Clinical Nutrition xxx (xxxx) xxx

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

# A ketogenic diet consumed during radiotherapy improves several aspects of quality of life and metabolic health in women with breast cancer

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ARTICLE INFO

*Article history:*
Received 17 November 2020
Accepted 18 January 2021

*Keywords:*
Blood parameters
EORTC-QLQ30
KETOCOMP
Nutrition

SUMMARY

*Background & aims:* Ketogenic diets (KDs) have been proposed as complementary nutritional treatments for cancer patients. Because it is important to gain knowledge about the safety of KDs adopted during cancer therapy, we studied the effects of KDs on quality of life and blood parameters in women with early-stage breast cancer undergoing radiotherapy.

*Methods:* A total of 29 patients consuming a KD were compared to 30 patients consuming their standard diet (SD) with respect to EORTC-QLQ30 questionnaire scores and different metabolic and hormonal blood parameters that were obtained prior to, in the middle of and at the end of radiotherapy. Baseline-to-end differences were assessed using Wilcoxon tests, and longitudinal changes were analyzed using linear mixed effects models.

*Results:* Compared to the SD, women consuming a KD experienced significant improvements in emotional functioning, social functioning, sleep quality, future perspectives and systemic therapy side effects (all $p$-values $<0.01$). While breast symptoms increased significantly in both groups, the increase was less pronounced in the KD group. There was no hint of a detrimental effect of the KDs on either liver or kidney function; in contrast, biomarkers of metabolic health (gamma-glutamyl-transpeptidase, creatinine, triglycerides, IGF-1, free T3) significantly improved in the KD, but not the SD group.

*Conclusions:* These data support the hypothesis that consuming a KD during radiotherapy is safe for women with breast cancer and has the potential to improve quality of life and metabolic health.

*ClinicalTrials.gov identifier:* NCT02516501.



## 1. Introduction

Most tumor cells possess a preference to take up and ferment large amounts of glucose from their environment, even in the presence of sufficient oxygen that would normally shift metabolism from glycolysis to oxidative phosphorylation in healthy cells. This is called the Warburg effect after Otto Warburg who had systematically studied this phenomenon in the 1920s [1,2]. In addition, many tumor cells are responsive towards insulin and insulin-like growth factor-1 (IGF-1), so that chronically elevated glucose levels may cause tumor cell proliferation by elevating the availability of these growth factors [3–5]. These facts have built the basis for proposals to reduce glucose supply to tumor cells through dietary manipulation by severely restricting carbohydrates either through fasting [6,7] or high-fat ketogenic diets (KDs) [8–10]. While fasting has its limitations stemming from the associated weight loss and risk of nutrient and mineral deficiencies [11], a well-formulated KD in principle allows for an adequate energy and micronutrient intake [12]. Nevertheless, many oncologists and nutritionists are also skeptical towards applying KDs to cancer patients, listing fear of weight loss, fatigue and nutritional inadequacy as arguments [13,14]. Clinical studies examining the safety and feasibility of KDs are therefore important to inform about potential risks and pitfalls for patients who want to adopt such diets during their cancer treatment.

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https://doi.org/10.1016/j.clnu.2021.01.023
0261-5614/

Please cite this article as: R.J. Klement, M.M. Weigel and R.A. Sweeney, A ketogenic diet consumed during radiotherapy improves several aspects of quality of life and metabolic health in women with breast cancer, Clinical Nutrition, https://doi.org/10.1016/j.clnu.2021.01.023

After having gained first experiences with cancer patients who adopted a KD during radiotherapy [15], in 2015 we initiated a controlled clinical trial (the KETOCOMP study) to investigate the effects of KDs on body composition, blood parameters and quality of life (QoL) in patients with breast, rectal and head and neck cancer [16]. We recently published the results of this study for the cohort of breast cancer patients concerning changes in body composition which was the primary outcome of the KETOCOMP study. Besides confirming the safety of this intervention, we were able to show that a KD consumed during radiotherapy induced significant gradual weight and fat mass reductions of approximately 0.4 kg/week while fat free and skeletal muscle mass did not change significantly after an initial rapid drop associated with water losses [17]. We also reported that the KDs did significantly reduce free T3 hormone levels, but not insulin, IGF-1 or glucose. Here, we investigate further the effects of the KDs on QoL and several blood parameters which were the secondary outcome measures of the KETOCOMP study.

## 2. Materials and methods

### 2.1. Patients

The KETOCOMP study was designed as a non-randomized, controlled phase I study. Women with early stage breast cancer being referred to our clinic for curative radiotherapy were principally eligible for participation. Exclusion criteria consisted of Karnofsky index <70, metallic implants (because of possible interference with body composition measurements), pregnancy, cognitive impairment, inability to speak or understand German and metabolic defects posing a contraindication against consuming a KD. We recruited 32 women into a KD group and 31 women into a standard diet (SD) control group. Of these, 29 and 30 patients, respectively, finished the study and contributed to the analysis. For a detailed description of the study protocol and its amendments, the reader is referred to the original study protocol [16] and the previous publication of the body composition results [17].

### 2.2. Measurements

Baseline measurements were performed prior to the first irradiation and consisted of (i) weight and bioimpedance analysis (BIA) on a seca 515/514 medical Body Composition Analyzer (mBCA; seca Deutschland, Hamburg, Germany); (ii) an EORTC QLC-C30 questionnaire version 3.0 together with the BR23 module; (iii) blood draw with subsequent analysis in the hospital laboratory. BIA and weighing were repeated weekly during radiotherapy, while laboratory blood analysis and completion of the EORTC QLC-C30 questionnaire were repeated once during and in the final week of radiotherapy. In the KD group, we also measured capillary β-hydroxybutyrate and glucose concentrations at least once per week at the time of BIA measurements using the FreeStyle Precision device (Abbott Diabetes Care Ltd., Range Road, Witney, UK). The study length was determined by the length of radiotherapy. Thirteen patients received hypofractionated radiotherapy (16–20 fractions), and 46 normofractionated radiotherapy (25–31 fractions).

The early (acute) breast skin toxicity (erythema and/or desquamation) at the end of radiotherapy was assessed by an oncologist and rated according to the RTOG (Radiation Therapy Oncology Group) scale [18].

### 2.3. Dietary intervention

Details about the KDs had been reported previously [17]. The KDs were individually designed according to principles that were explained to the patients by a registered dietician with experience in implementing KDs and in handouts including food choices and cooking recipes (Supplementary File 1). Patients also had the option to borrow recipe books and a popular book on the KD and cancer [19]. MCT oil was recommended (Kanso 100% MCT, Dr. Schär AG, Burgstall, Italy) and given to the patients for free. Our guidelines suggested replacing carbohydrates with fat, consuming 75–80% calories from fat, and limiting carbohydrates to 50 g per day and 10 g per meal. The goal was to promote the consumption of a whole food KD *ad libitum*. High-quality protein of animal origin and micronutrient-dense foods were emphasized. Patients were advised to avoid any industrial and processed foods (with the exception of MCT oil), vegetable oils (except virgin coconut and olive oil), grains, and legumes. Dairy products were suggested only in moderation and preferably in the form of butter, cheese, and fermented products. Patients in the KD group were requested to start the KD after baseline measurements, but at least 2 days prior to their first radiotherapy treatment. For 15 patients, the KD was supplemented with 10 g of an essential amino acid supplement (MAP, re-branded as MyAMINO, dr. reinwald health-care gmbh + co kg, Altdorf, Germany) on radiation days. Patients in the SD group received no specific dietary advice. However, patients could ask for dietary counseling, which was requested by four patients. These individuals received standard recommendations according to the German Nutrition Society (DGE), which promote consuming mostly unrefined foods of plant origin (in particular whole grains, vegetables, and fruits) and limiting fats to 30–35% daily energy intake, with an emphasis on reducing fats from animal origin.

### 2.4. Statistical analysis

The answers given by the patients in the EORTC QLC-C30 questionnaires were converted to the functional and symptom scores defined by Aaronson et al. [20,21].

Within- and between group differences between baseline and final measurements were tested for being consistent with the null hypothesis of no changes using the Wilcoxon signed rank test and the Wilcoxon rank sum test (equivalent to the Mann–Whitney test), respectively. For simplicity, we decided to investigate baseline-end differences independent of the length of the study, since the distribution of fractionation patterns was very similar between both groups (hypofractionation: 6 patients in KD, 7 in SD group; normofractionation: 23 patients in both groups). Because $p$-values overstate the evidence against the null hypothesis [22], we decided to only consider $p$-values $\leq 0.01$ indicating "significant" findings.[1]

In case of a significant difference between baseline and final measurements within the KD group, an additional longitudinal analysis was performed, assuming a linear gradual change. To this aim, we used linear mixed effects models with the slope of the variable $t$ (time since start of RT) as a random effect varying by the individual patient. Let $y_{ij}$, $i = 1, \ldots, n_j$, denote the $i$th measurement on patient $j = 1, \ldots, N$ at time $t_i$ during the study. We constructed simple models predicting an individual measurement $y_{ij}$ based on time, group (0 = SD; 1 = KD), their interaction and the corresponding baseline measure $y_{1j}$:

[1] This threshold was chosen based on the conversion between p-values and minimum Bayes factors [22]. Bayes factors (or likelihood ratios in case of simple hypotheses) measure the strength of evidence between two competing hypotheses [52]. In exploratory analyses, a $p$-value of 0.01 corresponds to a minimum Bayes factor of 1/6.5, providing moderate to strong evidence against the null hypothesis [22].

$$y_{ij} = \beta_0 + (\beta_1 + U_j) * t_i + \beta_2 * KD_j + \beta_3 * KD_j * t_i + \beta_4 * y_{1j} + \varepsilon_{ij},$$
$$U_j \sim N\left(0, \sigma_U^2\right),\ j = 1, \ldots, N$$
$$\varepsilon_{ij} \sim N\left(0, \sigma_\varepsilon^2\right),\ i = 0, \ldots, n_j \quad (1)$$

The average time trends of patients in the SD and KD group are therefore given by $\beta_1$ and $\beta_1 + \beta_3$, respectively.

All analyses were carried out in R, version 4.0.2.

## 3. Results

Baseline characteristics of all patients included in the analysis are given in Supplementary File 2 and have also been described previously [17]. The groups did not differ significantly in any of the anthropological, tumor- or treatment-related parameters, the greatest difference being that a larger percentage of patients had received accompanying therapy (antihormonal or antibody therapy) in the KD group ($p = 0.064$).

### 3.1. Quality of life

The baseline and final QoL scores are given in Table 1. The KD and SD groups appeared to be well balanced with regard to almost all scores at baseline, except for a higher symptom score of insomnia in the KD group that almost reached statistical significance ($p = 0.029$). However, at the end of the study the KD group had significantly improved its insomnia score, with the median being no different from the SD group. The KD group also achieved significant reductions in systemic therapy side effects, as well as significant improvements in emotional functioning, social functioning and future perspectives. In contrast, no significant reductions of symptom scores or improvements in function scores were observed in the SD group. Notably, two patients from the KD group explicitly mentioned the complete vanishing of their chronic migraine at the end of the study. The KD group also achieved improvements in the median score of role functioning, body image and the overall QLQ-C30 summary score as well as reductions in the score for pain and arm symptoms; while these changes were not statistically significant, it is noteworthy that the changes of these scores showed the opposite direction in the SD group, i.e., pointing towards a reduction in QoL (Table 1).

In the linear mixed effects models analysis, there were no significant time effects of the KD on QoL scores, indicating that the QoL changes associated with the KD did not occur linearly.

### 3.2. Skin toxicity

Because ketone bodies are hypothesized to protect against radiotherapy (and chemotherapy) side effects [23,24], we investigated early breast skin toxicity at the end of radiotherapy. Table 2 shows the skin toxicity experienced by the women at the end of radiotherapy according to treatment group. Only acute erythema was observed, but there was no significant difference in the severity of skin toxicity among both groups.

### 3.3. Blood parameters

Figure 1 shows the capillary blood concentrations of β-hydroxybutyrate and glucose according to the week of radiotherapy. Median β-hydroxybutyrate levels rose until week 2, then remained rather stable until week 5, and dropped in week 6.

The baseline and final blood parameters are given in Table 3. There were no significant differences between both groups with respect to most blood parameters except for significantly higher total and LDL cholesterol levels in the KD group. However, at the end of the study, these differences were less pronounced and no longer statistically significant. As expected, β-hydroxybutyrate levels rose significantly in the KD group, but glucose levels did not change significantly. Both the KD and the SD group experienced a significant reduction in leucocyte and platelet counts as well as gamma glutamyl transpeptidase (GGT), whereby the changes in GGT were significantly greater in the KD than in the SD group (Fig. 2). In addition, creatinine, triglycerides, IGF-1 and free T3 levels had dropped significantly in the KD, but not the SD group. At study end, both groups were comparable with respect to most blood

**Table 1**
Baseline and final quality of life (QoL) scores for the ketogenic diet (KD) and standard diet (SD) groups.

| QoL score | Keto | | | Control | | | Keto vs. Control | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Final | Difference ($p$-value) | Baseline | Final | Difference ($p$-value) | Baseline difference ($p$-value) | Final difference ($p$-value) |
| Global health status | 66.7 (33.3–100) | 75 (33.3–91.7) | 0.598 | 66.7 (0–100) | 66.7 (33.3–100) | 0.704 | 0.868 | 0.397 |
| Physical functioning | 93.3 (40–100) | 93.3 (60–100) | 0.533 | 93.3 (40–100) | 86.7 (40–100) | 0.979 | 0.553 | 0.270 |
| Role functioning | 66.7 (16.7–100) | 83.3 (33.3–100) | 0.081 | 83.3 (0–100) | 66.7 (0–100) | 0.288 | 0.833 | 0.023 |
| Emotional functioning | 58.3 (25–100) | 75 (50–100) | 0.00017* | 66.7 (25–100) | 66.7 (33.3–100) | 0.944 | 0.053 | 0.431 |
| Cognitive functioning | 83.3 (50–100) | 83.3 (50–100) | 0.829 | 100 (33.3–100) | 83.3 (33.3–100) | 0.704 | 0.901 | 1 |
| Social functioning | 66.7 (0–100) | 83.3 (33.33–100) | 0.0098* | 66.67 (0–100) | 66.7 (33.3–100) | 0.023 | 0.987 | 0.206 |
| Fatigue | 22.2 (0–66.67) | 33.3 (0–77.78) | 0.117 | 33.33 (0–100) | 38.9 (0–88.9) | 0.108 | 0.652 | 0.0996 |
| Nausea and vomiting | 0 (0–16.7) | 0 (0–33.3) | 0.407 | 0 (0–33.3) | 0 (0–16.7) | 0.824 | 0.670 | 0.692 |
| Pain | 33.3 (0–66.7) | 16.7 (0–66.7) | 0.683 | 16.7 (0–100) | 25 (0–100) | 0.045 | 0.364 | 0.459 |
| Insomnia | 66.67 (0–100) | 33.33 (0–100) | 0.0072* | 33.3 (0–100) | 33.3 (0–100) | 1 | 0.029 | 0.654 |
| Appetite loss | 0 (0–33.33) | 0 (0–66.67) | 0.437 | 0 (0–100) | 0 (0–66.7) | 0.608 | 0.843 | 0.095 |
| Constipation | 0 (0–66.7) | 0 (0–66.67) | 0.832 | 0 (0–100) | 0 (0–33.3) | 0.572 | 0.153 | 0.903 |
| Diarrhea | 0 (0–66.7) | 0 (0–66.67) | 0.588 | 0 (0–66.67) | 0 (0–66.7) | 1 | 0.288 | 0.475 |
| Financial difficulties | 0 (0–66.7) | 0 (0–66.67) | 0.276 | 0 (0–66.67) | 0 (0–66.7) | 1 | 0.695 | 0.396 |
| QLQ-C30 Summary Score | 80.2 (57.7–100) | 84.1 (63.0–97.0) | 0.020 | 82.8 (33.5–100) | 79.2 (49.6–98.7) | 0.374 | 0.315 | 0.363 |
| Body image | 75 (25–100) | 83.3 (50–100) | 0.066 | 91.7 (16.7–100) | 87.5 (16.7–100) | 0.979 | 0.144 | 0.294 |
| Future perspective | 33.3 (0–100) | 66.7 (0–100) | 0.0024* | 66.7 (0–100) | 66.7 (0–100) | 0.018 | 0.109 | 0.293 |
| Systemic therapy side effects | 19.1 (0–71.4) | 19.0 (0–38.1) | 0.0079* | 16.7 (0–52.4) | 23.1 (0–61.9) | 0.290 | 0.189 | 0.510 |
| Breast symptoms | 20.8 (0–75) | 33.3 (8.3–83.3) | 0.0034* | 16.7 (0–50) | 41.7 (8.3–100) | 0.00012* | 0.548 | 0.364 |
| Arm symptoms | 13.9 (0–66.7) | 11.1 (0–77.8) | 0.856 | 11.1 (0–66.7) | 22.2 (0–66.7) | 0.151 | 0.98 | 0.441 |

*$p \leq 0.01$ (statistically significant).

**Table 2**
Number of skin toxicity events in the ketogenic diet (KD) and standard diet (SD) groups according to RTOG grade.

| RTOG grade | 0 | 1 | 2a | 2b |
|---|---|---|---|---|
| KD group | 3 (10.3%) | 15 (51.7%) | 10 (34.5%) | 1 (3.4%) |
| SD group | 3 (10.0%) | 17 (56.7%) | 7 (23.3%) | 3 (10.0%) |

parameters except for significantly lower T3 levels and significantly higher β-hydroxybutyrate levels in the KD group. Figure 2 shows the absolute changes of GGT, creatinine, insulin, IGF-1, triglycerides and free T3 in both groups, showing that metabolic parameters improved to a greater degree in the KD group.

In longitudinal analysis, no significant time × KD effects were detected for the parameters that had changed significantly from baseline to the final measurement except for T3 levels which decreased by an average of 0.07 pg/ml per week in the KD group (Table 4). There was also a general significant decrease of both leucocyte and platelet counts by 190/μl and 4400/μl per week, respectively. The KD was associated with an additional, but non-significant, gradual decrease of these particle counts.

Correlation analysis revealed inverse correlations between the ketone body β-hydroxybutyrate and IGF-1 (Spearman's $r = -0.116$, $p = 0.127$), age-adjusted IGF-1 $z$-scores ($r = -0.132$, $p = 0.095$), insulin ($r = -0.138$, $p = 0.068$) and free T3 levels ($r = -0.327$, $p = 1.2 \times 10^{-5}$) as well as a significantly positive correlation between insulin and IGF-1 ($r = 0.30$, $p = 5.2 \times 10^{-5}$).

## 4. Discussion

The aim of this analysis was to investigate the impact of a KD consumed during radiotherapy on QoL and blood parameters of early stage breast cancer patients. Women in the KD group experienced significant improvements in several dimensions of QoL during the study, while no significant changes occurred in the control group. The overall QoL improvement in the KD group was also reflected in an almost statistically significant ($p = 0.020$) increase of the QLQ-C30 summary score [25] by roughly 4 points (Table 1). In addition to these subjective improvements, the KD group also improved in some blood parameters, most notably GGT, creatinine, triglycerides and IGF-1 (Table 3). This study has been the first to investigate the effects of a KD during radiotherapy on QoL and blood parameters in women with breast cancer, a group of patients that is particularly interested in complementary diet interventions.

### 4.1. Effects on quality of life

We have previously shown that the KD led to an overall improvement of body composition, in particular with respect to a significant body weight and fat mass reduction of approximately 0.4 kg/week each [17]. These anthropometric changes could have been responsible for the improvements in social functioning and body image, although the latter was not statistically significant ($p = 0.066$). In addition, emotional functioning improved, while insomnia and systemic therapy side effects decreased significantly during the study in the KD group. KDs have many beneficial effects on neurological functions which may include stabilizing effects on mood and improvement of sleep disorders [26]. Improved emotional functioning and less insomnia after adopting a KD was also found in two studies involving advanced stage cancer patients who were not on chemo- or radiotherapy [27,28]. These and our data thus provide some confirmation for the hypothesis that a KD improves emotional functioning and

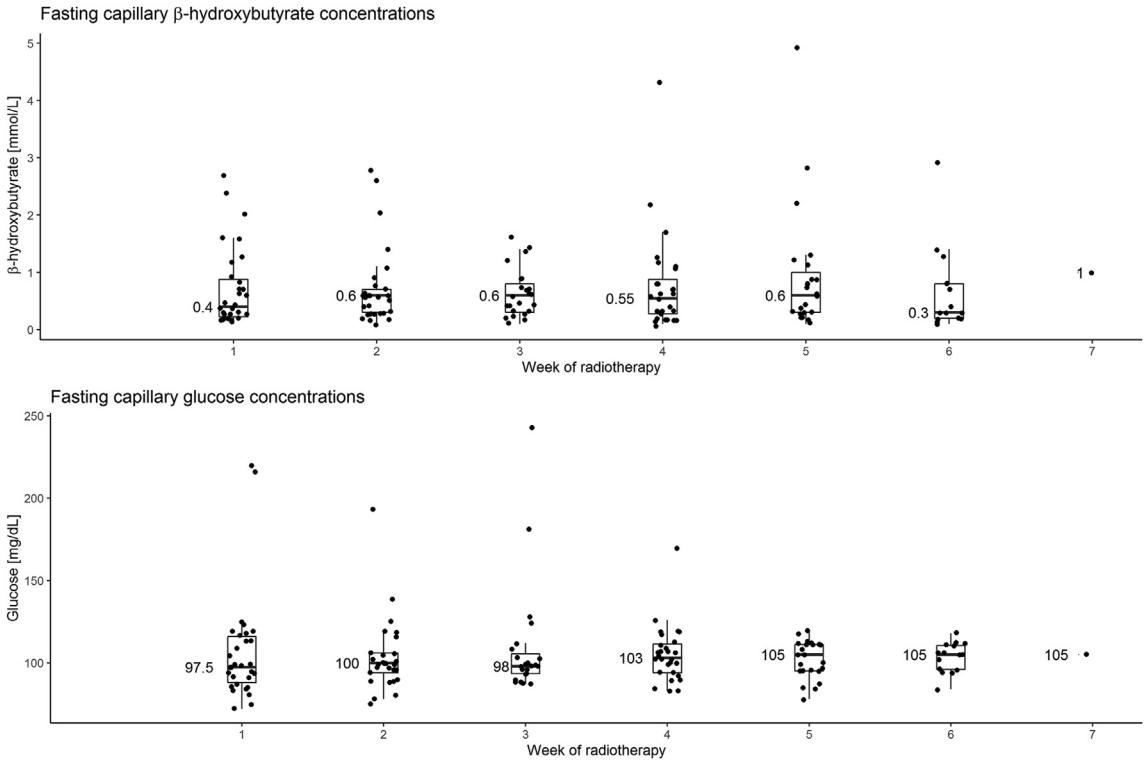


**Fig. 1.** Boxplots showing the course of fasting capillary β-hydroxybutyrate and glucose concentrations over the weeks in the KD group. Jittered points are individual measurements, and the weekly median is given as text.

**Table 3**
Blood parameters at baseline and end of the study in the ketogenic diet (KD) and standard diet (SD) group.

| Blood parameter | Keto | | | Control | | | Keto vs. Control | |
|---|---|---|---|---|---|---|---|---|
| | Baseline | Final | Difference (*p*-value) | Baseline | Final | Difference (*p*-value) | Baseline difference (*p*-value) | Final difference (*p*-value) |
| Erythrocyte count [$10^6$/μl] | 4.5 (3.3–5.2) | 4.7 (3.7–5.4) | 0.059 | 4.6 (3.6–5.6) | 4.6 (3.8–5.1) | 0.317 | 0.779 | 0.432 |
| Leucocyte count [$10^3$/μl] | 5.7 (2.9–10.8) | 4.8 (2.8–8.5) | $7.7 \times 10^{-5}$ * | 5.8 (3.0–12.1) | 4.9 (3.1–8.6) | 0.00048* | 0.834 | 0.430 |
| Platelet count [$10^3$/μl] | 244 (72–430) | 214 (131–371) | 0.00032* | 226 (178–381) | 206 (139–318) | 0.0011* | 0.276 | 0.439 |
| Aspartate transaminase (AST) [U/l] | 23 (15–191) | 22 (10–37) | 0.712 | 22 (13–43) | 23 (13–36) | 0.560 | 0.600 | 1 |
| Alanine transaminase (ALT) [U/l] | 23 (11–266) | 23 (12–54) | 0.876 | 19 (11–76) | 21.5 (11–61) | 0.474 | 0.027 | 0.078 |
| Gamma glutamyl transpeptidase (GGT) [U/l] | 23 (10–549) | 15 (9–42) | $5.7 \times 10^{-6}$ * | 21 (9–50) | 19 (6–43) | 0.0031* | 0.192 | 0.184 |
| Albumin [g/dl] | 4.55 (4.12–5.35) | 4.53 (4.06–5.24) | 0.949 | 4.56 (4.08–4.90) | 4.53 (4.00–5.06) | 0.455 | 0.749 | 0.575 |
| Creatinine [mg/dl] | 0.82 (0.50–1.04) | 0.76 (0.52–0.97) | 0.00034* | 0.83 (0.61–1.15) | 0.82 (0.65–1.15) | 0.0918 | 0.324 | 0.028 |
| Bound urea nitrogen [mg/dl] | 14 (9–18) | 14.5 (9–24) | 0.015 | 13 (7–19) | 13 (7–24) | 0.260 | 0.371 | 0.071 |
| Urea [mg/dl] | 4.96 (2.95–6.61) | 4.62 (3.11–7.16) | 0.867 | 4.61 (2.89–6.36) | 4.69 (2.91–6.93) | 0.838 | 0.534 | 0.907 |
| Total cholesterol [mg/dl] | 222 (166–296) | 217 (134–327) | 0.279 | 198 (129–282) | 193 (142–277) | 0.992 | 0.0074* | 0.156 |
| HDL cholesterol [mg/dl] | 70 (39–115) | 67 (43–141) | 0.263 | 67 (42–91) | 67 (38–100) | 0.546 | 0.342 | 0.762 |
| LDL cholesterol [mg/dl] | 141.1 (70.4–230.4) | 135 (64.8–256.8) | 0.400 | 115.2 (64.9–184.0) | 109 (74.5–184.0) | 0.639 | 0.0078* | 0.011 |
| Triglycerides [mg/dl] | 108 (55–222) | 76 (44–143) | 0.00092* | 85 (51–218) | 92 (48–275) | 0.537 | 0.441 | 0.158 |
| HbA1c [%] | 5.2 (4.3–7.5) | 5.3 (4.5–6.7) | 0.450 | 5.2 (4.5–5.9) | 5.3 (4.6–6.1) | 0.203 | 0.313 | 0.988 |
| C-reactive protein [mg/l] | 1.7 (0.1–18.9) | 1.3 (0.3–24.4) | 0.296 | 1.6 (0.2–6.6) | 1.0 (0.1–21.6) | 0.209 | 0.231 | 0.116 |
| IGF-1 [ng/ml] | 197 (45–364) | 175 (38–413) | 0.009134* | 212 (116–348) | 176 (90–350) | 0.078 | 0.901 | 0.392 |
| Insulin [mU/l] | 7.7 (2.0–45.6) | 6.7 (2.0–32.8) | 0.290 | 8.1 (2.5–27.2) | 7.2 (1.9–22.2) | 0.175 | 0.928 | 0.565 |
| T3 [pg/ml] | 3.13 (2.63–4.13) | 2.78 (2.24–3.68) | $1.1 \times 10^{-5}$ * | 3.16 (2.04–4.50) | 3.03 (2.37–3.86) | 0.171 | 0.828 | 0.0016* |
| T4 [ng/dl] | 1.21 (1.00–1.59) | 1.27 (0.95–1.65) | 0.407 | 1.215 (0.94–1.82) | 1.20 (0.86–2.09) | 0.559 | 0.932 | 0.414 |
| TSH [mU/l] | 1.67 (0.35–6.02) | 1.63 (0.20–4.12) | 0.229 | 1.31 (0.13–4.03) | 1.60 (0.12–3.12) | 0.777 | 0.462 | 0.852 |
| Glucose [mg/dl] | 97 (82–176) | 100 (80–146) | 0.721 | 96 (81–113) | 97 (77–115) | 0.664 | 0.197 | 0.177 |
| BHB [mmol/l] | 0.11 (0.01–0.45) | 0.52 (0.02–2.26) | $4.5 \times 10^{-6}$ * | 0.06 (0.02–0.29) | 0.06 (0.02–2.6) | 0.637 | 0.019 | $1.4 \times 10^{-7}$ * |

BHB: β-hydroxybutyrate. *$p \leq 0.01$ (significant difference).

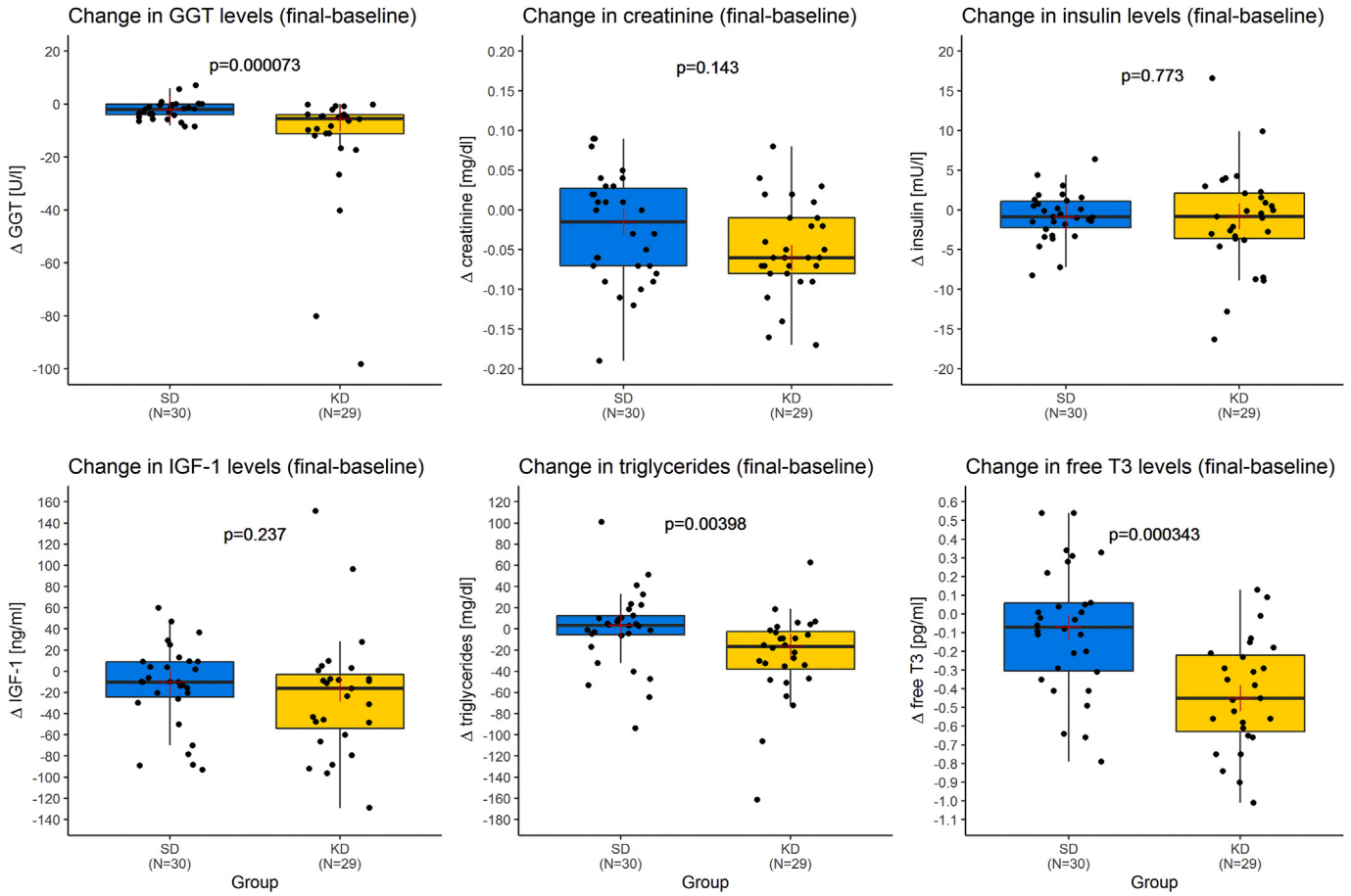


**Fig. 2.** Changes in metabolic parameters within both groups. The *p*-values refer to a between-group comparison of these changes. GGT: Gamma glutamyl transpeptidase; IGF-1: Insulin-like growth factor-1.

**Table 4**
Regression coefficients of linear mixed effects models for longitudinal changes of blood parameters.

| Parameter | Time | | KD | | Time × KD | |
|---|---|---|---|---|---|---|
| | $\beta_1$ | $p$-value | $\beta_2$ | $p$-value | $\beta_3$ | $p$-value |
| Leucocyte count [$10^3/\mu l$] | −0.19 ± 0.05 | $9.8 \times 10^{-5}$ * | −0.07 ± 0.14 | 0.628 | −0.0026 ± 0.070 | 0.970 |
| Platelet count [$10^3/\mu l$] | −4.4 ± 1.4 | 0.0012* | 3.2 ± 3.4 | 0.335 | −1.1 ± 1.9 | 0.560 |
| Gamma glutamyl transpeptidase (GGT) [U/l] | −0.5 ± 2.1 | 0.822 | −0.6 ± 2.8 | 0.820 | −5.0 ± 3.0 | 0.095 |
| Creatinine [mg/dl] | −0.005 ± 0.003 | 0.082 | −0.014 ± 0.007 | 0.054 | −0.004 ± 0.004 | 0.277 |
| Triglycerides [mg/dl] | −0.6 ± 1.4 | 0.686 | −6.5 ± 3.4 | 0.059 | −3.8 ± 2.0 | 0.054 |
| IGF-1 [ng/ml] | −2.4 ± 1.9 | 0.210 | −1.4 ± 3.9 | 0.713 | −1.7 ± 2.7 | 0.529 |
| Free T3 [pg/ml] | −0.01 ± 0.01 | 0.246 | −0.06 ± 0.04 | 0.119 | −0.06 ± 0.02 | 0.0018* |

*$p \leq 0.01$ (significant difference).

sleep quality in cancer patients. The KD is also hypothesized to improve migraine symptoms [29]. In line with this, two patients with chronic migraine experienced a complete cessation of their symptoms.

A previous study of locally advanced or metastatic breast cancer patients undergoing chemotherapy had evaluated EORTC-QLQ30 and BR23 scores before and after 6 and 12 weeks on a KD [30]. After 6 weeks, the KD group had a higher global QoL and physical functioning score than the control group. At 12 weeks, however, most functioning scores had decreased in the KD group, and there was a significant increase in fatigue, nausea and vomiting and systemic therapy side effects. Rather than being due to the diet, these symptoms most probably stemmed from the chemotherapy these women underwent as similar trends were observed in the control group [30]. In contrast, in our study many opposing trends in function and symptom score changes were observed between the KD and SD group, so that the KD likely had a role in mediating these changes. However, although some significant improvements were observed within the KD group, there were no significant differences in QoL scores between the KD and SD group at study end. It is possible that due to the fact that the study only lasted for a few weeks and some patients received hypofractionated radiotherapy, the observation period was too short for more pronounced differences between diet groups to appear. It is also possible that the rise in ketone bodies in the KD group was not large enough to induce more improvements in some QoL dimensions such as pain reduction. Finally, more patients had received accompanying antibody or antihormonal treatment in the KD group which could have attenuated some QoL improvements in this group. On the other hand, the possibility must be considered that the longer consultation times spent with patients in the KD group might have played a role in improving quality of life in these patients via psychological effects.

### 4.2. Effects on skin toxicity rates

As a more objective measure of side effects, we also evaluated the maximum skin toxicity at the end of radiotherapy which was restricted to acute erythema, but no desquamation. We were not able to detect any difference in the severity of skin toxicity between the KD and SD group (Table 2). In theory, by elevating anti-inflammatory ketone bodies and affecting several molecular pathways, KDs have been attributed the potential to protect against radiotherapy side effects [23,24]. However, skin toxicity may be influenced by a variety of other factors that we were not able to account for in the analysis. A recent modeling study revealed higher BMI, greater breast size, positive smoking status (ever) and higher number of fractions as significant predictors of greater odds for acute skin toxicity [31]. However, these factors only allowed for a moderate discrimination (area under the curve = 0.65) when applied to an independent validation cohort [31], and also were not significantly different between the KD and SD group in our study. This points to other unknown factors such as genetics that may have an important role in predisposing patients to radiotherapy-induced skin erythema. A small hint towards a protective effect of the KD is that subjective breast symptoms increased to a lesser extent in the KD than in the SD group (Table 1).

### 4.3. Effects on metabolic health and their relation to breast cancer outcomes

We also evaluated several blood parameters as objective measures of our patient's physiological functioning (Table 3). As expected, β-hydroxybutyrate concentrations were significantly higher in the final compared to the baseline measurement in the KD group, but fasting glucose levels showed no significant changes. As Fig. 1 shows, dietary compliance appeared to deteriorate towards the end of the study. Other studies conducted over similar timeframes in which KDs had been prescribed isocalorically or *ad libitum* have also failed to detect significant drops in blood glucose concentrations. For example, only small and non-significant decreases in glucose levels had occurred after 4–5 weeks on a KD in advanced stage cancer patients [32] and glioblastoma patients [33] or after 6–8 weeks in the ERGO trial [34], while non-significant increases in glucose levels were found by Tan-Shalaby et al. [28] in a mixed cancer patient cohort. Higher reductions of glucose levels on a KD may be facilitated by additional calorie restriction and/or a stricter reduction in carbohydrates; the latter was demonstrated by a Japanese study in which blood glucose levels of cancer patients quickly decreased after switching to a KD with only 10 g carbohydrates per day for one week and remained significantly reduced while allowing 20 g carbohydrates per day from the second week to the third month [35].

There was no indication that the KD had any detrimental effects on either liver or kidney function. The kidney function parameters bound urea nitrogen and urea did not change significantly and were comparable to the SD group at study end. Creatinine significantly decreased in the KD group only. Because higher creatinine levels have been associated with insulin resistance and metabolic syndrome even within their reference ranges [36,37], the observed changes in creatinine levels may be indicative not only of renal function, but also metabolic improvements in the KD group. Liver enzymes also tended to stay stable or normalize in the KD group, with a significant reduction of GGT. This shows that together with triglycerides and body weight, which were also reduced significantly in the KD group (see Table 3 and Klement et al. [17]), three main predictors of nonalcoholic fatty liver disease (NAFLD) [38] were significantly reduced on the KD. Previous studies have shown that with 15–45% prevalence, NAFLD is significantly more common in breast cancer patients compared to healthy controls [39–41] and associated with breast cancer recurrence after surgery [40]. GGT initially was above its reference range (40 U/l) in six patients of the KD group of which all but one were able to normalize their levels

(the one patient only having slightly elevated GGT of 42 U/l at the final measurement). Although we do not know the prevalence of NAFLD in our patient cohort, we hypothesize that the significant reduction of fat mass, GGT and triglycerides is indicative of an overall improved metabolic state and a reduction of liver fat depots, consistent with other studies showing a beneficial effect of KDs on NAFLD independent of calorie intake [42].

Given the beneficial changes of NAFLD markers in the KD group, we would also have expected a concurrent reduction in insulin levels [42]. Although insulin had decreased overall in the KD group, this was not statistically significant, and a decrease was also observed in the SD group. Previous studies had found more prominent reductions of insulin levels in women with gynecological cancers [43] or advanced stage breast cancer [44] after consuming a KD for 12 weeks. It is possible that the short study duration of our patients, in particular of that receiving hypofractionated radiotherapy, precluded a greater reduction of insulin levels. The cited studies also found reductions in IGF-1 levels (from 151 ± 52 to 133 ± 61 ng/ml in the breast cancer cohort of Khodabakhshi et al. [44] and from 120 ± 9 to 101 ± 10 ng/ml in the cohort of Cohen et al. [43]), although these changes were not statistically significant according to our definition ($p > 0.01$). We here found a significant reduction in IGF-1 levels from a median of 197 ng/ml to 175 ng/ml at the end of the study in the KD group, but the gradual reduction associated with the KD was not significant in the mixed effects model analysis (Table 4). Changes in IGF-1 concentrations are usually a marker for changes in nitrogen balance that depends on protein intake, but also on total energy intake [45–47]. Therefore it is not expected that IGF-1 concentrations would change markedly on a longer-term *ad libitum* KD with sufficient protein intake [5]. However, we hypothesize that the elevated ketone bodies may have improved IGF-1 sensitivity, thereby lowering the demand of circulating IGF-1. In line with this hypothesis, Cohen et al. found a significant negative correlation between changes in IGF-1 levels and changes in β-hydroxybutyrate concentrations after 12 weeks on a KD [43]. When we correlated IGF-1 levels with β-hydroxybutyrate concentrations, we also found a negative, but not significant correlation (Spearman's $r = -0.116$, $p = 0.127$) that became somewhat stronger when using age-adjusted IGF-1 *z*-scores instead ($r = -0.132$, $p = 0.095$).

Since insulin and IGF-1 are known growth factors for breast cancer cells [5] and predictive of shorter overall survival [48,49], the observed reductions in the KD group could be rated as beneficial. It is also interesting that higher T3 levels have been associated with increased breast-cancer specific death [50] and a more aggressive breast cancer phenotype [51]. Insofar, the significant absolute and gradual reductions of T3 levels induced by the KD could also be rated as beneficial.

## 5. Conclusions

We found that compared to a SD, women consuming a KD during curative radiotherapy experienced significant improvements in emotional functioning, social functioning, sleep quality, their future perspectives and systemic therapy side effects. While breast symptoms increased significantly in both groups, the increase was less pronounced in the KD group. There was no hint of a detrimental effect of the KDs on either liver or kidney function; in contrast, several biomarkers of NAFLD or metabolic syndrome significantly improved in the KD, but not the SD group. It is noteworthy that these improvements occurred within such a relatively short timeframe, and no negative effects of the KD could be detected. Overall, our data support the hypothesis that consuming a KD during radiotherapy is safe for women with breast cancer and has the potential to improve quality of life and metabolic health.

## Author contribution

RJK: Conceptualization, Data curation, Formal analysis, Supervision, Writing – original draft. MMW: Resources, Writing – review & editing. RAS: Conceptualization, Resources, Writing – review & editing.

## Funding statement

This study received no specific funding.

## Data availability statement

All data used in this analysis are available from the corresponding author upon reasonable request.

## Conflict of interest

All authors declare that they have no conflicts of interest associated with this research.

## Acknowledgments

We thank Petra Koebrunner, Kelly Krage and Nanina Brehm for helping us to collect the data.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2021.01.023.

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