Peer Review File

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Reviewer A

Baghdadi and colleagues report an important work to investigate the clinical efficacy of ketogenic diet in children with refractory epilepsy in Saudi Arabia population. It is of great implication to clinical use of KD. I only have minor comments to be addressed.

Comment 1: Abstract: please indicate how many patients were included in the study.

Reply 1:

Thank you for your kind comment. The abstract was updated with the total number of children recruited for the study.

Changes in the text: lines 62-63.

Comment 2. Introduction: It would be helpful to introduce why KD is efficient and its mechanism of action beyond ketone body production.

Replay 2: Thank you for your comment. The KD mechanism and efficiency was summarized in the introduction (lines 117-123); the efficiency of KD was highlighted in lines (153-158). The mechanism of action was discussed in detail in the discussion (lines 474- 493).

Changes in the text: The KD mechanism and efficiency was summarized in the introduction (lines 117-123). Possible mechanisms were discussed in detail in the discussion (lines 474- 493).

Comment 3: KD protocols: How was KD administered for infants in the protocol used?

Replay 3: Thank you for your question. The KD protocol was given in detail under "study measure" in lines 215- 248. In summary, KD was initiated in the inpatient setting according to a protocol-based on the John Hopkins over 3-4 days.

Changes in the text: Details about the KD protocol used by physicians and nutritionists at KFMC was given in details in Appendix B, lines 216- 218, 223- 229, 231- 243 and 247- 248.

Comment 4: How to introduce blind rules in the overall study design and methods?

Replay 4: Thank you for the comment. Our study is an observation non-experimental study (cross-sectional study), where blinding is not expected. We will consider blinding in our future randomized trial.

Changes in the text: none.

Comment 5. Results and Discussion: Are there differences in the duration of ketogenic diet? Will it affect the KD efficacy?

Replay 5: Thank you for your input. Our study showed that the KD duration was up to 12 months (line 215), and the KD was given a period of 3 months to determine its ability to produce adequate ketone and /or its effectiveness in decreasing seizures (lines 227- 229); however, we were not able to obtain more accurate data about the duration as the data was collected from the hospital database, physicians and dietitian notes, and patients' records. Despite this limitation, we included patients who were exposed to KD up to 12 months and insured that they

were on KD for at least 3 months. Our results were reflected in table 3, where we reported the distribution of the KD ratio, the change in diet ratios and the reasons for discontinuation. We then analyzed if changes in KD affected the reduction of seizures after adjusting for KD duration in tables 4 and 5.

Our methodology sought to ensure a fair assessment of the study by including variable analysis of exposure to KD and eliminating its effect on seizure outcome (lines 297- 304), which is reflected in the information provided in Tables 4 and 5. The effect of KD duration was also discussed in the discussion in lines 539- 543.

We conducted an observational cross-sectional study, and we acknowledge the limitations that this presents. Therefore, we plan to conduct a randomized control trial in the future in order to better assess the efficacy of KD, especially among children with refractory epilepsy.

Changes in the text: KD duration was up to 12 months (line 215). Its effect was adjusted in the multiple regression model to eliminate its effect on the seizure's outcome (lines 299- 304). This information was added under Table 4 and 5.

Comment 6. Lines 484-486, the discussion on KD cost has insufficient relevance to the comparison between KD and KD discontinuation.
Replay 6: Thank you for your comment. The main point for discussing the cost is that patients from low-income families may experience less improvement in their condition during KD treatment, possibly due to difficulties accessing essential equipment and food supplements. Additional information was added as requested (lines 553- 559).
Changes in the text: Additional information was added as requested (lines 553- 559).

Comment 7. Line 499, "counties", did the author mean "countries"?
Replay 7: Thank you for your comment and noticing this typo; yes, it is countries.
Changes in the text: it was corrected in line 600.

Comment 8. Table 1: What is the relapse rate after stopping KD? This is not visible in Table 1. A figure rather than table will be better for visualization.
Replay 8: Thank you for your comment. We collected data about relapse history (line 266). Only 1 patient had a history of relapse, and it was reported by the parent (i.e., might introduce self-report bias; therefore, this patient was excluded from the study. Although reporting the relapse rate would be beneficial, we conducted an observational **cross-sectional study** meaning that the outcome (improvement of seizure) and the exposure (KD) in the study participants were measured at the same time. The data was collected from the hospital database, physicians and dietitian notes, and patient's' records. Moreover, to assess the relapse rate among children especially those with refractory epilepsy, we need a longer follow up period and the drug-resistant epilepsy population should be followed prospectively (i.e. it is best to examine the relapse rate by conducting a prospective cohort study); relapse in a drug-resistant epilepsy has been examined in a prospective cohort study where the follow up period was up to 24 months https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3147304/ following long period of remission

https://jamanetwork.com/journals/jamaneurology/fullarticle/798231.

Most importantly, I would like to highlight that the main aim of this study is to examine the prevalence of improvement of seizure among children following the KD. However, we are planning for our future prospective cohort study and the relapse rate is one of the main outcomes.
Changes in the text: none.

Reviewer B

This article discusses the effects of a ketogenic diet on pediatric patients with refractory epilepsy in Saudi Arabia. Its sample size is large. In addition, the sociodemographic information of the patient's parents is examined in detail. This article shows that parents' backgrounds significantly impact KD treatment in pediatric patients with refractory epilepsy. It also suggests successful KD treatment requires multidisciplinary support for the patient's parents. This article is well-written, and the arguments are clear. It has a clinically useful message.
Reply: Thank you for your kind words. We are looking forward to publishing our study in such a respected journal.

Reviewer C

I read with great interest the manuscript "Effect of a Ketogenic Diet on Decrease of Seizures 1 in Refractory Epilepsy among 2 Children (Infancy to 14 Years Old) in Saudi Arabia: A Cross-sectional Study". The authors tried to study their experience of using the classic ketogenic diet in children with medically refractory epilepsy.

My observations:

Comment 1. This is a retrospective study. This topic has been studied a number of times, and the literature is replete with single-center experiences of using classic KD in children with epilepsy. As such, I am afraid, there is no novelty in this study.
Replay 1: Thank you for your comment. We agree with the reviewer that many studies have investigated the effect of KD in children with epilepsy. However, to date in **Saudi Arabia**, there is scarce evidence of the effect of KD on **refractory** epilepsy; this was highlighted in the manuscript (lines 160- 171). Additionally, few hospitals in Saudi Arabia with a specialized epilepsy center that offers KD treatment as a treatment option for refractory epilepsy and all cases of epilepsy requiring KD management are referred to the center, we selected to recruit the patients. This was highlighted in the methodology (lines 191- 195).

Moreover, our study was designed to assess the effect of KD on decrease of seizure frequency in children with **refractory** epilepsy and to investigate its effect on epilepsy control, depending

on various **social determinants**, including age, gender, socioeconomic status, and clinical risk factors. Determining the precise origin of these nation-specific discrepancies remains a challenging task due to possible variations in the social determinants of health influenced by geography, genetic and epidemiology of chronic diseases such as epilepsy, cultural idiosyncrasies, and types of lifestyles influencing the type and quality of diets. The effect of sociodemographic factors was discussed in details in the discussion (lines 529- 583).

Changes in the text: none.

Comment 2. What is mentioned under "key findings', 'what is known and what is new', and 'what is the implication and what needs to change' are all known to the medical community and not new.

Replay 2: Thank you for your kind comment. The "key findings', 'what is known and what is new', and 'what is the implication and what needs to change' were updated as requested.

Although many studies have investigated the effect of KD in children with **epilepsy,** there is insufficient evidence of the effect of KD on **refractory epilepsy** in Saudi Arabia up to date. Additionally, few hospitals in Saudi Arabia with a specialized epilepsy center that offers KD treatment as a treatment option for **refractory** epilepsy and all cases of epilepsy requiring KD management are referred to this center. Although this treatment approach is not common in a Saudi context, it could help in the treatment and prognosis of this disease. It might provide insight into the potential effectiveness of this dietary approach in comparison to other treatments available and its feasibility for long-term use.

Changes in the text: "key findings', 'what is known and what is new', and 'what is the implication and what needs to change' were updated in page 5, lines 83- 84.

Comment 3. I am very concerned about certain sentences which are against even the basic concepts of epilepsy/seizure (introduction). Epilepsy is no longer a disorder; it is a disease. The definition of seizure is inaccurate. The sentence "Although medical or surgical approaches have been effective in treating children with seizures, 20–30% of childhood epilepsies are not completely controlled and considered medically refractory seizures ", is inaccurate. Surgical treatment is not considered for the diagnosis of MRE.

Replay 3: Thank you for highlighting this unintentional error about the disease. It was corrected accordingly. The sentences explaining the definition and diagnosis of refractory epilepsy were unclear and gave a false meaning. We apologize for that, and the sentences were re-written, and correct meaning was given in the introduction (lines 87- 108) and abstract (lines 46- 49).

Epilepsy had traditionally been referred to as a disorder/family of disorders, rather than a disease, to emphasize that it is comprised of many different diseases and conditions. The term disorder implies a functional disturbance, not necessarily lasting; whereas the term disease may (but not always) convey a more lasting derangement of normal function. The ILAE and the

International Bureau for Epilepsy (IBE) have agreed that epilepsy is best to be considered a disease for practical reasons (DOI: 10.1111/epi.12550).

Epilepsy surgery is indicated in 30% - 40% of patients with refractory (pharmaco-resistant) seizures despite being on one-year adequate dosage of two appropriate anti-seizure medications (DOI: 10.14581/jer.18001). Unfortunately, surgical intervention is still one of the common treatment options in Saudi Arabia and it was one of the exclusion criteria (line 207); few hospitals in Saudi Arabia with a specialized epilepsy center that offers KD treatment as a treatment option for refractory epilepsy. Although this treatment approach is not common in a Saudi context, it could help in the treatment and prognosis.

In fact, this issue was one of the driving factors influenced our decision to assess the effect of KD on the frequency of seizures and then write recommendations to policy makers and hospital guidelines representatives and to run clinical trials to change the clinical practice; even though limited hospitals in Saudi Arabia offer KD therapy for refractory epilepsy, it may improve treatment and prognosis for children with epilepsy and should be more widely available.

Changes in the text: the term disease was inserted in line 87. Information about refractory epilepsy was rewritten in lines 87- 108.

Comment 4. There are unnecessary details about the basics of KD. In 2023, that is not needed in a medical article.

Replay 4: Thank you for your comment. The information about the KD was updated, and the most important information about Atkins diet and its comparison with the KD and the KD ratios was retained (lines 117- 123); because, unfortunately, surgical intervention is still one of the common treatment options in Saudi Arabia, where few hospitals with a specialized epilepsy center that offer KD treatment as a treatment option for refractory epilepsy. Although this treatment approach is not common in a Saudi context, it could help in the treatment and prognosis of this disease.

Changes in the text: The information was updated, and the most important information about KD was retained (lines 117- 123).

Comment 5. Method of initiation of KD is not detailed. Over how many days? Did they check blood or urine ketones? What were the adverse side effects?

Replay 5: Thank you for your comment. The KD protocol was given in detail under "study measure" in lines 215- 248. In summary, KD was initiated in the inpatient setting according to a protocol-based on the John Hopkins over 3-4 days. Urine ketones were assessed to monitor the patients' progression and ketonuria was one of the variables assessed and it was mentioned in the methodology (lines 223 and 233). Data about KD adverse effects such as gastrointestinal symptoms, hypoglycemia, dehydration, diarrhea etc. were reported (lines 223- 225), and their effects on discontinuing the KD were compared in table 3; where the prevalence of adverse effects were comparable in patients who improved on KD compared with those not improved (47 % vs. 52 %, respectively). It was discussed in lines 504- 505.

Changes in the text: Details about the KD protocol used by physicians and nutritionists at KFMC was given in details in Appendix B, lines 216- 218, 223- 229, 231- 243 and 247- 248. Information about urine ketones in monitoring the patient's progression was added in lines 223 and 225- 229. Information regarding KD adverse effects was added in methodology (lines 223- 224), and results (lines 357- 360).

Comment 6. There is no rationale for using different initiating ratios in different age groups as outlined by the authors.

Replay 6: Thank you for the comment. We acknowledge the reviewer's point of view. Although this protocol was developed based on an international guideline (lines 216- 218), it was personalized to the Saudi population because sociodemographic, and genetic cultural background varies between populations. This approach of personalized management has been previously used (16) (lines 236- 248). Initiation of classic KD were explained in detail under "study measure" in Appendix B, lines 216- 218, 223- 229, 231- 243 and 247- 248.

Changes in the text: Supporting evidence was added in Appendix B, lines 216- 218, 223- 229, 231- 243 and 247- 248.

Comment 7. Did they stick to the original initiating ratio? Or what parameters and strategy was used to increase the ratio subsequently?

Replay 7: Thank you for your comment. No, we did not stick to the initiation ratio but go up gradually. The ratio is increased gradually monitoring both blood glucose levels and specific gravity to avoid hypoglycemia and dehydration respectively. The ratio is intended to regulate the degree of ketosis with higher ratio theoretically stimulating higher ketosis. The higher the ratio, the lower the protein and carbohydrate content of the diet. The ratio can be manipulated during the course of the KD therapy to achieve nutrition therapy goals and optimize seizure control. It is important to keep in mind that the degree of ketosis may vary among individuals. Two different individuals of the same age and weight may experience a completely different level of ketosis on the same ratio. The difference is due to individual's variations in energy metabolism and expenditure.

Changes in the text: gradual increase in the KD ratio was explained in lines 230- 235. KD protocol was explained in lines 217- 229.

Comment 8. There is enough evidence to suggest 2.5:1 and 4:1 ratios work equally well (Raju et al 2011). Hence, it is difficult to accept the authors' findings that the 2:1 ratio did not work.

Replay 8: Thank you for the comment. We followed the John Hopkins protocol by Kossof which increase the KD ratio gradually through days 1 to 4 without waiting for urine ketone to appear which is why we did not stop at lower KD ratios i.e., 2.5:1 and monitor for adequate ketosis over weeks to months (lines 217- 235).

Also, there were only 5 patients who were following 2:1 ration in our study, which might explain why these children have not shown a reduction in the frequency of seizures while 44% of patients on 3:1 diets and 4.5:1 diets showed a decrease in seizure frequency. We conducted an observational study to examine the prevalence of patients improved on KD, and we

acknowledge the limitations that this presents. A randomized control trial is needed to examine the efficacy of KD in reducing seizures in epilepsy.

Changes in the text: Discussion was updated with more explanations (lines 474- 493 and 510-514).

Comment 9. Children who are non-ambulatory are likely to have a more severe brain dysfunction and hence their seizures are inherently resistant to any form of therapy.
Replay 9: Thank you for the comment. We acknowledge the reviewer's point of view. There is emerging evidence highlighting the importance of early application of KD to children with refractory status epilepticus or epilepsy related syndromes (Lin et al. 2020). Due to their critical status and neuro-protective benefits, which can be extended to other neurological illnesses, ketogenic diets should be administered in pediatric intensive care units (DOI: 10.1016/j.bj.2020.02.002).

Moreover, the efficacy of KD might vary based on sociodemographic, and genetic cultural background factors (16); hence, our protocol was personalized to the Saudi population, and we will explore the response rate of KD in these patients with severe brain dysfunction (i.e., who are non-ambulatory) in our upcoming manuscript examining the efficacy of KD for syndromes and genetic mutations.

Changes in the text: none.

Comment 10. What is probably more important is to look at the response based on syndromes, maybe there were more patients with EMAtS in the responder group.
Replay 10: Thank you for your comment. We collected data about syndromes such as Infantile epileptic encephalopathy, Angelman syndrome, Lennox–Gastaut syndrome (LGS), MMFSI, Dravet syndrome etc. and none of them showed statistically significant association with improvement of seizures.

In this manuscript the main aim is to examine the prevalence of improvement of seizure among children following the KD where the data was collected from the hospital database, physicians and dietitian notes, and patient's' records. We are planning to examine the effect of exposure of KD among epileptic patients based on syndromic diagnoses at the time of KD initiation in our future prospective cohort study. We will also examine specific gene mutations and their effects on responder rate to KD considering social determinants and lifestyle factors (please see my reply to your first comment above).

However, the result section was updated with a summary of the main finding and keep details for the upcoming manuscript examining the efficacy of KD for syndromes and genetic mutations.

Changes in the text: We updated the methodology (lines 267- 269), and the results with a brief summary of the findings (lines 331- 334).

Comment 11. Did the authors include neonates?

Replay 11: Thank you for your kind comment. No, we included children (infancy to 14 years old). We added neonates to the exclusion criteria.

Changes in the text: Neonates were added as one of the exclusion criteria (line 204).

Comment 12. We all know MAD and LGIT work very well in seizure control. If we calculate the ratio in them it would be less than 2:1. Only difference is, these diet types contain more protein compared to carbohydrates thereby increasing the ketogenic potential.

Replay 12: Thank you for your input. We totally agree with the reviewer. However, this study was conducted to focus mainly on how the KD affects intractable epilepsy. In the methodology the protocol of classic KD was explained (lines 216- 248). We highlighted this fact in the introduction (lines117- 126) and explained the mechanism of KD in the discussion under "explanations of findings" (lines 474- 493).

Changes in the text: none.