Problems associated with a highly artificial ketogenic diet: Letter to the Editor Re: van der Louw EJTM, Olieman JF, van den Bemt PMLA, *et al*. 'Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study'

Ther Adv Med Oncol
2019, Vol. 11: 1–3
DOI: 10.1177/1758835919879268

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Dear Editor,

Despite extensive research efforts and multimodal treatments utilizing radiotherapy, temozolomide, or electromagnetic fields, prognosis of patients with glioblastoma multiforme (GBM) remains extremely poor. According to preclinical data, metabolic therapy using ketogenic diets (KDs) may constitute an additional, nontoxic, treatment option that could potentially enhance the antitumor effects of such treatments by applying a steady 'press' against tumor cells.[1,2] We therefore read the recently published paper by van der Louw and colleagues with great interest.[3] In it, the authors report results of administering a KD to nine GBM patients during radiotherapy plus temozolomide, and 6 weeks thereafter. The study group was comprised of patients with several good prognostic factors: they were relatively young, had high performance status, had undergone total or subtotal resection, were free of dexamethasone use at study entry, and had no major metabolic or inflammatory comorbidities. Furthermore, patients were able to achieve high nutritional ketosis during treatment, resulting in average concentrations of ketone bodies and glucose of 4.3 ± 1.2 mmol/l and 4.7 ± 0.17 mmol/l, respectively. Despite these positive factors, overall survival (OS) was not improved in comparison to historical values, and the median OS time of 12 months was even lower than the 15–20 months expected from other published data of patients being treated with the same protocol.[4,5] The authors hypothesized whether this finding was the result of all tumors having confirmed IDH1-wildtype status, and speculated that other (unobserved) confounders could have negatively influenced OS. While we basically agree with this statement, we want to discuss here the hypothesis that the prescription of a highly artificial KD over 6 weeks could have been one of the confounders negatively influencing OS.

During the first 6 weeks of the study, all patients had received almost exclusively KETOCAL, a liquid KD formula with the main ingredients consisting of refined vegetable oils from sunflower, soy, and palm fruit, among many other highly processed ingredients. While nutritional ketosis is an evolutionary ancient and normal physiological state for the human body, none of the main ingredients of KETOCAL (except water) would have been ingested by any human for at least 99.99% of human evolution. The same is true for some of the minor ingredients, such as emulsifiers or the vitamin B12 version cyanocobalamin. While this is not an argument *per se* that such a diet might be harmful, many of the ingredients of KETOCAL are indeed known as potentially harmful. For example, high amounts of refined sunflower and soy oil promote the production of lipid peroxide radicals that can attack an array of biomolecules, leading to formation of reactive and damaging compounds and inflammation.[6] Tumors are known to thrive in a pro-inflammatory environment. Furthermore, the possibility exists that emulsifiers and organic solvents present in

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KETOCAL could promote gut dysbiosis and increase intestinal permeability.[7] An association between an altered gut microbiome and brain cancer was first demonstrated in *Drosophila*,[8] and several connections between the gut microbiome, the immune system and the brain suggest that dysbiosis could attenuate brain cancer therapy efficacy.[9] Finally, there is strong reason to believe that, for optimal functioning and antitumor defense, the human body depends on many factors that were derived from natural foods during the course of human evolution, and that no artificial food can completely mimic in both amount or optimal ratio. Such factors include, but are not limited to, radical-scavenging furan fatty acids,[6] countless phytochemicals, several trace minerals, and food sources promoting a healthy gut microbiome that are not present in KETOCAL.

Achieving ketosis is a measurable outcome of a KD; however, there is a variety of methods to reach this endpoint. Focusing exclusively on achieving ketosis with no consideration of diet quality is an example of medical reductionism, an unfortunately dominant line of reasoning in medicine.[10] Reductionism means that complex systems such as a tumor and its host are reduced to lower-level entities, in this case the GBM cells that are thought to be targeted by ketone bodies, and ketosis and blood glucose levels as biomarkers of the KD. While reductionism has its value when trying to decipher causal mechanisms, such reasoning is problematic in treating complex diseases because it neglects that the human body is a highly complex system whose different components interact and influence each other,[11] as illustrated by the interaction between several prognostic factors and outcomes after treatment for GBM.

While we perceive the study by van der Louw and colleagues as an important further step towards showing that KDs, even such highly artificial ones, appear to be feasible in GBM patients,[3] we are deeply concerned with the safety and rationale behind administering a highly artificial and monotone diet over longer time periods. Although this study cannot provide evidence for (or against) our hypothesis that the KETOCAL diet had a negative influence on overall patient health and prognosis, we think it is important to consider this hypothesis and discuss it further. We also believe our arguments justify caution against basing a KD on artificial and highly processed foods.

Funding

The author(s) received no financial support for the research, authorship, and publication of this article.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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