Low Carb (LCD) and Ketogenic (KD) Diets Increase Quality of Life, Physical Performance, Body Composition and Metabolic Health of Women with Breast Cancer Better Than a Standard Diet (SD)

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Abstract

Background:

Breast Cancer (BC) patients often ask for a healthy diet. Here, we compared three different diets which could support BC patients during the rehabilitation process: a healthy standard diet (SD), a low carb diet (LCD) and a ketogenic diet (KD).

Patients and Methods:

KOLIBRI was a one-site nutritional intervention trial, combining inpatient and outhouse phases for 20 weeks. Female BC patients (n=152; mean age 51.7 years) could select their diet. Data collected were: quality of life (QoL), spiroergometry, body composition, blood biochemistry. 30, 92 and 30 patients started the KD, LCD and SD, respectively. Of those, 20, 72 and 25 completed the final examination.

Results:

Patients rated all diets as feasible in daily life. No adverse effects occurred in any diet group. KD offered the highest amount of energy and protein. All groups improved in QoL, body composition and physical performance. KD was superior in improving fatigue, insomnia and physical functioning. KD participants finished with the best physical performance and the highest muscle/fat ratio. Despite their increased cholesterol, KD patients had the best triglyceride/HDL ratio and HOMA-IR. Most metabolic parameters significantly improved in the LCD group. SD participants ended with remarkably low cholesterol levels, but did not improve triglyceride/HDL or HOMA-IR.

Conclusions:

A well-defined KD and LCD are safe and beneficial for BC. Both diets could thus be recommended for patients wanting to self-support their rehabilitation process.

Trial registration ID

NCT02092753

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Ketogenic Or LOGI Diet In a Breast Cancer Rehabilitation Intervention (KOLIBRI)

URL: https://clinicaltrials.gov/ct2/show/NCT02092753?cond=KOLIBRI&draw=2&rank=1

Background

Breast cancer (BC) is one of the most common cancer types worldwide with over 2 million new cases each year (www.wcrf.org). Despite a generally good prognosis, the disease itself as well as its standard treatments via surgery, radiation and chemotherapy can have a negative influence on the health and fitness of affected patients. Typical problems such as weakness and loss of muscle mass (sarcopenia) are related to the particular cancer patient's whole body metabolism, which may be characterized by an increased inflammatory environment [1]. Parallel to inflammation, peripheral insulin resistance occurs and leads to a decreased ability of healthy tissue to metabolize glucose for energy demands [2, 3]. In compensation, fat oxidation rate increases [4, 5].

In the hope to support their healing process and long-term survival, many BC patients ask their health care providers about the possibility to integrate a healthy eating pattern. In general, physicians and cancer societies advise a healthy standard diet (SD) which is low in fat and rich in high-fiber starchy carbohydrates, fruits and vegetables [6]. Such a SD typically contains at least 50% energy from carbohydrates, 0.8 grams/kg body weight protein and approximately 30% energy from fat [7].

In recent years, "high fat, low carb" diets were discussed as a metabolically adapted therapy by several clinical nutrition societies [8]. Indeed, preliminary studies have shown that a fat-rich diet is able to protect muscle mass in the presence of catabolic stimuli [9–11].

The most stringent nutritional regime high in fat and low in carbohydrates is the ketogenic diet (KD). It provides at least 75% of daily calories from fat, is adequate in protein (1.0-1.4 g/kg body weight/day) and very low in carbohydrates (20–50 grams per day). This diet is still a matter of concern and debate among oncologists and nutritionists, which expect cardiovascular side effects and loss of quality of life due to the high amount of fat [12].

A less strict but also fat enriched diet is the LCD (low carbohydrate diet). Its idea is to keep insulin levels low to prevent or reduce the metabolic syndrome, which has been linked to worsening cancer outcomes [13]. The LCD allows up to 120 grams of carbohydrates, is balanced in protein (20% of energy/day) and rich in fat (remaining calories) [14, 15].

All three diet types avoid refined sugar, alcohol and highly processed food and include higher amounts of fiber than regularly eaten in the Western Diet. Thus, all three diets seem to have the potential to support cancer patients. In this respect, the aim of our open-label trial was to compare the three diet types (SD, KD and LCD) in BC patients and to assess feasibility, safety and tolerability. Our focus was on quality of life, body composition, physical performance and serum biochemistry during the rehabilitation phase.

Patients And Methods

The "Ketogenic Or LOGI Diet In a Breast Cancer Rehabilitation Intervention" (KOLIBRI) trial (ClinicalTrials.gov Identifier: NCT02092753) was approved by the Ethics Committee of the Bavarian Medical Association (Bayerische Landesärztekammer; No. 13082). All study participants signed informed consent.

Study design (Fig. 1):

This was an open label non-randomized nutritional intervention trial for 20 weeks consisting of three phases:

1.
Three weeks of an inpatient multimodal intervention in the rehabilitation center (initial examination T0) followed by implementation of the allocated diet and training of the patients in diet calculation, cooking and realization of the diet regimen in routine daily life.
2.
16 weeks outhouse phase: continuing the selected nutritional regime under close contact and supervision of the study team accompanied by food diaries and daily urine measurements of ketones (KD group).
3.
One week of intervention at the rehabilitation center (final examination: T20).

Patients:

In total 152 women, aged 26–69 years (mean age 51.7 years) were enrolled in the study during the standard rehabilitation in one specific center after treatment of primary or recurrent BC. All patients gave written informed consent. Baseline characteristics of the patients are shown in Table 1.

Table 1
Baseline characteristics of the patients comprising the three intervention groups.

Parameter	KD ($n = 29$)	LCD ($n = 92$)	SD ($n = 31$)	p-value
Age [yr]	53 (38−64)	52 (26−66)	53 (37−60)	0.65
Karnofsky index	100 (90−100)	100 (80−100)	100 (80−100)	0.92
Body mass index [kg/m^2]	23.4 (18.1−35.4)	27.2 (18.0−41.0)	26.6 (17.6−40.2)	**0.001***
Menopause	5	22	10	0.28
Premenopause	14	54	16	
Postmenopause	10	16	5	
Unknown				
Neoadjuvant Chemotherapy	20	75	26	0.30
No	9	17	5	
Yes				
Metastases	19 (76.0%)	86 (96.6%)	27 (93.1%)	**0.006***
No	6 (24.0%)	3 (3.4%)	2 (6.9%)	
Yes	4	3	2	
Unknown				
Estrogen receptor status	8	14	3	0.16
Negative	20	78	28	
Positive	1	0	0	
Unknown				
Progesterone receptor status	9	15	4	0.13
Negative	19	77	27	
Positive	1	0	0	
Unknown				
HER2/neu status	23	77	23	0.48
Negative	6	15	8	
Positive	0	0	0	
Unknown				
Anti-Hormon Therapy	10	54	19	0.035
Tamoxifen	6	23	6	
Aromatase Inhibitor	13	15	6	
non				
Heceptin	5	13	6	0.74
Yes	24	79	25	
No				

Continuous variables are given as median and range and categorical variables as absolute and relative frequencies. Missing values were omitted when computing these summary statistics. The null hypothesis of no differences between the three groups was tested using the Kruskal-Wallis test and Fisher's exact test for continuous and categorical variables, respectively.

The exclusion criteria included Karnofsky Index < 70 and/or expected life span < 12 months, additional malignant tumors at the time of recruitment, participation in other trials, unwanted weight loss and BMI < 18, dementia or other clinically relevant alterations of the mental status that could impair the ability of the patient to cope with the diet, not being able to understand German at a level allowing to follow instructions, metabolic alterations contraindicating a fat-rich diet such as insulin dependent diabetes mellitus, decompensated heart failure (NYHA > 2), myocardial infarction within the last 6 months, symptomatic atrial fibrillation, severe acute infection, pregnancy, pancreatic insufficiency.

Procedure:

At start of the rehabilitation program, patients were introduced to the study aims and procedures. Certificated dietitians presented the three different diet regimens in a neutral lecture as healthy diet choices. At the morning of day two, all patients who gave written consent to participate underwent the primary

examination (T0: weight, size, body composition, serum blood parameters, physical performance, quality of life questionnaires, assessment of individual dietary history) and then selected their dietary regime (no random selection) which immediately started with the first lunch. Of the 152 patients, 30 selected KD, 92 LCD and 30 SD. At the first evening, one patient switched from KD to LCD and one from LCD to SD. One patient stopped participation at day three, resulting in 29 KD, 92 LCD and 31 SD patients throughout the 3 weeks of in-house rehabilitation (Fig. 1).

The composition and guidelines for the three dietary patterns are given in Supplementary Table S1

After 16 weeks of an outpatient phase, patients underwent another week of a "rehabilitation refresher" while maintaining their diet until final examination. Unfortunately, in five cases, health insurances refused to cover the costs of this week and therefore four KD and one SD patients could not participate in the final examination. Here, telephone interviews revealed that all five persons adhered to their diet until T20. Additional reasons for dropouts included lack of motivation, personal (not medical/health) reasons and health problems (Fig. 1). At T20, there were 20 patients in KD, 76 in LCD and 25 in SD

Parameters analyzed at T0 and T20

At day one of phase 1 (T0) and day 4 of phase 3 (T20), weight and size were measured after an overnight fast followed by taking blood and serum samples. Then, bioimpedance analysis (BIA; Nutriguard-M Data-Input GmbH, Pöcking, Germany) and Dual-Energy X-Ray Absorptiometry (DXA; Horizon DXA system Explorer S/N 90425, HOLOGIC, Marlborough, Massachusetts, USA) were performed. After breakfast, quality of life (QoL) data were assessed with standardized questionnaires (EORTC QLQ-C30 version 3.0 + EORTC QLQ BC23) and finally, physical performance was assessed via spiroergometry testing with a bicycle ergometer and a standard ramp protocol (Ergoline 900 digital, ergoline GmbH, Binz Germany) supervised by the experienced team of the rehabilitation center.

Parameters analyzed throughout the study

Average energy and macronutrient intake per day through the outpatient phase were calculated based on food diaries. Per patient, a trained dietitian analyzed 3–5 randomly selected days with the PRODI 5 program (Nutri-Sciences GmbH, Freiburg, Germany).

Ketosis was documented daily in the KD group per urine test (Ketostix, Bayer, Basel, Switzerland)

Data collection and statistical analysis

A routine clinical lab analyzed blood and serum samples. BIA was analyzed with the Thetis V3.1 software (FORANA GmbH, Frankfurt, Germany), DXA with the QDR for Windows XP 12.5 software (HOLOGIC) and Spiroergometry with the SDS104 software (Ganshorn, Niederlauer, Germany).

A study nurse collected all data into the database.

Parameter values are given as mean ± standard error of the mean (SEM). Comparison of diet types was performed with the Mann Whitney U test without adjustment, rating $p < 0.01$ as significant. Within-group differences between T0 and T20 of patients were evaluated using the Mann Whitney U test ; between-group differences at T0 and T20 were evaluated using the Kruskal-Wallis test. Due to the high number of tests, p-values were adjusted following the Benjamini-Hochberg procedure with a false discovery rate of 25% resulting in Benjamini-Hochberg critical values (BHcv). BHcv < 0.05 was rated significant. Data were analyzed with Prism 6.05 (GraphPad Software, San Diego, CA, USA).

Results

Choice of diet type

Analysis of diet history questionnaires revealed that 22 of the 29 patients in the KD group already had experience with consuming a LCD or KD over 6–24 months. In contrast, patients in the LCD or SD group started from a Western diet. The majority of patients selected LCD.

Energy and protein uptake

Since cancer patients need a considerable amount of energy and an increased daily intake of protein [16] we analyzed both components on the basis of the food diaries maintained by the patients in the outpatient phase. All three diets reached the goal intake of 25–30 kcal/kg/d for ambulatory patients Fig. 2A). However, the KD supported the patients with a mean of 32.5 ± 1.5 kcal/kg/d, which was significantly higher than the energy supply obtained with LCD (24.3 ± 0.7 kcal/kg/d; $p < 0.0001$) as well as with SD (26.4 ± 1.2 kcal/kg/d; $p = 0.0005$). Both KD (1.33 ± 0.07 g/kg/d) and LCD (1.2 ± 0.03 g/kg/d) supplied sufficient protein, while SD (0.98 ± 0.04) failed to reach the goal of 1.0 – 1.5 g/kg/d protein (Fig. 2B). Patients in the KD group reached the intended ketogenic ratio (KR; grams of fat divided by grams of carbohydrates plus protein) of 1.6:1 (1.65 ± 0.08) and exhibited stable ketosis according to the daily urine measurements (not shown). As expected, LCD patients had a higher KR than SD patients (Fig. 2C).

Physical performance

Because the majority of the participants in the KD group already were on a high fat diet at study entry, this group had a lower respiratory quotient (RQ; 0.79 ± 0.01) than LCD (0.85 ± 0.01) and SD (0.88 ± 0.02) at T0. During the intervention, the RQ in the KD group further decreased to 0.76 ± 0.01, almost reaching the 0.7 value of pure fat oxidation. The RQ in the LCD group remained stable (0.85 ± 0.01), while that of the SD group increased (0.9 ± 0.02), in line with the carbohydrate rich diet (Fig. 3A).

All three groups improved their physical performance during the intervention reflecting effects of the multimodal therapy. However, despite being the group with the highest percentage of advanced diseases, patients in the KD group performed best in the treadmill test at T0 with higher maximal oxygen uptake (VO2max/kg; 24.7 ± 1.2; Fig. 3B), and maximal workload (142 ± 5.8 Watt; Fig. 3C) as well as longer time to exhaustion (8.5 ± 0.4 min; Fig. 3D). At T20, the KD

remained the fittest group. All three diet groups increased their VO2max/kg from T0 to T20 which was significant in both the LC (BHcv = 0.02) and SD groups (BHcv = 0.03). Improvements in workload and time to exhaustion missed significance. In all three groups, lactate (3 min after exhaustion) in peripheral blood was slightly higher (4.1–4.4 mmol/l) at T20 compared to T0 (3.7–3.8 mmol/l) without any significant inter- or intra-group differences (not shown).

Body composition

There was no significant intergroup difference in body mass index (BMI) at T0 but all three interventions induced a significant reduction until T20 (Fig. 3E). BMI decreased from 23.9 ± 0.7 kg/m^2 to 22.9 ± 0.7 kg/m^2 (BHcv = 0.05) in the KD group, from 27.3 ± 0.5 kg/m^2 to 26.1 ± 0.5 kg/m^2 (BHcv = 0.017) in the LCD group and from 26.8 ± 0.8 kg/m^2 to 26.0 ± 0.9 kg/m^2 (BHcv = 0.033) in the SD group.

The phase angel was very similar in all diet groups (KD/LCD/SD) at T0 (5.69 ± 0.12 /5.56 ± 0.05/5.68 ± 0.10) and remained stable until T20 (5.68 ± 0.14/5.57 ± 0.05/5.63 ± 0.10; Fig. 3F).

Neither at T0 nor at T20 was there a significant difference in bone density between the groups (Fig. 3G). Bone density slightly decreased in the KD (T0: 1.11 ± 0.02 g/cm^2; T20: 1.09 ± 0.02 g/cm^2) and LCD group (T0: 1.08 ± 0.01 g/cm^2; T20: 1.07 ± 0.01 g/cm^2) and remained stable at the lowest level in the SD group (T0: 1.06 ± 0.02 g/cm^2; T20: 1.06 ± 0.02 g/cm^2).

All three diet groups improved their muscle/fat mass ratio based on a significant reduction of total body fat (16.7% in KD; 10.5% in LCD and 5% in SD) and only a slight reduction in muscle mass (2.5% in KD; 1.4% in LCD and 1.8% in SD) during the intervention (Fig. 3H). The KD group exhibited the best ratio at T0 (2.07 ± 0.15) and further improved to 2.43 ± 0.14 at T20, which was significantly higher (BHcv = 0.025) compared to LCD and SD at T20.

Patients in the KD group had a lower amount of visceral fat mass at T0 (10.0 ± 0.9 kg) and further reduced it to 7.9 ± 0.8 kg at T20. While LCD patients had lost around 1.6 kg of visceral fat (from 14.3 ± 0.5 to 12.6 ± 0.6 kg, BHcv = 0.017), the reduction was 0.6 kg in the SD group (12.7 ± 0.9 to 12.1 ± 1.0; Fig. 3I). The percentage of visceral fat of total body fat improved in the KD (from 44.2 ± 1.3 to 42.37 ± 1.3) and LCD groups (from 48.9 ± 1.0 to 48.1 ± 1.2) while it remained stable in the SD group (46.8 ± 1.1 to 46.9 ± 1.3; Fig. 3J).

Quality of life (QoL)

QoL assessed with the EORTC-QLQC30 and BR23 questionnaires improved in all three diet groups. At T0, the KD group had a significantly higher global quality of life and lower fatigue than the other two groups, while all other parameters were without a significant difference (Table 2).

Table 2
Quality of life (EORTC-QLQ C30, version 3 + BR23)

	KD			LCD			SD			T0 Intergroup	T20 Intergroup
	T0	T20	BHcv	T0	T20	BHcv	T0	T20	BHcv	BHcv	BHcv
Glob. health/QoL	61.2 ± 3.4	71.3 ± 4.5	**0.006**	47.2 2.1	64.7 2.4	**0.006**	55.1 ± 3.1	64.2 ± 3.7	0.042*	0.016*	0.055
Physical funct.	77.9 ± 3.0	88.7 ± 4.3	0.060	66.7 ± 2.3	79.2 ± 1.9	**0.006**	70.3 ± 3.0	80.0 ± 2.9	0.024*	0.063	**0.003**
Emotional funct.	56.6 ± 5.0	74.2 ± 6.3	0.036*	41.9 ± 3.2	62.0 ± 3.1	**0.006**	46.5 ± 5.1	58.0 ± 5.2	0.065	0.070	0.047*
Cognitive funct.	66.7 ± 5.6	70.1 ± 6.4	0.167	57.4 ± 3.3	64.7 ± 3.2	0.095	52.2 ± 6.2	61.8 ± 4.6	0.071	0.078	0.117
Social funct.	56.9 ± 4.9	70.0 ± 6.6	0.077	57.2 ± 3.3	68.5 ± 3.4	0.030*	57.0 ± 5.8	75.0 ± 4.6	0.024*	0.18	0.148
Role funct.	57.5 ± 5.1	70.8 ± 7.3	0.107	50 ± 3.2	63.6 ± 3.5	0.012*	56.5 ± 5.8	61.8 ± 5.3	0.119	0.125	0.109
Fatigue	42.9 ± 5.3	20.6 ± 5.7	0.060	62.6 ± 2.8	40.9 ± 3.2	**0.006**	57.0 ± 4.7	46.3 ± 4.3	0.083	0.023*	**0.008**
Pain	41.4 ± 6.0	29.2 ± 7.4	0.107	50.2 ± 3.7	40.2 ± 3.6	0.054	49.5 ± 6.2	31.9 ± 4.6	0.036*	0.125	0.086
Dyspnea	46.0 ± 5.6	30.0 ± 7.6	0.101	49.6 ± 3.4	34.2 ± 3.7	0.018*	43.0 ± 6.6	33.3 ± 5.7	0.077	0.133	0.156
Insomnia	58.6 ± 6.5	28.3 ± 7.3	0.048*	63.6 ± 3.1	56.9 ± 3.8	0.119	51.6 ± 6.5	47.2 ± 8.9	0.155	0.094	0.039*
Nausea/Vomiting	8.6 ± 3.8	5.0 ± 2.7	0.077	7.2 ± 1.5	4.5 ± 1.2	0.131	14.0 ± 3.9	7.6 ± 3.1	0.083	0.102	0.133
Appetite loss	12.6 ± 4.2	8.3 ± 4.1	0.161	17.0 ± 2.6	7.6 ± 2.0	0.060	16.1 ± 4.9	13.9 ± 4.5	0.137	0.141	0.102
Constipation	14.9 ± 4.8	10.0 ± 4.3	0.113	14.4 ± 2.8	9.8 ± 2.5	0.125	16.1 ± 4.9	12.5 ± 5.2	0.179	0.172	0.164
Diarrhea	12.6 ± 5.1	11.7 ± 4.4	0.173	15.5 ± 2.9	12.0 ± 2.9	0.143	12.9 ± 3.7	8.3 ± 3.6	0.149	0.148	0.156

Benjamini Hochberg corrected p-value (BHcv): BHcv < 0.05*; BHcv < 0.01**

The improvement in fatigue was not significant in the KD group upon intervention, but still superior to the other groups; furthermore, global QoL improved significantly (BHcv = 0.006) and remained the highest among the diet groups. The same could be observed for emotional functioning (BHcv = 0.036) and insomnia (BHcv = 0.048); the latter improvement resulted in a significant advantage of the KD compared to the LCD and SD groups (BHcv = 0.039). Participants in the LCD group significantly improved in nine of the 14 parameters of QoL, and SD participants in four of those nine aspects, which were global QoL (BHcv = 0.042), pain (BHcv = 0.036), physical (BHcv = 0.024) and social (BHcv = 0.024) functioning. Symptoms of dyspepsia (nausea/vomiting, appetite loss, constipation and diarrhea) improved on all three dietary regimens resulting in an equal outcome at T20.

Blood parameters

Results of blood chemistry are shown in Table 3.

Table 3
blood parameters at start and end of intervention

Parameter and dimension		Normal range	KD			LCD			SD			Between-group differences	
			T0	T20	Within-group difference (BHcv)	T0	T20	Within-group difference (BHcv)	T0	T20	Within-group difference (BHcv)	T0 BHcv	T20 BHcv
TG	(mg/dl)	< 150	78.1 ± 5.1	82.0 ± 6.6	0.130	128.3 ± 8.0	106.5 ± 7.3	0.005**	105.3 ± 8.9	106.0 ± 10.9	0.146	0.008**	0.156
Chol	.(mg/dl)	< 200	234.6 ± 8.5	239.1 ± 11.4	0.135	233.5 ± 4.8	221.6 ± 4.8	0.005**	215.2 ± 6.1	203.6 ± 5.5	0.047*	0.125	0.047*
HDL	(mg/dl)	> 65	79.9 ± 3.7	78.6 ± 4.2	0.078	64.5 ± 1.5	68.2 ± 1.6	0.026*	65.2 ± 2.7	64.6 ± 6.2	0.057	0.016*	0.055
LDL	(mg/dl)	< 130	141.8 ± 7.1	146.9 ± 8.7	0.010*	152.0 ± .9	141.2 ± 3.7	0.005**	137.2 ± 5.6	125.4 ± 4.8	0.052	0.109	0.047*
LDL/HDL	(ratio)	< 2,5	1.9 ± 0.1	2.0 ± 0.2	0.177	2.5 ± 0.1	2.1 ± 2.3	0.005**	2.2 ± 0.1	2.0 ± 0.1	0.089	0.023*	0.102
TG/HDL	(ratio)	< 1.25	1.1 ± 0.1	1.1 ± 0.1	0.156	2.2 ± 0.2	1.7 ± 0.1	0.005**	1.9 ± 0.2	1.8 ± 0.2	0.151	0.008**	0.039*
BG	(mg/dl)	74−106	86.5 ± 1.8	85.3 ± 1.8	0.167	91.2 ± 1.4	88.7 ± 1.1	0.016*	86.0 ± 1.4	85.5 ± 1.8	0.125	0.070	0.148
Crea	(mg/dl)	0.7−1.1	0.83 ± 0.02	0.79 ± 0.02	0.052	0.78 ± 0.01	0.73 ± 0.01	0.010*	0.79 ± 0.03	0.80 0.03	0.109	0.094	0.031*
GFR	(ml/min)	60−150	82.0 ± 2.9	85.6 ± 25	0.042*	88.6 ± 1.6	92.9 ± 1.4	0.010*	84.6 ± 3.8	83.9 ± 3.5	0.172	0.117	0.031*
Uric acid	(mg/dl)	2.6-6.0	4.8 ± 0.2	4.8 ± 0.2	0.083	5.3 ± 0.1	5.0 ± 0.1	0.031*	5.3 ± 0.2	5.2 ± 0.3	0.156	0.094	0.188
BUN	(mg/dl)	17−43	30.5 ± 1.2	33.1 ± 1.1	0.021*	29.0 ± 0.7	32.5 ± 0.9	0.005**	28.8 ± 1.3	29.1 ± 1.4	0.063	0.172	0.164
AP	(U/l)	30−120	66.6 ± 4.7	64.2 ± 4.4	0.130	68.8 ± 2.4	67.0 ± 2.9	0.036*	65.9 ± 4.8	65.3 ± 5.0	0.068	0.180	0.195
AST	(U/l)	< 31	28.8 ± 4.8	25.7 ± 4.0	0.089	30.1 ± 2.1	28.2 ± 1.9	0.094	24.2 ± 1.8	23.9 ± 1.8	0.167	0.086	0.133
CRP	(mg/l)	< 5.0	1.6 ± 0.4	0.83 ± 0.2	0.078	2.2 ± 0.23	1.9 0.2	0.052	2.3 ± 0.5	1.7 ± 0.4	0.112	0.195	0.133
TSH	(mU/l)	0.3−3.5	1.5 ± 0.2	1.6 ± 0.2	0.141	1.7 ± 0.1	1.6 ± 0.1	0.073	1.0 ± 0.1	1.2 ± 0.2	0.104	0.063	0.078
Protein	(g/dl)	6.6−8.3	6.7 ± 0.09	6.7 ± 0.09	0.182	6.8 ± 0.04	6.8 ± 0.04	0.182	6.9 ± 0.08	6.7 ± 0.09	0.042*	0.148	0.24
Hemoglobin	(g/dl)	12-15.5	13.1 ± 0.2	13.4 ± 0.2	0.167	13.2 ± 0.1	13.4 ± 0.1	0.125	13.2 ± 0.2	13.0 ± 0.2	0.250	0.250	0.125
Lekocyte	$(10^3/\mu l)$	3.9−11	4.68 ± 0.25	5.17 ± 0.29	0.083	5.41 ± 0.16	5.82 ± 0.20	0.042*	5.27 ± 0.31	5.56 ± 0.35	0.208	0.063	0.188
Insulin	(µU/ml)	2−25	12.8 ± 2.0	12.3 ± 1.6	0.177	16.3 ± 0.9	14.0 ± 0.8	0.031*	16.9 ± 2.3	16.6 ± 1.9	0.172	0.188	0.086
HOMA-IR	index*	1.9/2.9	2.73 ± 0.4	2.79 ± 0.4	0.151	3.55 ± 0.3	3.14 ± 0.3	0.016*	3.68 ± 0.5	3.58 ± 0.4	0.182	0.086	0.156

TG: triglycerides; Chol: total cholesterol; HDL: high density cholesterol; LDL: low density cholesterol; BG: blood glucose; Crea: creatinine; GFR: glomerular filtration rate; BUN: bound urea nitrogen; AP: alkaline phosphatase; AST: aspartate transaminase; CRP: C-reactive protein; TSH: thyoid-stimulating hormone; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance *index: 1.9−2.9 = early insulin resistance; >2.9: significant insulin resistance

Blood parameters for the three intervention groups measured at T0 and T20. Parameter values are given as mean ± standard error of the mean (SEM). The other columns give p-values derived from various tests: (i) within-group differences between T0 and T20 were evaluated using the Mann-Whitney-U test; (ii) between-group differences at T0 and T20 were evaluated using the Kruskal-Wallis test; p-values were adjusted following the Benjamini-Hochberg procedure with a false discovery rate of 25% resulting in Benjamini-Hochberg critical values (BHcv). *BHcv ≤ 0.05; **BHcv ≤ 0.01

At T0, the KD group had the lowest triglycerides (TG; 78.1 ± 5.1 mg/dl) and highest HDL concentrations (79.9 ± 3.7 mg/dl) compared to LCD (128.3 ± 8.0/64.5 ± 1.5) and SD (105.3 ± 8.9/65.2 ± 2.7), while LDL was similar between groups, resulting in significantly higher HDL/LDL (BHcv = 0.023) and TG/HDL (BHcv = 0.008) ratios. TG and HDL remained relatively stable until T20 in the KD and SD group, but there was a significant decrease of TG (BHcv = 0.005) and increase of HDL (BHcv = 0.026) in the LCD group. Of note, total cholesterol was highest in the KD group and remained high, while in the LCD and SD groups a significant reduction of cholesterol was observed, corresponding to a decrease in LDL with only a slight increase (LCD) or decrease (SD) in HDL. However, the

final TG/HDL ratio in either the LCD (1.7 ± 0.1) or SD (1.8 ± 0.2) group did not reach the recommended ratio of < 1.25 that was only achieved in the KD group (1.1 ± 0.1). Due to the distinct changes in LDL and HDL, the LDL/HDL ratio was nearly the same in all three groups at T20 (2.0-2.1).

Throughout the intervention, no significant change occurred for blood glucose and insulin in the KD and SD groups. Here, blood glucose concentration was comparable in KD and SD, but insulin remained lowest in KD and highest in SD, resulting in the lowest HOMA-IR (2.8 ± 0.4) in the KD group and highest (3.6 ± 0.4) in the SD group at T20. There was a significant decrease of blood glucose in the LCD group (from 90.2 mg/dl to 88.7; BHcv = 0.016) which was accompanied by a significant decrease in insulin (from 16.3 to 14.0 µU/ml; BHcv = 0.031) and reduction of HOMA-IR to 3.14 ± 0.3 (BHcv = 0.016).

Concerning markers of kidney function, all thee intervention groups started from comparable ranges. While there was no influence of diet type on creatinine, glomerular filtration rate (GFR), uric acid and bound urea nitrogen (BUN) in the SD group, creatinine decreased (BHcv = 0.01) and GFR significantly increased in the KD (BHcv = 0.04) and LCD (BHcv = 0.01) group. Uric acid remained stable in the KD and SD groups and decreased in the LCD group (BHcv = 0.03); BUN increased on the KD (BHcv = 0.02) and LCD (BHcv = 0.005); however all parameters stayed within the normal range.

The liver parameters alkaline phosphatase (AP) and aspartate transaminase (AST) did not differ between groups at T0 and remained stable throughout the intervention with the exception of a significant decrease of AP in the LCD group (BHcv = 0.036).

At T0 and T20, c-reactive protein (CRP) was lowest in the KD group without significant differences within or between groups. Serum protein remained stable in the KD and LCD group but decreased in the SD group (BHcv = 0.04).

Hemoglobin remained relatively stable upon intervention, slightly raised on the KD (from 13.1 ± 0.2 g/dl to 13.4 ± 0.2) and LCD (from 13.2 ± 0.1 to 13.4 ± 0.1), and decreased on the SD (from 13.2 ± 0.2 to 13.0 ± 0.2). In all three groups, there was a positive development in leukocyte count that was significant in the LCD (from 5.41 ± 0.16 to 5.82 ± 0.2; BHcv = 0.042) and without significance in the KD (from 4.68 ± 0.25 × 10^3/µl to 5.17 ± 0.16; p = 0.04) and SD (from 5.27 ± 0.31 to 5.56 ± 0.35) group.

Discussion

In this study we were able to show that the three diets compared (KD, LCD, SD) were all well tolerated and safe and supported quality of life and physical performance of BC patients in the rehabilitation process.

The excellent compliance of our subjects during the outpatient phase is proven by the analysis of food diaries, the match between the measured respiratory quotient with that expected for a given diet and changes in serum parameters (especially the TG/HDL ratio) which are in line with previously published data obtained for LCDs and KDs [17] compared to SDs. All three diets were well implementable for our participants as judged by phone interviews, email exchanges and the questionnaires throughout the outpatient phase as well as personal interviews during their stay in the rehabilitation center.

Limitations and strengths of the study

Our study has several limitations. The most obvious is the lack of a clear randomization with the bias of the pre-existing experience of the majority of KD patients with LCDs or even KDs for a longer period prior to T0. This group was highly motivated to participate in the study in order to maintain their diet throughout the rehabilitation procedure. To ensure maximal compliance, we let patients choose their diet since realization of the diets throughout the outpatient phase needed a high motivation and active realization (food preparation, calculation) by the participants. Further, due to the highest rate of advanced cancer patients, KD participants had the highest impetus to achieve good performances in the study.

Another point for critique could be the lack of control regarding the amount of exercise in the outpatient phase. We cannot rule out the possibility that some participants increased their training volume and/or intensity during this phase, although subjects affirmed this not to be the case. Nevertheless, our results indicate that for all subjects, physical performance improved during the intervention and was not compromised by the low (LCD) or very low (KD) carbohydrate content of their diet. This is in accordance with published data from healthy subjects and athletes, which also performed well under LCD and KD regimes [18–21]. While some studies showed a negative impact when switching to LCDs or KDs on physical performance in the short term (21–30 days; [22]) and up to 10 weeks [23], the duration of 20 weeks in our study allowed the patients to adapt to the profound change in energy metabolism. Accordingly, at T20, none of the KD and LCD patients reported "lack of energy", and their physical performance was even superior to patients in the SD group.

On the other hand, strengths of the study include the well-controlled dietary intervention, the uniform multimodal treatment of patients within the closed setting of the rehabilitation center and a tight supervision in the outpatient phase by the study team (physician, dietitian, study nurse). Furthermore, the 20-week intervention ensured a profound adjustment of fuel utilization according to diet type. This allowed us to measure effects at T20, which were free of problems with metabolic adaption. The diet effects were reflected in objective parameters (serum analysis, spiroergometry, DXA and BIA) as well as in patient reported outcomes determined by validated questionnaires.

Energy uptake/body composition

Since muscle loss [24] and increased fat mass (in particular visceral fat [25]) are negatively associated with the outcome of breast cancer patients, we were interested how the individual diet types influenced body composition. All three diet groups were able to reduce body weight, which was one of their personal goals since their physicians told them that normalizing body weight might improve outcome based on international guidelines [26]. Weight loss consisted mainly of fat mass. Accordingly, the muscle/fat mass ratio improved, with the SD group showing the weakest effect and the KD group the most prominent effect. This finding is in accordance with the previously published superiority of KD to SD in reducing central obesity in female cancer patients [27]. LCD patients, who started from the worst ratio, managed to improve nearly as well as patients on a KD. This indicates that a protein and fat enriched LCD could be a good choice for cancer patients wanting to improve their body composition without the need to be as strict as patients on the KD. Very recently, the weight

loss benefits of a LCD were also shown in overweight men with prostate cancer [28]. A reason for the superiority of fat-rich diets could be that they are better adapted to the increased fat oxidation rates found in cancer patients [4, 5]; the latter correlates with a decreased ability to use glucose in the periphery due to insulin resistance [2]. In our study, the KD was the only regimen that covered the recommendations for energy and protein intake during chemotherapy and radiation [29] and thus could be considered as a possible supportive diet during cancer treatment in such cases.

Physical performance

The RQ is a strong indicator of fuel utilization. Due to the prevalent pre-existing adaption to a LCD in the KD group, the RQ was the lowest already at T0. However, the RQ declined further until T20, possibly reflecting the influence of a well-designed KD calculated by the trained dietitian compared to the self-prescribed LCDs consumed before the intervention. This decline in the RQ reflected a further shift in fuel utilization towards fat oxidation in line with the findings of previous studies in obese [30] or lean [31] subjects after at least three weeks on a KD. Maximum RQ values tended to be lower at T20 compared to T0 on the LCD and higher on the SD, also confirming the correct dietary intervention for the respective groups.

It is interesting to note, however, that patients reached similar lactate concentrations at T20 compared to T0 despite the different nature of the diets. This indicates that glycogen stores were not fully depleted during the exercise protocol even in the KD group and that adaption to a KD did not impair glycolysis and performance during high-intensity exercise. VO2max/kg values are frequently used in the literature to compare exercise capacity after an intervention. Increases in VO2max/kg could correlate partially to the decreases in body weight of our patients and thus alone did not necessarily confirm an increase in physical performance. However, as workload and time to exhaustion improved in parallel, all three parameters together clearly indicate a positive effect of the rehabilitation process in general and of the combination with dietary interventions in particular. Patients in the KD group were able to further extend their higher fitness from T0 to T20 compared to those in the LCD and SD groups. Finally the KD participants ended up in VO2max/kg comparable to age related healthy women [32]. This indicates that high amounts of carbohydrates in the diet were not necessary for the fitness demands we placed on our study participants.

Quality of life

The positive impact of the 3 weeks inpatient rehabilitation program used in our study on QoL of breast cancer patients has already been published [33]. In this study, no special dietary intervention was used, but the other parameters of the comprehensive multi-modal program were the same as in the KOLIBRI study. All three of our groups reached or outreached the mean QoL values achieved in the previously published papers that did not include a dietary intervention at the end of the fist inpatient phase (T3; **supplementary Figure S1**). This allows us to speculate that any type of nutritional counselling should be included in rehabilitation programs to further improve results. Functional scales remained relatively stable during the outpatient phase on all three diets. However, in parallel to the increase in physical performance, the KD group had the best physical functioning value, reaching the mean value of healthy persons published as the "reference scale" [34]. This positive effect of KD on physical functioning was also seen in women with endometrial and ovarian cancer [35] highlighting this important aspect as general.

Further, a clear discrepancy was seen in the development of some of the symptoms amongst the groups during the outpatient phase (T3-T20). While fatigue and insomnia scores remained stable in the LCD and SD groups, they further improved in the KD group to T20, almost reaching the reference values of healthy age-matched adults. This remarkable reduction in fatigue was also seen in other cancer patients eating a KD [35]

Blood/serum

Although evidence exists that fat-rich diets do improve rather than worsen cardiovascular risk factors and especially increase HDL and decrease triglycerides [17, 36, 37] some oncologists fear that such diets have a detrimental effect on blood lipid profiles and liver- and kidney function. Here, a remarkable positive effect of the LCD on nearly all parameters could be observed – a significant improvement in lipid profile and optimization of the liver profile and kidney function parameters. Together with the positive effects on body composition and physical performance this would speak in favor of a LCD as a recommendable diet for patients with metabolic syndrome in general or BC patients in particular who are frequently overweight and could benefit from reducing their body weight and improving their metabolic health [38]. Apart from a minimal increase in LDL, KD patients had the highest HDL and lowest triglycerides of all groups with no out-of-reference values in any other parameters, indicating the safety of a KD. In addition, KD patients had low insulin concentrations as observed for healthy persons [39]. Taking into account that insulin is discussed to be a growth factor in neoplasia [40], the KD appears to be the most effective strategy to attenuate insulin-mediated growth stimuli to tumor cells.

It is noteworthy that the effects on biochemical parameters were more prominent in the long time intervention (T20) compared to the "short time" intervention at T3 (**supplementary Figure S2**), again pointing out the advantage of a 20 weeks dietary intervention compared to short-term interventions that might not allow a full judgement of profound metabolic changes.

In summary, we could show that a well-defined KD as well as a less strict LCD exhibited positive effects on body composition, physical performance and quality of life of BC patients during the rehabilitation phase. In contrast, a SD following the current guidelines of nutritional societies was inferior for physical performance and body composition improvements and also failed to meet the recommended energy and protein intake for cancer patients. A reason could be that SD guidelines are intended for healthy persons, which have other metabolic needs than cancer patients.

Based on the known metabolic situation in cancer patients, we expect both the KD and the LCD to better account for the metabolic alterations compared to the SD regimen recommended thus far. In addition, the KD was reported to be safe for cancer patients in several clinical settings [27, 35, 41] and to improve overall survival in a group of breast cancer patients compared to a SD [42]. Thus, our work provides further evidence supporting the safety and benefits of this dietary approach for BC patients.

Conclusion

Besides the effects of local and systemic therapies, normal BMI, a positive body composition and physical performance are important predictors of outcome. Oncologists therefore often enforce their patients to normalize their body weight by a healthy diet and increased physical activity. Fat rich low carb diets (LCDs) and ketogenic diets (KDs) are able to induce profound positive changes in body weight and composition. The question whether LCDs and KDs are safe and compatible with physical performance and quality of life in cancer patients can be answered with yes in BC patients during their rehabilitation process according to the data of the KOLIBRI trial. Further trials should now test LCDs and KDs for BC patients to support systemic therapies by improving quality of life and physical fitness, and thus compliance and treatment response in BC patients.

Abbreviations

AP
alkaline phosphatase
AST
aspartate transaminase
BC
breast cancer
BHcv
Benjamini-Hochberg critical value
BIA
bioimpedance analysis
BMI
body mass index
BUN
bound urea nitrogen
CRP
c-reactive protein
DXA
Dual-Energy X-Ray Absorptiometry
GFR
glomerular filtration rate
HDL
high density lipoprotein
HOMA-IR
Homeostatic model assessment of insulin resistance
KD
ketogenic diet
LCD
low carb diet
LDL
low density lipoprotein
NYHA
New York heart association
QoL
Quality of life
RQ
respiratory quotient
SD
standard diet
SEM
Standard error of mean
TG
triglycerides
VO2max
maximal oxygen uptake

Declarations

Ethics approval:

The "Ketogenic Or LOGI Diet In a Breast Cancer Rehabilitation Intervention" (KOLIBRI) trial (ClinicalTrials.gov Identifier: NCT02092753) was approved by the Ethics Committee of the Bavarian Medical Association (Bayerische Landesärztekammer; No. 13082). All study participants signed informed consent.

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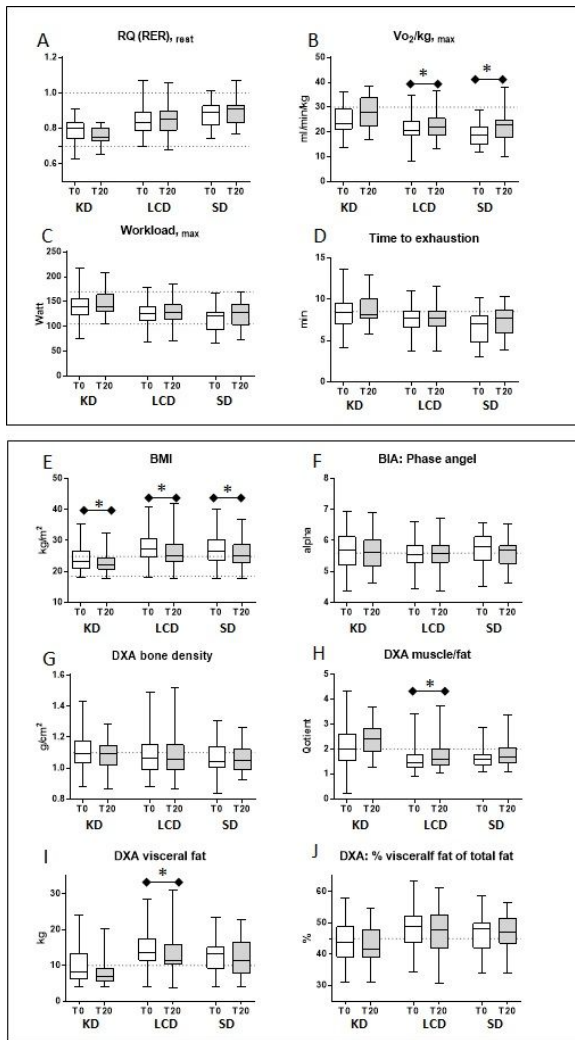
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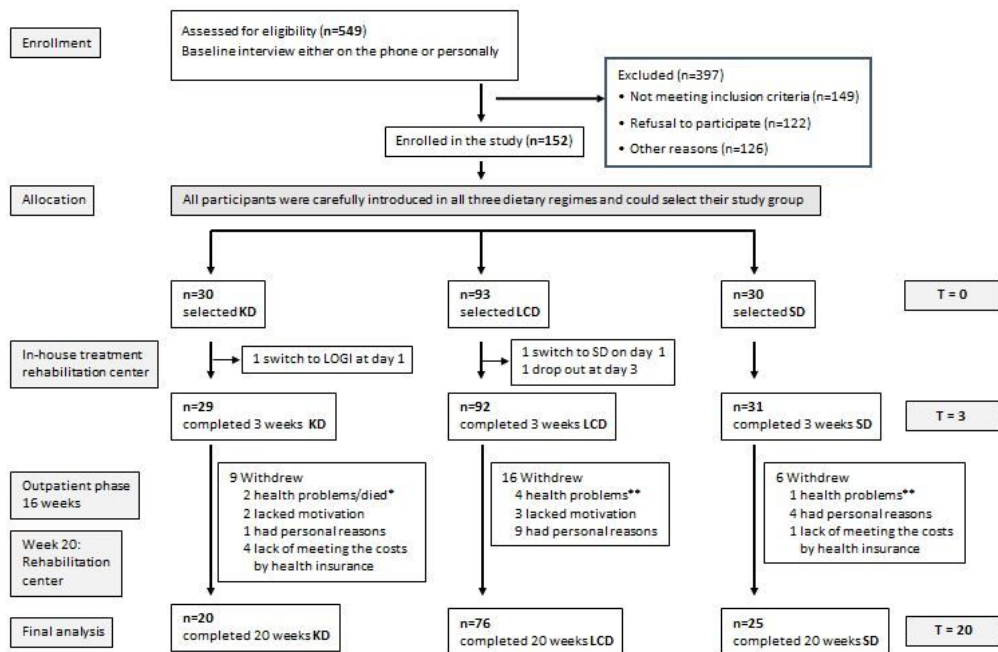
Figure 1

Trial profile with dropouts * 1 patient had to resume chemotherapy directly after T3 due to progress, one died because of advanced metastatic disease ** Patients reported health problems without further specification
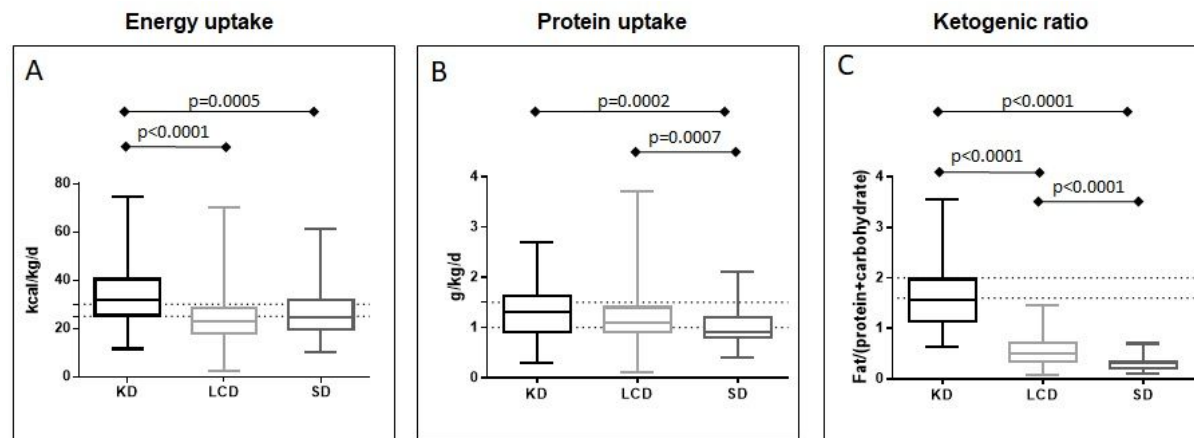
Figure 2

Energy and protein uptake Energy and protein taken up by the patients per day per kg body weight as calculated by analysis of the food diaries. A) Energy in kcal/kg body weight/day. Dashed lines: optimal daily energy intake (25-30 kcal/kg/d) as recommended for ambulatory patients by Muscartoli M, 2019 (16) B) Protein uptake per day per kg bodyweight. Dashed lines: goal for daily protein intake in cancer treatment (1-1.5 g/kg/day) according to Muscartoli M, 2019 (16) C) Ketogenic ratio. Dashed lines: goal in the study 1.6-2:1

Figure 3

Physical performance and body composition Data obtained at start of intervention (T0) and at end (T20) by spioroergometry (A-D), boioimpedance analysis (BIA; F) and Dual-Energy X-Ray Absorptiometry (DXA; G-J) . A) Respiratory quotient (RQ/RER). Dashed lines indicate pure fat oxidation (0.7) and pure carbohydrate respiration (1.0) respectively. B) Body weight related oxygen uptake. Dashed line indicates VO2/kg max for healthy age-matched women calculated by −0.35 × age (years) + 46 (ml/min/kg) (32). C) Maximal workload, lines mark expected upper and lower results for age-related healthy women and D) time to exhaustion, dashed line: median of KD group at T0. E) Body mass index (BMI) with lines indication lower and upper limit of normal BMI. F) Phase angle alpha obtained via BIA. Line gives medium phase angle for age adjusted women. G) Bone density measured by DXA. Line shows mean bone density of comparable healthy women. H) Result of DXA analysis of muscle mass and fat mass resulted in the muscle/fat quotient. A quotient of 2:1 (line) or higher should be reached for optimal health. I) Visceral fat. As health goal, visceral fat should not extend 10 kg (line) or 45% of total body fat (line; J). *BHcv≤0.05; **BHcv≤0.01

Supplementary Files

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

- SupplFigS1QoLT0T3T20.pptx
- SupplFigS2serologyT0T3T20.pptx
- SupplTable1Dietcomposition.docx