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Indicators of metabolic syndrome in normotensive normoglycemic asthmatic patients

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1st editorial decision
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Dear Prof Lutfi,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below. The editorial board specifically would like you to pay particular attention to the comments of reviewer 1, who is an expert in the field and who has raised some points that the editorial team fully endorses.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript.Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Jul 17, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This study evaluates the indicators of metabolic syndrome in normotensive normoglycemic asthmatic patients. As compared with non-asthmatics, patients with asthma have higher waist circumference, triglyceride levels and lower insulin sensitivity index. These finding suggest association of metabolic syndrome /pre-diabetes with asthma. In general, the study appears to be carefully conducted and offers new data and supports the role of multimorbidity /metabolic dysfunction/ systemic inflammation already in early phases of asthma. However, there remains room for improvement.

Major:
1. The asthma population was limited to otherwise healthy, non-smoking patients of 20-40 years of age. Given the study question and hypothesis, this is acceptable. However, given the reality in adult asthma clinic, often patients have smoking history, they are older, have comorbidities (diabetes, depression, obesity, hypertension, cardiac etc). Recently, specific obesity-related phenotypes with diabetes, depression etc have been described (see e.g. Ilmarinen P, et al. JACI In Practice 2017), as well as multimorbidity and systemic inflammation (that is usually related to metabolic syndrome, diabetes, etc) (see e.g. Ilmarinen P, et al. Eur Respir J 2016). This aspect is not well discussed even though it appears to be a direct continuum to what is found in the current study). Instead I consider the discussion on the pathogenetic similarities between BA and hypertension out of place and it could be mostly removed. Furthermore, I do not agree with the conclusion that SABA/LABA use would explain 10 mmHg difference in blood pressure. It can lower blood pressure in acute situations but there is no evidence for such long-term effect (if there would be, it would be used as blood pressure lowering drug!). The focus of the current paper is on metabolic disorder and insulin resistance, not so much blood pressure.
2. Patient characterization is not good enough (Table 1): ICS use? LABA? OCS? previous smoking? Asthma history? Asthma-onset age? ACT? Given that the lung function of asthmatic patients was clearly lower than those of controls, it appears that they are on insufficient therapy. As one speculates the role of steroids in obesity and insulin sensitivity, more detailed characterization of therapy or its absence is necessary. The proportion of IR patients is higher on those with ICS+LABA, but the IR level is still high on SABA only group (Fig 3). What is off-treatment asthmatic patients? Not even SABA? Why they are off-treatment. N-values in the groups?
3. Given that this study evaluates relatively healthy persons with 20-40 years of age, 61% of them show insulin resistence. This sounds very high percentage. Is that correct in general population?
4. Results section: the authors much repeat the results on the markers. The values can be found in the tables, it is not necessary to repeat all in the results text.

Minor:
1. Please, give the proportions of patients with IR in tables also
2. Figures need n-values for all groups.

3. Give lung function + demographic data for different therapy groups (not treated, SABa-only, ICS-LABA) e.g. in supplement
4. Define the ACT cutpoint for uncontrolled asthma.
5. Abstract: results, please state what the numbers in parentheses mean. IQR? 95% CI?
6. How was asthma diagnosed?

Author's rebuttal

The editor
Thank you for the valuable comments from the reviewer. Below are point to point response of the authors to the reviewer's comments:

Major:
Reviewer comment
1. The asthma population was limited to otherwise healthy, non-smoking patients of 20-40 years of age. Given the study question and hypothesis, this is acceptable. However, given the reality in adult asthma clinic, often patients have smoking history, they are older, have comorbidities (diabetes, depression, obesity, hypertension, cardiac etc). Recently, specific obesity-related phenotypes with diabetes, depression etc have been described (see e.g. Ilmarinen P, et al. JACI In Practice 2017), as well as multimorbidity and systemic inflammation (that is usually related to metabolic syndrome, diabetes, etc) (see e.g. Ilmarinen P, et al. Eur Respir J 2016). This aspect is not well discussed even though it appears to be a direct continuum to what is found in the current study). Instead I consider the discussion on the pathogenetic similarities between BA and hypertension out of place and it could be mostly removed. Furthermore, I do not agree with the conclusion that SABA/LABA use would explain 10 mmHg difference in blood pressure. It can lower blood pressure in acute situations but there is no evidence for such long-term effect (if there would be, it would be used as blood pressure lowering drug!). The focus of the current paper is on metabolic disorder and insulin resistance, not so much blood pressure.

Authors response

1. Yes, we do agree. The asthmatic patients examined in the present study were limited to healthy, 20-40 years of age, non-smokers so as to control for possible risk factors of hypertension and insulin resistance. The drawback of these adjustments in the studied groups was raised in study limitations and we recommend to consider the modulatory effects of smoking, age and comorbidities related to obesity in future studies. Please, see the track changes in the first paragraph under the subtitle **study limitations**.
2. The authors think that it is necessary to mention the pathogenetic similarities between BA and HTN because when only normotensive asthmatic patients were included the present study, their blood pressures were proved to be less than the control group. It can be hypothesized that if we control for the common etiological mechanisms of BA and HTN, asthmatic patients are likely to have lower blood pressure than the controls. This is important because some people may think that hypertension associated with BA may extend to the normal physiological range of blood pressure.
3. We do agree that beta agonist therapy would **not** explain as much as 10 mmHg difference in blood pressure between asthmatic and the control group, but it contributes to this difference. During data collection, we did not exclude patients with a recent dose of beta agonist and consequently these patients may still be under the short effects of beta agonist therapy. The authors added few sentences to clarify this point. Please, see the track changes in the last paragraph under the subtitle **blood pressure**.

4. The authors would like to stress that the aim of the present study was to evaluate **all components** of MS in patients with BA, including blood pressure. Theoretical speaking and based on the pathogenetic similarities between BA and HTN as stated earlier, one may think that blood pressure is likely to be higher in asthmatic than non-asthmatic even within normal physiological range of blood pressure. However, the present results showed the reverse.

Reviewer comment

2. Patient characterization is not good enough (Table 1): ICS use? LABA? OCS? previous smoking? Asthma history? Asthma-onset age? ACT? Given that the lung function of asthmatic patients was clearly lower than those of controls, it appears that they are on insufficient therapy. As one speculates the role of steroids in obesity and insulin sensitivity, more detailed characterization of therapy or its absence is necessary. The proportion of IR patients is higher on those with ICS+LABA, but the IR level is still high on SABA only group (Fig 3). What is off-treatment asthmatic patients? Not even SABA? Why they are off-treatment. N-values in the groups?

Authors response

1. Table 1 characterized all studied groups and may be difficult to add features related to BA to it. A new table showing the characteristics of the studied asthmatic patients was added (please see table 2). The questionnaire we used for data collection contained no much details about the drugs used e.g. short or long acting. Due to many reasons like financial issues and poor education, most of the studied patient were not following physician instructions. Being from poor developing country, the patients were taking the cheapest drugs they can afford, mostly short acting inhalers. Unfortunately, most of the drugs actually taken by the patient were not following NAEPP. Twenty patients were not taking any asthma medications because they claimed that they are symptoms free. No significant variations in types of beta-agonist/steroid therapy were observed between the patients we studied. Because of these reasons and to facilitate statistical analysis and adjustment, we used the simple classification of drugs in table 2.
2. We would like to stress that the aim of the study was to evaluate indicators of MS in patients with BA regardless of intensity of treatment. The increased intensity of treatment is offered to patients with severe BA, which put patients on high stress. Physical and psychological stress associated with BA, especially in patients with repeated attacks, increases risk of IR probably more than BA medications which are mostly inhalational. Please, see Borsi SH, et al. The effects of inhaled corticosteroid on insulin sensitivity in asthmatic patients. Monaldi Arch Chest Dis. 2018;88(1):892. Published 2018 Feb 19. doi:10.4081/monaldi.2018.892. This gives another explanation why we did not elaborate on the details of asthma medications during data collection and put the classification mentioned in table 2.

Reviewer comment

3. Given that this study evaluates relatively healthy persons with 20-40 years of age, 61% of them show insulin resistence. This sounds very high percentage. Is that correct in general population?

Authors response

Yes, this value is comparable with some studies. For example, using the QUICKI and a cut-off point of < 0.357 in a Saudi study, 64.6% of the studied population were considered to have high insulin resistance. Please, see Bahijri SM, et al. Estimation of insulin resistance in non-diabetic normotensive Saudi adults by QUICKI, HOMA-IR and modified QUICKI: a comparative study. Ann Saudi Med. 2010;30(4):257-264. doi:10.4103/0256-4947.65252.

Reviewer comment

4. Results section: the authors much repeat the results on the markers. The values can be found in the tables, it is not necessary to repeat all in the results text.

Authors response

Yes, thank you for the comment. Results were revised. Please, see the track changes in the section of results.

Minor:

Reviewer comment

1. Please, give the proportions of patients with IR in tables also

Authors response

Done. Please, see table 4.

Reviewer comment

2. Figures need n-values for all groups.

Authors response

N-values were inserted in all figures.

Reviewer comment

3. Give lung function + demographic data for different therapy groups (not treated, SABa-only, ICS-LABA) e.g. in supplement

Authors response

Done. Please, see table 4.

Reviewer comment

4. Define the ACT cutpoint for uncontrolled asthma.

Authors response

Patients with ACT < 19 were considered uncontrolled. Please, see the track changes in the section of methods.

Reviewer comment

5. Abstract: results, please state what the numbers in parentheses mean. IQR? 95% CI?

Authors response

Yes, thank you. It is done. Please, see the track changes in the abstract - section of results.

Reviewer comment

6. How was asthma diagnosed?

Authors response

Diagnosis was based on clinical examination and spirometric evaluation. All patients were diagnosed by their physicians at least for two years before we see them. Please, see the track changes in the section of methods.

2nd editorial decision
7-Jul-2020

Ref.: Ms. No. JCTRes-D-20-00038R1
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Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly

review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger
Editor-in-Chief
Journal of Clinical and Translational Research

Comments from the editors and reviewers:

Reviewer #1: The authors have developed the manuscript further. Eventhough I do not fully agree with their comment on the blood pressure, I do understand it as part of metabolic syndrome. This reviewer does not see where the current study was done (authors and country blinded) but supposing it was done in a developing country with poor resources, I congratulate the authors for good idea and important results! I have no further comments.

Reviewer #2: The study has highlighted the importance of metabolic syndrome and its impact on asthma and is clinically relevant. More understanding of the inflammatory mediators, its complex interaction and relationship to biomarkers may pave the way for better therapeutic options.