Author’s response to reviews

Title: Association between Serum Uric Acid and Metabolic Syndrome Components in Prepubertal Obese Children (Tanner Stage I) from Nuevo León, Mexico - A Preliminary Study

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Version: 1 Date: 08 May 2017

Author’s response to reviews:

May 8, 2017

We would like to thank the editors and the two reviewers for their patience and detailed recommendations to revise the manuscript. We have taken specific steps to revise the manuscript as per their recommendations. These changes are described in blue. We also had this manuscript read by Prof. Robertino Mera, an epidemiologist, from Vanderbilt School of Medicine who helped strengthen the manuscript in terms of epidemiologic expressions.

I hope that the editors will find the revised manuscript acceptable for publication.

Chandan Prasad, PhD
Reviewer reports:

Peter Hosick, Ph.D. (Reviewer 1): In this study researchers examined the relationship between specifically pre-pubertal obesity, hyperuricemia and the Metabolic Syndrome. Authors argue that previous research in this area is confounded by separating subjects in separate categories by age rather than pubertal status. This is an interesting premise, however the data does not appear to disagree or refute with previous findings. Please see below for additional comments.

General Comments

1. References 3-11 have been used to call into question previous research in this area as well as to support the findings of the present investigation. While these studies do include pre and peri-pubertal subjects from both overweight and obese populations, if their results support your findings can you discuss more specifically how does this research extends or adds to what is currently know about hyperuricemia and obesity?

The following additional description of results in references 3-11 has been added. “While the above studies [3-11] support the conclusion that the odds ratio of having metS or one or more its components is associated with sUA, seven of the studies [3, 4, 6,7,9,10,11] include data from pre-pubertal, post-pubertal and post-pubertal children ranging in age between 4 and 18 years making it difficult to assess the role of sUA in MetS in just pre-pubertal children. The remaining two studies [5, 8] included peri-pubertal children ranging in age between 10 and 13 years.”

Specific comments

1. Page 7, line 22. What time of day were the blood draws performed?

Additional information has been introduced.

2. Page 10, line 21: Authors state that hyperuricemia increases the risk for developing MetS. This is at least misleading and likely false. The data presented does not show cause and effect. What has been shown is the odds are higher that a pre-pubertal child with hyperuricemia will also have MetS. Even in the authors discussion on purine handling (page 12, lines 3-9) it is the increased
adipose tissue that leads to increased uric acid production and not uric acid which increases adipose tissue expansion.

We agree with the reviewer. We have re-written this section so that the conclusion reflects the data.

3. Page 9, paragraph beginning on line 21: This paragraph discusses the influence that sex hormone play in uric acid regulation particularly as children go through puberty. However, this manuscript was specifically design to focus on pre-pubertal children that have immature hypothalamic-pituitary-gonadal axes and low levels of sex hormone. With the focus of this research being on pre-pubertal children this reviewer has a difficult time understanding the relevance of a discussion on the effect that sex hormones have on hyperuricemia.

The entire discussion about role of gonadal hormones in uric acid metabolism has been deleted.

4. The results found in table 3 are quite staggering. Further discussion of these finding and implications they can have on the diagnosis of MetS or if uric acid can be used a predictor of MetS in specifically pre-pubertal children would be interesting.

The entire discussion section has been written in a concise manner with a discussion relevance of our findings.

5. Table 4. This review has trouble following the information and relevancy of this table. Please include a more apt discussion of it content within the manuscript itself. If a clear designation for it cannot be supplied consider removing.

Table 4 has been deleted.
Ju-Sheng Zheng (Reviewer 2): The authors presented an interesting work on the cross-sectional correlation between serum uric acid and MetS and its components. My major concerns are the appropriate usage of epidemiologic terminology, such as prevalence, incidence, odds ratio, and reporting of the results with sufficient details, such as sample size and covariates for each analysis /model.

1. Abstract: Page 4, line 22. "Increase in each unit of sUA": please provide the exact unit for the sUA you mentioned here; "higher probability of the presence of MetS" please change the sentence to "higher odds ratio of MetS".

Changes have been made as recommended. 1 Unit of sUA refers to 1mg/dL. This has been introduced.

2. Abstract: Page 5, line 5 conclusion. Please change "hyperuricemia" to "uric acid". Hyperuricemia is a binary status, which you did not examine in the paper.

Changes have been made as recommended.

3. Background: Page 5, line 17. Please change "incidence of MetS" to "prevalence of metabolic syndrome (MetS)", and then use the abbreviation MetS next time you mentioned metabolic syndrome.

Changes have been made as recommended.

4. Page 7, line 16-17. Please provide a reference for the definition of Metabolic syndrome

Reference has been added and MetS fully defined as per IDF.
5. Page 9, line 2. Please change "odd-ratio" to "odds ratio".

Changes have been made as recommended.

6. Page 10, line 6. "each unit of sUA", unit of the sUA should be given here.

Unit of the sUA has been introduced.

7. Page 10, line 7-8. "increase in sUA aslo raise the probability": this is the observational study, you could not use word like "increase" or "raise", which imply causality. Please change to "higher in sUA is associated with higher odds ratio of high waist circ., high TG and low HDLc"

Agree. Changes have been made as recommended.

8. Page 10, line 17. Change "incidence" to "prevalence"; line 20,21: change "hyperuricemia" to "sUA".

Changes have been made as recommended.

9. Page 12, before conclusion section. Please add a paragraph discussing the limitation of the study, which a common rule in reporting the results from epidemiological studies.

A paragraph discussing the limitation of the study has been added.

10. Page 12, line 21. please change "hyperuricemia" to "sUA".

Changes have been made as recommended.
11. Table 3: please change "95% IC" to "95% CI" in the table. Please also provide the unit for the variables listed in the table, including age, uric acid and BMI. For gender, please be clear it is women compared with men or men compared with women in the model. In addition, please change "Waist circumference" to "Abdominal obesity (waist circumference>90th percentile)", and change "Triglyceride" to "High triglyceride (≥150 mg/dL)", and change "HDL-C" to "low HDL-C (<40 mg/dL)". Please do not use Model 1 Model 2 Model 3 or Model 4, which would confuse the readers. Replace them directly with the sample size of the analysis, such as Metabolic syndrome (n=59).

12. Please check across the manuscript that describe abbreviation when first mentioned and then use the abbreviation thereafter, such as MetS and sUA. Please do not mix abbreviation and full name across the manuscript.

Changes have been made as recommended.

13. Please also consult with an epidemiologist for appropriate usage of epidemiological words.

We have consulted with Prof. Robertino Mera MD, PhD, an expert in epidemiology from Vanderbilt School of Medicine. He has examined this manuscript and his recommendations have been incorporated. Please see acknowledgement section above the references.