**Title:** A Nutritional Perspective of Ketogenic Diet in Cancer: A Narrative Review

**ABSTRACT**

The predominant use of glucose anaerobically by cancer cells (Warburg effect) may be the most important characteristic the majority of cancer cells have in common, and therefore a potential metabolic pathway to be targeted during cancer treatment. As this effect relates to fuel oxidation, dietary manipulation has been hypothesized as an important strategy during cancer treatment. As such, the concept of a ketogenic diet (KD) in cancer emerged being conceived as a “metabolic therapy” (i.e. targeting cancer cell metabolism) rather than a dietary approach. The therapeutic mechanisms of action of this high fat, moderate to low protein, and very low carbohydrate diet may potentially impact cancer treatment/prognosis. Considering the lack of a dietetics focused narrative review on this topic, this manuscript reviews the evidence related to the use of this diet in humans with diverse cancer types and stages, also focusing on the nutrition and health perspective. The use of KD in cancer shows potentially promising, but inconsistent results. The limited number of studies and differences in study design and characteristics contribute to overall poor quality evidence, limiting the ability to draw evidence-based conclusions. However, the potential positive influences a KD may have on cancer treatment justify the need for well-designed clinical trials to better elucidate the mechanisms by which this dietary approach affects nutritional status, cancer prognosis and overall health. The role of the dietitian is demonstrated to be crucial in planning and implementing KD protocols in oncology research settings, while also ensuring patient’s adherence and optimal nutritional status.

**INTRODUCTION/BACKGROUND**

In the 1920s Otto Warburg observed that most cancer cells, regardless of oxygen availability and functional mitochondria, capture and metabolize large amounts of glucose and convert it to lactate rather than fully oxidizing it (as in the case of healthy respiring cells) to carbon dioxide. This phenomenon, now termed the “Warburg effect”,1 represents an inefficient use of glucose since the theoretical yield of adenosine triphosphate (ATP) generated by aerobic glycolysis (2 ATP/mol glucose) is lower than that theoretically obtained through mitochondrial respiration (36 ATP/mol glucose). This inefficient use of glucose may be countered by an increased rate of glucose uptake, which alters levels of the intermediates and substrates associated with glycolysis, and consequently promotes growth, survival, proliferation, and maintenance of tumor cells.2, 3 This distinctive metabolic feature of cancer cells is the basis for the imaging of tumor tissue by positron emission tomography (PET) using the radio-labeled glucose analogue 18F-ﬂuorodeoxyglucose (18F-FDG).4

Considering that cancer is a highly heterogeneous disease, by reason of its distinct genotypes, the Warburg effect is an important characteristic that the majority of cancer cells have in common, representing a susceptible metabolic pathway that could be targeted during cancer treatment. Despite being known for several decades for its broad applicability to diverse cancers, there have been few systematic clinical investigations of the phenomenon,5 and the development of treatment strategies based on an understanding of the implications of the Warburg effect has likewise been limited.

Since the Warburg effect relates to fuel oxidation, dietary manipulations have been hypothesized as important strategies to prevent and treat cancer. As such, the ketogenic diet (KD) has emerged as a potential “metabolic therapy” (as opposed to simply a dietary approach) with the aim of exploiting the aforementioned metabolic vulnerability of cancer cells: overreliance on glycolysis.6 Although the evidence of its impact on cancer is limited, a KD approach has been extensively studied for the treatment of epileptic seizures.7 The initial application of KD to epilepsy stemmed from the observation that seizures were reduced or absent when affected individuals were fasting.8 A ketogenic dietary pattern can simulate a fasted state since reliance on fat metabolism is a key characteristic under both dietary conditions.9, 10 Although mechanisms of action are not fully understood, metabolic consequences of a KD to cancer include its impacts on cancer cell epigenetics, growth-factor signaling pathways including insulin, reactive oxygen species (ROS) production, angiogenic factors, and inflammatory state,6, 11 as described by Klement and Kammerer.6 Its use has been extensively studied in cell and animal models,12 and a few clinical trials in humans have aimed to establish feasibility and safety and to assess efficacy.13, 14

In general, the KD is characterized by high fat, moderate to low protein, and very low carbohydrate content. The conventional fat to carbohydrate and protein ratio of this diet is 4:1 and 3:1 respectively, which gives a macronutrient distribution of approximately 90% fat, 2% carbohydrate, and 8% protein.11 However, alternative macronutrient distributions have been recently developed to increase flexibility and palatability (e.g. lower fat to carbohydrate and protein ratio; medium-chain triglyceride KD; low glycemic index treatment).11, 15 The increased fat metabolism and limited carbohydrate metabolism of a KD induce a state of physiological ketosis with increased production of ketone bodies levels in the blood (18-90 mg/dL [1-5 mmol/L]),13 decreased glucose (65-80 mg/dL [3.6-4.4 mmol/L])11, 16 and insulin (6.6-9.4 µU/L [45.8-65.2 pmol/L]),11, 16 and maintenance of blood pH levels (pH=7.4).11, 16

The macronutrient distribution range of KD is not ideal for maintenance and promotion of health and prevention of chronic diseases according to the Acceptable Macronutrient Distribution Range (AMDR) recently published in the Dietary Guidelines for Americans (10-35% of protein, 45-65% of carbohydrate, 20-35% fat).17 However, its therapeutic mechanisms of action may transcend this concern in the clinical setting. In fact, beneficial impacts of KD have been observed in the context of conditions such as epilepsy18 and other neurologic diseases,19 obesity,20-27 diabetes,28-31 polycystic ovary syndrome,32 cancer,11 respiratory conditions,33 and cardiovascular disease.26, 34-38 In these and other contexts, decreased morbidity and mortality may exceed potential acute or chronic side effects observed with a ketogenic dietary pattern.11 In view of the potential impact of a KD on cancer treatment/prognosis and the lack of a dietetics focused narrative review on this topic, this review describes the evidence related to the use of this diet in cancer therapy research, either as a standalone treatment or in conjunction with other therapies, focusing on the nutrition and health perspective.

**METHODS**

The focus of this review is to describe original human studies conducted in individuals diagnosed with cancer consuming a ketogenic diet. A literature search was performed in PubMed/MEDLINE from its inception until May 2016. The search strategy consisted of two separate components, each involving key words related to “cancer” and “ketogenic diet” individually. The key words in each component were linked using “OR” as a Boolean function, and the results of the two sections were combined by utilizing the “AND” Boolean in final search. Non-original articles, *in vitro* studies, studies with animal models, studies with children, studies in which cancer originated because of a previously diagnosed disease, and studies in languages other than English were excluded. All studies meeting the inclusion criteria were reviewed, from case-studies to randomized controlled trials, in spite of statistical approach. Titles and abstracts of retrieved studies were screened to select potentially relevant articles. Full text of the remaining studies was then analyzed independently to determine whether they met the established criteria. References of eligible articles were then searched manually for additional articles which could have been missed by the electronic search. A flow chart of the literature selection process is shown in **Figure 1**.

**STUDIES INVESTIGATING KETOGENIC DIET IN CANCER**

A total of 14 studies between 1988 and 2016 including 206 individuals (94 female, 106 male, six not defined) assessed effects of KD in cancer, **Table 1**. The age and sex of participants were not mentioned in one study.39 The mean sample size was 15 participants (ranging from one to 78). Study designs included: two clinical trials,40, 41 one controlled clinical trial,42 one randomized controlled trial,43 five case reports,44-48 one retrospective study,39 one prospective, single-arm pilot study,14 one pilot clinical study,13 one systematic, prospective cohort study,49 and one prospective observational pilot study.50

Cancer types varied substantially among studies. The use of concurrent standard cancer treatments were not mentioned in four studies.40, 41, 44, 49 Concurrent treatment included chemotherapy (one study)43 and radiation + chemotherapy (four studies).14, 39, 46, 47 Five studies used KD as the sole therapy.13, 42, 45, 48, 50 The duration of the dietary interventions ranged from five days to 12 months, and consisted of oral KD,13, 39, 43, 47, 48 oral KD plus supplements (vitamins, minerals, carnitine, arginine, high fermented yogurt drinks, vitamin D3 and/or omega-3 fatty acid),14, 40, 44-46, 50 and parenteral KD feeding.42, 44 No details of diet administration were provided in two studies.41, 49

Nine studies assessed effects of KD on tumor metabolism and/or disease progression.13, 14, 41, 42, 44, 46, 48-50 Among them, two reported negative results,46, 48 two showed diverse results among participants,13, 49 four did not report any difference between treatments,14, 42, 44, 50 and one demonstrated an alteration in cancer cell metabolism (not related to 18F-FDG) associated with the ketogenic dietary intervention.41 The remaining five studies assessed effects of the KD on metabolic and health outcomes as well as its safety and feasibility.39, 40, 43, 45, 47

**Ketogenic Diet and Disease Progression**

 The two studies reporting negative results were case studies conducted in patients with glioblastoma (World Health Organization grade IV).46, 48 In the first study, an older woman followed a KD for 14 days,46 compared to a 12-week intervention in two adult men.48 In spite of discrepancies in the length of the dietary intervention, cohort and diet characteristics, both studies failed to demonstrate efficacy, which could be explained by the aggressiveness of the tumor type being studied (one and a half year median survival).51, 52 Additionally, Schwartz *et al*.48 reported a positive expression of ketolytic enzymes in participants’ tumor cells, suggesting an ability to metabolize ketone bodies to produce energy. These findings are supported by a recent human study reporting that malignant glioma cells are genetically heterogeneous, and have different ketolytic and glycolytic enzyme expression.53 Therefore, as concluded by the authors, expression of ketolytic enzymes may also determine the response/success of KD approach; this could help explain some of the inconsistencies in the literature findings53.

Two studies demonstrated variable disease response among participants.13, 49 Fine *et al*.13 conducted a four-week pilot study to evaluate safety and feasibility of a KD in subjects diagnosed with different cancer types. Fine *et al*.13 found that for those participants whose disease remained stable or partially remitted, their ketotic response (measured by serum β-hydroxybutyrate concentration) was, on average, three-fold higher when compared to those with progressive disease (p=0.018). This variation in disease response may be explained by the observed difference in the degree of ketosis achieved. The second study reporting mixed findings relating to the impact of a KD on disease progression had the largest sample size of all human studies conducted to date;49 however very poor dietary adherence (17%) and the omission of several relevant factors (diet access, diet composition, participants’ energy and nutrient intake, metabolic measurements, level of ketosis, tumor size) limit the conclusions that may be drawn from the study. In spite of these limitations, transketolase-like-1 (TKTL1) levels were assessed, which have been associated with aerobic glycolysis in cancer cells, and reduced levels were reported in individuals ingesting a KD compared with increased levels during active disease. High levels of TKTL1 are associated with worse prognosis and development of end-stage disease. The authors concluded that TKTL1 may be a useful marker of aerobic glycolysis and disease progression. Furthermore, it was found the ketogenic dietary intervention to be feasible and likely beneficial, reinforcing the need for further investigation of the unique metabolic characteristic of tumor cells and its response to low-carbohydrate and high fat-diet.49

 Among four studies14, 42, 44, 50 showing no difference in disease progression with a KD intervention, two administered the KD via parenteral nutrition.42, 44 The provision of readily available nutrients through parenteral nutrition and their potential impact on increasing tumor growth has been an unresolved concern for over 30 years.54 As shown in **Table 1**, despite similar feeding access, these studies differed on design, sample size, cancer type, length of intervention, protein content of the diet, and medication utilized by participants. Both of these studies failed to show a positive impact on disease progression. Similar to studies previously mentioned, Schmidt *et al*.50 could not demonstrate a positive effect of KD, but noted a higher prevalence of stable disease among participants who adhered to the KD intervention, compared to the observed disease progression among dropouts. The authors indicated that a statistical evaluation of the effect of the diet on tumor characteristics was not feasible due to the small sample size and participant heterogeneity. Lastly, Rieger *et al*.14 observed that when a KD was consumed some participants presented with stable disease, and the ones with stable ketosis experienced a trend for longer progression-free survival (six vs. three weeks, p=0.069). The trend towards significance may infer a potential clinical benefit to be explored in larger future studies investigating synergistic effects of a KD and chemotherapy on disease progression. Another interesting finding reported by these authors was that two participants did not achieve a ketotic state in spite of adherence to the dietary intervention, which could be explained by genetic or other unknown factors affecting the impact of a KD, also an important factor to be explored in future studies.14

Considering that some studies have shown that KDs lead to decreased blood glucose levels and insulin secretion, glucose uptake is altered, making FDG a suboptimal PET tracer to evaluate the impact of this diet on cancer cell metabolism4. As such, in order to better understand cancer cell metabolism and the inconsistent findings in the literature regarding KD interventions, the authors are developing positron-emitting fluorine-18 labeled ketone body radiotracers (similar to existing carbon-11 versions)55 to investigate the uptake of ketone bodies by tumor tissue through PET imaging.

**Alterations in Cancer Cell Metabolism**

Schroeder *et al*.41 reported decreased lactate levels in tumor tissue when compared to tumor-free mucosa after five days on a KD. Considering that high lactate levels in tumor cells are related to worse prognosis in patients with head and neck squamous cell carcinoma, this finding highlights one way in which nutrition can impact cancer cell metabolism, and that KD may be a promising therapeutic dietary approach for this cancer type. However, important limitations of the study included sample size, length of intervention, absence of a control group and lack of information regarding diet adherence, composition, feeding access, participant nutrient intake, level of ketosis, and effect on disease progression.

**Metabolic Outcomes**

Ketogenic diet interventions were associated with blood glucose levels that decreased in four studies,39, 40, 44, 46 did not change in six studies,13, 14, 41, 42, 47, 50 were unstable in one study,48 and were not measured in three studies.43, 45, 49 It is expected that individuals consuming a KD would experience decreased blood glucose levels that, nevertheless, are maintained within physiologically safe levels (65-80 mg/dL [3.6-4.4 mmol/L]) because gluconeogenesis can provide sufficient glucose for normal function, including nervous system requirements.16 Frequent use of steroid medication may alter glucose metabolism, and also gluconeogenesis potentially explaining the conflicting results. Additionally, low adherence to the dietary intervention is another factor to be considered.

In regards to lipid profile, blood lipid levels were not measured in eight studies,13, 39-41, 43, 45, 46, 49 worsened in two studies,44, 48 improved in one study,50 and were unaltered in three studies.14, 42, 47 Considering the high fat content of a KD, adverse effects on blood lipid levels might be expected; however, a considerable number of studies have shown improvements in blood lipid profile during KD. This includes elevated high-density lipoprotein blood levels (HDL), decreased triglycerides, and unchanged or slightly elevated low-density lipoprotein (LDL) along with reduction in LDL density.26, 34-38, 56, 57 Moreover, improvements of participants’ cholesterol and LDL/HDL values observed in the study conducted by Schmidt *et al*.50 could be partially explained by the inclusion of omega-3 fatty acids in the diet, as supported by another study.58

No differences in liver or kidney function were observed in three studies assessing these variables,40, 44, 50 with lengths of intervention ranging from 13 days to five months. Nitrogen balance remained stable among participants in one study40 and was increased in another,44 with 13 and 150 days of ketogenic dietary intervention, respectively.

**Anthropometrics and Body Composition**

Changes in body weight were not measured in two studies,41, 45 not reported in one study,49 unchanged in two studies,42, 44 decreased in seven studies,13, 14, 39, 46-48, 50 and increased in two studies.40, 43 Only two studies assessed the impact of a KD on body composition, both using bioelectrical impedance analysis (BIA).43, 47 Breitkreutz *et al*.43 demonstrated that the group that received the intervention increased body weight, body mass index, fat free mass and preserved body cell mass, when compared to the control group. Total body fat and extracellular mass did not differ between groups and the extracellular mass/body cell mass quotient was lower in the group that received the KD.43 However, the most recent study showed that two out of six patients receiving the KD lost weight (although all participants lost weight, the loss was only significant in these two individuals).47 Among patients who presented with weight loss, body composition analysis showed this loss was mainly of fat mass, with a significant decrease observed in three patients.47 Fat-free mass increased in three patients and was stable in the remaining.47 As measured by BIA, no significant changes were observed in patients’ extracellular water, total body water and hydration; however, intracellular water decreased in three patients and increased in one.47 Moreover, phase angle was decreased in one patient.47 Although the amount of protein offered is considered adequate for cancer patients59 and positive results were demonstrated by the authors, the body composition measurement technique used was BIA, which is not a gold-standard method and of questionable accuracy in cancer patients.60 Furthermore, changes in hydration status are known to directly impact BIA measurements.61, 62 As KD may decrease glycogen stores, altered hydration and changes in electrolyte concentrations might have occurred (diuretic effect) - considering each gram of glycogen is bound to 2-4 grams of water and 0.45 mmol of potassium.63, 64

**Quality of Life**

Quality of life was evaluated in three studies.43, 47, 50 Although the randomized controlled trial did not demonstrate differences in quality of life between groups, within analysis showed improvement in the group receiving the KD, and worsening in the control group.43 Klement *et al*.47 did not observe any differences in patients’ overall quality of life in a single-arm pilot study. Although Schmidt *et al*.50 reported that emotional functioning and insomnia were improved in some participants receiving the KD, other quality of life parameters (global health status, functional score, global symptom score, digestive functions, fatigue and pain) remained stable or worsened. The latter could be reflected by the advanced stage of the disease (most presented with progressive disease).50 The authors hypothesized that some of the improvements observed among patients receiving the diet may have been related to their motivation, and the increased levels of the ketone body β-hydroxybutyrate50, which was shown to cause mild euphoria.65

**Adverse Events and Diet Tolerance**

Diet-related adverse events were assessed in seven studies,13, 14, 39, 46-48, 50 but were reported in only three studies, which included one episode of grade II fatigue,39 and headache between weeks six and eight of cancer treatment48 and short-term reversible fatigue, constipation and leg cramps.13 Furthermore, the diet was well tolerated by participants in five studies,39, 40, 44, 46, 47 while in three studies tolerance was variable,14, 49, 50 and was not mentioned in six studies.13, 41-43, 45, 48

**DISCUSSION**

**Nutritional Perspective**

 Dietary manipulations or the use of “food as medicine” has been practiced since Hippocrates, in order to prevent or treat many pathological conditions. With modern advances in science and technology, the field of nutrition has increasingly become an evidence-based therapeutic approach that develops alongside the growing knowledge-base of biochemistry. The possibility of supplementing or even replacing the use of pharmacological treatments with dietary manipulation in pathological conditions may be promising. Moreover, using nutrition as an adjuvant therapeutic approach has the potential to enhance drug effects in a synergistic way which could lead to decreased side effects and dependency.

The recommended contribution of carbohydrate, protein, and fat to total caloric intake of respectively 45-65%, 10-35%, and 20-35% has been associated with reduced risk of developing chronic disease and provision of adequate intakes of essential nutrients.15 Macronutrient distributions outside this recommendation have nonetheless been shown to benefit health in many pathological conditions.11, 18-38 Although the therapeutic application of KD is not novel, as mentioned previously with regard to epilepsy, emerging evidence suggests its potential benefits in numerous diseases, including cancer.11 The interest on the impact of KD in cancer is growing, and a list of relevant, ongoing KD trials can be found in a recent review paper.66

The physiological response achieved by the KD (characterized by high-fat, moderate to low-protein and very low-carbohydrate content) includes increased fat and limited carbohydrate metabolism with consequential impact of normal blood pH levels, elevated levels of ketone bodies, and decreased levels of glucose and insulin (ketosis).7, 11

In obesity, the KD has been shown to positively modify appetite sensations through diverse mechanisms,20-22 regulate adipose tissue metabolism,23, 24 and improve metabolic function.25-27 In cardiovascular diseases, this diet has been shown to improve blood lipid profile,26, 34-38 and in type 2 diabetes, to improve insulin sensitivity, glycemic control, and to stimulate weight loss.28-31 As mentioned earlier, KD may also positively impact other conditions, but further research is needed to better elucidate the physiological mechanisms conferring its benefit in different clinical scenarios.16, 67 Whether a KD is able to prevent certain disease states, especially metabolic-driven ones is currently unknown.

Studies described in this review assessed the effects of a KD in cancer. Potentially promising, but inconsistent results were shown. The limited number of studies and differences in study designs and characteristics (length of intervention, sample size and characteristics, lack of a control group, diet composition, feeding access, cancer type, stage and therapy, methodologies and techniques used to assess the results) contribute to a poor overall quality of evidence and limit the ability to draw evidence-based conclusions. However, the positive impact KD might have on cancer treatment justifies the need for well-designed randomized controlled trials investigating its physiological mechanism of action. Additional considerations to test the therapeutic impact of KD in cancer include the following:

* Length of intervention no shorter than three weeks to allow for ketoadaptation (depletion of glycogen stores,63, 64 increased ketone body levels, initial increase followed by eventual decrease in gluconeogenesis—paralleling the reduction in physiological requirement for glucose, blood glucose level reaching a low-normal range, and decreased triglyceride levels) and detectable differences in tumor size and metabolism;
* Assessment of ketosis state by measuring ketone body levels, which is also an indicator of adherence to the dietary intervention;
* In studies in which the primary purpose is cancer treatment, a measure of tumor size and/or metabolism is essential;
* Ideally, the KD intervention should be the only treatment being tested to determine the unique contribution of ketosis and insulin inhibition. While withholding standard treatment may pose ethical concerns and also would serve as an impediment to accrual, in the pre-surgical setting or among cancer patients in which active surveillance is an option, i.e., women diagnosed with ductal carcinoma in situ or men diagnosed with non-aggressive prostate cancer, such protocols could be instituted;
* In studies where KD is employed as a sole therapy, inclusion and exclusion criteria should include failure to respond to standard therapies and end organ failure, respectively.13

The macronutrient distribution characteristic of KD could cause unfavorable short-term side effects (gastrointestinal discomfort including constipation, lethargy, hypoglycemia) or chronic adverse effects (worsening lipid profile in susceptible populations, kidney stones, renal damage).11 Acute effects are observed during the transition phase which lasts for approximately one to three weeks, as the body adapts to the higher fat and lower carbohydrate content of the diet. Moreover, prophylactic approaches can be adopted in order to counteract these side effects (e.g. potassium citrate supplementation for kidney stones68 and gout;69 magnesium citrate for constipation70). Long-term adverse effects may be avoided if the diet is offered to patients only during the anticancer therapy, (to explore its synergistic effects).71 Certainly, researchers should bear in mind the interaction of ketotic metabolism with the presumed mechanism of action of a chemotherapeutic to judge compatibility, before prescribing this diet. As studies evolve, the benefits and side effects of this dietary manipulation must be weighed in view of its potential treatment advantage in research populations for whom the therapeutic actions may transcend the side effects. As in any scenario, the potential benefits and risks should be clearly discussed among the health care team and disclosed to the patient.

**Body Composition**

The potential of the KD to lead to favorable changes in body composition is an emerging area of interest. As mentioned previously, two studies reported an increase in fat-free mass.43, 47 In spite of methodological limitations, this is a promising finding as high fat-free mass is associated with better response to therapy and survival.72 In addition to providing an adequate amount of protein (1.0-1.5 g of protein/kg of body weight/day, as recommended for cancer patients),59 a KD elicits changes in fuel oxidation. Through its impact on nutrient partitioning, the replacement of energy source from dietary carbohydrate to fat may ultimately influence body composition by preserving fat-free mass and reducing fat mass; this body composition phenotype is associated with better treatment response, physical function and quality of life.72 Importantly, at a eucaloric level, the increase in energy expenditure would be unlikely to lead to substantial weight loss.73 The impact of this diet on body composition should be further studied using state-of-the-art body composition techniques such as dual energy X-ray absorptiometry (DXA) or computerized tomography (CT) analysis.74

It is important to note that the protein content of KD offered to cancer patients needs to be further explored. Protein intake guidelines for oncology patients are not evidence-based, and are provided as a range adjusted based on kg of body weight. As such, the large variability of body composition (amounts of fat-free versus fat mass) in this population,75, 76 as well as the metabolic alterations induced by the KD (amino acids enter in the citric acid cycle generating glucose and NADPH through gluconeogenesis) may impact protein requirements in this population. It is worthwhile mentioning that the protein content of a KD is different from the Atkins diet, which is higher (~30% of total caloric intake),15 and may not confer the same potential benefits to cancer, considering the higher amino acid content may contribute to glucose and NADPH generation.

**Practical Considerations for Implementing a Ketogenic Diet Protocol**

 If KD is proven to confer benefits to the care of the cancer patient, its implementation in will require close supervision by registered dietitians. As an example, guidelines have been published to provide support for dietitians when implementing KD in the context of epilepsy.77-80 However, only six out of 14 studies hereby reviewed described the provision of nutritional counseling,13, 14, 43, 47, 50 with only one specifically mentioning such counseling was done by registered dietitians.48

Before implementation of this dietary manipulation, a blood and/or urine analysis for disorders of fatty acid metabolism and organic acidurias will be needed, considering that fat is the primary source of energy of this diet. These disorders include carnitine deficiency (primary), carnitine palmitoyltransferase I or II deficiency, carnitine translocase deficiency, β-oxidation defects, pyruvate carboxylase deficiency, and porphyria. Furthermore, complicating factors, such as presence of kidney stones, dyslipidemia, liver disease, failure to thrive, gastroesophageal reflux, poor oral intake, constipation, cardiomyopathy, and chronic metabolic acidosis must also be evaluated.

A comprehensive assessment of nutritional status should be done including anthropometrics, body composition, and record of food intake (online tools and apps can be used; as reviewed elsewhere).81-83 The recommended ketogenic ratio (or percentage of medium-chain triglycerides oil) individualized based on participants’ preferences increases diet adherence.78, 80 Due to the complexity of the dietary regimen and potential low palatability, patient adherence depends upon their commitment, motivation, and support throughout diet implementation and follow-up.

Considering KD has limited amounts of fruit, vegetables, enriched grains, and calcium-rich foods, micronutrient and fiber ingestion are often below recommendations.78, 84 While the American Cancer Society recommends an intake of at least 2.5 cups of vegetables and fruits per day for cancer survivors85 the shortcoming in these necessary food groups, may be met, at least short-term by a multivitamin supplementation with minerals (and trace minerals), and calcium with vitamin D, as recommended by the International Ketogenic Diet Study Group78 and a practical guide80 for epilepsy. As mentioned earlier, once implemented, patient adherence has to be monitored in order to ensure that they have reached and maintained a state of ketosis. Some of the studies included in this review periodically monitored blood glucose and ketone bodies in both urine and blood. These markers can additionally be used to evaluate the metabolic alterations required to inhibit disease progression.13, 14, 39, 40, 44, 46, 48, 50 Although commonly used, urinary ketone body measurement is inferior to serum analysis since the latter is measured quantitatively and is a better general measure of ketosis.86 With ketoadaptation, urinary excretion of ketone bodies falls and the ratio of β-hydroxybutyrate to acetoacetate increases, whereas acetoacetate is the only ketone body detected in certain urine tests. Additional blood parameters such as serum electrolytes and creatinine and liver function tests may also be used to determine hepatic and renal effects of the diet as reported in the protocol as originally developed by Fine *et al*.87

**CONCLUSION**

Considering the prevalence of the Warburg effect across a wide range of human cancers, it would seem sensible to target this distinctive and general feature of cancer metabolism with a metabolic therapy. It is surprising, therefore, that this review shows the relative lack of well-designed rigorous trials testing the impact of specific nutrition interventions to treat cancer or optimize its treatment. Evidence-based research is needed to better elucidate the effects of KD on nutritional status, as well as its impact on cancer prognosis and overall health. Research themes should additionally include its mechanisms of action, dose-response effects, types of cancer impacted, required length of intervention, and prognostic effect. Dietitians play an important role in planning and implementing ketogenic protocols in oncology research settings, as well as ensuring patients’ adherence and optimal nutritional status.

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