Author's response to reviews

Title: Ethnicity and elevated liver transaminases among newly diagnosed children with type 2 diabetes

Authors:

Omar D Hudon (ohudson@yahoo.com)
Martha Nunez (marthanu@gmail.com)
Gabriel Q Shaibi (gabriel.shaibi@asu.edu)

Version: 2 Date: 9 October 2012

Author's response to reviews: see over
October 8th, 2012

Emily Crow, PhD
Executive Editor
BMC-Pediatrics

Dear Dr. Crow,

We appreciate the opportunity to revise our manuscript, *Ethnicity and elevated liver transaminases among newly diagnosed children with type 2 diabetes*, and respond to the reviewers’ comments / suggestions. Please extend our gratitude to the reviewers, as we believe their efforts have contributed to a greatly improved manuscript. Below you will find point-by-point responses to each of these comments and revisions are identified in the marked version of the revised manuscript. In addition to these comments we have revised the statistical approach and edited the manuscript for language.

Sincerely,

Gabriel Q. Shaibi, PhD
Assistant Professor and Southwest Borderlands Scholar
Arizona State University

Phone: 602-496-0909, email: Gabriel.Shaibi@asu.edu
500 N 3rd St Phoenix AZ 85004

Gabriel Q. Shaibi, PhD
Assistant Professor and Southwest Borderlands Scholar
Arizona State University

Director of Research
Division of Endocrinology and Diabetes
Phoenix Children’s Hospital
REVIEWER 1

AUTHOR RESPONSE: We thank the reviewer for this suggestion and have incorporated these recent papers throughout the revised discussion.

REVIEWER 2
REVIEWER COMMENT: The authors investigated the association of ethnicity and transaminases levels with NAFLD risk in children affected by T2D. Although the aim of the study is critical for the early diagnosis of children with NAFLD, data reported are insufficient to solve this question. Where is the novelty of this manuscript? The study appears to be preliminary.

AUTHOR RESPONSE: We appreciate the reviewer’s comments and agree that these data alone are insufficient to solve the issue of early diagnosis of NAFLD in youth with T2D. However, the novelty of this investigation lies in it being the first to examine potential ethnic differences in NAFLD risk in youth with T2D. We acknowledge the limitations of using transaminase levels to assess NAFLD risk but we hope that our findings will serve as a springboard for future prospective studies that include more precise and proximal measures of hepatic health in larger samples. We also agree that these findings are preliminary rather than confirmatory and have added this terminology throughout the revised manuscript to temper any conclusive statements in regards to NAFLD in our sample.

REVIEWER COMMENT: There are no data about the glucose and insulin levels of patients. These measures are relevant for T2D diagnosis, but also to make a correlation with ethnicity and NAFLD.

AUTHOR RESPONSE: We agree that glucose and insulin data would aid in interpreting the degree of hyperglycemia and insulin resistance and whether these factors contribute to underlying mechanisms of the ethnic differences in NAFLD risk. Unfortunately, these data are not available. As discussed in our manuscript, it is well established that Hispanic and African-American youth are more insulin resistant than their Caucasian peers. However, insulin resistance alone does not explain ethnic difference in NAFLD risk as Hispanics are at highest risk and African-Americans appear to be at lowest risk even after controlling for insulin sensitivity (See JD Browning et al Hepatology. 2004 Dec;40(6):1387-95). Therefore, mechanisms other than insulin resistance may be contributing to the observed disparities. Nevertheless, we have added the lack of glucose and insulin measures as a limitation in the revised manuscript.

REVIEWER COMMENT: NAFLD risk is evaluated only by transaminases levels. It is a strong limitation to the study, because NAFLD diagnosis requires at least ultrasound to evaluate steatosis, and eventually liver biopsy to evaluate damage severity (as also stated by the authors in discussion).
AUTHOR RESPONSE: We agree that relying on transaminases is a key limitation of the study and also agree that more sophisticated imaging studies are necessary to quantify liver fat content, NAFLD risk, and ultimately evaluate steatosis. Like most pediatric liver centers in the US, liver biopsies are not routinely done at our institution unless a high suspicion of NASH is present. Even then, it is likely that this procedure would not be performed upon diagnosis of diabetes but rather after initiation of therapeutic intervention and lifestyle counseling has been attempted and failed to significantly lower transaminases. The reviewer’s point about using ultrasound or other imaging techniques to better evaluate steatosis is well taken and we have added some discussion related to imaging to the limitations section in the revised manuscript.

REVIEWER COMMENT: Statistical approach is poor. Univariate and multivariate analysis should be performed.

AUTHOR RESPONSE: We re-analyzed our data using general linear modeling. This approach did not impact the interpretation of our results for the effect of ethnicity on transaminase levels ($R^2 = 0.20$, $F = 6.768$, $P = 0.002$ for ALT and $R^2 = 0.24$, $F = 8.804$, $P < 0.001$ for AST). Furthermore, when we included BMI and HbA1c as additional independent variables in this model, the overall effect of ethnicity on transaminase levels was attenuated but remained significant ($F = 3.487$, $P = 0.039$ for logALT and $F = 3.557$, $P$