Author’s response to reviews

Title: Recombinant Growth Hormone Therapy in Children with Short Stature in Kuwait: A Cross-sectional Study of Use and Treatment Outcomes

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Author’s response to reviews:
Response to Reviewers is attached below and separately as a PDF file in the attached files section of the submission

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To: Journal Editorial Office, BioMed Central
From: Authors; Dalia Al-Abdulrazzaq, Abdullah Al-Taiar, Kholoud Hassan, and Iman Al-Basari

We would like to thank The Reviewers and The Editor for their constructive and insightful comments on our manuscript. Indeed, we are grateful for their comments which have improved our manuscript.
Point-by-point responses to the reviewers’ comments follow. Comments requiring change/response with appropriate references were included in this letter.

Reviewer Dr Elżbieta Petriczko

We would like to thank Dr Elżbieta Petriczko for the time she spent on reviewing our manuscript. We appreciate her valuable comments.

1. Small study group size despite the fact that this department has a large coverage area in the country and serves a total pediatric population of approximately 250,000, only 60 children were treated with rhGH in the center. (Major limitation of this analysis).

Response:

We agree with the reviewer’s comment that the small sample size is a limitation of our study. We have acknowledged this in the original manuscript, please see Results – page 9-lines 190-191 & Discussion – page 10 – lines 230-232, and Discussion – page 12 – lines 269-271). We also now modified the conclusion to recommend large multi-center study to investigate the outcome of rGH therapy in Kuwait and the region. (Please see Conclusion – page 13 – lines 303-304).

It is worth noting that rGH therapy was introduced recently in Kuwait compared to other parts of the world and that there are only limited number of practicing pediatric endocrinologists. This may explain the small number of children on rGH despite the large coverage area of the hospital. (Please see Introduction – page 5 – lines 104-106).


Response:

The poor response of children with ISS to rGH therapy at 1-year was demonstrated by the fact that 40% of children with ISS had significant response to therapy (height SDS change of ≥ 0.3). Also they had the lowest median height SDS change 0.17. (Please see Results section – page 8 - lines 178-183 & Table 2; and Discussion page 11 – lines 233-235). We have made slight
modifications to the manuscript to make this clearer (Please see Results section – page 8 - lines 178-183)

3. All patients came from only one pediatric endocrine center.

Response

We agree with the comment; and the pros and cons of working in a single center were outlined in the original manuscript. On one hand, the fact that this study was conducted in one center limits the generalizability of the findings as we highlighted in the discussion section– page 12 lines 280-282). On the other hand, conducting study in one center will introduce some standardization in data collection and less variability in anthropometric measurements (Please see Discussion – page 12 – lines 289-290). Finally, we have now modified the conclusion section to suggest a larger multi-center study to investigate the outcome of rGH therapy in the country and the region. (Please see Conclusions – page 13 – lines 303-304)

4. No data on several important parameters (e.g. mid-parental height, target height, bone age, IGF-1 levels, and GH doses), what the authors themselves mention in the discussion.

Response

We agree with The Reviewer that these missing pieces of information are limitations in the study. This is outlined in the Discussion section in the original manuscript (pages 12-13 – lines 282-286). However, this problem is inherent weakness of all studies that use data from medical records and not unique to our study. Despite these missing data, our findings are valuable in the evaluation of rGH treatment outcome; hence guiding decision makers to optimally use the resources. The missing data, may help explain why the outcome of rGH therapy was good or poor (act as potential confounders), and this would be of secondary interest. We have now recommended to conduct a prospective study with which it will be possible to collect data on all important parameters, see conclusion, pages 13-14 – 303-308. Also, because rGH dosing protocol used in our center at initiation of therapy is known, we have added this to the method section. (Please see Methods – pages 6-7 – lines 136-139).

5. Comparing this study with other much larger European and American groups of patients is not really possible due to the above limitations.

Response
Like-to-like comparison between different research studies is hardly possible. Differences in study design, study population, baseline characteristics, and data collections methods, etc make such comparison in medical research indeed very rare. However, comparing findings from different studies while taking into account the other factors have been a major source for generating hypothesis hence guiding further research. For example, in our study we did not find strong gender differences in rGH therapy like other studies; and this may warrant further investigation. We highlighted the fact that comparison between our findings and results of other studies you mentioned should be interpreted with caution in various places in the discussion- e.g. Page 10 – lines 230-232.

6. The phrase „production” in line 95 should be replaced with „secretion”.

Response
Done, see Introduction – page 5 – line 94.

Reviewer Dr Ana M Ramos-Levi

We would like to thank Dr Ana M Ramos-Levi for the time she spent on reviewing our manuscript. We appreciate her valuable comments.

1- One of the major limitations of the study is its retrospective nature.

Response
We agree with The Reviewer that retrospective studies have their own inherent weaknesses. We highlighted this as a limitation along with its ramifications in the discussion section in the original manuscript. (Please see Discussion – pages 12-13 – lines – 282-286). We have also modified the conclusions section to suggest a future prospective study. (Please see Conclusion – page 13 – lines 303-304)

2- Also, although the clinical setting is properly introduced and the references to the literature are correctly chosen, perhaps some more information regarding the healthcare system in Kuwait and in the hospital area could be interesting and should be discussed, in order to be able to better interpret and explain the main results obtained.
Response

Thank you for this comment. More details on the healthcare system in regards to rGH therapy in Kuwait are added to the revised manuscript in the Introduction section as suggested. (Please see Introduction – page 5 – lines 104-107). More details about diagnostic criteria and dosing protocols of rGH in the center are added to the revised manuscript. (Please see Methods section – pages 6-7 – lines 130-139)

3- Other minor corrections: -Abbreviation "AOR" in the abstract should be explained.

Response

Thank you. We spelled this out now in the revised manuscript: Abstract section – page 3 – line 70 & the list of abbreviations section – page 14 – line 319.

4- Which is the period of analysis? 60 patients were included, but only 44 were analyzed. Why were these patients under treatment not included? (Because of absence of information, withdrawal of treatment or follow-up…?)

Response

As outlined in the manuscript, the study included those children treated with rGH in between December 2013 and December 2014. To make the study period clearer we have slightly edited the aims at the introduction section (Please see Introduction – pages 5-6 – lines 114-115).

As demonstrated in the manuscript (See Discussion section – page 13 – lines 286-288), we had 16 patients with no follow-up data, of whom 8 patients did not yet complete one year since the start of therapy. In order to verify whether those who did not complete their follow-up differ from the rest who did complete their follow-up, we compared the characteristics of the two groups and found the groups to be similar (See Discussion section – page 13 – lines 286-288).

Reviewer Dr Mieczyslaw Szalecki

We would like to thank Dr Mieczyslaw Szalecki for the time he spent on reviewing our manuscript. We appreciate his valuable comments.
1- Interesting study of an experiences the major hospital in Kuwait in growth hormone therapy. Authors analyzed results of one year therapy in children with Isolated Growth Hormone Deficiency (diagnosed based on two stimulation tests with a peak GH concentration <7.5 ng/ml), Idiopathic Short Stature and Small for Gestational Age but they did no answer which criteria was used to determined others than GHD recommendation to use GH.

Response

Thank you for the comment. We revised manuscript to include criteria on diagnosing children with ISS and SGA along with information on rGH dosing protocol used in the center for different diagnoses as suggested. (Please see Methods section – pages 6-7 – lines 130-139)

2- They analyzed the influence of gender, age at initiation, pre-pubertal status at initiation, height SDS and BMI at initiation. Unfortunately they did not analyzed the influence of IGF-1 and IGFBP-3 concentration, bone age, mid-parental height and especially growth hormone doses. The last point is very important because we don't know if the doses use in therapy of ISS and IGHD children were similar or different. May be here is the key to understand the poor answer in therapy of ISS children (also the qualifications this group for treatment).

Response

We totally agree with the comment above. With respect to growth hormone doses in different groups, this is now added to the revised manuscript (Please see Methods – pages 6-7 – lines 136-139). For other missing data, please see our response to comment # 4 from Dr Elżbieta Petriczko.

3- For all children the same growth chords (WHO) were used in spite of fact that children were not the same origin and the group was multiethnic.

Response

Due to the lack of locally established growth standards in Kuwait, the Ministry of Health in Kuwait has approved the use of the WHO growth standards as a reference (Please see Methods – page 7– lines 141-145). Currently, these growth standards are the official standards in all hospitals and healthcare facilities in Kuwait. The WHO growth standards were published after a multi-center study was conducted within which a representative sample of children from our region was included. Most of our patients were Kuwaitis (see table 1).
4- Of course one year period is too small to assess the final results but some observations are interesting for example no influence of gender, influence of age at initial, very good answer in IGHD group and very poor in ISS group. Some more details is necessary to understand the results especially GH doses in both group and criteria in ISS and SGA groups (for example genetic, SHOX gene and so on).

Response

With respect to GH doses and diagnostic criteria for ISS and SGA, these have been added to the revised manuscript, (see our response to the comments # 1 & 2 above). We agree with The Reviewer that a one-year follow-up period is short and this is highlighted in the manuscript as a limitation (see Discussion – page 12 – lines 279-280). We also now recommended conducting a prospective study and extend the follow-up and include data on adult heights after therapy (see Conclusion – page 13 – lines 303-304).

With regards to genetics studies, this is indeed a valid point in interpreting response to rGH in children. However, genetic studies are not part of the routine work-up for children considered for rGH in Kuwait. Nevertheless, we thank you for raising this point and we have included it as a potential variable for consideration in future studies in the modified manuscript (See Conclusion – pages 13-14 – lines 304-308).

Finally, as suggested by the reviewers, we have re-edited the manuscript for language.

We appreciate the time and effort The Reviewers and The Editor are spending on our revised manuscript and we hope that we have addressed all of their concerns.

Best Regards,

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