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EDITORIAL

Addressing the controversial role of ketogenic diets in cancer treatment

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1. Introduction

There is a growing interest in a particular metabolic state and its influence on cancer therapy: ketosis. Ketosis denotes the physiological rise in ketone bodies that is proportional to fat oxidation and thus occurs when insulin levels are low, which is the case during fasting or very low carbohydrate (≤50 g/day), high-fat (>60% energy) diets, also known as ketogenic diets (KDs). KDs have a long history in both human evolution and clinical medicine with treatment applications including cancer, cardiovascular and endocrine diseases, gastrointestinal, neurological and psychological disorders [1]. Concerning cancer, ketone bodies have been shown by some studies to inhibit tumor cell growth *in vitro*, and indeed there is evidence that feeding a KD can delay tumor growth in many, although not all, animal models of implanted tumors (reviewed in [2]). However, many patients who want to undertake a KD are left alone or discouraged by their physicians. This may be the result of some controversies about the KD itself and the available clinical data. My aim here is to briefly discuss skepticism about using KDs during cancer treatment and identify further steps needed to gain better evidence about the KD's antitumor effect hypothesis.

2. Skepticism about KDs and cancer

First of all, it is helpful to distinguish two kinds of skepticism: one I call *methodological skepticism*, referring to the statement that the evidence for efficacy of KDs is absent or weak, because randomized controlled studies are missing. The other I call *fundamentalist skepticism* which, as the name implies, is of a more fundamental nature and refers to a general rejection of KDs for cancer patients due to putative side effects, avoidance or inclusion of certain foods, their extreme macronutrient ratios, confusion between ketosis and ketoacidosis or some ideological reasons.

2.1. Fundamentalist skepticism

An example for fundamentalist skepticism is a review on KDs and cancer by Erickson et al. [3] in which the authors claim that 'it is important to know that all forms of the KD are considered nutritionally inadequate'. However, the authors fail to justify this claim with data or references to other studies. Quite contrary, other authors have argued that a well-formulated KD should be considered safe and nutritionally adequate [1,4], refuting the above claim by Erickson et al.

A second example of fundamentalist skepticism is a recent study by Lareida et al. [5] which found that weight loss in patients with brain metastases exceeding 5% within six months after diagnosis was associated with a significant reduction in overall survival (14 months versus 22 months, $p = 0.004$). Without any information on the patient's diet, the authors conclude that 'regimens associated with weight loss such as ketogenic diet may be detrimental.' However, a literature search on PubMed and Google Scholar revealed not a single study showing that KDs cause excessive weight loss in patients with brain metastases – quite contrary, there is both clinical and mechanistic evidence that they may counteract weight loss in frail and cachectic patient populations [6]. Furthermore, cachectic weight loss must not be confused with KD-associated weight loss; the former is characterized by high insulin levels and excessive protein degradation [7], the latter by low insulin levels and anti-catabolic signaling [8]. Therefore the claim of a causal connection between KDs and shorter survival based on mere and biologically not comprehensible associations (KDs putatively associated with weight loss which in turn is associated with shorter survival) is not supported by the data from that particular or any other study and can best be interpreted as a fundamental skepticism about KDs by these authors.

Fundamentalist skepticism should be rejected based on the following arguments:

2.1.1. A mechanistic argument

This argument is what is usually summarized in mechanistically oriented reviews on this topic, drawing from a wealth of *in vitro* and *in vivo* data. There are some central mechanisms how a KD has been shown to affect tumor growth and host metabolism [2]. Given these data, the probability of an antitumor effect hypothesis is much higher than a pro-tumor effect hypothesis. In addition, from a Bayesian reasoning perspective, these data may be used to justify a higher *a priori* probability for the efficacy of a KD as compared to any standard diet. This rejects fundamental skepticism that KDs could be dangerous by promoting tumor growth.

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2.1.2. A heuristic argument

Heuristics can yield frugal results when one has to choose from several options in situations of uncertainty [9], which applies to patients trying to choose the 'optimal' diet to support their therapy. KDs conform to the simple heuristic that the macronutrient most attractive for cancer cells is carbohydrate (glucose), while normal tissue preferentially utilizes fats and ketone bodies (cancer patients are frequently insulin resistant [10]). The notion that cancer has a 'sweet tooth' can easily be explained to patients and serves as a heuristic for avoiding blood glucose and insulin spikes that are associated with worse outcomes in a variety of cancers [10]. Together with the fact that there is no human requirement for dietary carbohydrates [1], this rejects fundamental skepticism against a diet with very low carbohydrate content.

2.1.3. A safety argument

Some authors have cautioned against KDs for cancer patients based on side effects observed in epileptic children who are often on extreme versions of a KD. Such extrapolation is highly problematic since these children are frequently on drugs predisposing them to the development of side effects, and the diets used are too restrictive in nature and contain a high proportion of artificial foods. Clinical studies on well-formulated KDs in cancer patients have so far shown no serious side effects associated with the diet even in advanced stages of the disease [6], so that warnings against the safety of KDs during cancer therapy appear unjustified.

2.1.4. An evolutionary argument

During most parts of their evolution (as hunter-gatherers), humans probably have encountered frequent periods of limited carbohydrate consumption or fasting [11]. This is still reflected in our physiology as ketone bodies provide an essential fuel for the brain and muscles in these situations [11]. Besides their role as metabolic substrates, recent research has revealed new important roles of ketone bodies as signaling molecules with a variety of salutary functions [12]. This shows that general skepticism against diets inducing physiological ketosis is unwarranted.

2.2. Methodological skepticism

An example of methodological skepticism is a systematic review of Maisch et al. [13] concluding in the abstract: 'Based on the current data, a ketogenic diet cannot be recommended to cancer patients because prospective, randomized trials are missing.' This conclusion exemplifies the strict application of rigid 'evidence hierarchies' to complex interventions such as KDs. However, the epistemological value of evidence hierarchies has been questioned from different perspectives (see e.g. [14–16], and references therein). The non-consideration of studies from lower stages of evidence hierarchies in evidence amalgamation constitutes a violation of the principle of total evidence, one of the epistemological principles of modern evidence-based medicine. Methodological skepticism, i.e. the strict rejection of a new approach based on the lack of randomized clinical trials, should therefore be rejected.

2.3. Current state of the research

When counseling cancer patients it is important to take into account the totality of evidence about the safety, costs, efficacy and other potential benefits or problems associated with the KD. Unfortunately the early studies, while being able to show the safety of a KD even for advanced cancer patients, were not designed to derive valid conclusions about its efficacy. They lacked clinical relevance since they did not combine KDs with established tumor therapies and failed to collect clinical end points such as overall or progression free survival. However, more recently higher-quality clinical studies have been published. Table 1 gives an overview of the controlled clinical trials published to date and their endpoints [17–22].

We now have some evidence for beneficial effects of a KD on body composition in gynecological cancers [19,21], pancreatic cancer [23] and head and neck cancer patients [21]. We also have some evidence for synergistic effects between KDs and other therapies, in accordance with predictions from animal studies [2]. In stage IV non-small cell lung cancer patients a KD combined with hyperthermia, hyperbaric oxygen, and short-term fasting prior to chemotherapy resulted in a 3 – 8 times longer overall and progression-free survival than expected from other studies applying the same type of chemotherapy [24]. In metastasized pancreatic cancer patients, the same combination of complementary treatments together with gemcitabine or FOLFIRINOX chemotherapy resulted in a median overall and progression-free survival of 15.8 months (95% CI, 10.5–21.1) and 12.9 months (95% CI, 11.2–14.6), respectively [25]. Finally, a randomized controlled trial in breast cancer patients receiving neoadjuvant chemotherapy found that a KD resulted in significantly longer overall survival compared to a control diet over a follow-up period of 30 months [22]. As a drawback, only some of these controlled studies have also been randomized, patient numbers were

Table 1. Controlled clinical trials using the KD in cancer patients published until October 2019. See Klement et al. [6] for more details. HGG: High grade glioma; HNC: Head and neck cancer; N_KD: Number of patients in KD group included in the analysis; N_CTRL: Number of patients in the control group included in the analysis.

First Author	Year	Tumor entity	N_KD	N_CTRL	Simultaneous treatment	Overall survival?	Tumor progression?	Body composition?
Rieger [17]	2014	HGG	7	28	Bevacizumab	No	Yes	No
Santos [18]	2018	HGG	17	15	Intranasal perillyl alcohol	Yes	Yes	No
Cohen [19]	2018	Ovarian, endometrial cancer	25	20	Chemotherapy (24% of the patients)	No	No	Yes
Furukawa [20]	2018	Rectal cancer	7	13	Chemotherapy	No	Yes	No
Klement [21]	2019	Breast, rectal, HNC	20	61	Radiotherapy ± chemotherapy	No	No	Yes
Khodabakhshi [22]	2019	Breast cancer	30	30	Chemotherapy	Yes	No	Yes

small, diets were not well described and ketosis not reached by all patients [6].

Some studies have also provided disappointing results. In the ketolung and ketopan studies [26] which combined a KD with radiochemotherapy, only seven lung cancer and two pancreatic cancer patients could be recruited and not even half of them finished the study. A recent study from the Netherlands tested the administration of a KD during and six weeks after radiochemotherapy in eleven high grade glioma patients, of which six completed the study [27]. Median overall survival was only 12.8 months which is less than expected from studies utilizing the same radiochemotherapy protocol. A strength of these three studies was that patients reached high ketone body levels, yet none showed an extraordinary response to the diet. Noteworthy, ketosis was achieved using highly artificial KDs devoid of vegetables and their phytonutrients, with very low high quality protein content and including artificially hydrogenated oils. The hypothesis that such artificial diets are detrimental to health should be considered in the design of future trials.

3. Conclusion and expert opinion

I have argued that both fundamentalist and methodological skepticism about the clinical application of KDs for cancer patients should be rejected, so that the totality of evidence can be objectively evaluated. There is weak, yet positive evidence for improved efficacy of cancer treatments when KDs are used as complementary therapies. However, there is strong evidence for the safety of this approach, so that patients who want to support their treatment by a KD should not be discouraged, but ideally be supported by dieticians and oncologists that are well-trained in a systemic view of cancer and metabolism. Such patients should also be followed prospectively and their outcomes documented, so that we can gather more evidence on the efficacy of the KD. Ultimately, we need more studies from all levels of the evidence hierarchy, counterbalancing the strengths of different study types concerning internal validity (rigor and the removal of bias) and external validity (generalizability) [14].

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Declaration of Interest

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