Ketogenic and low-carbohydrate diets in people with cancer

A statement by the Working Group on Prevention and Integrative Oncology (PRIO) in the German Cancer Society (GCS) and the German Society for Nutritional Medicine (DGEM)

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**Abstract**

For several years, people with cancer have been offered so-called "cancer diets" that are low-carbohydrate or ketogenic to varying degrees. The rationale for these diets is that the metabolism of tumor cells is dependent on carbohydrates. Depending on the interpretation of the study data, these diets promise a direct influence on tumor growth (and metastasis) as well as an improvement in the efficacy and tolerability of chemotherapy and/or radiotherapy (especially chemotherapy). However, there is a lack of methodologically high-quality studies and thus of reliable evidence for the ketogenic diet. For this reason, the authors of the statement conclude that at the present time, the use of a low-carbohydrate or ketogenic diet for this indication must be discouraged.

**Keywords:** nutritional medicine, ketogenic diet, carbohydrate reduction, cancer, malnutrition, side effects, tumor therapy.

**Introduction**

The importance of a low-carbohydrate diet or – if carbohydrates are largely avoided – a ketogenic diet has been discussed in oncology for years. These diets are thought to reduce tumor growth, improve the efficacy of tumor therapies, and/or reduce the side effects of tumor therapy by protecting healthy cells. A ketogenic diet is a significant dietary restriction. Therefore, the question of the benefits and risks of this type of diet in tumor patients is highly relevant.

**Definition of ketogenic and low carbohydrate diets**

Ketogenic or low-carbohydrate diets in different variants currently exist under different names. Their common feature is that they are all characterized by a high fat content combined with a low carbohydrate content of mostly < 70 g daily compared to the national recommendations for nutrient intake of the German Nutrition Society (DGE) [1–5].

In the therapeutic form (used in the treatment of epilepsy), the fat content is increased to 90% energy (En%) and the protein and carbohydrate content is reduced to 5 En% each. As a result, the body cannot be adequately supplied with glucose as an energy source and must switch fat metabolism [6], resulting in increased formation of ketone bodies (β-hydroxybutyrate, acetoacetate, and acetone), which are then used as an energy source.
Ketogenic diet in oncological diseases

For several years, ketogenic or low-carbohydrate diets have also been recommended for patients with oncological diseases. Reduced blood glucose levels, a decrease in insulin levels and cell proliferative signals, as well as an increased effectiveness of chemotherapy/radiation with simultaneous protection of healthy cells are postulated as the active principle [6].

The basis of the hypotheses on antitumor effects of a ketogenic or low-carbohydrate diet is the "Warburg effect". This states that malignant cells preferentially meet their energy needs via glycolysis rather than oxidative phosphorylation. A low-carbohydrate or ketogenic diet should therefore reduce the energy substrate of the tumor cells by decreasing glucose availability [8].

Based on a systematic review [9], the S3 guideline Complementary Medicine for Oncological Patients [10], and an updated systematic literature search, the Working Group Prevention and Integrative Oncology in the German Cancer Society (PRIO) in the German Cancer Society (DKG) and the German Society for Nutritional Medicine (DGEM) take the following position on this issue:

At this time, there are no scientific studies that demonstrate that a ketogenic or low-carbohydrate diet:

- prevent or repress tumor growth or metastasis in people with cancer; or
- improve the efficacy or tolerability of chemotherapy and/or radiation therapy.

Preclinical evidence

A number of cell and animal experiments are available on low-carbohydrate or ketogenic diets. The results of these experiments are inconclusive and sometimes contradictory. In some studies, tumor growth was slowed down, but in other studies it was shown that after some time on a ketogenic or low-carbohydrate diet, stem cell-like changes in tumor cells occurred [8, 11–17].

In animal experiments, accelerated growth of tumor cells sometimes occurred after initial slowing. In addition, some experiments show that initial tumor growth slowing was seen only in those animals that also experienced weight loss. However, it was shown that the decisive factor for tumor growth slowing was weight loss and this was independent of the diet (low carbohydrate or low fat) [12, 18–20].

In another animal experiment, increased tumor growth of BRAF V600E1-expressing melanomas occurred on a ketogenic diet [21].

Clinical evidence

At first sight individual clinical studies could find a positive effect. However, a closer look shows that none of these studies offers reliable data:

The KETOCOMP study is a non-randomized controlled trial in which patients with rectal cancer, breast cancer, or neck and head tumors were included. This study tested the hypothesis of whether a ketogenic diet during radiotherapy can have a positive effect on body composition and metabolic parameters [22]. However, for all publications from the study, the results should be critically questioned because the participants in the intervention group received an energy-containing drinkable food as well as the option of nutritional counselling on the ketogenic diet. In addition, the lack of randomization and likewise lack of disclosure of the algorithm of assignment to the two study arms may have led to substantial bias.

- According to the authors, an interim analysis [23] showed first positive effects. In addition to the above-mentioned criticisms, patients from the control group also showed ketosis at times, which mostly occurred due to reduced energy intake as a result of therapy-related side effects. Therefore, the mentioned results could also be explained by the more intensive care (nutritional counselling and hydration) and not by the ketogenic diet.
- A second publication [24] describes the ketogenic diet (n = 24) vs. standardized diet (n = 25) in patients with non-metastatic rectal cancer undergoing neoadjuvant radiotherapy. Although meals were not controlled and energy content was not restricted, the authors report that in patients, the ketogenic diet significantly reduced body weight and body fat, while muscle mass remained [24]. The study results may have been influenced by the aforementioned problem of lack of randomization, the offer of a sip diet, and nutritional counselling.
- In the third publication [25], the quality of life of breast cancer patients undergoing adjuvant radiotherapy was compared with a ketogenic diet (n = 29) versus a standard diet (n = 30). Compared with the standard

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1 The BRAF gene ("proto-oncogene B-Raf") encodes the serine/threonine protein kinase B-Raf, which plays a role in the regulation of a signalling pathway that affects cell division and differentiation.
diet (DGE recommendation), the authors reported that the intervention group showed significant improvement in emotional and social function, sleep quality, and improved perspective on the future and reduced side effects. Therefore, the authors concluded, a ketogenic diet could potentially improve the quality of life of this intervention group. Indeed, a difference in total score on the EORTC QLQ-C30 was seen in the intervention group between study start and end (p = 0.020; significance level of ≤ 0.01), but not between groups (pstart = 0.315 and pend = 0.363, respectively) [25]. In the absence of randomization, unclear allocation of patients to the study arms, and attention in the form of counselling alone in the intervention arm, an improvement in quality of life can be explained by these effects alone and thus not in direct relation to the ketogenic diet.

A randomized controlled trial published for the first time in 2020 investigated the effect of the ketogenic diet in patients (n = 80) with locally advanced and metastatic breast cancer undergoing neoadjuvant or palliative chemotherapy. As a result, a 12-week ketogenic diet was reported to have decreased tumor size as well as several biomarkers in the ketogenic-fed group compared to the control group [26–28]. In addition to the small number of participants and the very different patient groups and treatment approaches, there are other criticisms of this study. These include the high dropout rate of 25% in the intervention group (20% due to side effects such as nausea, hypoglycemia, weakness, hunger) and the per-protocol analysis. In addition, the patients’ oncological therapy may not have been optimal during the study intervention. The intervention and control groups contained 7 and 15 participants, respectively, in tumor stage IV at baseline, with 2 more patients in tumor stage IV at the end. In addition, the average tumor size at baseline was much smaller in the intervention group than in the control group. Accordingly, tumor regression assessment results in a greater change from baseline in this group (table 5 of the original publication; [29]). In addition, the authors report overall survival data in a manuscript submitted 5 months after completion of neoadjuvant chemotherapy [29]. Because of these methodologic flaws, unclear reporting, and poor patient care, this study is inadequate to demonstrate an effect or even a positive benefit of the ketogenic diet.

A randomized controlled trial examined 73 patients with ovarian or endometrial cancer at baseline and after 12 weeks. The effects of a ketogenic diet or a standard diet (American Cancer Society recommendations) on body composition, fasting insulin, insulin-like growth factor 1 (IGF-1), and β-hydroxybutyrate were compared.

- The first publication reported lower total fat mass (35.3 vs. 38.0 kg, p < 0.05) and visceral fat (−21.2% vs. −4.6%, p < 0.05) and no difference in lean mass [30]. However, due to the lack of p-values for demographics at baseline, the significant results at study end are not interpretable. Furthermore, despite the high dropout rate (32% in the intervention group vs. 44% in the control group), a per-protocol analysis was performed, further limiting the significance.

- The second publication reports, among other things, the side effects of the participants. In the intervention group, these were hunger, constipation, fatigue, muscle cramps, diarrhea, and a feeling of coldness in the extremities. The control group also showed hunger and fatigue [31]. All side effects are described as mild, with no severity indicated and, moreover, a clustering in the intervention group is evident.

In comparison to these studies, a randomized controlled trial of 32 overweight to obese patients examined the effects of weight loss before breast cancer surgery. The control group received baseline nutrition counselling and upper body strength training, while the intervention group was offered additional weight and calorie reduction counselling and aerobic activity (with a weight loss goal of 0.68–0.92 kg/week). Compared with the control group, the intervention group had higher weight loss (−3.62 vs. −0.52 kg), higher body fat loss (−1.3 vs. 0%), and engaged in more moderate to intense physical activity (+224 vs. +115 min/week). There was also lower serum leptin (−12.3 vs. −4.0 ng/dl), upregulation of FLT1 (VEGFR1), SPRY1, and THBS1 (all associated with progression in breast carcinoma), and no effect on FGFβ, IL-6, VEGF-C, caspase 3, NFkB, p16, 4E-BP, pSK6, VEGF, PCNA, or Ki67 parameters. Statistical analysis (mixed model) suggests an unclear benefit of preoperative caloric restriction but possible benefits of physical activity [32].

**Systematic reviews**

The critical discussion of the ketogenic diet is steadily increasing. Various systematic reviews could not identify any positive effects in the studies and therefore do not recommend a ketogenic diet in tumor patients [33–36]. A systematic review published in 2017 on the isocaloric ketogenic diet in people with malignant tumors included a total of 15 studies (8 prospective studies, 2 retrospective studies, and 5 case reports) with a total of 330 patients. The endpoints of the included studies were feasibility, patient quality of life, and adherence, but not the antitumor effect of a ketogenic diet. No study was able to demonstrate tumor regression, prolonged survival, improved treatment response, or reduced side effects with the ketogenic diet [5].

Another systematic review from 2021 examined 39 publications with a total of 770 cancer patients. Again, no conclusive evidence of an antitumor effect or improved overall survival was found, but significant weight loss and mild to moderate side effects were found. The authors concluded that due to the heterogeneous study results and methodological limitations, clinical evidence for the effectiveness of the ketogenic diet in cancer patients is lacking [37].
Risk of malnutrition

Ketogenic and low-carbohydrate diets increase the risk of malnutrition already within a few days to weeks.

Fine et al. already observed a weight loss of 4% (± 6.1%) within 28 days in 2013 [38]. Tan-Shalaby et al. reported that 73% of study participants lost an average of between 7.5 ± 5.8 kg of body weight over a 16-week period [39]. Urbain et al. 2017 reported a weight loss of 2.0 ± 1.9 kg in a study in healthy subjects, although average energy intake was not reduced, confirming early evidence that isocaloric ketogenic diets may also contribute to weight loss due to metabolic changes [40]. The aforementioned weight losses have been reported in studies with intensive nutritional monitoring of patients. In all likelihood, the losses are even more pronounced in patients following these diets under less optimal conditions.

In accordance with the European Society for Parenteral and Enteral Nutrition (ESPEN) (2015), oncology patients should be classified as malnourished at 5% unintentional weight loss in a three-month period and treated with nutritional therapy [41]. Although the guidelines advocate increasing fat intake in patients with tumor cachexia to increase energy density, the authors emphasize that this should be done without carbohydrate restriction [42, 43].

In the S3 guideline "Complementary Medicine in the Treatment of Oncological Patients" published in 2021, the implementation of the ketogenic diet is clearly not recommended. According to this guideline, "a ketogenic diet [...] should not be recommended in normal-weight and underweight female patients." Likewise, a ketogenic diet should not be recommended with the goal of improving quality of life or slowing disease progression in prostate cancer or in patients with breast cancer with the goal of improving survival [10].

In a joint position paper, the Prevention and Integrative Oncology Working Group of the German Cancer Society together with several associations pointed out the considerable medical and psychological importance of malnutrition [44].

Conclusion

Based on current data, low-carbohydrate or ketogenic diets cannot be recommended as complementary therapy and in general for people with oncological diseases.

- Diets that inevitably lead to restriction of food intake and choice are not an option for tumor patients because of the intrinsic weight loss and the worsening prognosis that has been shown to result.
- Patients interested in low-carbohydrate or ketogenic diets should be counselled early and intensively about the potential negative effects.
- Oncology patients with weight loss should be actively asked if they are following such a diet and counselled if necessary.
- Should patients follow a low-carbohydrate or ketogenic diet despite intensive nutritional counselling, close interdisciplinary supervision and checks of weight, body composition, and laboratory parameters are indicated in order to intervene in a timely manner. However, this is hardly feasible in everyday clinical practice.

FLT1 (VEGFR1) = vascular endothelial growth factor-receptor FLT1, SPRY1 = protein sprouty homologue 1, THBSL = thrombospondin ligand, FGFβ = fibroblast-growth factor-beta, IL-6 = interleukin 6, VEGF-C = vascular endothelial growth factor C, NFκB = (nuclear) nuclear factor-kappa-B, 4E-BP = 4E-binding protein, pSK6 = phytosulfokines 6, VEGF = vascular endothelial growth factor growth factor, PCNA = proliferating cell nuclear-antigen
Conflict of interest
Position papers and statements reflect the views and assessments—i.e. also the interests—of the organization(s) named in the author’s line. The authors declare that there are no further conflicts of interest in connection with the contents of this statement.

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References

28. Khodabakhshi A, et al.: Does a ketogenic diet have benefi-


