Does a ketogenic diet have any adverse effect on quality of life, physical activity, or biochemical factors in patients with breast cancer? A randomized controlled trial.

Adeleh Khodabakhshi (khodabakhshiadeleh@yahoo.com)
Kerman University of Medical Sciences
Mohammad Esmaeil Akbari
Shaheed Beheshti University of Medical Sciences
Thomas N. Seyfried
Boston University
Maryam Mahmoudi
Tehran University of Medical Sciences
Miriam Kalamian
Dietary Therapy Hamiltton, MT, USA
Nariman Moradi
Iran University of Medical Sciences
Maryam Beheshti
Mofid Hospital
Sayed Hossein Davoodi
Shaheed Beheshti University of Medical Sciences

Research

Keywords: Ketogenic diet, breast cancer, quality of life, physical activity, lactate, alkaline phosphatase

Posted Date: March 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-19350/v1

Version of Record: A version of this preprint was published on August 22nd, 2020. See the published version at https://doi.org/10.1186/s12937-020-00596-y.

Abstract

Introduction: Despite the potential benefits of ketogenic diets (KDs) for cancer**,** evidence of its effects on quality of life is lacking. This study has aimed to find out whether KD has adverse effects on quality of life, physical activity, and biomarkers in patients with breast cancer.

Method: A total of 80 patients with locally advanced or metastatic breast cancer were randomly assigned to either a KD or a control group for this 12-week trial. Concurrent with the first, third, and fifth chemotherapy sessions (12-week), the quality of life, physical activity, and biomarkers (thyroid function tests, electrolytes, albumin, ammonia, ALP, lactate and serum ketones) were assessed. Dietary intake was also recorded on admission and the end of the treatment.

Results: No significant differences were seen in the quality of life or physical activity between the two groups after 12 weeks; however, the KD group showed a better global quality of life compared to the control group at 6 weeks (P=0.02). Also, serum lactate and ALP levels decreased significantly in KD group compared to the control group after intervention (10.7±3 vs 13.3±4, 149±71 vs 240±164, P=0.02 and P=0.007, respectively). KD did not have any negative impact on thyroid hormones, electrolytes, or physical activity. Compliance among KD subjects ranged from 66.7% to 79.2% as assessed by dietary intake and serum ketones levels of >0.5.

Conclusion: According to our results, chemotherapy combined with KD does not negatively impact the quality of life, physical activity, or biomarkers tracked during our study. Ketosis may improve the effectiveness of chemotherapy in patients with breast cancer in part by decreasing lactate and ALP.

Introduction

Ketogenic diets (KDs) are high in fat and very low in carbohydrate (CHO). They have been used as a dietary treatment for childhood epilepsy for nearly a century (1). Recently, KDs have gained the attention of cancer researchers due to their potential impact on cancer cell metabolism (2). Despite the growing evidence of possible anti-tumor benefits, there are still some concerns about potential side effects of KDs in cancer patients, including micronutrient deficiencies, appetite reduction, nausea, constipation (3), fatigue (4), hyperlipidemia and especially unintended weight loss (3, 5). KDs are perceived as restrictive in nature which may add to the burden of patients who already suffer from considerable physical, emotional, and financial stress, all of which are known to negatively impact quality of life (QoL). In addition, alterations in physical and mental function during cancer treatment are prevalent. It is estimated that 25–99% of patients undergoing cancer treatment suffer from cancer-related fatigue (6). Prior studies have found that KD may improve physical and mental well-being (7). Less fatigue has been reported in overweight and obese adults following low-glycemic compared to high-glycemic diets (8). Results of three studies assessing the QoL with validated European Organization for Research and Treatment core QoL questionnaire were inconsistent (9–11). A small trial among advanced cancer patients has shown

improved insomnia and emotional function after a three-month KD intervention (12). Other studies have suggested enhanced cognitive function (9, 13).

Hunger is a reported side effect of restricted KDs. Previous research demonstrates that low-CHO diets compared to low fat diets reduce feelings of hunger (14). To date, only four studies have assessed quality of life in adult patients with cancer (7, 9–11). A recent systematic review has highlighted the need for additional, larger investigations in this field (15).

The goal of this clinical trial was to determine whether KD adversely affects QoL, dietary intake, physical activity, and specific biomarkers in individuals with breast cancer while also evaluating compliance to KD guidelines in these patients.

Methods

Complete details of the study methods have previously been published (16). The study protocol was approved by the National Nutrition and Food Technology Research Institute (NNFTRI), Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran (IR.SBMU.NNFTRI.REC.1396.187). Prior to participation in the study, all participants provided written informed consent. This study was a randomized controlled open-label clinical trial open to breast cancer patients with locally advanced or metastatic breast cancer and receiving chemotherapy for at least 12 weeks at the medical oncology clinic at Shohada-e-Tajrish hospital, Cancer Research Center, Tehran, Iran from May to October 2018. Inclusion was limited to patients between 18 and 70 year old. Exclusion criteria excluded patients with significant cardiac, renal or neurologic comorbidities, those with malnutrition or diabetes, pregnant women, and those with a Karnofsky index less than 70. Using block balanced randomization method, patients were assigned to the intervention (n = 40) or control (n = 40) groups. Randomization was computer-generated by a statistician who was not working with the patients. The project coordinator enrolled and assigned participants to their interventions. Both the KD and the control diet were calculated to be eucaloric. The KD consisted of 6% of calories from CHO, 19% from protein, 20% from medium-chain triglyceride (MCT) oil, and 55% from fat. Diet-specific nutritional counseling was prescribed by a dietitian to each participant in individual face-to-face meetings. Patients received weekly counseling via phone or app (WhatsApp) and were evaluated for compliance and possible side effects. To enhance patient adherence, diet recommendations were further individualized and appropriate recipes were provided to patients. Patients were asked to refrain from eating any grains, grain products, starchy vegetables, or sugar. Dietary CHO were limited to nonstarchy vegetables, and dietary proteins were obtained primarily from egg, meat, poultry and fish. Small amounts of lower sugar berries and nuts were allowed as long as they did not exceed the CHO limit in the diet prescription. Subjects were encouraged to increase their fat intake from a variety of sources, including olive oil, butter, cream cheese, and cream. Patients were asked to choose only the foods indicated in the diet provided to them. Patients were also encouraged to use medium-chain triglyceride (MCT) oil. MCT oil, an odorless and tasteless saturated fat, does not require bile or pancreatic enzymes for digestion. It is easily converted to ketones in the liver thereby enhancing ketosis. Every two weeks, 500 ml of MCT oil from Nutricia (Erlangen, Germany) was given to each subject in this KD group.

For better tolerance, initial dosage of MCT was kept low and increased daily over a 6 day period until maximum tolerable dosage was achieved. Stable ketosis was defined beta-hydroxybutyrate (βHB)concentrations of > 0.3 mmol/l.

Patients in the control group were instructed to follow a standard diet containing 55% of calories from CHO, 15% from protein, and 30% from fat. Dietary compliance was checked by assessing blood βHB levels every 3 weeks and dietary intake at baseline and end of the study.

Quality of life (QOL) assessment
The patients' QoL was assessed using the EORTC QLQ-C30 (version 2) and IORTC QLQ-BR23 questionnaires developed by the European Organization for Research and Treatment of Cancer. The validity and reliability of the questionnaires has previously been evaluated in Iran (17, 18). The questionnaires were completed at enrollment, at 6-weeks, and at the end of the intervention.
Dietary intake assessment
A 24-hour dietary recall was obtained for a total of three days (one weekend day and two workdays) both at the beginning and end of the study. Dietary intake was analyzed by Nutritionist IV software (xxx).
Physical activity assessment

Physical activity was measured by the IPAC (International Physical Activity) questionnaire at baseline, at 6 weeks, and at the end of the study.

Biochemical (biomarker) assessment

Fasting blood sampling for serum Na^{+}, K^{+}, Ca^{++}, P^{+}, lactate, Mg^{++}, LDH, albumin, ammonia, and ALP were performed at baseline, middle of the intervention (6-weeks), and at 12 weeks. Also T_3, T_4, and TSH were measured at baseline and the end of the intervention.

Statistical analysis

Considering the 80% power and α = 0.05, the sample size was calculated as 30 individuals per group. Assuming a 20% dropout during the 12 weeks of the study, the final number of participants was calculated as 40 patients in each group.

Statistical analysis was carried out according to the intention-to-treat protocol. Continuous variables were tested for normal distribution by the Kolmogorov-Smirnov test and then reported as mean ± standard deviation or median as appropriate. Student t-test or Mann–Whitney U test was used to compare the continuous variables between the two groups. Paired sample t-test or Wilcoxon was used to compare the continuous variables within the two groups. The ANCOVA test was used to eliminate the effect of confounding factors.

Data were analyzed using the SPSS version 18.0 software (Chicago, IL, USA) and Stata version 13. $P < 0.05$ was considered as statistically significant.

Results

Detailed patient demographics were reported previously (19). A total of 80 women with breast cancer were enrolled and randomly assigned to either the intervention (n = 40) or control (n = 40) groups. Three patients in the control group withdrew before beginning their assigned diet while10 patients in the KD group and 7 patients in the control group withdrew from the study after beginning their assigned diet. Ultimately, 30 patients in each group completed the study. No significant differences were seen between the two groups with regard to age, cancer type, metastasis, and marriage and education status (P > 0.05). The intervention group included 25 neoadjuvant and 5 metastatic patients while the control group consisted of 19 neoadjuvant and 11 metastatic patients (P = 0.08).

Data related to QoL are shown in Tables 1, 2 and 3. No significant differences were seen in QoL between the two groups after 12 weeks; however, the KD group showed better QoL compared to the control group in week 6 (P = 0.02). Diarrhea increased in the control group compared to the KD group (P = 0.02). There was a within-group decrease in hunger from baseline to 12 weeks in the KD group (P = 0.02). A within-group decrease was also seen in physical performance measures from baseline to 12 weeks in both groups but this was significant only in the KD group (P = 0.04). In addition, role functioning and social functioning significantly decreased in the control group compare to the KD group (p = 0.02 p = 0.02). (Table 1.) After adjusting for baseline values and chemotherapy status, no significant change was observed in either group.

Table 1

qulity of life in breast cancer patients' before and after intervention in KD group and control group as measured by the EORTC QLQ-C30*

Functioning*		**KD□□□□**	**□□□□**	**P**
Physical functioning	Week 0	89±11*	76±20	004/0
	Week 12	78±19	68±20	06/0
	p-value	04/0	05/0	
Role functioning	Week 0	86±16	79±28	24/0
	Week 12	75±25	66±29	23/0
	p-value	10/0	02/0	
Cognitive functioning	Week 0	85±16	71±28	03/0
	Week 12	75±19	72±21	59/0
	p-value	03/0	1	
Emotional functioning	Week 0	67±21	66±21	84/0
	Week 12	62±23	60±21	73/0
	p-value	34/0	11/0	
Social functioning	Week 0	94±17	93±17	93/0
	Week 12	91±17	87±17	45/0
	p-value	38/0	02/0	
Global quality of life	Week 0	68±16	65±16	41/0
	Week 12	70±20	62±20	16/0
	p-value	64/0	49/0	
after adjusted for baseline value and chemotherapy status was not observed any significant change.				
Student t-test was used to compare the continuous variables between the two groups. Paired sample t-test was used to compare the continuous variables within the two groups				
*The higher values indicate higher level of functioning and quality of life				

Table 2

qulity of life in breast cancer patients' before and after intervention in KD group and control group as measured by the EORTC QLQ-C30

Symptoms*		KD□□□□	□□□□	P
Fatigue	Week 0	22(8–33)[a]	33(11–44)	10/0
	Week 12	33(19–55)	33(33–55)	66/0
	p-value	01/0	02/0	
Nausea and vomiting	Week 0	3±13[b]	5±9	71/0
	Week 12	16±24	16±21	92/0
	p-value	01/0	02/0	
Pain	Week 0	16(0–50)	16(0–33)	59/0
	Week 12	16(0–50)	33(16–50)	59/0
	p-value	62/0	38/0	
Appetite loss	Week 0	14±24	21±26	37/0
	Week 12	30±36	23±28	48/0
	p-value	02/0	41/0	
Sleep difficulties	Week 0	16(0–33)	0(0–66)	1
	Week 12	0(0–41)	33(0–50)	81/0
	p-value	63/0	88/0	
Dyspnea	Week 0	0(0–33)	0(0–33)	31/0
	Week 12	33(0–41)	16(0–33)	43/0
	p-value	05/0	73/0	
Constipation	Week 0	10±23	16±27	31/0
	Week 12	19±34	20±27	90/0
	p-value	18/0	39/0	
Diarrhea	Week 0	6±18	4±11	57/0
	Week 12	10±18	8±17	69/0
*The higher values indicate a greater degree of symptoms a: median (b: mean±SD				
Mann–Whitney U test was used to compare the continuous variables between the two groups. Wilcoxon was used to compare the continuous variables within the two group				

Symptoms*		KD□□□□	□□□□	P
	p-value	71/0	20/0	
Financial	Week 0	13±29	8±19	49/0
	Week 12	17±28	26±27	28/0
	p-value	87/0	01/0	
*The higher values indicate a greater degree of symptoms a: median (b: mean±SD				
Mann–Whitney U test was used to compare the continuous variables between the two groups. Wilcoxon was used to compare the continuous variables within the two group				

Table 3
qulity of life in breast cancer patients' before and after intervention in KD group and control group as measured by the EORTC QLQBR23*

*Functioning		KD	□□□□□	P
Body image	Week 0	91 (37–100)	87	59/0
	Week 12	79	91	86/0
	p-value			
Future perspective	Week 0	66 (33–100)	66 (33–66)	60/0
	Week 12	66 (33–66)	33 (33–100)	85/0
	p-value	45/0	76/0	
**Symptoms+				
Arm symptoms	Week 0	11 (0–36)	11 (0–22)	36/0
	Week 12	11 (0–36)	22 (0–33)	88
	p-value	70/0	59/0	
Breast symptoms	Week 0	8 (0–33)	8 (0–25)	34/0
	Week 12	8 (0–10)	8 (0–16)	55/0
	p-value	01/0	34/0	
Systematic therapy side effects	Week 0	9 (4–17)	14 (4–23)	54/0
	Week 12	42 (20–52)	42 (33–52)	33/0
	p-value	001/0<	001/0<	
Upset by hair loss	Week 0	0	0	20/0
	Week 12	66 (33–100)	33 (33–100)	50/0
	p-value	001/0<	001/0<	
*The higher values indicate higher level of functioning and quality of life				
**The higher values indicate a greater degree of symptoms				
Mann–Whitney U test was used to compare the continuous variables between the two groups. Wilcoxon was used to compare the continuous variables within the two groups				

Mean dietary intake is shown in Table 4 and Fig. 1.The mean calorie intake and CHO decreased significantly at the end of the study (P = 0.003 and P < 0.001, respectively), while fat intake increased significantly in the KD group compared to the control group (P < 0.001). After adjusting for total energy

intake, this difference remained significant. When data from both groups was combined, a significant inverse association was observed between total CHO intake and serum βHB at 12 weeks (r= -0.77 P < 0.001), although this effect was not observed when the KD group was analyzed separately.

Table 4
Compare of mean ±SD macronutrient intake in baseline and 12-week by two trial arms in breast cancer patients

Variable	KD SD ± Mean	Control SD ± Mean	p-value
Energy (Kcal/day) Before After	1743±305 1245±360	1789±323 1600±304	60/0 003/0
p-value	001/0<	001/0	
Carbohydrate (gr) Before After	235±52 22±11	238±54 208±60	85/0 001/0<
p-value	001/0<	03/0	
Protein (gr) Before After	73±13 61±61	71±22 72±71	76/0 08/0
p-value	02/0	003/0	
Fat (gr) Before After	56±11 101±32	61±15 53±11	23/0 001/0<
p-value	001/0<	007/0	
Student t-test was used to compare the continuous variables between the two groups. Paired sample t-test was used to compare the continuous variables within the groups			

Within-group analysis showed significant decreases in energy, CHO, and protein intake in both groups compare to the baseline. Fat intake increased significantly compared to the baseline in the KD group (P < 0.001) and decreased significantly in the control group (P = 0.007).

During the intervention, 96% of the subjects in the KD arm limited CHO to < 50 g and 79.2% of subjects consumed < 10% of calories from CHO.

At 12 weeks, 66.7% of patients in the KD group had serum βHB > 0.5 mmol/L; at 6-weeks, 70.4% had βHBlevels of > 0.5 mmol/L. As previously reported, serum βHB concentrations increased significantly in the KD group (0.007 ± 0.026 to 0.923 ± 0.699 mmol/l, P < 0.001) (19).Physical activity did not show any significant difference in the between or within-group analysis. (Data not shown.) No significant difference was observed in the between or within-group analysis of thyroid hormones (Fig. 2), electrolytes, albumin,

urea, and LDH. However, lactate and ALP decreased significantly after the intervention in the KD group compared to the control group (P = 0.02 and P = 0.007, respectively). (Table 5. Data on electrolytes not shown.)

Table 5
Changes of different outcomes across different time interval by two trial arms

Variable	Trial Arms	Baseline	middle	12 weeks	P value middle vs BL	P value 12weeksvs middle	P value 12weeks vs BL
Lactat	KD	13.3±11	10.8±4	10.7±3	1	1	1
	Control	13.8±4	14.7±6	13.3±4	0.94	0.93	1
	MD	-0.51	-2.8	-3.8	1	0.10	0.02
LDH (u/l)	KD	680±643	666±770	535±517	1	0.48	0.58
	Control	706±560	627±556	472±148	1	0.36	0.12
	MD	-25	39	62	1	1	1
Amonia (micg/dl)	KD	58±17	60±17	66±15	1	1	0.69
	Control	75±27	71±36	75±24	1	0.92	1
	MD	-17	-11	-9	0.03	0.43	0.49
Albumin ((g/dl	KD	4.5±0.33	4.5±0.26	4.5±0.33	1	1	1
	Control	4.4±0.43	4.5±0.37	4.5±0.37	1	1	1
	MD	0.08	0.04	0.04	1	1	1
ALP	KD	197±126	169±76	149±71	1	1	0.99
	Control	325±375	333±440	240±164	1	0.11	0.51
	MD	-127	-164	-90	0.19	0.12	0.007

BL: Baseline, middle: 1st follow-up or week 6, 12 weeks or Last follow-up, MD: Mean Difference, CI: Confidence Interval. Analysis type: Repeated measure, all of p values were calculated based on Bonferroni correction for multiple comparisons * Ancova: Adjusted for base line value

Discussion

The effects of KD on QoL, physical activity, dietary intake, and specific biomarkers in patients with locally advanced and metastatic breast cancers were evaluated in this study. Based on our findings, the KD did not adversely impact QoL significantly after 6 weeks; in fact, diarrhea was more frequent in the control group than the KD group. No significant differences were seen in QoL, physical activity, and biomarkers

between the two groups after the12 week intervention. Of note, lactate and ALP were lower in the KD group than in the control.

Effect of diet on QoL

In our study, KD improved the global QoL at 6 weeks. No adverse effects were observed in those participants assigned to the KD compared to the control group after 12 weeks. Within-group analysis showed decreased hunger and physical function in the KD group compared to the base line. In the control group, role functioning decreased significantly compared to baseline. Results of a systematic review and meta-analysis have shown that KDs suppress appetite (14). Decrease in hunger or appetite in our study may have been due to the high fat content of the KD as it decreases ghrelin release which in turn may lower appetite. Previously we have shown that KD results in weight loss (19). As a clinical benefit, KD-induced decreases in appetite, weight, and body fat may result in favorable responses in breast cancer patients, notably in overweight or obese women (20, 21) .

In contrast with our findings, Cohen found that a KD significantly enhanced physical function scores in women with ovarian or endometrial cancer compared to the control group but appetite did not change at the end of the study compared to the baseline (7). Part of this inconsistency between our study and Cohen's trial may be explained by the design of the study. While only 25% of the participants in the Cohen study were undergoing chemotherapy, all of our patients were receiving treatment. Also, timing of the administration of the questionnaires and whether the participants were in positive or negative energy balance may have influenced our findings.

No significant difference was reported in QoL at the end of a study reported by Tan-Shalaby et al when compared to the baseline (22). However, in a separate study, Tan-Shalaby reported a slight decrease in physical and role functioning as well as temporary constipation and fatigue in the KD group (9). In our study, constipation was noted by 6 number of participants in the KD arm during the early days; this was managed by dietary means. Furtthermore, the KD had no measurable negative impact on physical activity.

Dietary intake and adherence

Our study data showed a significant decrease in CHO intake and a significant increase in fat intake in the KD group compared to the control. Protein intake was not significantly different between the two groups but decreased overall in both groups when compared to baseline. Total daily CHO intake was similar to results in the Cohen study (23). We also assessed serum βHB: In the KD group, 66.7 % of patients at 12 weeks and 70.4% at 6-weekshad serum levels >0.5 and 89 % patients at 6 weeks and 12 weeks had serum levels >0.3 mmol/l. Cohen reported that 57% of patients had βHB concentrations >0.5 mmol/l.

A recent systematic study of KDs in adult cancer patients reported a range of 23% to 100%, with a 49% adherence rate overall reported by Sremanakova (15). According to our data, the level of adherence to the

KD intervention suggests that the diet is a feasible option for women with breast cancer who are receiving chemotherapy.

Despite the lack of any restriction in caloric intake in the study design and consistent with findings of Cohen (24), the KD group showed a significant reduction in calorie intake compared to the control group. The decrease in calorie intake may be due to reductions in appetite associated with ketosis, as the subjects in the KD arm did not consume all the fat calculated for their diet. This may also be due in part to customary practices surrounding meal preparation which favor lower than the prescribed amount of fat. A decrease in appetite and subsequent inadvertent calorie restriction most often results in weight loss; in the absence of malnutrition or cachexia, this may have anti-inflammatory and pro-apoptotic properties which in turn may exert a positive effect on cancer outcomes. Ketosis may also enhance the effectiveness of chemotherapy while reducing the side effects of treatment (25, 26).

Effect of KD on specific biomarkers

Consistent with the outcomes of the previous studies, our results revealed that the KD had no adverse effect on thyroid hormones, electrolytes, LDH, urea, and albumin while significantly decreasing lactate and ALP. Lactate depletion results in lower availability of lactate as a substrate for biomass synthesis. Downregulation of glycolysis also reduces acidity of the tumor microenvironment which in turn may slow metastasis (27). Furthermore, higher ALP levels in breast cancer patients often indicate metastatic disease progression (28). More research is needed to assess whether lower ALP or lactate as seen in this study is associated with slower rates of disease progression.

To our knowledge, this is the first randomized controlled trial examining the effects of a KD on QoL in breast cancer patients with locally advanced or metastatic disease.

The primary limitation of this study was the heterogeneous nature of the sample in regards to cancer classification and hormone sensitivity. A secondary limitation was the small sample size.

Conclusion:

Our results suggest that a KD implemented alongside standard of care chemotherapy has no adverse effects on patient QoL, physical activity, or specific biomarkers. Future studies are needed to determine if ketosis may enhance the effectiveness of chemotherapy by decreasing lactate and ALP in patients with locally advanced and metastatic breast cancer.

Declarations

Acknowledgments: We would like to give special thanks to Thomas N. Seyfried, PhD, for his input into the study design. We would also like to thank all the participants for taking part in this study.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable

Ethical Approval and Consent to participate : All participants provided written informed consent. The study protocol was approved by the National Nutrition and Food Technology Research Institute (NNFTRI), Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran (IR.SBMU.NNFTRI.REC.1396.187)

Consent for publication: Not applicable

Availability of supporting data: Data described in the manuscript, code book, and analytic code will be made available upon request pending

Authors information:

Adele Khodabakhshi**,** Department of Nutrition, School of Public Health, Kerman University of Medical Sciences, Kerman, Iran.

Mohammad Esmaeil Akbari , Cancer Research Center, Shahid Beheshti University of Medical Sciences,Tehran

Thomas N. Seyfried, Biology Department, Boston College, Chestnut Hill, MA, United States

Maryam Mahmoudi, Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran

Miriam Kalamian, Dietary Therapies LLC, Hamilton, MT, USA

Nariman Moradi, Cellular and Molecular Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran. And Department of Clinical Biochemistry, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran.

Maryam Beheshti , Department of Nutrition and Dietetics, Mofid children's hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Sayed Hossein Davoodi, Cancer Research Center, Shahid Beheshti University of Medical Sciences,Tehran, Iran and Department of Cellular and Molecular Nutrition, Faculty of Nutrition Science and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran

*Correspondence to:

Sayed Hossein Davoodi, MD, MPH, PhD

Authorship:

Khodabakhshi carried out the conception, Methodology, performed the experiments, design of the diet and wrote the article. Mirzaei, Akbari, Davoodi and Seyfried collaborated in the design of the study. Akbari

and Mirzaei provided patients. Davoodi supervise on the thesis. Mahmoudi, Beheshti and Kalamian collaborated in the design of the diet. Kalamian gave critical review on the manuscript. Moradi collaborated in performing the lab test. All authors have read and approved the final manuscript

References

1. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of childhood epilepsy: a randomised controlled trial. The Lancet Neurology. 2008;7(6):500-6.
2. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutrition & metabolism. 2007;4(1):5.
3. Huebner J, Marienfeld S, Abbenhardt C, Ulrich C, Muenstedt K, Micke O, et al. Counseling patients on cancer diets: a review of the literature and recommendations for clinical practice. Anticancer research. 2014;34(1):39-48.
4. Champ CE, Palmer JD, Volek JS, Werner-Wasik M, Andrews DW, Evans JJ, et al. Targeting metabolism with a ketogenic diet during the treatment of glioblastoma multiforme. Journal of neuro-oncology. 2014;117(1):125-31.
5. Zuccoli G, Marcello N, Pisanello A, Servadei F, Vaccaro S, Mukherjee P, et al. Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report. Nutrition & metabolism. 2010;7(1):33.
6. Andrykowski MA, Schmidt JE, Salsman JM, Beacham AO, Jacobsen PB. Use of a case definition approach to identify cancer-related fatigue in women undergoing adjuvant therapy for breast cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2005;23(27):6613.
7. Cohen C, Fontaine K, Arend R, Soleymani T, Gower B. Favorable Effects of a Ketogenic Diet on Physical Function, Perceived Energy, and Food Cravings in Women with Ovarian or Endometrial Cancer: A Randomized, Controlled Trial. Nutrients. 2018;10(9):1187.
8. Breymeyer KL, Lampe JW, McGregor BA, Neuhouser ML. Subjective mood and energy levels of healthy weight and overweight/obese healthy adults on high-and low-glycemic load experimental diets. Appetite. 2016;107:253-9.
9. Tan-Shalaby JL, Carrick J, Edinger K, Genovese D, Liman AD, Passero VA, et al. Modified Atkins diet in advanced malignancies-final results of a safety and feasibility trial within the Veterans Affairs Pittsburgh Healthcare System. Nutrition & metabolism. 2016;13(1):52.

10. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kämmerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. Nutrition & metabolism. 2011;8(1):54.
11. Klement RJ, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC research notes. 2016;9(1):1.
12. Schmidt M, Pfetzer N, Schwab M, Strauss I, Kämmerer U. Effects of a ketogenic diet on the quality of life in 16 patients with advanced cancer: A pilot trial. Nutrition & metabolism. 2011;8(1):1.
13. Tóth C, Clemens Z. Halted Progression of Soft Palate Cancer in a Patient Treated with the Paleolithic Ketogenic Diet Alone: A 20-months Follow-up. American Journal of Medical Case Reports. 2016;4(8):288-92.
14. Gibson AA, Seimon RV, Lee CM, Ayre J, Franklin J, Markovic T, et al. Do ketogenic diets really suppress appetite? A systematic review and meta-analysis. Obesity reviews. 2015;16(1):64-76.
15. Sremanakova J, Sowerbutts A, Burden S. A systematic review of the use of ketogenic diets in adult patients with cancer. Journal of Human Nutrition and Dietetics. 2018;31(6):793-802.
16. Khodabakhshi A, Akbari ME, Mirzaei HR, Kazemian E, Kalantari K, Kalamian M, et al. Effects of ketogenic diet for breast cancer treatment. a protocol for randomized controlled clinical trial. J Biochem Technol. 2018;9:90-4.
17. Montazeri A, Harirchi I, Vahdani M, Khaleghi F, Jarvandi S, Ebrahimi M, et al. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30): translation and validation study of the Iranian version. Supportive Care in Cancer. 1999;7(6):400-6.
18. Montazeri A, Harirchi I, Vahdani M, Khaleghi F, Jarvandi S, Ebrahimi M, et al. The EORTC breast cancer-specific quality of life questionnaire (EORTC QLQ-BR23): translation and validation study of the Iranian version. Quality of Life Research. 2000;9(2):177-84.
19. Khodabakhshi A, Akbari ME, Mirzaei HR, Mehrad-Majd H, Kalamian M, Davoodi SH. Feasibility, safety, and beneficial effects of MCT-based Ketogenic diet for breast Cancer treatment: a randomized controlled trial study. Nutrition and cancer. 2019:1-8.
20. Champ CE, Volek JS, Siglin J, Jin L, Simone NL. Weight gain, metabolic syndrome, and breast cancer recurrence: are dietary recommendations supported by the data? International journal of breast cancer. 2012;2012.
21. Sherwin R, Hendler R, Felig P. Effect of ketone infusions on amino acid and nitrogen metabolism in man. The Journal of clinical investigation. 1975;55(6):1382-90.
22. Tan-Shalaby J, Seyfried T. Ketogenic diet in advanced cancer: a pilot feasibility and safety trial in the veterans affairs cancer patient population. Journal of Clinical Trials. 2013;2013.
23. Cohen CW, Fontaine KR, Arend RC, Gower BA. A Ketogenic diet is acceptable in women with ovarian and endometrial cancer and has no adverse effects on blood lipids: a randomized, controlled trial. Nutrition and cancer. 2019:1-11.
24. Fine EJ, Segal-Isaacson CJ, Feinman RD, Herszkopf S, Romano MC, Tomuta N, et al. Targeting insulin inhibition as a metabolic therapy in advanced cancer: a pilot safety and feasibility dietary trial

in 10 patients. Nutrition. 2012;28(10):1028-35. Epub 2012/07/31.

25. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer. Nutrition & metabolism. 2007;4(1):1.
26. Mukherjee P, Mulrooney TJ, Marsh J, Blair D, Chiles TC, Seyfried TN. Differential effects of energy stress on AMPK phosphorylation and apoptosis in experimental brain tumor and normal brain. Molecular cancer. 2008;7(1):37.
27. Gatenby RA, Gawlinski ET, Gmitro AF, Kaylor B, Gillies RJ. Acid-mediated tumor invasion: a multidisciplinary study. Cancer research. 2006;66(10):5216-23.
28. Singh A, Pandey A, Tewari M, Kumar R, Sharma A, Singh K, et al. Advanced stage of breast cancer hoist alkaline phosphatase activity: risk factor for females in India. 3 Biotech. 2013;3(6):517-20.

Figures

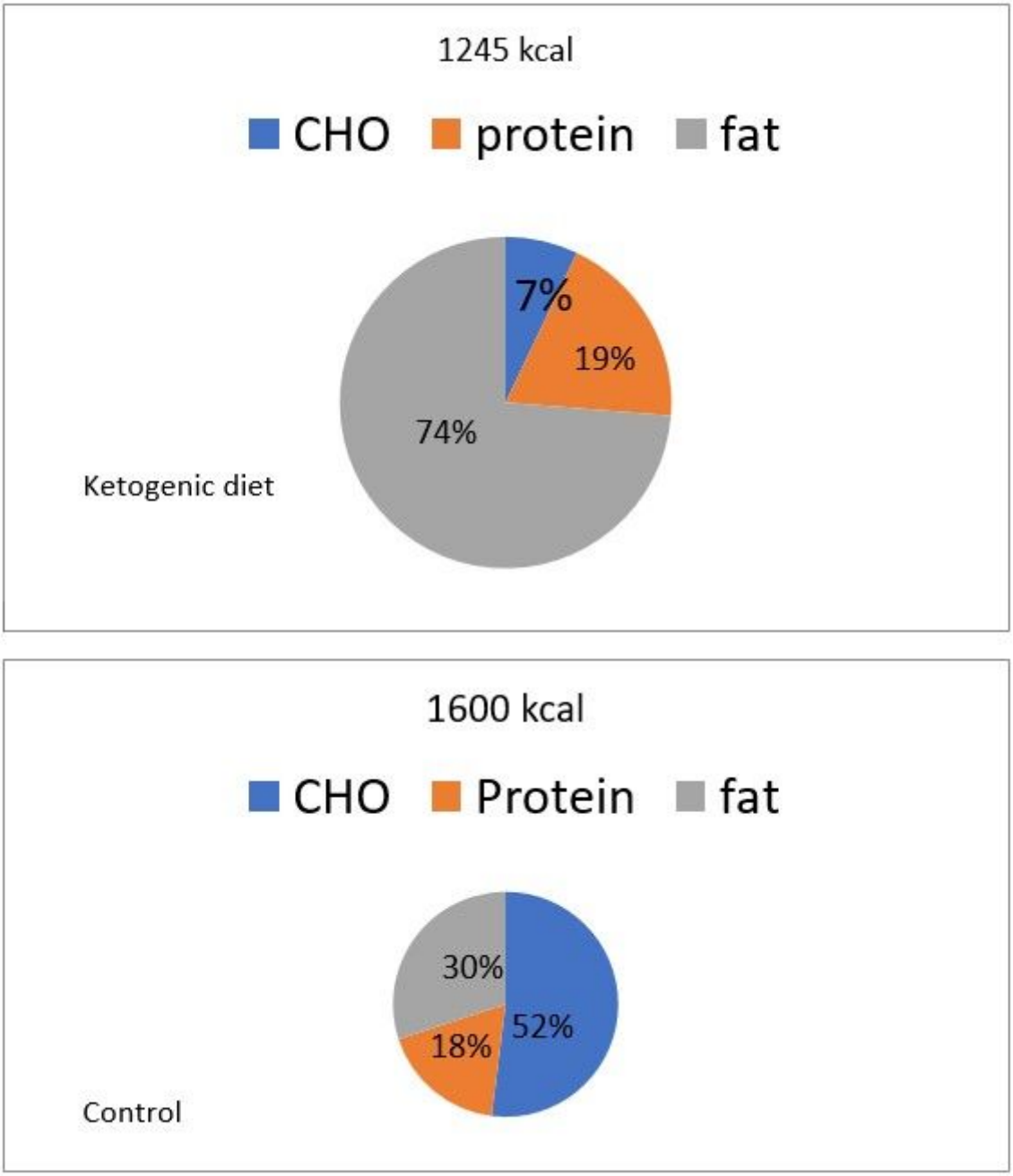

Figure 1

Mean caloric intake and distribution of macronutrients (as percentage of total kilocalories) in Breast cancer patients

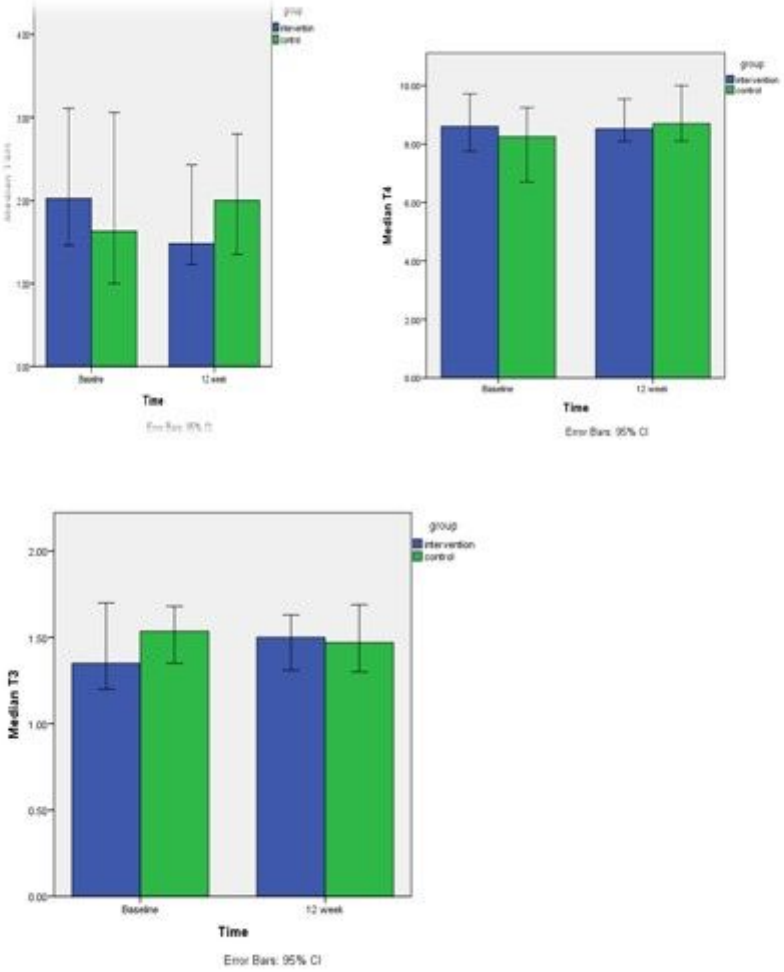

Figure 2

Median (confidence interval) tyroid hormones in baseline and 12-week by two trial arms in breast cancer patients

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist3.doc