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Author response to '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"'

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Dear Editor,

We are pleased to submit a response to the Letter to the Editor you have received from Klement *et al.* on our study "Ketogenic diet treatment as adjuvant to standard treatment of glioblastoma multiforme: a feasibility and safety study."[1] We thank them for their interest in our study. In their letter, they comment that their major concern is the prescription of a highly artificial ketogenic diet (KD) over 6 weeks that could have negatively influenced the overall survival (OS) in our study. Regarding the OS, we agree that it was lower than average reported results, but we expand further on this point. However, we disagree with many of the other points raised.

First, we would like to rectify certain numbers presented in their summary of our manuscript:

- Page 2, lines 2–3: ketone and glucose levels were different during the study period; the presented average numbers only correspond to the first 6 weeks of the study.
- Page 2, lines 4–5: a careful look at our article shows that the median survival was 12.8 months (IQR 12.3–17.7, range 9.8–19.02 months), when rounding off, it becomes 13 months and not 12 months.

Furthermore, we would like to emphasize that the small cohort size of our study ($N = 11$), which was focusing on KD feasibility and safety, not KD efficacy, precludes any statistical evidence of a cause–effect relationship between the diet and survival. Nine out of 11 patients were able to start the study protocol and 6 were able to finish the study period of 14 weeks.

Although our patients had good prognostic factors, as mentioned by the authors of the letter, all of our patients' histology results were identified as isocitrate dehydrogenase (IDH) wild-type glioblastoma multiforme (GBM), which is known to have a very poor prognosis. Only recently Gittleman *et al.* reported a median survival of 12.4 months (95% CI 10.9–13.3) in their cohorts with IDH wild-type GBM,[2] which places the OS of our small cohort in another perspective. Unfortunately, we were not able to confirm the status of another negative prognostic factor reported by Gittleman *et al.*, the MGMT promotor methylation status, which was negative in 2/9 and missing in 7/9.[2]

We disagree with the statement that our prescription of the KD is highly artificial and monotone. According to the study protocol, as described in our article,

> 'Patients consumed an exclusively fluid KD with a 4:1 diet ratio (4 g fat *versus* 1 g protein plus carbohydrates, 90% energy from fat) from baseline to end of chemoradiation. Once a ketone level >3 mmol/l was reached and sustained for 3 days, the patient was allowed a snack with the same 4:1 diet ratio once a day.'

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Patients were able to vary their liquid menu with a shake, soup, or smoothie, consisting of different ingredients with the same nutritional composition and a 4:1 ratio. Next to the liquids, a KD snack with 4:1 ratio was allowed. Different recipes (with different natural ingredients) were proposed from a ketogenic cooking book.[3] Although this recipe book is in Dutch, it can be ordered at the Department of Dietetics at the Erasmus MC. Moreover, the varied liquid KD was prescribed for only 6 weeks, which to our opinion cannot be defined as a long time period.

Klement *et al.* argue that some specific nutrients and ingredients used in KD might have inflammatory effects. However, there is growing evidence from laboratory studies that the KD itself has neuroprotective and anti-inflammatory effects.[4] These are based on the metabolic pathways that are related to ketone bodies, mitochondrial functioning, neurotransmitters, glycolytic restriction, oxidative stress, anaplerosis, fatty acid oxidation, and polyunsaturated fatty acids.[5–7] Moreover, during our study protocol, anti-inflammation marker IL-6 was examined at baseline, after 6 weeks (all liquid KD use) and at the end of the study, and were within normal limit levels (<10 pg/ml) at all measurements [unpublished data].

The KD, despite its composition being different from a natural diet for healthy individuals, as addressed by Klement *et al.* probably has additional metabolic benefits (i.e. by alteration of the gut microbiome), although the effect and the underlying mechanisms are still to be elucidated.[8,9]

Finally, in nutritional clinical practice, research groups face difficulties with patient inclusion and for that reason studies on KD are still ongoing or are published based on small patient cohorts. One of the major problems is that patients recently diagnosed with GBM are under major stress, which is a factor limiting their ability to cope with all the information and education that is required for successful implementation of KD. Earlier studies on KD patients also reported that a supporting family member or partner, in addition to counseling by the dietician and nurse, was of high importance in daily life to cope with the complex situation of combined treatments.[10–12] Therefore, we are convinced that simplification of KD (at least during the most hectic time of daily chemo-radiation) may be very helpful. We acknowledge that future KD intervention studies could further explore the right balance between nutritional adequacy of the diet and matching the patient preferences and needs in daily life without compromising beneficial effects when treatment modalities are combined. In our study, quality-of-life data and coping data confirmed there were no major negative effects during the two different trial periods and diet types.

Moreover, it is important to mention that our study protocol was also evaluated and approved by the Dutch Cancer patient organization KWF. Their opinion has been very valuable to us. This supported us to initiate this study but also convinced us about the integrity of the choices we made in our study design.

Our study has been designed as a feasibility and safety study. As we concluded in our manuscript: 'This study suggests that the use of KD as adjuvant to standard treatment, with chemo-radiation after first surgery, is feasible and safe in patients with GBM'. However, based on the small sample size of our cohort, no direct effect of KD (neither positive nor negative) on OS could be determined.

With kind regards,

On behalf of the research group,

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Conflict of interest statement

The author(s) declare that there is no conflict of interest.

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