RESPONSE TO REVIEWERS

Reviewer 1:

1. The introduction to Biogenic amines reference only one review which clearly points out the uncertainty of the TMAO story. This would be better summarized. It is a 2016 article and allows the authors to detail advances in Knowledge since then.

   We appreciate the reviewer's comments. We have added several recently published journals (Kanitsoraphan et al, 2018, Schugar et al, 2017, and Barrea et al, 2018) to summarize recent data on TMAO and its pathways. We use these papers to provide some recent updates on the role of TMAO in metabolic diseases. However, we would like to point out that the role of the TMAO story still remains unresolved despite this updated research, which is noted in these recently published journals.

2. For example Ref 8 which is wrongly reported shows that CRP IL6 and TNFa are lower in subjects whose level is more than 310mg/dl. This might be in keeping with the new studies which suggest that high fat diet might not be that bad in atherosclerotic terms.(PURE study for example).

   We have rechecked this reference (Detopolou et al 2008) and we believe that we've correctly reported that those who consumer >310 mg/dl of choline had decreased inflammatory biomarkers.

3. Ref 9 does not examine supplementation. The sentence "Other studies have shown it has a role in CVD" should be referenced critically. Since betaine is a metabolite of choline metabolism is it not a given that there an inverse relationship between Betaine and Choline? Insulin resistance in mice and choline deficient diet interesting Ref 10 2006 but what about Gao R et al nutrition 2017 showing that in humans a high choline diet is associated with insulin sensitivity? Would the article by Roe AJ et al 2017 Am J Clin Nutr and Svinger GF 2016 Clin Chem 2016 not be worth a mention?

   Thank you for these suggestions. We have expanded on Reference 9 to further Support its inclusion in our paper. Reference 9 will be our major other study that will be referenced critically. Gao 2017 and Roe 2017 have been included to further substantiate choline's association with insulin sensitivity.

4. The section on amino acids might also benefit from some more up to date references. A suggestion Wang S et al Clin Chim Acta 2018 tHart lM J Clin Endocrinol Metab 2018 Paprott R et al J Diab Res 2018 Choi YS et al 2018etabolic Syndr rel disorders, Further articles worth considering Ganz T Diabetes Metabolism Res Rev 2017 Deveaux AJ J Nutr 2016

   Thank you for these suggestions. tHart and Wang S et al have been added to the BCAA section and provide more recent evidence that isoleucine, valine, and leucine are increased in a diabetic setting. Wang has also been referenced in the section on Alanine, Glutamine, and Glutamate in order to further support the association between the glutamine/glutamate ratio and hyperglycemia. Ganz and Deveaux were incorporated into the section on arginine as they provide further evidence that arginine may mitigate endothelial dysfunction and could be

decreased in T2DM, despite being increased in obesity. We didn't find that Paprott 2018 directly pertained to the metabolites being discussed in this review

5. The conclusion is reasonable but perhaps more in the text about metabolomics and what they have so far shown would be helpful to support the conclusion. In conclusion a very interesting article but the reader is too often left with the idea that nothing much has changed in our knowledge in the last 10 years.

   This is a valid point. We incorporated several sentences on choline and TMAO. Additionally, a recent study regarding utilization of metabolomics to Predict onset of MetS was added to give an example of future directions of metabolomics. However, because the review is so broad, more details regarding metabolomics were not added. Though the reviewer is reasonable to ask for a more straightforward conclusion, there is still ongoing research and unexplored areas in the metabolomics of MetS. The conclusion we are making is that this is a critical area that should be explored in more depth so that we can identify biomarkers that will identify MetS or its proinflammatory state .

Reviewer 2:

1. The proposed mini-review by Lent-Schochet et al. entitled "Exploratory metabolomics of metabolic syndrome: A status report" gives a snap-shot of the current knowledge of the role of various metabolites in the development, diagnosis and treatment of metabolic syndrome as well as of their potential to interfere with inflammatory signaling pathways. The review starts with an introduction section defining the pathophysiology of the metabolic syndrome and related pathological conditions, followed by sections for specific biogenic amines, amino acids, branched chain amino acids, and aromatic amines. Based on the provided information, the authors of the manuscript conclude that the analysis of particular metabolites may help to better characterize metabolic syndrome and its pathogenesis. This review follows straight logic and is written in a clear language. Main weakness of the present work in my opinion as a peer reviewer is the lack of specific details when previous studies are described. Information about what specific dose and time period of stimulation, way of administration type of solvent used, concentrations in circulation, etc. is important to be provided when discussing supplementation with a specific agent.

   We thank the reviewer for these insights. However, we disagree with the reviewer's comment. The purpose of this paper was to provide a translational perspective on the applicability of metabolomics in Metabolic Syndrome. The paper was not written from as a methodological stand point since there are numerous publications on methodology, and therefore, we believe that details related to the methodologies of the cited papers to be unnecessary. We have included the time period of treatments and dosages of supplements used in various cited research studies, when available. We hope this satisfies the reviewers request.

2. Also, when describing a change of particular analyte, the magnitude of change also needs to be given.

a. Few examples of such lack of information include: p. 3 ("LC supplementation in humans…", "…positively correlated…", "…inversely to the important anti-inflammatory adipokine…"),

Thank you for this comment. We have added the dosage of LC used as well as the p values for the explicit results mentioned in the Lee et al, 2015 article. To our knowledge, the authors of this article did not give explicit magnitudes of change. We have added that there was a 2.5-fold increase in the median values of LC in nascent MetS based on the Lent-Schochet et al, 2018 article.

b. p. 5 ("…glutamate levels were down-regulated compared to controls"),

Thank you for this insight. We have added to the text that glutamate levels were downregulated by a magnitude of 0.8-fold peak integral change in PCOS/controls in the RoyChoudhury et al, 2016 article.

c. p. 6 ("…supplementation of L-arginine…", "…L-arginine treatment improves…", "…decreases pro-inflammatory cytokines…"),

We thank the reviewer for this comment. Additional details have been added to the text. Specifically, we added the p values and magnitudes of change for factors mentioned in the text for the Korish 2010 article. We also included dosage and length of treatment to the text. Our apologies, the portion discussing "decreased pro-inflammatory cytokines" was removed from the text, as this was cited incorrectly.

d. p. 7 ("…histidine supplementation…", "…decreased inflammation and oxidative stress…"), etc.

Thank you for this comment. The information was updated to accurately reflect the cited data. We have now included the percent change for all factors mentioned in the article by Feng et al 2013.

3. Minor comments: - p. 7, Histidine section, "…after bariatric surgery": Please be specific about the type of bariatric surgery.

Thank you for your comments. The requested information is now included in the text.

4. p. 7, Methionine/Cysteine section, "Adams et al.": Is this the same reference # 44 (Adams as a single author) or a different reference?

Thank you for bringing this to our attention. The reference and author's name has been updated appropriately.

5. p. 8, Lysine section: Reference for Ilda et al. (reference # 50) is missing in the text.

Thank you for bringing this to our attention. The reference for #50 (Iida et al) has been added to the text.