Author’s response to reviews

Title: Impaired awareness of hypoglycemia in children and adolescents with type 1 diabetes mellitus in North of Jordan

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Author’s response to reviews:

Editor Comments:
1) Please include a sample size calculation to demonstrate that your study is sufficiently powered to detect differences.

Author's comment: As indicated in Methods section, this study was conducted at outpatients' clinics of Princess Rahma Pediatric Hospital which is the only pediatric referral hospital in the North of Jordan and it receives cases from the four northern governorates of Jordan (Irbid, Ajloun, Jerash and Mafraq). According to hospital's records, 130 Type 1 diabetic children and adolescents (age ≤ 16 years) receive their treatment at these clinics. So, this number represents most of the diagnosed cases of Type 1 diabetes in this area of Jordan. Accordingly, our sample size was calculated according to the previously reported prevalence (22.4%) of Impaired Awareness of Hypoglycemia (IAH) in children and adolescents as determined by Graveling et al study [1] using Clarke's method.

We used the following formula which was determined by Bartlett et al [2]:
\[ n = \frac{[t]^2 (p) (1-p)/(d)^2]/(1+[t]^2 (p) (1-p)/(d)^2)]/N \]

\( n \) = sample size.
\( t \) = 1.96 (t-value corresponding to 95% confidence interval).
\( p \) = 0.224 (the estimated prevalence of IAH in children and adolescents determined by Graveling et al [1].
\( d \) = 0.05 (the acceptable margin of error based on a confidence interval of 95% and 5% error).
\( N \) = population size (130).

Consequently, the calculated sample size was 87. However, we tried to recruit all patients (\( n = 130 \)) but we only included 94 patients as reported in Methods section. Our sample size was comparable to other
similar studies including Graveling et al [1] where n was 98 children and adolescents with Type 1 diabetes and Clarke et al (1995) where n was 78 patients with Type 1 diabetes.

Change to manuscript:
- Title: replace "Jordan" by "North of Jordan".

- Sample size calculation was included in the revise manuscript in Methods section under Participants subheading (highlighted in yellow).

2) Please note that we require all manuscripts to have a complete Declarations section, our submission guidelines outlines how to complete this section (https://bmcendocrdisord.biomedcentral.com/submission-guidelines/preparing-your-manuscript/research-article#declarations).

Author's response: Declaration section was added to the end of manuscript as required.

Reviewer #1:
Andrea Fischl, PhD, MPH, BS (Reviewer 1): Hypoglycemia is a common acute complication seen in Type 1 Diabetes. In addition to significant physiological issues associated with hypoglycemia in children, there may be significant psychological issues experienced by both the child with T1D as well as their caregivers.

There are several areas that need addressed before publication. These include:
1) More detail is needed to describe this population. What was the age range of this group? What constitutes the age of a child versus the age of an adolescent? you eliminated children below the age of 5 so did the population include children >5 years of age? What is the oldest adolescent that was seen? Does your clinic see pediatric patients through age 18? 19? etc.

Author's response: Outpatient pediatric clinics of PRPH receive Type 1 DM patients who are ≤ 16 years old. Patients who are ≥ 17 years old are considered as adults by the Ministry of Health and they receive medical treatment at the diabetic clinic of adults. We excluded children who are < 5 years old as described in Methods as it was difficult for them to describe their feeling of hypoglycemia. So, the age range of our study participants was 5-16 years. According to the WHO definition of adolescence (≥ 10 years old), children participants were from 5-10 years old while adolescents participants were from 10-16 years old.

Change to manuscript: “So, the age of our study participants ranged from 5-16 years”. This statement was added to the paragraph under Participants subheading in Methods.

Continued reviewer comment 1: Table 1 is confusing and needs to be re-constructed to show what statistic is used for each of the variables and each of the age groups. The authors report what statistics are used at the bottom of the table.

When generating the table, please delineate what the statistic is, ie, %, mean, range etc. While interquartile range shows where the bulk of the cohort lies, in describing age for example it would be more descriptive to report range, mean, median and then the interquartile range.

When looking at the age, what does the first column report for the n=94: what does the number 10 refer to as well as the numbers in the parenthesis 8-13. It was difficult to tease out what statistics were addressed with each of the variables. Also if you can provide more detail in the table for the age range
definition for children versus adolescent. This table is very difficult to interpret.

Authors response: Age ranges for children and adolescents were defined in the heading of Table 1. Mann Whitney U test was used to find differences between children and adolescents in continuous variables (age, BMI, duration of DM or insulin therapy and HbA1c), Chi-square test or Fisher’s exact test were used to find association between age groups and categorical variables (insulin regimen, adherence to insulin, maintenance of regular meals, frequency of hypoglycemia and development of severe hypoglycemia). Data of continuous variables for both children and adolescents were expressed as median (25th-75th percentiles) but not as mean ± standard deviation because these continuous variables are not normally distributed. So, median (interquartile range) is more statistically representative compared to mean ± standard deviation in this situation. Data of categorical variables for both children and adolescents are expressed as frequency (%).

The first column that contains n= 94 represent data for all study participants including both children and adults. For age, 10 represents the median age and (8-18) represents the 25th -75th percentiles of age. Again median (interquartile range) is used to describe continuous variables when they are not normally distributed.

Change to manuscript: Age ranges for children and adolescents were defined in the heading of Table 1. Children (5-10 years old) and adolescents (10-16 years old).

The bottom of Table 1 was changed to: Mann Whitney U test was used to find differences between children and adolescents in continuous variables, Chi-square test or Fisher’s exact test were used to find association between age groups and categorical variables (P<0.05 is considered significant). Data are expressed as median (25th-75th percentile) for continuous variables and as frequency (%) for categorical variables.

Continued reviewer's comment 1: Table 2 again has the statistics listed at the bottom of the table. Please reconstruct to show in detail the variable with its measure.

Author's response: Same comment as for Table 1.

Change to manuscript: The bottom of Table 2 was changed to: Mann Whitney U test was used to find differences between aware and IAH participants in continuous variables, Chi-square test or Fisher’s exact test were used to find association between hypoglycemia awareness and categorical variables (P<0.05 is considered significant). Data are expressed as median (25th-75th percentile) for continuous variables and as frequency (%) for categorical variables. IAH: impaired awareness of hypoglycemia.

Continued reviewer's comment 1: Does Table 2 report the Clark Survey results? Does Table 3 report the results of the Edinburgh survey. Tables need to be reconstructed and titled appropriately.

Author's response: Yes. Table 2 reports the Clarke survey results and table 3 reports Edinburgh survey results.

Change to manuscript: Table titles were changed accordingly.

2) Measures: The author states that the Clark and Edinburgh were modified. What does this mean? Again this section would benefit from greater detail. Does that mean modification was the translation into Arabic? or were questions or scoring modified? Some discussion as to whether these tools can be
used in a pediatric population is also needed.

Author's response: No. questions and scoring were not modified. Both surveys were only translated as described in Methods.

Regarding the use of these surveys in pediatric population, yes these tools were used previously in children and adolescents. E.g. Graveling et al [1] and LY TT et al [3] studies.

Change to manuscript: The word “modified” was removed.

3) Measures were self-report Clarification is needed as to if the parent or caregiver also was asked about hypoglycemia events. Where is your evidence that these surveys can be taken and interrupted appropriately by a child great than 5 years of age. Can a child greater than 5 understand/read the survey and answer appropriately?

Author's response: Yes our data were obtained by self-reporting. As described in Methods, the questionnaires were applied to participants and/or their parents. The age of 5 is the school age in Jordan. So, we believe that children at this age can speak well and they can express their feelings too. However, responses were obtained from participants themselves when they were able to do this or by getting assistance from their parents. Also, a well-trained researcher was available to explain the purpose of the study and answer any inquiry revealed by participants and/or their parents. Applying the survey to children or their parents was also performed in other studies that used the same survey. For example, the age of participants in LY TT et al study [3] was between 6 months – 19 years. However and to make our results more reliable we excluded all subjects who are < 5 years old.

Change to manuscript: no change.

4) Conclusion and discussion: Because of the lack of detail in the body and Tables presented, it is difficult to say if the conclusions drawn are correct.

Author's response: We respect the reviewer’s comment although we think that it is not accurate. We used well-validated surveys that were used previously by many researchers in children and adolescents. Results from these surveys were described well in the Results section which was supported by Tables that were modified according to the previous reviewer’s comments mentioned above. Unfortunately, the prevalence of type 1 DM in children and adolescents is not very high compared to Type 2 DM in adults. So, our sample size was only 94 out of 130 patients who receive treatment in North of Jordan. However, other similar studies (e.g. Graveling et al [1] ) have comparable sample size as our and they used the same survey to detect IAH. Therefore and compared to such studies, we believe that our conclusions are reliable and deserve acceptance for publication as this is the first report form the Middle East that reports IAH in children and adolescents with Type 1 DM.

Change to manuscript: no change.

Reviewer #2: Neil White

In this manuscript, Alkhatatbeh et al from Jordan report a low rate of Impaired Awareness of Hypoglycemia (IAH) in children and adolescents with type 1 diabetes (T1D). Their reported rate is 15.96%, lower than that reported in many other studies. Importantly, and more important than the rate of IAH, they report that IAH is associated with having reported more hypoglycemia during the
preceding 6 months. Based on what we already know about IAH (also known as hypoglycemia unawareness and as a component of hypoglycemia-associated autonomic failure [HAAF]), this is not an unexpected finding and has been reported many times. The only elements of this report that are novel are the report from a different population and the surprising conclusion that IAH was not associated with HbA1c or with the frequency of severe hypoglycemia (SH). I have problems with these latter conclusions.

My problems with some of the conclusions in this manuscript are the lack of association of IAH with HbA1c, the presence of SH during the preceding year, insulin regimen and adherence to the regimen. In all these cases, I think that the sample is too small to reliably conclude that their result are different from prior reports. In the case of HbA1c, the p-value between the Aware and the IAH group is p=0.12; with more subjects this would likely be significant and this study is underpowered to detect the difference. In the case of insulin regimen, only 6 subjects were not using Mixtard; too few subjects not using Mixtard to make any conclusions related to the insulin regimen. In the case of adherence, no definition of the categories are given and there is likely a difference between the groups if the sample size were larger; the p-value (0.06) is approaching significance. Most importantly, in the case of SH, which is an important conclusion, the number of events is small with a p-value of 0.14; again, with a larger number of events, this would likely be significant in the direction expected; IAH would be associated with more SH. To conclude the lack of an association in contrast to other studies, some determination of power for the sample size would be important. I suspect that the power to detect a difference between groups in HbA1c and SH would be low. The studies to which the authors compare their results and came to different conclusion related to duration, HbA1c and SH were much larger studies (Hoi-Hansen et al: N=372; Ly et al: N=656; Abraham et al: N=413).

Author's response: We would like to thank the reviewer for this comment but we do not agree that the low prevalence of IAH reported in our study compared to other studies is of low importance. In fact and compared to Graveling et al [1] which has similar sample size, our study has reported a lower IAH by 6%. (from 15.96% to 22.4%). We think that this finding is important and should be reported because it may reflect differences between different populations especially our finding is the first one reported from the Middle East. As well, we explained in the discussion a possible cause for the low rate of IAH in our study which was the relatively shorter duration of Type 1 DM in our participants compared to other studies. It is expected that IAH could be more frequent in patients with longer duration of DM. As the reviewer said, the association between IAH and the frequency of hypoglycemia is expected and we were able to confirm this association in our study. I.e. when hypoglycemia becomes frequent, patients may lose sensation of hypoglycemic symptoms and thus they may develop IAH. The association between IAH and HbA1c was not confirmed in all previous studies. For example, Graveling et al [1] did not show any significant association while LY TT et al [3] had reported an association between IAH and HbA1c. Similarly, the later study had also confirmed an association between IAH and frequency of severe hypoglycemia. The difference between the later study and our study was the sample size as the reviewer said. While, there was no much difference in sample size between our study and the former study. So, it seems that it is expected to get significant association between IAH and other parameters mentioned by the reviewer if we increased the sample size. Although, the calculated sample size mentioned above was relevant, we will add the small sample size compared to other studies as a limitation.

Change to manuscript: This sentence was added to the study limitations: “Although the calculated sample size appears to be relevant, the small number of participants compared to other studies [3] may not be enough to report significant associations between IAH and other expected variables including HbA1c and severe hypoglycemia”
continued reviewer comment: Secondly, in this manuscript, they have excluded subjects <5 years old who "were not mature enough to express their feeling of hypoglycemia." On one hand, this is an arbitrary age cutoff. In addition, I am not sure that all the other studies to which they compare their results used the same exclusion.

Author's response: We selected this age cutoff as it is the age at which children start their school. So, we believe that children at this age can speak well and they can express their feeling during hypoglycemia. Exclusion of subjects who are < 5 years was also added as a limitation.

Change to manuscript: This sentence was also added to limitations: “As well, the exclusion of children who are < 5 years old may also be considered as a limitation when we compare our results to other studies that they did not consider this exclusion”.

Specific reviewer 2 comments:

1. Many of the references, especially #6 and #14 in the Introduction, are certainly not the best references to cite in support of the statements to which they refer. There are much more robust references.

Author's response: Yes we agree with this.

Change to manuscript: References were changed to more robust ones.

2. They should state specifically whether the cutoffs used on the questionnaires were the same as were used in the other studies. Any differences would certainly make the comparisons weaker if not meaningless.

Author's response: We have used well-validated questionnaires without any modifications. As mentioned in Methods, cutoffs that determine the level of hypoglycemia awareness (number of R responses for Clarkes’ survey) are used exactly as previous studies. Similarly, cutoffs that determine the intensity of hypoglycemic symptoms (1-7 scale) was similar to that was used by previous studies. These cutoffs are clearly defined in Methods section.

Change to manuscript: no change.

3. On the first page of the Results section (line 25), they state that self-monitoring was done on a "daily basis". More detail about the frequency of monitoring should be given and there needs to be some analysis of hypoglycemia frequency for different monitoring frequencies. The frequency of monitoring will certainly affect the frequency of hypoglycemia reported.

Author's response: Unfortunately, we did not collect data about the number of times they monitor blood glucose every day. We asked participant if they monitor blood glucose every day, every other day, twice a week, once weekly or if they do not monitor glucose at all. All responses were that they monitor glucose daily. However we have to consider this issue for future studies.

Change to manuscript: no change.

4. The percentages reported to 2 decimal places is inappropriate (15.96, 18.01, 65.96); one decimal
place (16.0; 18.0; 66.0) is more than adequate.

Author's response: We changed these to one decimal place.

5. Last paragraph of Results (line 20): "lest" should be "least".

Author's response: corrected.

6. Were all patients on insulin from the time of diagnosis, as hopefully would be the case for T1D? If so, in Table 1, "duration of DM" and "Duration of insulin therapy" are redundant, and only one is needed.

Author's response: Yes they were. Redundancy was removed from the table.

7. Also, in Table 1, to report a p-value for the difference in age between children and adolescents is meaningless since the groups were defined by age and there would be no overlap.

Author's response: p-value for age was removed.

8. In Table 3, what is meant by "Mean Rank" in the column headers?

Author's response: Statistically when we compare 2 groups we use students’ t-test if the continuous variable is normally distributed and we use the mean to compare between the 2 groups. When the continuous variable is not normally distributed, we use a nonparametric analysis to compare between the 2 groups (a test called: Mann Whitney U test). When you perform this test it gives us a rank for each group of the 2 groups (like the mean in t-test). If the mean ranks for the 2 groups are similar, this mean there is no difference between the 2 groups. If the mean ranks are different and the P-value is significant, this means that the variable is statistically different between the 2 groups. For example hunger has a mean rank of 56.2 in children compared to 36.7 in adolescents (p<0.01). This means the intensity of hunger during hypoglycemia is much more than that in adolescents.

References: