Reviewer's report

Title: Plasma branched-chain and aromatic amino acid concentration after ingestion of an urban or rural diet in rural Mexican women.

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Reviewer: SEAN ADAMS

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Summary:
Lopez et al. describe post-prandial differences in selected plasma essential and non-essential amino acids in rural Mexican women fed either a typical Mexican “rural” diet versus an “urban” diet. In a crossover design, Lopez et al. reported significantly higher post-prandial AUC for isoleucine, valine, total BCAA, tyrosine, and proline after consumption of the “urban” diet. The results are not unexpected, but they do provide a clear example of how mixed meals of different composition can impact blood amino acid patterns in humans. Such examples may prove useful in the literature in terms of design of diets that alter amino acids for research purposes, and thus the paper may be better suited for a modest nutrition-specialty journal. A major flaw that requires attention for any revision and for any journal format is the assertion that BCAA etc. patterns acutely following each meal somehow promotes dysmetabolic phenotypes, which is far too speculative and does not have a solid foundation in the literature. The urban vs. rural diets have a huge variety of differences beyond protein, and physical activity is also a factor in driving insulin resistance and obesity outcomes. Changes in BCAA etc. seem to reflect, not cause insulin resistance.

Comments:
1. Lines 85-86: Please report BMI; in the statistics, presumably a paired t-test was employed (this is not clear from the write up)
2. Was there any attempt to determine historical dietary data in these women? Also, in the Introduction there is an assertion that a diet more rich in protein or certain proteins would lead to the associations of BCAA, Phe, and Tyr and insulin resistance; yet, the latter literature was conducted during the overnight-fasted period and so it is not clear how that would impact overnight-fasted amino acid patterns.
3. It is not clear how the test meal (i.e., after time 0) was administered. Table 1 appears to provide the total daily composition of urban or rural diets, but the plasma measurements occurred presumably after single meal ~ 7am. Was the test meal administered and consistent among participants? What was the composition of the meal before the post-prandial measurements?
4. Was glucose or insulin measured? These measurements would provide context for many of the author’s conclusions.
5. There is very little discussion about the other macronutrient differences between the “rural” and “urban” diet. In addition to differences in protein, there are stark differences in carbohydrates, lipids and dietary fiber; all of which will impact insulin and energy dynamics. This is a major confounder in terms of interpretations and must be fully acknowledged.

6. The authors conclude that the elevations in post-prandial plasma BCAA concentrations seen after consumption of an “urban” diet may increase the risk of obesity and diabetes. Contrary to this conclusion, there is considerable evidence that diets high in leucine improve insulin sensitivity. There is, actually, a far stronger case that elevations in BCAA, Phe, Tyr in the insulin resistant state are a result, not a cause of the resistance (see, e.g., S.H. Adams, Advances in Nutrition). Additional discussion about the counter evidence is needed.

7. The data presented herein is really insufficient (i.e., a single post-prandial meal response) to draw such conclusive statements regarding obesity and diabetes risk. Although the reviewer agrees that the risk of obesity and diabetes is greater in a Mexican “urban” environment compared to a “rural” environment, a single post-prandial BCAA response is not enough evidence to justify the final sentence of the manuscript (lines 183 through 185, and last lines in the Abstract), or the bulk of L. 164-179. This reviewer suggests an alternative conclusion that addresses the limitation in their study and a statement regarding the need for future controlled longitudinal studies.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No conflicts