate these but in the majority of radio-, chemo-, pharmaco- and immunotherapies’ side-effects could not be removed. Nutritional therapy, more precisely the low carbohydrate-containing food or nutrition (low carb diet; LCD) offered a chance in improvement of success of the traditional oncotherapeutic interventions. This intervention does not intend to replace conventional therapeutic forms but – based on the Warburg effect – may limit proliferation of the glucose-dependent cancer cells. Therapeutic nutrition with isocaloric low or moderately low carbohydrate + high fat containing food (eg. modified Atkins diet) or nutrients recently became an intensively searched field in the nutrition research. Low carb diet, in general, means all diets and enteral nutrition modalities containing less than 50% carbohydrate-originated energy (50~150 g/day) and more than 35% fat-driven energy (>100 g/day), including the ketogenic diet (KD)/ ketogenic enteral nutrition (KEN). Ketogenic diet is represented by the serum levels of ketogenic compounds, characteristically by the concentration of beta-hydroxybutyrate. In a recent study different isocaloric ketogenic diets with 5%, 15% and 25% carbohydrate content were compared in 77 healthy adult participants. During the 3 weeks’ test period beta-hydroxybutyrate (BHB) serum concentrations measured upon awakening rose with an overall value from baseline by 0.62, 0.38 and 0.27 mmol/L, respectively [1]. This demonstrate that all kind of low carb diets exert ketogenic effect with different efficiency. To date strong KD and KEN (<10% of carbohydrate content) are used as standard nutritional therapeutic tools in intractable epilepsy since 1921, however they are used in weight control, in migraine therapy and other illnesses as well. Here we focus on the oncological attempts published so far, based on the PubMed data base.

Brief Overview of Physiology and Pathophysiology of Ketogenic Diet

In healthy individuals physiological blood ketone concentration is below 0.2–0.3 mmol/L. Ketone bodies (KBs) are synthetized in the mitochondria of the hepatocytes and serve as alternative energy source for peripheral tissue. Under this condition some peripheral organs (hear muscle, kidney) prefer oxidize ketone bodies to glucose. When patients are fasting or permanently eat food with drastically reduced carbohydrate content, serum ketone levels rise to 2–8 mmol/L. When serum ketone body levels exceed 4 mmol/L brain starts to utilize ketone bodies in a significant manner. This change results in modified control of energy homeostasis [2]. Transient ketosis is in the range of normal physiological conditions and also called as “physiological ketosis”. If natural sources of glucose production (sugars, starches and other carbohydrates) are missing, glucose reserves gradually exhaust and the necessary glucose is made from aminoacids (glucogenic AAs) and from glycerol originates from fat decomposition. This is the situation after consumption of ketogenic diet as well. The liver produces ketone bodies, mainly acetocacetate that convert to acetone and BHB. The former one is volatile therefore it is exhaled but BHB can turn back with help of BHB dehydrogenase to acetocacetate and further on to two molecules of acetyl-CoA (Figure 1). This compound is precursor for the Krebs-cycle (citric acid cycle) in order to make energy via oxydative phosphorylation. If this latter pathway is blocked due to lack of carbohydrates or it is overloaded with acetyl-CoA as result
of hyperutilization of fats, the liver switch to ketogenetic pathway. This is an economical switch as 100g acetooacetate and 100g BHB may generate 9,400 and 10,500 g of ATP, respectively. In contrary 100g glucose produces just 8,700g ATP. Thus energy need of the body for synthetic processes, other cellular functions and cell division is ensured. BHB is not just an energetic metabolite but also a signaling molecule that integrates the metabolic status of the cell [3]. But energy is not the only requirement of cell proliferation. When pyruvate to acetyl-CoA transformation fails exogenous glutamate via alpha-ketoglutarate may serve as lipid-synthesis supporter as well as energy and nitrogen source [4]. Nitrogen is badly needed to expansion of tumor cell mass. The pentose-phosphate pathway also generates building blocks for the proliferation. As demonstrated, there are several alternative pathways to tumor-cell propagation.

**Theoretical Consideration about Ketogenic Diet Therapy**

In the group of special diets LCD and its extreme form, the classical ketogenic diet plays a specific role. The selective capacity of neurons in utilization of ketone bodies makes this type of food and enteral nutrition able to support antiseizure therapy. In the oncology impact of KBs was highlighted by the discovery of Warburg effect in cancer cell metabolism. 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 rose as preferred or dispreferred choice of treatment beside the members of continuously developing pharmacotherapy. The oldest efforts were registered in the field of neurological disorders, inclusive epilepsy, where low carb diet and the extreme low carb diet (classical ketogenic diet) is still accepted therapeutic modality. Some types of epilepsy, especially certain drug-therapy resistant epilepsies and the status epilepticus can favorably be treated by this intervention. In case of the genetic defect glucose transporter 1 (GLUT1) deficiency induced epileptic seizures the mechanism of action is obvious but the exact mechanism in other cases is even today not really known. There are several suggestions, eg. Elamin M suggested that increased NAD during the ketolytic metabolism may be the primary mechanism behind the beneficial effects in a variety of brain disorders [5]. General safety of this type of nutritional treatment is, however, not a query and numerous artificial nutrition products have been developed by manufacturers in order to make this nutrient efficient and palatable. After therapeutic success with ketogenic diet in epilepsy attempts have been made to cure patients suffering from various forms of cancer diseases, too. Ketogenic diet has also been tested as treatment option in several other illnesses in the past: patients with obesity, NAFLD/NASH, heart failure, neurological and neurodegenerative diseases, inborn errors of metabolism and exercise performance were the main subjects of clinical trials with LCD [6]. Even today ketogenic diet and other LCDs are being used in further health conditions like cardiovascular diseases, obesity (metabolic syndrome) therapy, etc. as well. Main features of these therapies are as follows.

**Non-epileptic and Non-cancer Disorders**

The most obvious way of obesity-treatment is restriction in calories. As carbohydrates set out majority of western diet, carbohydrate-restriction together with calory restriction is one of the leading form of obesity management. Human studies generally demonstrate a slow loss of both fat mass and lean mass during low calory low carb diet. Some authors suggest that reduced energy intake that often accompanied with low carb, high fat (LCHF)

![Figure 1 The ketone body formation.](image)

*Ketone body formation starts when serum glucose frantically decreases and the acetyl-CoA production from proteins and mainly from fat increases. The process runs in the liver but kidney is also able to produce small amounts of ketone bodies. Final products enter the systemic circulation. HMG-CoA, hydroxymethylglutaryl-CoA*
diet, is responsible for weight loss and related metabolic and functional improvements [7]. Effect of LCD including KD in non-alcoholic fatty liver disease, which is present in 90% of obese, is after all, controversial. In contrast type 2 diabetes mellitus (T2DM) patients profit from low carb diet because of the better control of glucose homeostasis and reduction in antidiabetic medication [8]. The low carb diet seems to be beneficial also to kidney function. Juraschek SP et al. published a randomized controlled study (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 in diet increased glomerular filtration rate of the patients [9]. Low carbohydrate diet in human beings exerts an effective anti-hyperlipidemic effect as well. Authors report reduction in total cholesterol, triglyceride and LDL-cholesterol levels whereas the HDL-cholesterol improves during and after introduction of low carb diet. Heart failure patients also may benefit from low carb ketogenic diet due to the ketone bodies which are good fuels for the heart muscle [10].

Ketogenic Diets and Cancer

As most conventional cancer therapies (chemotherapy, radiation therapy and immunotherapy) are usually associated with several adverse effects alternatives or additional treatment methods are badly desired. Mounting individual experiences underpin that dietary restrictions, particularly the restriction of carbohydrates, can exert benefit for cancer patients [11]. Thus nutritional therapies may belong to these efforts and offer positive solution.

About 100 years ago, Otto H. Warburg revealed a specific phenomenon of cancer cells, later referred to as “the Warburg hypothesis” or “Warburg effect” that firstly intended to explain specific cancer cell energy metabolism. He stated based on his research activities in sarcoma cells that cancer cells use a specific glucose-utilization pathway called aerobic glycolysis, in presence of sufficient oxygen, to support their proliferation (Figure 2a).

To elucidate details of the metabolic pathways of cancer cells intensive research activity was initiated and maintained during the past 100 years but the mechanism is still not fully understood. 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 of that in normal cells. It means theoretically by carbohydrate restriction ATP-production as well as the synthesis of building bricks for cancer cell proliferation can (temporarily?) limited. But in fact, some cancer cells, eg. MCF-7 breast cancer cells get 80% of ATPs from oxidative and only 20% from glycolytic reactions [12]. Glucose dependent cancer cells use the aerobic glycolysis that provides much less energy but 10-100x quicker in contrast to cell respiration thus energy production per time-unit is nearly the same or more [13]. According to the Warburg hypothesis the glycolytic pathway in cancer cells is - due to the increased ATP-demand - upregulated even under normal oxygen tension and before pyruvates reach mitochondria, majority of energy-carrier substrates disappeared in other pathways like PPP and lactate production (Figure 2b). As a consequence, upregulation in GLUT transporters and increase of enzymes of glucose utilization is to be detected. Due to the pre-mitochondrial leakage of energy substrates ATP-output in oxidative phosphorylation pathway does

![Figure 2](image-url)

**Figure 2** The “Warburg-shift”. According to the Warburg effect of cancer cells ferment pyruvate originating from aerobic glycolysis to lactate. Besides, the pentose phosphate pathway is activated which produce carbon equivalents for macromolecular synthesis of the tumor biomass. PPP, pentose phosphate pathway; CO₂, carbon dioxide; ATP, Adenosine triphosphate; CAFs, cancer cell associated fibroblast cells; CC-cells, cancer cells
not increase but the lactate fermentation via lactate dehydrogenase and the aerobic glycolysis. The leaking of lactic acid in the surrounding of cancer cells make local environment proliferation-friendly. Some cancer-cell line adapt to the changed metabolic circumstances or have genetically determined enzyme deficiency and remain proliferative even under glucose-poor conditions. As learned from a recent study eg. low expression of the ketolytic enzymes 3-hydroxybutyrate dehydrogenase and succinyl-CoA:3-oxoacid CoA transferase in certain cancer cells might be in the background of the resistance [14]. We know that tumor cells are able to develop resistance toward anticancer interventions as tumor-aspecific attribution. We observe a very similar result in this situation: a part of tumors are glycotropic, other part of that cell-lines are non-glycotropic thus certain cancer cells exhibit flexible metabolic phenotype. Genetic alterations in the cancer cells result in metabolic deviations eg. in BRAF gene mutations detectable in melanoma, colorectal cancer and multiple myeloma and hairy cell leukemia. HMGCL which converts HMG-CoA to Acetyl-CoA and acetoacetate is upregulated in BRAF-V600E-expressing melanoma cells [15,16]. This alteration reorganize metabolism and signaling of the cancer cell selectively promoting their proliferation. Or, for instance, acetate originating from glutamate, can also be utilized by cancer cells for proliferation [4,17,18]. Moreover, cancer cells are able to let produce energy carriers by adjacent healthy cells. This is the reverse “Warburg effect” where cancer cells induce (mainly oxidative) stress situation in neighboring healthy cells (stroma cells) and trigger these cells to produce surplus high energy substrates (ATP, fatty acids and lactate) which via upregulated monocarboxylate transporters turn back to the cancer cells (Figure 2c). Due to the versatility of tumor cells their survival is still good enough [19]. On a whole, there are a lot of alternative pathways embedded in a complex metabolic network (Figure 3). All these processes can explain the diverse results seen in various preclinical studies made with LCDs. The real driver of the switches is not discovered yet.

**Preclinical Studies in Cancer Models**

Beneficial effects of LCD, inclusive ketogenic diet in preclinical studies have been demonstrated several years ago in various health disorders. Tumor cell culture experiments as well as animal models were developed for test the effect of LCD to tumor metabolism for decades. Much more studies were published with use of extreme low carbohydrate content (ie. classical KD) than with the moderate carbohydrate consumption presumably due to the more definitive ketonemia and the good results in epilepsy. In 2014 evaluation of nine studies with KD treated animals was published. Eight out of 9 studies with various tumors resulted in tumor reduction [20]. Three years later results of preclinical studies published till the end of 2017 were summarized by Weber DD et al. They reviewed 13 animal studies with various cancer types and demonstrated that some of them respond not at all (eg. medulloblastoma, melanoma, kidney, etc.), some respond partly (eg. glioblastoma, medulloblastoma, prostate cancer, pancreas, etc.) and others respond well (eg. colon tumor, neuroblastoma, lung- and breast cancer) to ketogenic nutritional interventions, in summary majority of studies resulted in positive effect [21]. However, in another study glioblastoma responded well to low carb diet in animal studies [22]. Other animal studies with neuroblastoma demonstrated synergistic effect of KD with chemotherapy.

![Figure 3 Metabolic summary](image-url). Cancer cells, in contrast to healthy cells, support protein synthesis more intensively and efficiently via several "abnormal" metabolic pathways inclusive the consumption of exogenous aminoacids, mainly glutamate and pentose phosphate pathway product ribose-5-phosphate. PPP, pentose phosphate pathway; OxPhos, oxidative phosphorylation; GLUT, glutamate; ribose-5P, ribose-5-phosphate
(cyclophosphamide) in xenografted mice [23]. The peritoneal dissemination of tumor cells was decreased in carbohydrate-restricted animals and the KD-fed mice had longer survival time, smaller ascites-production, improved behavior and also blood cell count, hematocrite and hemoglobin improved [24]. These and many other positive results indicate the use of LCD in cancer therapy. Nonetheless it seems 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 even different melanoma cell-lines react differently to the same nutritional intervention. Moreover, a 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 [25]. In some cases, ketogenic diet may aggravate neurodegeneration via mitochondrial damage, too [26]. Based on this finding the question arise maybe precision diet based on individual genetic background could prevent or attenuate cancer risk and/or the cancer progression in patients? Other negative effects were also demonstrated. Huang and coworkers demonstrated that hepatocellular cancer cell culture could utilize ketone bodies and the increased ketolysis enhanced tumor growth [27]. Certain kidney tumor models in rats react also with increased tumor growth after high fat containing ketogenic diet [28]. These and other negative results encourage scientists to search for the reason of controversial effects.

In the course of evaluation of preclinical studies, one important aspect should also be considered: noteworthy that results of rodent and human studies often do not correlate. Kosinski pointed out that the cardiovascular parameters basically differ, eg. total cholesterol (TC), LDL and HDL cholesterol and triglyceride (TG) levels move just opposite in the two species ie. KD increases TC, LDL-C and TG in rodents but decreases in humans and HDL is decreased in rodents but increases in humans after ketogenic diet [29]. Moreover, some changes in organ functions and pathogenesis are to be observed in rodents, but never detected in human beings, eg. 6 days of KD induced impairment in glucose tolerance and insulin sensitivity, but in human studies, this is not relevant even after long term use of KD. Preclinical studies supported so far to make sense of organizing clinical trials in order to evaluate capacity of dietary interventions to synergize with treatment modalities in oncology [30].

Clinical Experiences

Low carb diet exert beneficial effect in various disease models as described above. Already more than 10 years ago various industrially manufactured clinical nutrition products supported the human use of ketogenic nutrition [31]. According to Shi HP and Miao MY, tens of thousands of patients with advanced cancer having tried a ketogenic diet for the treatment of their disease by themselves in China [32]. In a review of 10 articles including data of 214 patients were analyzed in order to conclude effectiveness and safety of KD in humans [33]. This analysis found improvement of body weight while tumor-progression markers reduced. The QoL did not change in the average. Overall judgement was, however, moderately positive due to the inconsistent results. Tolerability of the classical ketogenic diet is often poor [34] in contrast to the low carb diet [35]. In the latter study, 16 patients with metastatic cancer received low carb diet (less than 70g carbohydrate per day) for 3 months, and the majority of them completed the trial moreover their quality of life improved. More studies performed in patients with epilepsy clarified that in this disease, effectiveness of moderately ketogenic diet (modified Atkins diet) was inferior to classical ketogenic diet [36]. Despite of that due to the better adherence, this type of treatment can be preferred from therapeutic point of view. Moreover, the very artificial classical ketogenic diets may initiate pathophysiologic changes that could compensate beneficial effect of this type of nutrition therapy [37]. A very recent publication reported about a randomized controlled study in gynecological patients treated with moderately ketogenic diet (70% fat, 25% protein and 5% carbohydrate) [38]. 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 (ovarian 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 [39].

Case reports of two pediatric patients with astrocytoma displayed 50% success after 12 months of KD [40]. In another report one patient with glioblastoma verified by contrast-enhanced MRI and histology received standard combination therapy of radiotherapy + chemotherapy + LCD and after 2 months of treatment course, her malignant lesio disappeared but after termination of KD tumor recurrence was detected [41]. Gliomas are highly heterogenous metabolically active tumors, therefore the ketogenic diet is very interesting research target within the neuro-oncologists [42]. Glioma, especially glioblastoma, is a highly aggressive tumor with poor survival of just one or two years. As glioma cells consume mainly glucose, the low carb diet seems to be advantageous for patients suffering from this type of tumor. Results in a group of glioma patients on standard chemoradiation receiving adjuvant LCD were positive even if the QoL, neurological functioning and impairment did not change over time [43].

Glucose restriction - eg. the extreme of low carbohydrate load as strongly ketogenic compositions usually contain less than 10% carbohydrate in energy density - support the Warburg hypothesis and can stop or inhibit tumor-cell proliferation in selected tumors. It seems that we have a progression in nutritional recommendations.
The extreme low carbohydrate is not good for certain cancer types but low carb diet, containing caloric ratio of 20%-50% carbohydrate-origin energy source maybe better [22]. Recently, positive therapeutic effect (overall survival) was reported in an RCT involving 40 breast cancer patients taking KD and 40 controls under conventional chemotherapy [44]. In this homogenous cancer group, patients received MCT-fortified ketogenic diet of 75% fat, 19% protein and 6% carbohydrate and overall survival were better after 12 week MCT-KD-nutrition therapy than those in controls. Another study from 2014 also confirmed the better tolerability of the moderate LCD, the more displayed a positive interaction with bevacizumab therapy [45]. Recent clinical experiences demonstrate further synergic effect of LCD with conventional cancer-therapeutic modalities [46]. A metabolically supported chemotherapy treatment (MSCT) is artificially induced hypoglycemic condition during the chemotherapeutic 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 [47]. The combination of KD and other glucose restrictive modalities with antioxidant therapy (eg. N-acetylcystein) significantly reduced anaplastic thyroid tumor growth \textit{in vitro} as well as \textit{in vivo} [48]. The systematic review of the published results, however does not support that LCD or other dietary interventions could significantly mitigate recurrence or mortality of breast cancer [49]. To sum up, the results of clinical data, we can set out that conclusions of the many divergent trials and case reports are not comparable. Patients, diseases, nutritional interventions and endpoints are divergent, therefore neither predictivity nor reliability is not on the expected level.

\textbf{Safety}

Research of safety data on low carb diet and its extreme form the ketogenic diet goes back to 100 years ago. Ketogenic diet was first applied as treatment attempt in epileptic patients and since that it became an accepted, relatively safe and effective therapeutic modality in the treatment of therapy-resistant epilepsy. However, KD may be too drastic metabolic intervention in other disorders, therefore some scholars suggest to use “light low carb diet” (eg. modified Atkins diet) instead. According to Rezaei S et al, its efficacy seems to be similar to KD in epileptic children [50]. In case of nutritional treatment, similarly to medical treatments, contraindications should be taken into account: LCD is not recommended for patients having uncontrolled diabetes, pancreatitis, liver failure, dysfunction of fat-metabolism, carnitine deficiency. And there are side effects as well. Kossoff EH recently summarized the side effects of KD in epileptic patient in the frame of a Consensus Statement [51]. He concluded that “Like all medical therapies KDs have potential adverse effects. Overall, the risk of serious adverse events is low; KDs do not need to be discontinued for most adverse effects. Gastrointestinal complaints are often the most common, but can be mostly remedied.”

The first safety concern of LCD for cancer patients is weight loss. KD is often reported as successful form of slimming diets and this assumes a dangerous weight reduction in frailty population, accidentally in cancer cachexia. Indeed, in this patient group, increase of body weight (BW) would be advantageous, but in the course of anticancer treatment preservation of body weight would also be acceptable. In cancer cachexia, LCD cannot increase body weight especially not the fat free mass but in a randomized controlled study of gynecological tumor patients’ maintenance of BW was observed [39]. Concerns about the weight loss induction of LCD/KD in cancer patients were not affirmed by a recent systematic scoping review [52]. In patients with normal or pre-cachectic phase, LCD does not accelerate weight loss. Animal studies supported the hypothesis that ketone bodies reaching the brain stimulate food intake [2]. The main problem is that majority of LCDs, especially KD is not a tasty food, therefore the adherence to these diets is relatively low. Alternative solutions are being intensively searched (see later).

Earlier, there was an obscurity whether KD represents an increased risk for hypoglycemia in patients, especially having instable carbohydrate metabolism like diabetes. Recently, Loew ZZK and colleagues 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 average euglycemia was observed [53]. Despite the positive effects, a lot of patients discontinuous KD therapy because of the unpalatability of this food [54]. This can be ameliorated with various kitchen-techniques, but more successful attempts have been made with ketone esters or balanced ketone electrolyte formulations [55,56]. Today new approaches appeared in the market eg. in form of ketogenic drinks [57]. 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 necessary. 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 [58].

Further, 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 [59]. These symptoms are mostly reversible if the diet is stopped after 1-2 years.
[60]. In contrast, obese patients on shorter course of low carb diet present improvement (decrease) in se-cholesteric levels. Interestingly, the lipid profile differs between rodents and humans as KD in rodent models associate with worsening of serum-lipid parameters [29].

**Discussion**

Low carb diets, used on the Warburg effect concept, are effective adjuvants in certain tumors according to their glucose consumption. Majority of brain tumors are like this. The results of recent studies show that effectiveness of this kind of nutritional intervention depends on several factors, inclusive mutations, normal metabolic program of the tissue-of-origin or the enzyme-defects [61]. Preclinical studies and clinical trials in the past were done without regard to the genotypic and phenotypic features of the cancer cells concerned. Therefore, the results of these studies were very diverse and offered no chance to draw particular conclusion. Moreover, the duration of a specific nutrition and the composition of the nutrition (ketogenic potential) were also diverse. Attempts to analyse tumor biopsies in order to learn enzyme expression and predict whether ketogenic diet may act as anti-tumor intervention did not bring positive results so far. Therefore, even ESPEN was not able to give far sighted recommendation for nutritional support. The actual ESPEN guidelines advise: “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” [62]. This is a careful formulation which comprise the positive result, we realized in increasing number of studies at the same time aware of the missing evidences. It is clear that more and more experiences preferably ensue from RCTs are needed with different types of cancer. Maybe this is not so far away.

**Conclusion**

The nearly 100 years old discovery of Warburg effect was the first initiative to map mysteries of energy metabolism of cancer cells. During this century, we have learned a lot but we do not know enough. The huge amount of preclinical studies provided us with diverse results. In some cancer-types, we have seen very positive outcomes. Due to the partial positive preclinical achievements, human trials were started to elucidate the risks of various forms of low carb diets that finished with success and we know that LCD is a safe treatment modality. By the help of published examples, researchers could demonstrate successful synergies with various conventional anticancer therapies. The real position of the nutrition therapy is, however, not yet found in cancer management. Nutrition is often not regarded as therapeutic intervention, therefore, in many studies composition, quality and quantity of the food/clinical nutrition was/is not defined as precisely as drugs are defined in clinical trials. Subsequently studies performed so far with low carb diets are very heterogenous and are not suitable to draw conclusions. All these facts put us on start clinical studies with patients having same type of cancer, taking the same type of nutrition and get the same conventional therapy. Only in this case shall we be able to find evidence and offer the clinicians evidence-based additional nutrition that support the treatment of tumor patients. In short, LCD still being a promising safe adjuvant therapy, but the real indication is not yet clear.

**Conflict of interests**

The author declare no conflict of interests.

**References**


47. Salih lyikesici M. Feasibility study of metabolically supportes che-
therapy with weekly carboplatin/paclitaxel combined with ketogenic
diet, hyperthermia and hyperbaric oxygen therapy in metastatic non-

48. Aggarwal A, Yuan Z, Barletta JA, Lorch JH, Nehs MA. Ketogenic
diet combined with antioxidant N-acetylcysteine inhibits tumor
growth in a mouse model of anaplastic thyroid cancer. Surgery 2020
Jan;167(1):87-93.

49. Weigl J, Hauner H, Hauner D. Can nutrition lower the risk of recur-

50. Rezaei S, Abdurahman AA, Saghzadeh A, Badv RS, Mahmaudi M.
Short-term and long-term efficacy of classical ketogenic diet and modi-
fied Atkins diet in children and adolescents with epilepsy: a systematic

51. Kossoff EH, Zupec-Kania BA, Auvin S, Ballaban-Gil K, Bergquist
AGC. Optimal clinical management of children receiving dietary ther-
apy for epilepsy: updated recommendations of the International Keto-

Ness A, Atkinson C. Dietary restrictions during the treatment of cancer:

53. Leow ZZX, Guelfi KJ, Davis EA, Jones TW, Fournier PA. The
glycaemic benefits of a very-low-carbohydrate ketogenic diet in adults
with type 1 diabetes mellitus may be opposed by increased hypoglyce-

54. D’Andrea Meira I, Romaio TT, Pires do Prado HJ, Krüger LT, Pires
MEP, da Conceiesao PO. Ketogenic diet and epilepsy: what we know so

55. Hashim SA, VanItallie TB. Ketone body therapy: from the ke-
togenic diet to the oral administration of ketone ester. J Lipid Res

56. Poff AM, Rho JM, D’Agostino DP. Ketone administration for sei-
zure disorders: history and rationale for ketone esters and metabolic

57. Stubbs B, Cox PJ, Evans RD, Santer P, Miller JJ, Faulk OK, Ma-
gor-Elliott S, Hiyama S, Stirling 4, Clarke K. On the metabolism of
exogenous ketones in humans. Front Physiol 2017;8:848-60.

NA, Kohler M, Pratsinis SE, Gerber PA. Guiding ketogenic diet with

59. Lima PA, de Brito Sampaio LP, Damasceno NR. Ketogenic diet in
children: impact on lipoproteins and oxidative stress. Nutr Neurosci
2015;18(8):337-44.

60. Kossoff E. Danger in the pipeline for the ketogenic diet? Epilepsy

61. Myers JR, Vander Heiden MG. Nature and nurture: what deter-