Author's response to reviews

Title: The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants

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Editorial Office
Nutritional Journal

Dear Editor,

We have uploaded the revision of our original manuscript, titled “The effects of varying protein and energy intakes on the growth and body composition of very low birth weight infants”, through the electronic system according to the suggestions of the reviewers.

The manuscript describes original research and has been submitted to the Original Articles section for consideration by the Editorial Board of the Nutritional Journal. Neither the entire paper nor any of its content have been published previously or have been submitted to another journal. All authors have contributed to the study according to international criteria on authorship and have seen and approved the final submitted version. There are no conflicts of interest.

In the revised manuscript, we have underlined the paragraphs added to the original text. The responses to the reviewers are described below.

1. How many were approached to join the study?:
   - We calculated the desired sample size to be 12 newborns per group (10 plus 2 for possible drop-outs), and we applied the “intention to treat” policy without substitution for the dropouts. We had 4 dropouts due to the wishes of the parents; unfortunately, all of them were in group A. Two dropped out after the first-week exam, and the other two dropped out after the second-week exam. As they did not reach the third-week exam, they were excluded. Considering that there were 8 infants in the control group and 12 infants in the study group, the “Power and sample size calculation” program gives the following description: “We are planning a study of a continuous response variable from independent control and experimental subjects with 0.7 control(s) (8/12) per experimental subject. In
a previous study, the response within each subject group was normally distributed with a standard deviation of 3.14 (with averages of 2.14 and 4.15). If the true difference in the experimental and control means is 4.76 (19.85 minus 15.09), we will need to study 10 experimental subjects and 7 control subjects to be able to reject the null hypothesis that the population means of the experimental and control groups are equal with a probability (power) of 0.8. The Type I error probability associated with this test of this null hypothesis is 0.05”. Therefore, our sample size (12 experimental subjects and 8 control subjects) is adequate.

We have added in the text “(10 cases plus 2 for possible drop-outs)”.  

2. How was the end of the intervention otherwise defined for each individual?:  
- The intervention lasted at least 24 days, which allowed us to perform the third-week exam. Sixteen patients attended the 4th-week exam, thereby finishing the intervention. The others were discharged from the Unit, and the results of the 3rd-week exam were considered the final ones. Because of this, we included the duration of the intervention as a covariate.

3. It would be helpful to also include a figure showing the changes in weight, length, Z-scores, FFM etc. between the 4 groups. This would also illustrate the trends in length Z-score changes that appear quite similar in size to the changes in weight.
- We have added a figure to the manuscript describing this information (Figure 1).

4. In the Methods section of the text, we included a statement that the study design was a “randomized clinical trial” instead of a “randomized interventional study”.

5. Can BMI Z-scores also be calculated?:  
- No, because the growth curves that we have used (reference 21) do not contain these reference values.

6. We have included the following weaknesses of the study in the discussion section:  
- “The macronutrient intake of breast milk was based on reports rather than direct measurements. Therefore, there may be some error in the estimated intakes”.
- “Body composition was measured using BIA. This is not a common methodology and is subject to some inaccuracies because of the assumptions that need to be made in the equations that relate impedance to water content, from which FFM is estimated”.

7. The methods give the trade/commercial names for the formula and preparation - we need to know exactly what nutrients those products contain.  
- Alprem (Nestlé): in 100 g = 506 kcal, protein 14.5 g, carbohydrate 53.6 g, fat 26.0 g.  
- Enfamil Human Milk fortifier (Mead Johnson): 1 vial = 5 mL = 5 g = 7.5 kcal,
protein 0.55 g, carbohydrate <0.3 g, fat 0.55 g.
- ProMod protein powder (Abbott): in 10 g = 42.4 kcal, protein 7.6 g, carbohydrate 1.0 g, fat 0.9 g.
- Duocal MCT (SHS): in 10 g = 12.4 kcal, carbohydrate 1.8 g, fat 0.58 g.

We have added this information to Table 2 in the manuscript.

8. Table 1 – As the numbers are small, we have deleted the percent sign in each column and the P-values in the last column.

9. Table 3 –
- We have reduced the number of significant digits used (1.9 instead of 1.93, etc.)
- It was just one measurement for each patient on one occasion. We have included the n of each group and an explanation in the table.
- Group A triglycerides have a much higher mean and a large SD - was there 1 child with a very high TG level? The TG figures in group A were 73, 115, 129, 236, 99, 84, 75 and 41. One newborn had a TG level of 236 mg/dl.

10. Table 4 – It has been simplified so that the key messages for clinicians can be easily identified. In the final column, P-values for the initial and duration terms have been erased, indicating that these were adjusted for in the model.

11. What was the rationale for analyzing the data after 5 subjects in the control group and 5 subjects in the combined protein/energy enriched groups and using the preliminary data to calculate the sample size?
- This method, described in Doménech JM (in Bioestadística, Ed. Herder, Barcelona, 1977), is used to calculate the sample size, taking into account the values obtained in a pilot study of a small number of patients (mean and standard deviation). The program “Power and sample size calculation” also permits using the same method, and the results of such calculations are similar.

12. Not sure of the value of the very small number of subjects fed human milk as a reference group.
- These 6 newborns are only considered a “descriptive reference group” and have not been included in the comparison between the three interventional groups. However, we believe that it may be valuable for clinicians reading the manuscript to get an idea about what might happen with breastfeeding.

13. There is no mention of the measurement of foot length although it was used to calculate the TBW.
- This measurement has not been analyzed because it is not used clinically.

14. Not sure of the rationale for the use of BMI in young infants especially in the VLBW infants?:
- Although not normally used in premature babies, we wanted to attempt a novel use of the technique. Unfortunately, the results of the technique in this population
were not promising.

15. Would the authors speculate on the possible reasons for the higher urea concentrations in the groups that received the higher protein intake?:

- If the renal function is normal, the levels of urea (or BUN) in blood are related to the metabolism of proteins from the diet. It is even possible to use urea or BUN values to administer an “individual adjustable fortification” to premature infants, with the goal of increasing protein intake while maintaining urea values. (citation: Arslanoglu S et al. Adjustable fortification of human milk fed to preterm infants: does it make a difference? J Perinatol 2006;26:614-621)

We greatly appreciate your attention to the revised manuscript submission and hope it will be considered suitable for publication.

Yours sincerely,

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