Author's response to reviews

Title: Metabolic Syndrome: Definitions and Controversies

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Author's response to reviews: see over
We would like to thank the Editor and the reviewers for their thoughtful evaluation of our manuscript and for the most welcome comments/suggestions. Accordingly, we have now revised our manuscript to reflect these comments. In the revised Text, all inserted changes/ modifications/insertions are marked in bold characters.

Reviewer 1

1. The authors should not hesitate to express their personal opinion on which definition of the metabolic syndrome they think is suited best for practical use in clinical medicine.

According the Reviewer’s suggestion we have now expressed our personal opinion on which definition of the MetS is considered most suitable for clinical practice, in the conclusion section (Page 17, Line 4-10)

2. A schematic image of all factors implicated in the pathophysiology of the metabolic syndrome would be helpful

Following the Reviewer’s suggestion we have now created a schematic image of all factors implicated in the pathophysiology of the MetS including the traditionally accepted and others that could also be implicated for which there is strong experimental and clinical evidence (see Figure 1).

3. The authors could elaborate a little more on the (potential) role of visfatin.

According to the Reviewer’ s suggestion we have now expanded further on the potential role of visfatin in the pathogenesis of MetS (Page 10, Line 24-28)

4. Page 3, line 18: “adulthood“ should be replaced by “young adulthood” or “adolescence”.

We have now replaced it as the Reviewer suggested.

5. The term “obesity“ should be used exclusively throughout the manuscript (not “adiposity“)

We have also replaced this term throughout the manuscript according to the Reviewer’s suggestion.

Reviewer 2
1. Whereas the essence of MetS needed to be described in greater detail along with the components’ role in conferring the risk for diabetes and cardiovascular disease, the various definitions, how they evolved and the resulting differences in the prevalence of and controversies around MetS seem to have been overemphasized.

Although this was one of the tasks that we were asked to address in the design of the paper following the Reviewer’s suggestion we have now reduced substantially this part of the manuscript.

2. Search for unified criteria applicable to all ethnicities is in vain and should not be stressed. As a consensus definition (listed in Table 1) agreed, abdominal obesity is population-specific. And even in Westerners, a difference of 14 cm in current abdominal obesity criteria across genders may be debatable, leading to dilution of MetS in women or a failure of encompassing men with MetS at increased cardiometabolic risk.

We have now discussed the difficulties in establishing unified criteria applicable to all ethnicities in Page 5, Lines 1-15.

3. The essence of MetS is wide waist circumference and elevated triglycerides; HDL-cholesterol varies depending on the associated pro-inflammatory state that may induce HDL dysfunction which further promotes HDL dysfunction. Hardly any dwelling on hypertriglyceridemia can be noted.

We have now briefly discussed the role of hypertriglyceridemia in the pathogenesis of the MetS, according to the Reviewer’s suggestion (Page 10, Line 29 – Page 11, Line 4).

4. Instead, several topics marginally relevant to MetS are discussed at length (pp. 9-12). These may well be omitted as may some one-third of the references.

According to the Reviewer’s suggestion we have now omitted several topics regarding the conditions contributing to the pathogenesis of MetS along with the relevant references.

5. The major shortcoming of current MetS definitions is that the pro-inflammatory state which should be an essential component and determinant of future cardiometabolic risk is left out of definitions on the –albeit justified- ground of lack of a unique biomarker. The greatest novel knowledge on MetS (and cardiometabolic risk) developed in the past decade has been the important role of pro-inflammatory state (reflected by hypertriglyceridemia) and for which various individual markers (CRP, GGT, uric acid, apoB, apoE, fibrinogen, SHBG etc.) have been documented, and the associated dysfunction of apoA-I and HDL (reviewed in Ref. 17, below). Most of this knowledge is derived from over a
dozen papers of the Turkish Adult Risk Factor study (a selection listed below) which have been totally overlooked.

We have now included in the manuscript factors others than those incorporated in the existing definitions of the MetS, that are essential components and determinant of future cardiometabolic risk (Page 9, Lines 17 – 29) having cited the relevant references.

6. Gender is a modulator of the pro-inflammatory state and the associated future cardiometabolic risk. This needs to be described.

We have briefly described the possible role of gender as a modulator of the pro-inflammatory state as suggested (Page 9, Line 14-16)

Editor’s comments:

1. Abstract: The abstract is a vital part of the article, to encourage browsing readers to download the full text, so must be engaging and informative. The current abstract is well written, however it is currently too detailed and may not immediately engage the target audience for this article. To enhance the impact of the abstract, you should aim give a short and succinct overview of the key points covered in the review ensuring that you keep this summary to a maximum of 170 words in length. I have suggested where you can cut the abstract to fit the word limit while retaining the key points of your review.

According to Editor’s suggestion, we have substantially reduced the length of the abstract in order to fit the required word limit (<170 words), while retaining the key points of the review.

2. Introduction: Please ensure that the introduction section addresses the points raised in the marked up copy of this manuscript. We particularly encourage you to ensure that this section highlights the pediatric metabolic syndrome element of this review article, as this will increase both the breadth and potential clinical impact of this piece.

According to the Editor’s suggestion, in this section we have addressed the points raised in the marked up copy of this manuscript and we highlighted the pediatric metabolic syndrome element of our review (Page 3, Line 10-22).

3. Main text – “Currently used criteria to define MetS”:
(a) Referee 2 has made a number of suggestions regarding this section of the manuscript. While the depth and flow of this portion of the manuscript are generally very good, this section would
benefit from some expansion to incorporate Referee 2’s point regarding the potential role of the pro-inflammatory state as an essential component of MetS and a determinant of future cardiometabolic risk. Adding this element to your discussion would both improve the scope of the article and further add to discussion of the controversies currently surrounding the definition of MetS. However, this is a discretionary revision, therefore we leave it to your judgment as to whether, and how many, of referee 2’s suggested papers you choose to cite in this section.

Please see replies to Reviewer 2.

(b) We also suggest repositioning a paragraph from the “Morbidities related to MetS” section to the end of the “Currently used criteria to define MetS” section. This paragraph naturally fits within the context of the discussion about the various definitions of MetS and provides a concise link to section concerning the epidemiology of MetS according to these various definitions.

We have now moved this paragraph as suggested by the Editor.

4. Main text ? Epidemiology of MetS according to the various definitions used?:
(a) Please make a statement following citation of Reference 13 that despite the differing prevalence estimates observed by the variety of definitions used to characterize MetS, they all add up to a shocking picture of a vast proportion of the population at high risk of developing CHD etc. Please ensure that you then lead into the rest of this section by mentioning the main criteria that show interesting trends, for example age and BMI.

We have made this statement following citation of Ref 14 (final revised version) (Page 6, Lines 6-9) as suggested by the Editor.

(b) In this section you briefly discuss the increase in the prevalence of MetS within developing countries, similar to western countries. This is a very interesting point, and would benefit from further discussion as to why this may be happening. We are not suggesting an in depth analysis of this issue, but we briefly highlighting this point further would increase the value of this review from a developing world point of view.

According to the Editor’s suggestion, we have further discussed the factors contributing to the increase in the prevalence of MetS within developing countries. Page 7, Lines 3-11.

(c) Please also ensure you add a sentence summing up the key points of this paragraph and leading into the following section discussing the variety of morbidities related to MetS. For example: “Thus the importance of identifying markers for MetS to supplement age- and obesity-related measures cannot be overstated. Understanding how to use definition criteria in clinical settings will aid physicians in treating the right cohort of at-risk patients.”
We add a sentence summing up the key points of this paragraph and leading to the following section, according to the Editor’s suggestion Page 7, Lines 14-17.

5. Main text ? Morbidities related to MetS?:
(a) Referee 2 has advised that your review article would benefit from further discussion on the components that make up MetS, with a specific focus on their role in conferring risk for diabetes and cardiovascular disease in affected patients, along with a reduced focus on the other aspects of your review.

According to the Reviewer’s suggestion we have expanded our discussion on the established components that make up MetS and their role in conferring risk for diabetes and CVD (Page 7, Lines 21-28).

(b) Removing sections of your review would not benefit this manuscript in our opinion, therefore we do not believe this to be a necessary revision to undertake. However, providing a summary for this section on MetS morbidities, including discussion on whether it is possible to use MetS status to guide treatment for cardiovascular disease, would both enhance the potential clinical impact of this manuscript and satisfy referee 2? s requested revision. Please also ensure that your summary gets the readers ready to think about what will be covered next in the review, what other co-morbidities need to be kept in mind that contribute to MetS status (that is, if not full blown DMT2, is IR also important to consider)?

We have made an attempt to exclude elements of the discussion that were not regarded crucial to the terms and conditions discussed without influencing the main flow of the manuscript.

6. Main text ? Conditions contributing to the pathogenesis of MetS?:
(a) This section is currently very long and would substantially benefit from breaking up the text with relevant subheadings. Not only would this increase the readability of this section, but would also provide pointers for browsing readers as to what the key conditions are without needing to read the whole section.

We have now divided the text into relevant subheadings, according to the Editor’s suggestion.

(b) Referee 2 notes in their review that your manuscript does not currently give a detailed appraisal of the role hypertriglyceridemia may play in the pathogenesis of MetS. We believe that formulating an in-depth discussion of hypertriglyceridemia?s role in MetS in this section of your review would both satisfy referee 2? s concerns, and significantly enhance the scope of this review- therefore we strongly encourage you to revise your manuscript to cover this point.
We have presented an appraisal of the role hypertriglyceridemia may play in the pathogenesis of MetS as the Editor suggested. Page 10, Line 29- Page 11, Line 4).

(c) Referee 1 suggests that your manuscript would benefit from further elaboration on the potential role of Visfatin in the pathogenesis of MetS. This may be taken as a discretionary revision as it may be considered out of scope for this review article, however further discussion of this point would increase the clinical utility of this article for our target audience.

According to the Referee’s suggestion we have elaborated a little more on the potential role of visfatin in the pathogenesis of Mets (Page 10, Line 24-28). See also reply to Reviewer 1.

(d) Please summarise the take home message for this long section of the manuscript for our readers. What are the important points for the readers to take away from this discussion? Please also ensure that you insert a sentence linking this section with the forthcoming section the Pediatric Metabolic Syndrome? i.e. children with MetS have got Pediatric MetS? a different class of MetS altogether.

We have now summarised the take home messages for this section and linked them with the forthcoming section in Page 13, Lines 15-21, according to the Editor’s suggestion.

8. Main text “Is the Pediatric Metabolic Syndrome True or Myth? A Developmental Perspective”:
(a) In the section subheaded ?MetS Consistency in Adolescence? please introduce within the text that your group studies this facet of MetS too. Please also revise the text so as to clarify whether the studies mentioned in this section of the review were undertaken solely by your group or not.

We have now introduced, as suggested by the Editor, that our group studies this too and revised the text appropriately. Page 15, Lines 23-26.

9. Conclusions:
(a) Please expand your concluding remarks section. This should not only summarize the research described in the review but also provide a discussion of future directions for the field. For example - What barriers are there to progress that must be overcome? When are the next set of clinical data going to be made available? What future directions could research take in light of this need for a uniform criteria of MetS?, How could future research potentially shape clinical practice/management of this condition?
We have now expanded our concluding remarks section, discussing future directions for the field as suggested by the Editor (Page 16, Line 22- Page 17, Line 13).

(b) Referee 1 has suggested that the authors may wish to express an opinion on which definition of the metabolic syndrome they believe is best suited for practical use in clinical medicine. This can be considered a discretionary revision, however if added to the text this opinion may help stimulate debate amongst our readers within the clinical field.

We have expressed our opinion on which definition is more suitable for practical use (Page 17, Line 4-10). See also relevant reply to Reviewer 1.

10. Figures:
(a) Referee 1 believes that your review would be suitably enhanced by providing a schematic image of all the factors implicated in the pathophysiology of the metabolic syndrome. One suggestion for this schematic may be to present these associated factors in the form of a flow listing their potential role in the pathophysiology of MetS and potential interactions with one another.

We believe this figure would help our non-specialist readers understand the topic without disturbing the flow of the article for expert readers. I have marked up on the text where I think this figure may be called out to best suit the manuscript (in the section titled “Conditions contributing to the pathogenesis of MetS”).

Thank you for your helpful suggestion. We have now provided a schematic image (Figure 1) of all the factors implicated in the pathophysiology of the MetS and their potential interactions. See also reply to Reviewer 1.