**Table 1.** Literature search of human studies investigating ketogenic diet in cancer.

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| **Reference****[Year]** | **Study Design** | **Sample Characteristics** | **Cancer type** | **Cancer Treatment** | **Intervention**a | **Measurements** | **Results** |
| Fearon et al.40[1988] | Clinical Trial. | Cachectic.N = 5Three women.Two men. | Female (ovarian, gastric, lung).Male (gastric, lung). | NMb | 13 days of intervention.Nasogastric feeding at a constant rate over 24 hours.Day 1 to 6 (normal diet):44 kcal/kg/day1.5 g protein/kg/day (whey protein)4 mmol arginine/kg/day55% carbohydrate21% fatDay 7 to 13 (ketogenic diet):44 kcal/kg/day1.5 g protein/kg/day (whey protein)4 mmol arginine/kg/day70% fat (MCTf) | Body weight | Day 6: NSc.Day 13: Sd (Increased). |
| Performance score | Day 6: No changee.Day 13: Increasede. |
| [Serum sodium] | Day 6: NSc.Day 13: Sd (Increased). |
| [Serum potassium] | Day 6: NSc.Day 13: NSc. |
| [Serum chloride] | Day 6: NSc.Day 13: NSc. |
| [Serum bicarbonate] | Day 6: Sd (Decreased).Day 13: Sd (Increased). |
| [Urea] | Day 6: NSc.Day 13: NSc. |
| [Creatinine] | Day 6: NSc.Day 13: NSc. |
| [Serum phosphate] | Day 6: Sd (Decreased).Day 13: Sd (Increased). |
| Liver function | Day 6: NSc.Day 13: NSc. |
| [Serum albumin] | Day 6: Sd (Decreased).Day 13: Sd (Increased). |
| Ketone bodies | Day 6: NSc.Day 8, 10 and 13: Sd (Increased). |
| Glucose | Day 6: NSc.Day 8, 10 and 13: Sd (Decreased). |
| Lactate | Day 6: NSc.Day 13: Sd (Decreased). |
| Pyruvate | Day 6: NSc.Day 13: Sd (Decreased). |
| FFAg | Day 6: NSc.Day 13: NSc. |
| Alanine | Day 6: NSc.Day 13: NSc. |
| Glutamine | Day 6: NSc.Day 13: NSc. |
| Insulin | Day 6: NSc.Day 13: NSc. |
| Nitrogen balance:Whole-body protein synthesis, degradation and turnover ratio | Day 6: NSc.Day 13: NSc. |
| Urinary creatinine excretion | Day 6: NSc.Day 13: NSc. |
| Diet toleration | Well tolerated. |
| Rossi-Fanelli et al.42[1991] | Controlled Clinical Trial. | N = 2713 women.14 men.N = 9 in each group. | Oesophageal (n = 9), gastric (n = 9), and colorectal (n = 9). | None of the patients had previously received anti-neoplastic therapy. | 14 days of intervention.Arm A (parenteral diet):Total caloric requirement entirely met by dextrose.0.24 g/kg/day of amino-acids.Vitamins and minerals.Arm B (parenteral diet):80% fat.20% dextrose.0.24 g/kg/day of amino-acids.Vitamins and minerals.Arm C (oral diet) – Control:Isocaloric.Isonitrogenous. | Cancer cell replication rate | Within: NSc.Between: NSc. |
| Total lymphocytes count | Within: Sd (Decreased in Arms A and B).Between: NSc. |
| Blood glucose | Within: NSc.Between: NSc. |
| Triglyceride levels | Within: NSc.Between: NSc. |
| Body weight | Within: NSc.Between: NSc. |
| Triceps skin-fold | Within: NSc.Between: NSc. |
| Mid-arm circumference | Within: NSc.Between: NSc. |
| Serum albumin | Within: NSc.Between: NSc. |
| Pre-albumin | Within: NSc.Between: NSc. |
| Transferrin | Within: NSc.Between: NSc. |
| Retinol-binding protein | Within: NSc.Between: NSc. |
| Bozzetti et al.44[1996] | Case Report. | N = 1Adult man. | Desmoid tumor. | NMb. | 5 months.Total parenteral nutrition.28 non-protein lipid kcal/kg/day (70% asLCTh and 30% MCTi).1.5 g amino acid per kg/day.Approximately 40 g/day of glucose (oral).4g/day of carnitine for one month. Vitamins and electrolytes provided. Hydrazine sulphate for 2 months. | Body weight | No changee. |
| Total protein | Decreased, but maintained within normal rangese. |
| Serum albumin | Increased, but maintained within normal rangese. |
| Cholinesterase | Increased, but maintained within normal rangese. |
| Lymphocytes | Decreased, but maintained within normal rangese. |
| Hemoglobin | Decreased and maintained below normal rangese. |
| Cholesterol | Increased, but maintained within normal rangese. |
| Triglycerides | Increased and maintained above normal rangese. |
| Total bilirubin | Decreased and maintained below normal rangese. |
| ASTi | Increased, but maintained within normal rangese. |
| ALTj | Decreased and maintained within normal rangese. |
| GGTk | Increased and maintained above normal rangese. |
| Alkaline phosphatase | Decreased and maintained within normal rangese. |
| Prothrombin time | Increased, but maintained within normal rangese. |
| Glucose | Decreased, but maintained within normal rangese. |
| Serum urea | Increased, but maintained within normal rangese. |
| Serum creatinine | No changee. |
| Urine ketone bodies | Increasede. |
| Respiratory quotient | Decreasede. |
| Lactate | No changee. |
| Tolerance to diet | Diet well tolerated. |
| Nitrogen balance | Increasede. |
| Tumor size | NSc. |
| Breitkreutz et al.43[2005] | Randomized Controlled Trial. | Moderately malnourished patients.N = 23Group A (n = 11)Group B (n = 12) | Gastrointestinal adenocarcinoma (colorectal and gastric). | Patients received chemotherapy. | 56 days of intervention.Group A (conventional natural diet):35 non-protein kcal/kg/day.1.1g of protein/kg/day.Group B (commercial fat-enriched drink + natural diet):35 non-protein kcal/kg/day.1.1g of protein/kg/day.Drink supplied at least 20 non-protein kcal/kg/day (9.3 grams of fat/ 100 mL).Nutritional counseling was provided to both patient groups every 14 days. | Body weight | Within: Sd (Increased in Group B).Between: Sd (Increased in Group B after 4 and 8 weeks). |
| FFMl | Within: NSc.Between: Sd (Increased in Group B). |
| TBFm | Within: NSc.Between: NSc. |
| BCMn | Within: Sd (Decreased in Group A).Between: Sd (Increased in Group B after 4 and 8 weeks). |
| ECMo | Within: NSc.Between: NSc. |
| Quotient ECMo/BCMn | Within: Sd (Increased in Group A).Between: Sd (Decreased in Group B). |
| [Serum albumin] | Within: Sd (Decreased in Group A).Between: NSc. |
| [Serum cholinesterase] | Within: Sd (Decreased in Group A).Between: Sd (Increased in Group B). |
| Total lymphocyte count | Within: Sd (Decreased in Group B).Between: Sd (Decreased in Group B). |
| Quality of life | Within: Sd (Decreased in Group A, and increased in Group B).Between: NSc. |
| Zuccoli et al.46[2010] | Case Report. | 65-year-old woman. | Glioblastoma multiforme. | Radiation and chemotherapy. | 14 days of intervention.Calorie-restricted ketogenic diet:600 kcal/day42 g fat/dayVitamins and minerals supplementation. | Body weight | 8 weeks after intervention: Decreasede. |
| Blood glucose levels | 8 weeks after intervention: Decreasede. |
| Urinary ketones | 8 weeks after intervention: Increasede. |
| Tumor | 10 weeks after suspension of the intervention: tumor recurrencee. |
| Diet-related adverse events | Not found. |
| Tolerance to diet | Well tolerated. |
| Schmidt et al.50[2011] | Prospective Observational Pilot Study. | N = 16.12 women.4 men. | Advanced/metastatic tumor stage of solid malignant tumors of different origins. | No established therapeutic option available(no chemo- or radiotherapy). | 90 days of intervention.Ketogenic diet:Less than 70 g carbohydrate/day.2.6 g/day of omega-3 fatty acid.3 tablespoons/day of olive, flaxseed and hempseed oils with the principle meals.Patients were instructed in the principals and practical realization of the diet. | Dropout | Did not tolerate the diet: 2 patients.Died early: 2 patients.Unable to stick to the diet: 1 patient.Stopped due to progress of the disease: 4 patients.Stopped due to treatment: 1 patient.Stopped due to weight loss and weakness: 1 patient. |
| Adherence to diet | 31% of the patients. |
| Emotional functioning and insomnia | Improvede. |
| Diet-related adverse events | Not found. |
| Ketonuria | Reached in 3 patientse. |
| Global health status and functional score | No changee. |
| Physical and role functioning | Decreasede. |
| Appetite loss, constipation or diarrhea | Increasede. |
| Fatigue and pain | Increasede. |
| Blood cholesterol | Sd (Decreased). |
| HDLp | Sd (Decreased). |
| LDLq | Sd (Decreased). |
| LDLq/HDLp relation | Sd (Decreased). |
| Serum triglycerides | NSc. |
| Blood glucose levels | NSc. |
| Creatinine | NSc. |
| Albumin | NSc. |
| Blood urea nitrogen | Sd (Increased, but still within normal range). |
| Liver parameters | Sd (Decreased, but still within normal range). |
| Total leukocyte count | Sd (Increased). |
| Body weight | Sd (Decreased). |
| Disease progression | Stable diseasee. |
| Fine et al.13[2012] | Pilot Clinical Study. | N = 10.7 women.3 men. | Incurable, advanced cancer (various types), with progressive disease after at least two conventional anticancer treatments. | Chemotherapy was discontinued for at least 2 weeks before trial initiation. | 26 to 28 days of intervention.The carbohydrate intake was targeted at no higher than 5% of total energy. Increased fat and protein ingestion was encouraged to attempt to maintain stable calorie intake and weight.Investigators instructed participants on how to consume the diet. | Mean caloric intake | Sd (Decreased when compared to baseline). |
| Body weight | Sd (Decreased). |
| Disease progression | Progressive disease in 4 patientse.Stable disease in 5 patientse.Partial remission in 1 patiente. |
| Dietary ketosis | Sd (Increased in patients with stable disease or partial remission). |
| Ketosis and serum insulin levels | Sd (Inverse relation between insulin secretion and β-hydroxybutyrate). |
| Blood glucose levels | NSc. |
| Diet-related adverse events | Short-term reversible fatigue, constipation and leg cramps. |
| Schroeder et al.41[2013] | Clinical Trial. | N = 11.1 woman.9 men. | Advanced stage cancer (stages III and IV). | NMb | 5 days of intervention.Ketogenic diet. | Urea | Increased in tumor tissue compared to tumor-free mucosae. |
| Glucose | Increased in tumor tissue compared to tumor-free mucosae. |
| Serum glucose | No changee. |
| Lactate | Decreased in tumor tissue compared to tumor-free mucosae. |
| Pyruvate | Increased in tumor tissue compared to tumor-free mucosae. |
| Circadian rhythm of the tumor metabolism | No changee. |
| Champ et al.39[2014] | Retrospective Study. | N = 6. | Glioblastoma multiforme (stages III-IV). | Treatment with concurrent chemoradiotherapy and adjuvant chemotherapy. | Intervention period varied between 3 and 12 months.Ketogenic diet:30 to 50 g of carbohydrate/day.77% of total energy intake of fat, 8% of carbohydrate, and 15% of protein. | Serum glucose levels | Sd (Decreased). |
| Diet-related adverse events | Grade I constipation and fatigue, grade II fatigue. |
| Diet tolerance | Well tolerated in all patients. |
| Survival | 4 patients alive at a median follow-up of 14 monthse. |
| Body weight | Decreasede. |
| Ketosis | Confirmed four out of six patientse. |
| Rieger et al.14[2014] | Prospective, Single-Arm Pilot Study. | N = 20.13 women.7 men. | Recurrent glioblastoma. | Treatment with radio and chemotherapy. | 6-18 weeks of intervention median time.Ketogenic diet:60 g of carbohydrate/day.500 mL of highly fermented yogurt/day provided.2 different plant oils/day provided.No calorie restriction (patients instructed to eat to satiety).Patients were instructed on how to prepare their diet. | Body weight | Sd (Decreased). |
| Detectable ketosis | At least once in 92% of the patients evaluatede. |
| Blood glucose | NSc. |
| HbA1cr | NSc. |
| Lipid profile | NSc. |
| Diet-related adverse events | Not found. |
| Leukocytopenia | Present in 2 patientse. |
| Disease progression | Stable disease in 3 patientse. |
| Median overall survival | 32 weeks after start of the interventione. |
| Adherence to diet | 85% of the patients. |
| Diet toxicity | Not observed. |
| Branca et al.45[2015] | Case Report. | N = 1.1 woman. | Recurrent breast cancer. | No treatment. | 3 weeks of intervention.Oral vitamin D3 (10,000 IU/day) + ketogenic diet rich in olive oil. | Human epidermal growth factorreceptor | Decreased expressione. |
| Progesterone receptor | Increased expressione. |
| Schwartz et al.48[2015] | Case Report. | N = 2.2 men. | Glioblastoma multiforme. | No treatment. | 12 weeks of intervention.Energy-restricted ketogenic diet:Commercial formula to provide a 3:1 ratio of fat grams to the grams supplied by protein and carbohydrate.0.6 g of protein/kg/day.20-25 kcal/kg/day + 20% calories restriction/day.Patients were trained by an experienced RD. | Disease progression | Tumor progression during the intervention in both patientse. |
| Body weight | Decreasede. |
| Blood glucose | Unstable (did not decreased enough to desired values)e. |
| Ketone bodies | Increased in both patientse. |
| Serum cholesterol | Increased in 1 patiente. |
| LDLq | Increased in 1 patiente. |
| Diet-related adverse events | Headache reported between weeks 6 and 8. |
| Jansen et al.49[2016] | Systematic, prospective cohort study. | N = 78.35 women.43 men. | Any type of tumor, or recurrence of a tumor or metastasizing disease during the 10 years previous to the initiation of the study. | NMb | 10 months of intervention.Ketogenic diet. | Adherence to diet | 17%(Partially ketogenic diet: 8%;Fully ketogenic diet: 9%). |
| Disease progression in patients who adhere to ketogenic diet | Improvement: 3 patientse.Stable disease: 7 patientse.Progressive disease: 1 patiente. |
| TKTL1s levels | Sd (Increased in active disease).Sd (Decreased in patients who adhered to ketogenic diet). |
| Klement et al.47[2016] | Case Report. | N = 6.2 women.4 men. | Various cancer types. Women (breast and rectum). Men (prostate, rectum, and lung) | Treatment with radio and/or chemotherapy. | 32 to 73 days of intervention.Self-administered ketogenic diet:<50 grams of carbohydrate per day (ratio less than 2:1, fat to carbohydrate + protein).Patients were instructed about the diet once per week. | General subjective feeling on the diet | “Good” for all patientse. |
| Diet-related side effects | Not reported. |
| Overall quality of life | No change in all patientse. |
| Body weight | Sd (Decreased in 2 patients). |
| Fat mass | Sd (Decreased in 3 patients). |
| FFMl | Sd (Increased in 3 patients). |
| Hydration status | NSc (No change in all patients). |
| Phase angle | Sd (Decreased in 1 patient). |
| Biochemical blood parameters (complete blood count, lipid panel, IGF-1t, and TSHu) | NSc. |
| β-hydroxybutyrate blood levels | Sd (Increased in all patients). |
| Correlation between β-hydroxybutyrate and glucose blood levels | Sd (Negative correlation). |

aUnless otherwise specified, a registered dietician (RD) was not involved, or the information was missing from the study.

bNM=not mentioned.

cNS=not statistically significant (p>0.05).

dS=statistically significant (p<0.05).

eNo statistical analysis conducted.

fMCT=medium-chain triglyceride.

gFFA=free fatty acids.

hLCT=long chain triglyceride.

iAST=aspartate aminotransferase.

jALT=alanine transaminase.

kGGT=gamma-glutamyl transpeptidase.

lFFM=fat free mass.

mTBF=total body fat.

nBCM=body cell mass.

oECM=extracellular mass.

pHDL=high density lipoprotein.

qLDL=low density lipoprotein.

rHbA1c=glycated hemoglobin.

sTKTL1=transketolase-like-1.

tIGF-1=insulin-like growth factor 1.

uTSH=thyroid-stimulating hormone.