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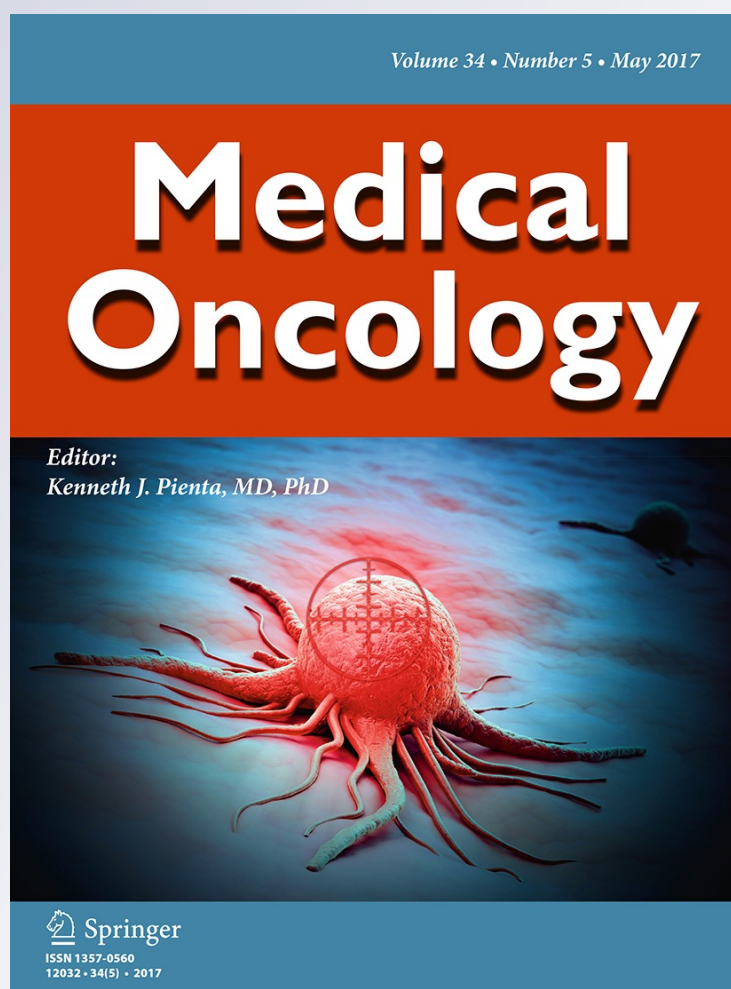
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## Need for new review of article on ketogenic dietary regimes for cancer patients

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### To the editor,

In a recent article entitled “Systematic review: isocaloric ketogenic dietary regimes for cancer patients” [1], Erickson et al. provide their summary of the use of ketogenic diets for treating cancer patients. As active researchers in this field, we find the Erickson paper to be inaccurate in its characterization of ketogenic diets. The writing is highly biased and contains a significant number of errors, some of an elementary nature. The overall tenor of the paper, rather than that of a balanced review, gives the impression of established experts warning patients about the risks of a new method. In fact, Dr. Erickson and co-authors are not acknowledged experts and, as far as we know, have no record of clinical or research experience in this area. We detail below the paper's faults and suggest the positive side of the issue which we feel remains

ignored. We think that the pertinent subject matter was not considered in the manuscript. In essence, failure to address these questions means that the paper could not have received adequate peer review. We suggest that some form of re-review of the paper be instituted. As it stands, Erickson et al. are likely to be misleading to patients and practitioners alike.

Erickson et al. are correct in describing the limited number of studies and the somewhat preliminary nature of work in the field. They nonetheless evaluated these papers as if they were part of an established, well-defined discipline and have largely tried to find fault. Their analysis has ignored the real promise and logical rationale behind the undertaking [2–4]. Equally important is the unstated implication that there exist effective, reliable cancer and epilepsy therapies, dietary or otherwise, with acceptable impact on quality of life. We do not think that this is the case. A balanced review would sensibly focus on the potential of ketogenic diets to go beyond the limitations on efficacy and adverse effects of current standards of treatment.

Our specific objections:

1. The methodology was based on rote library work with no analysis beyond the size and scope of each study and without recognizing differing foci. We find this a reflection of the long-standing bias against diets based on carbohydrate restriction of which KDs are an extension. Erickson et al. introduce the KD as a “cancer diet” equating it with non-scientific diets such as the Breuss cure. The metabolic anti-tumor effects of KDs are supported by significant preclinical data and preliminary clinical results. The KD should be characterized as a potential metabolic therapy and not simply a diet [2–5].

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2. Erickson et al. state that “ketogenic diets for cancer patients are implemented with the aim to reduce the energy production of cancer cells, thus decreasing tumor proliferation” (page 2). While this is one rationale employed by some of the included studies, several other mechanisms have been displayed in these studies, such as reducing inflammation, enhancing the efficacy of standard therapies, or accounting for the altered substrate utilization of cancer patients. Erickson et al. should know this, e.g., from reading their own reference No. 2 which focuses specifically on increased reactive oxygen species production and weakening of the anti-oxidative capacity of tumor cells [2]. This narrow view understates the promise of KDs which rests with the effectiveness of the method in other disease states, particularly diabetes and epilepsy, and depends, as well, on the associated anabolic role of insulin and IGFs [3, 6]. And, again, beyond the promise of improving the efficacy of current methods, a metabolic approach can avoid or reduce the adverse effects and, in many cases, debilitating declines in quality of life, that characterize chemo- and radiotherapy alone.
3. In the results section, Erickson et al. criticize the included studies for not having a “methodological rigorous design.” This follows from their assumption that all therapeutic methods are the same if they come up in a search on their key words. This appears somewhat disingenuous in that, as above, they have pointed out that this is a new approach with a relatively small number of studies where researchers are trying to find out what the key parameters are. As in many negative reviews on low-carbohydrate therapies that suggest “more work needs to be done,” the negative tone ensures that it will be difficult for that work to ever be done.
4. On body mass, Erickson et al. cite weight loss as a negative effect. An example is the mean weight loss of 1.5 kg after 2–3 days on the KD in the study by Tan-Shalaby et al. [7] (not “Tan and Shalaby” as written in the article—there are several such minor typos). KDs frequently show an initial weight loss in the form of water bound to glycogen. The longer-term weight loss of  $7.5 \pm 5.8$  kg is mentioned, but the authors do not state that all the patients in this study were overweight in the beginning (mean BMI  $29.46 \pm 5$  kg/m<sup>2</sup>). Reporting study results without considering the context indicates authors’ bias. In fact, there is evidence that KDs may counteract weight loss in the context of cachexia as was shown in the clinical trial by Fearon et al. [8] and mechanistically investigated in preclinical work [9].
5. The Discussion section warns against the application of KDs for cancer patients but provides no support from the extracted studies. The authors cite putative side effects, most of which derive from epilepsy studies in children. A strict KD in children with epilepsy cannot be generalized. None of us has personally experienced side effects such as hypoglycemia or metabolic acidosis during our studies or care of cancer patients. Table 3 “Reported adverse effects of KD” would be substantially shorter if restricted to events actually observed and reasonably attributed to KD in the cancer trials. Any real or potential side effects which derive mainly from the pediatric population are minor compared to the side effects of standard cancer treatments and are readily prevented and/or managed by a trained dietician. Finally, a great deal has been learned about the KD and potential side effects in cancer patients in recent years, which is not reflected in older papers on the subject.
6. Erickson lists a highly objectionable collection of parochial “concerns” that are conjectural, have never materialized but have continued to dog serious research in low-carbohydrate strategies:
  1. “it is important to know that all forms of the KD are considered nutritionally inadequate.” (page 5) This is without substance. No experimental evidence is supplied.
  2. “...the long-term application of the KD has been correlated with calcium deficits...” This is not true. If there are particular cases, the evidence is not presented.
  3. “...can exacerbate bone loss,” is particularly objectionable. It is not true, has never been seen and has been raised and answered innumerable times.
  4. “...and the metabolic state of acidosis...” is the most serious lapse. This is a constant feature of criticism found mostly in the popular media, and the statement is an elementary error in biochemistry. KDs do not cause acidosis. Blood pH is regulated. Ketoacidosis occurs only in untreated type I diabetes or in other states of absolute or relative insulin deficiency.
  5. The paper cites failure to conform to official dietary guidelines as fault, but ketogenic dietary approaches explicitly seek to avoid and to improve on the guidelines. In any case, at least in the USA, the guidelines have been strongly criticized and the increase in diabetes and obesity concomitant with the institution of the guidelines is commonly cited as evidence of their stature and effectiveness.



7. It is important to point out that researchers and clinicians in this field—again, in distinction to popular diets—have been circumspect about the current state of knowledge and have emphasized that KDs may be valuable as adjuvant to other modalities [2, 10, 11], and therefore, one must be careful in attributing adverse effects to the KD alone. Along these lines, Erickson et al. suggest that Klement and Sweeney [11] (not Sweeny as written) would have underrated the side effects of the KD in their study on six cancer patients. However, the two patients who experienced nausea and the one patient with diarrhea underwent radio-chemo therapy, a more likely cause of these side effects. Furthermore, no mention was made that all six patients reported subjective well-being and improvements in quality of life during the KD.
8. Erickson et al. conclude that “evidence on benefits regarding tumor development and progression as well as reduction in side effects of cancer therapy is missing.” Extraordinary responses of some cancer patients to the KD are reported [7, 12, 13] so that its efficacy must be considered a likely hypothesis in these cases.

An important trend in the medical literature is concerns about the actual quality and reliability of that literature [14–16]. We think Erickson et al. represent an example of the problem and an obvious cause: highly biased analysis without adequate editorial and reviewer oversight. The critiques of the literature recommend, as one potential remedy, post-publication review or, more generally, a more flexible method of publication where initial publication is more tentative. We think this paper should be re-reviewed and editors should obtain input from workers in KDs. The paper should be republished after all opinions—particularly from those authors whose work is cited—are examined. A novel format or mechanism for effecting this change in published papers may be required, but it seems necessary and the journal would receive approbation for bringing it about.

In summary, Erickson et al. represent an almost totally negative analysis of the ketogenic approach to therapy, and, while no particular credentials are required to summarize the literature, such a negative judgment is inappropriate given the authors' lack of direct experience with KD research, and lack of any communication with workers in the field. The net effect is to encourage patients to avoid a potential therapy that has significant promise and few side effects. The authors declare “This article does not contain any studies with human participants or animals performed by any of the authors and therefore did not require ethical approval.” We think that this lack of experience is precisely why there is an ethical question.

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#### Compliance with ethical standards

**Conflict of interest** All other authors declare that they have no conflicts of interest.

**Ethical approval** This article does not contain original data from human participants or animals performed by any of the authors.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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