Rationale, Feasibility and Acceptability of Ketogenic Diet for Cancer Treatment

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Ketogenic diet has been used for more than 80 years as a successful dietary regimen for epilepsy. Recently, dietary modulation by carbohydrate depletion via ketogenic diet has been suggested as an important therapeutic strategy to selectively kill cancer cells and as adjuvant therapy for cancer treatment. However, some researchers insist ketogenic diet to be highly undesirable as ketogenic diet may trigger and/or exacerbate cachexia development and usually result in significant weight loss. This review revisits the meaning of physiological ketosis in the light of this evidence and considers possibility of the use of ketogenic diet for oncology patients. Article search was performed from 1985 through 2017 and finally 10 articles were analyzed. The review focused on the results of human trials for cancer patients and checked the feasibility of using ketogenic diet for cancer patients as adjuvant therapy. The main outcomes showed improvement of body weight changes, anthropometric changes, serum blood profiles, and reduction in novel marker for tumor progression, TKTL1, and increase of ketone body. Lactate concentration was reduced, and no significant changes were reported in the measurements of quality of life. Ketogenic diet may be efficacious in certain cancer subtypes whose outcomes appear to correlate with metabolic status, but the results are not yet supportive and inconsistent. Therefore, it warrants further studies. (J Cancer Prev 2017;22:127-134)

Key Words: Ketogenic diet, Neoplasms, High-fat diet, Ketosis

INTRODUCTION

Diet and exercise interventions in cancer patients may be of benefit for ameliorating adverse events during cancer treatment and may improve overall survival.1-3 Metabolic processes in cancer are complex and highly regulated, and there is increasing evidence that dietary modulation can be efficacious in managing cancer, i.e., diet rich in fat and protein4 or calorie restriction.5,6 Calorie restriction has been shown to reduce the pro-growth signaling, partially achieved by temporarily reducing glucose and circulating insulin-like growth factor 1, which is highly associated with aging and cancer.7 Also, manipulation of the molecular pathways using calorie restriction has been shown to render cancer cells susceptible to standard cytotoxic treatment with radiation and chemotherapy especially strong for breast cancer. However, considering the high drop-out rate (25%), this indicates that adherence to this low-calorie diet requires high commitment to the study participants.

Ketogenic diet is designed specifically to result in ketosis and is emerging as a metabolic therapy for treating cancer. The mechanism can be explained by inducing shortage of glucose and/or lactate for tumor cells to survive. Vander Heiden et al.8 observed that tumors take up enormous amounts of glucose compared to the surrounding tissue and eventually produces lactate through aerobic glycolytic pathway. Therefore, limitation of glucose availability in cancer cell may reduce energy production of cancer cells, and thereby decreasing tumor proliferation.9
The aim of this review is to assess the clinical evidence of ketogenic diet intervention in cancer patients by analyzing human trials.

STUDY SEARCH AND SELECTION

1. Literature search

The eligible literatures were retrieved by searching through databases (PubMed, MEDLINE, and Springer link) from 1985 until July, 2017. Searching keywords included “ketogenic diet” or “ketone”, “cancer” or “tumor”, and “oncology” with no language restriction and was limited to human clinical trials.

2. Inclusion and exclusion criteria

Articles were included under the following criteria: (1) randomized clinical trials with/without control, (2) prospective cohort study, (3) adult population, and (4) ketone diet composition mentioned. The exclusion criteria were as follows: (1) articles with incomplete data, (2) case studies, and (3) reviews. Letters or comments were irrespective.

3. Data extraction

After the completion of article screening, two investigators independently extracted the data from the eligible studies according to the predesigned protocol. The extracted information was summarized by the first author’s name, journal name, publication year, geographical area of study population, mean age of the participants, sample size of the intervention and control groups, detailed dietary regimen and the length of the study, adherence rate, outcome measures, and results of each article, and finally reported side effects.

ELIGIBLE STUDIES

The process of search strategy is presented in Figure 1. The original search yielded a total of 468 citations (limited to clinical trials, human studies, and years from 1985-2017). First, there were 63 articles after removing the duplicates. Then, 47 articles were excluded because of obvious irrelevance after screening the title and abstract. Six among the remained 16 articles were removed after full-text review: 2 for case studies; 4 without available data. Finally, 10 articles were included in this review. The recommendation of the Cochrane Effective Practice and Organization of Care Review systematic review and meta-analyses, randomized controlled studies, and non-randomized controlled studies were included.10
### Table 1. Clinical trials (including prospective cohort study) using KD in cancer patients

| Author (journal and year) | No. of subjects and characteristics | Cancer type | KD intervention (duration and regimen) | Adherence | Outcome measures and results | Side effect |
|--------------------------|-------------------------------------|-------------|----------------------------------------|-----------|-----------------------------|------------|
| Fearon et al. 11 (Am J Clin Nutr 1988) | Total n = 5 Cachectic patients (mean age, 61 yr) Country: Italy | 2 Gastric cancer 2 Lung cancer 1 Ovarian cancer | 6 days balanced enteral formula (BD) → 7 days KD enteral formula (KD) BD: kcal: 44 kcal/kg/d prot: 1.5 g/kg/d (55% carbohydrate, 31% fat) KD: kcal: 44 kcal/kg/d prot: 1.5 g/kg/d (whey) 4.4 mmol arginine/kg/d (70% of calorie as MCT) | 100% | BD  No change of body weight  No change of nitrogen balance  No change of prot turnover  KD  Increased body weight  No change of nitrogen balance  No change of prot turnover | No GI upset |
| Rossi-Fanelli et al. 12 (Clin Nutr 1991) | Total n = 27 TNM staged Arm A: n = 9 (median age, 61 yr) Arm B: n = 9 (median age, 70 yr) Arm C: n = 9 (median age, 67 yr) Country: Italy | 9 Oesophagus 9 Stomach 9 Colorectal | 14 days intervention Iso-caloric regimen Arm A: parenteral nutrition 100% dextrose 0.24 g/kg/d amino-acid Vitamin minerals Arm B: parenteral nutrition 80% as fat, 20% as dextrose 0.24 g/kg/d amino-acid Vitamin minerals Arm C: oral diet | 100% | No group differences were found in S-phase fraction of cell cycle Total lymphocyte counts Blood glucose Triglycerides Body weight Midarm circumferences Serum albumin Pre-albumin Transferrin Retinol-binding prot | Not mentioned |
| Breitkreutz et al. 13 (Wien Klin Wochenschr 2005) | Total n = 23 Moderately malnourished cancer patients Group A: n = 11 (mean age, 60.6 yr) Group B: n = 12 (mean age, 58.8 yr) Country: Germany | 12 Colorectal 11 Gastric All metastases | 8 weeks of 35 kcal/kg/d, 1.1 g prot/kg/d (normal meals) Nutritional counseling every 14 days Group B 8 weeks of 20 kcal/kg/d, 1.1 g prot/kg/d (fat-enriched liquid diet + normal meals) Nutritional counseling every 14 days | 100% | Group A Average intake 1.556 ± 497 kcal Progressive weight loss Progressive loss of FFM Decrease in serum albumin No change TLC No change of QOL Group B Average intake 1.865 ± 317 kcal Increased body weight Progressive increase of FFM No change in serum albumin Significant decrease of TLC No change of QOL | Not mentioned |
| Author (journal and year) | No. of subjects and characteristics | Cancer type | KD intervention (duration and regimen) | Adherence | Outcome measures and results | Side effect |
|--------------------------|-----------------------------------|-------------|----------------------------------------|-----------|----------------------------|-------------|
| Schmidt et al. (Nutr Metab (Lond) 2011) | Total n = 16 Metastatic tumors (mean age, 50.4 yr) Country: Germany | 3 Ovarian cancer 1 Breast cancer 1 Osteosarcoma 5 Gastrointestinal cancer 2 Thyroid cancer 1 Endometrial 1 Lung cancer 1 Granulosa cell tumor 1 Parotis carcinoma | 3 months of low CHO diet (KD) - CHO limitation to 70 g/d, 20 g/meal - 2 liquid meals (21 g fat, 5 g CHO, 14 g prot)/meal | 91% (2 died, 9 dropped out) | KD 3 patients reached ketosis No change: Global health status Functional score Blood glucose, TG creatinine, Albumin Increase: appetite loss, constipation Decrease: fatigue, pain Decrease: insomnia | No diet related adverse events |
| Fine et al. (Nutrition 2012) | Total n = 109 Incurable, advanced cancer (mean age, 62.9 yr) Country: USA | 2 Breast cancer 3 Colorectal 1 Ovary 1 Fallopian tube 2 Lung 1 Esophagus | 26-28 days KD intervention - < 5% of kcal as CHO - Increase fat and prot encouraged | 100% | KD Increased weight loss (−3.0 kg) Energy deficit (−35%) No change of serum glucose Increased dietary ketosis Inverse relationship of insulin vs. β-hydroxybutyrate | No unsafe adverse effects Except constipation, leg cramps, reversible fatigue |
| Schroeder et al. (Nutr Cancer 2013) | Total n = 12 Head and neck cancer (mean age, 64 yr) Country: Germany | 2 Larynx 3 Oral cavity 2 Hypopharynx 3 Oropharynx Unknown primary | 5 days KD intervention Microdialysis | 100% | KD Increase of urea in tumor tissues No change in plasma glucose Decrease in lactate concentration in tumor tissues Decrease in lactate/pyruvate ratio | Not mentioned |
| Bieger et al. (Int J Oncol 2014) | Total n = 20 Patient from ERGO trial (mean age, 57 yr) Country: Germany | Recurrent malignant glioma | 36 days intervention KD diet: ketogenic ratio, 3.41 : 1 - CHO limitation to less than 60 g/d - No calorie restriction - 500 mL yoghurt + plant oil | 85% | KD Increased weight loss No change in blood glucose, HbA1c Lipid profiles Leukocytopenia in 2 patients Overall survival 32 weeks | Few reports on diarrhea, constipation but no major concern or toxicity |
| Jansen and Walch (Oncol Lett 2016) | Total n = 78 Prospective cohort study (mean age, 68 yr) Country: Germany | 18 Breast 16 Prostate 9 Colon 5 Lung 5 Othoharyngeal 25 Other | 10 mo-2 yr Not mentioned | Not mentioned | KD Reduction of TKTL1 (novel marker associated with tumor progression) | Not mentioned |
| Author(s) and Source | No. of subjects and characteristics | Cancer type | KD intervention (duration and regimen) | Adherence | Outcome measures and results | Side effect |
|----------------------|-------------------------------------|-------------|----------------------------------------|-----------|----------------------------|-------------|
| Klement and Sweeney19 (BMC Res Notes 2016) | Total n = 6 (mean age, 60.3 yr) Country: Germany | 1 Breast 1 Prostate 3 Rectum 1 Lung during RT | 32-73 d KD with weekly counseling - CHO limitation to 50 g/d - Encourage to consume olive oil, coconut oil, butter, fatty fish, cheese, meat | Not mentioned | KD - Decreased BW in 2 patients - Decreased fat mass in 2 patients - No change in hydration status - Decreased phase angle - Increased ketone body | Not mentioned |
| Tan-Shalaby et al.20 (Nutr Metab (Lond) 2016) | Total n = 17 Advanced cancer pts not on hemotherapy (mean age, 65 yr) Country: USA | 6 Gastrointestinal 2 Lung 3 Skin cancer 1 Prostate 1 Thyroid 2 Brain cancer 1 Head/neck 1 Renal | 16 weeks (checked every 4 wk) KD - CHO limitation to 20-40 g/d (no restriction of cal, prot, fat) | 64.7% (6 for 8 wk, 4 for 16 wk, 3 beyond 16 wk) KD | KD - 13% wt loss at week 16 No changes in glucose, creatinine, SBP/DBP, lipid profile, WBC count, urk acid, albumin, ALT Slight improvement of EORTC QLQ-30 | 8 Weight loss 7 Hyperuricemia 2 Hyperlipidemia 2 Pedal edema 2 Anemia 2 Halitosis 2 Pruritus 2 Hypoglycemia 2 Hyperkalemia 2 Hypokalemia 2 Hypomagnesemia 2 Flu-like symptom |

KD, ketogenic diet; BD, balanced diet; MCT, medium chain triglyceride; prot, protein; GI, gastrointestinal; FFM, fat free mass; TLC, total lymphocyte count; QOL, quality of life; CHO, carbohydrate; TG, total cholesterol; RT, radiation therapy; BW, body weight; wt, weight; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; ALT, alanine aminotransferase; EORTC QLQ-30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30.
SUMMARY OF THE STUDY OUTCOMES OF ELIGIBLE ARTICLES

The detailed information of ketone diets from the selected articles are summarized in Table 1.11-20 A total of 214 subjects were included in the review. Most of the studies were intervention trials except for one prospective cohort study. The mean age of the studies was mostly from late fifties to early seventies. Eight out of ten articles were submitted from European countries (Germany and Italy) and only two were from USA. The duration of experimental intervention ranged from 5 days to 2 years and the outcome measures were mainly focused on the body weight and composition and blood profile. One article measured quality of life (QOL). The adherence rate in 5 studies were 100%, and the rest were from 31% to 85%. Reported side effects in the studies were relatively minor and included only few reported constipation, leg cramps, diarrhea, etc. Subjects maintained on ketogenic diet for a relatively short period (2 weeks in the study by Rossi-Fanelli et al.; 1 week in the study by Fearon et al.; 5 days in the study by Schroeder et al.) did not show any significant changes of the markers, such as body weight or blood profile except for decrease in lactate concentration in the tumor tissues. Meanwhile, when subjects were maintained for a longer period, such as 8 weeks, ketogenic diet (normal meal + fat-enriched liquid diet) successfully showed increased energy intake and body weight of the subjects.13 Ketogenic diet in this study was used for only malnourished gastro-intestinal cancer patient with metastases, suggesting the possibility of application in specific cancer patients. Evaluation on anticancer biomarkers was not measured in most of the articles except for study by Jansen and Walach who found that TKTL1, a novel marker associated with tumor progression, was reduced by a 2-year ketogenic diet.

Notably, the results from Fine et al., Rieger et al., and Klement and Sweeney9 showed that ketone diet increased significant weight loss. These results showed that unlike the consistent ketogenic effects on epilepsy patients, ketogenic effects on cancer patients were not consistent in this review.

KETOCGENIC DIET AS A CANCER THERAPEUTIC STRATEGY

Recently, ketogenic diet has been newly emerged as a cancer therapy in both animal models and humans. Some of the preclinical studies have shown the effect of ketogenic diet to reduce tumor growth and improve survival in animal models of malignant glioma, prostate cancer, colon cancer, and gastrointestinal cancer. Low calorie diet, such as fasting inducing a state of ketosis, has been shown to enhance the responsiveness of cancer cells to chemotherapy in pre-clinical cancer therapy models and to ameliorate some of chemotherapy-induced side effects in normal tissues.29 More recently, numerous case reports were reported. First report was derived from confirmed glioblastoma multiforme treated with standard therapy together with a restricted ketogenic diet, and the response observed in the case suggested the possibility of calorie-restricted ketogenic diet.30 Ketogenic diet has been studied intensively in the European country including Germany. In these studies, the physical condition was successfully improved and tumor shrinkage was observed by ketogenic diet.14 The studies here reviewed lack greatly in the homogeneity of type of cancer, location of cancer, the stages of cancer, and the treatment course of the cancer, and thus the results cannot be generalized. Because ketogenic diet normally results in an increased weight loss, there are continuous concerns to apply this diet for cancer patients. In this review, however, we found that ketogenic diet showed no significant adverse effects. It may be possibly because the subjects were adults, while in children long-term ketogenic diet induces renal damage such as kidney stones.31 Any adverse effects reported in this review were constipation, diarrhea, fatigue, etc. In healthy obese adults with low-carbohydrate ketogenic diet for 6 months, the only adverse effects reported were an increase in the level of low-density lipoprotein cholesterol and some shakiness and uneasiness.32

Studies described in this review assessed the effects of a ketogenic diet in cancer patients. Only ten studies were analyzed and the characteristics and study design, the ketogenic diet regimen, the length of study, cancer type and stage, and site were heterogeneous, thereby contributing to a poor conclusion. As for ongoing clinical trials, there are currently 62 trials assessing low carbohydrate diets as a potential therapy for a variety of diseases of which 13 trials are assessing ketogenic diet as an adjuvant cancer therapy. Three of the studies are not initiated, but, one study with pancreatic cancer patients was terminated because of the low participation and adherence (Table 2).

CONCLUSION

Our main aim in this review was to assess the feasibility and acceptability of ketogenic diet and to assess the changes of outcome variables, such as body composition, biochemical blood
Table 2. Ongoing clinical trials from clinicalTrials.gov (https://clinicaltrials.gov) (accessed on 08/04/2017)

| Title                                                                 | Recruitment   | Study Results | Conditions                        | Interventions                                      |
|----------------------------------------------------------------------|---------------|---------------|-----------------------------------|----------------------------------------------------|
| 1 Ketogenic Diet for Recurrent Glioblastoma                          | Completed     | Has results   | Recurrent glioblastoma            | Dietary supplement: TAVARLIN                        |
| 2 Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: A Pilot Study | Recruiting    | No results available | Glioblastoma multiforme          | Other: ketogenic diet                               |
| 3 Ketogenic Diet and Prostate Cancer Surveillance Pilot               | Enrolling by invitation | No results available | Prostate cancer                  | Other: surveillance                                |
| 4 Ketogenic Diet Adjunctive to Salvage Chemotherapy for Recurrent Glioblastoma: A Pilot Study | Recruiting    | No results available | Glioblastoma multiforme          | Dietary supplement: ketogenic diet, standard diet   |
| 5 Impact of a Ketogenic Diet Intervention During Radiotherapy on Body Composition | Recruiting    | No results available | Neoplasms                        | Dietary supplement: ketogenic breakfast, standard diet, radiation, chemo/therapy |
| 6 Ketogenic Diet Phase 1 for Head & Neck Cancer                      | Terminated    | No results available | Head and neck neoplasms          | Dietary supplement: Ketogenic diet                 |
| 7 Ketogenic Diet With Concurrent Chemoradiation for Pancreatic Cancer | Terminated    | No results available | Pancreatic neoplasms             | Dietary supplement: ketogenic diet, standard diet   |
| 8 Ketogenic Diet Treatment Adjunctive to Radiation and Chemotherapy in Glioblastoma Multiforme: A Pilot Study | Recruiting    | No results available | Glioblastoma multiforme of brain | Other: ketogenic diet, standardized diet           |
| 9 Calorie-restricted, Ketogenic Diet and Transient Fasting During Radiation for Patients With Recurrent Glioblastoma | Recruiting    | No results available | Recurrent glioblastoma           | Dietary supplement: calorie-restricted ketogenic diet, fasting, standard diet |
| 10 Restricted Calorie Ketogenic Diet as a Treatment in Glioblastoma Multiforme | Recruiting    | No results available | Glioblastoma multiforme          | Other: MKD, MCT                                    |
| 11 Ketogenic Diets as an Adjuvant Therapy in Glioblastoma             | Recruiting    | No results available | Glioblastoma multiforme          | Other: MKD, MCT                                    |
| 12 Restricted Calorie Ketogenic Diet in Advanced Cancer               | Recruiting    | No results available | Cancer                           | Other: ketogenic diet                               |
| 13 Ketogenic Diet in Advanced Cancer                                  | Completed     | Has results    | Cancer                            | Other: ketogenic diet                               |

MKD, modified ketogenic diet; MCT, medium chain triglyceride ketogenic diet.

profiles, and QOL. From this review, we found further evidence that ketogenic diet in cancer patients is safe and feasible as an adjuvant therapy. As described above, we could conclude that in order to see any significant progression or improvement by ketogenic diet, at least 3 to 4 weeks of ketogenic diet is required. Additionally, we suggest that not only body composition but also biomarker or measures for tumor size or tumor metabolism assessment is essential. We also conclude that the acceptability for ketone diet may be better in some cancer type (better in glioblastoma than gastric cancer).

In conclusion, ketogenic diet can be safely used to cancer patients if carefully monitored. Most importantly, we have to establish standardized treatment protocol which include the length and regimen for ketogenic diet.

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CONFLICTS OF INTEREST

No potential conflicts of interest were disclosed.

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