

November 20, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 12998-edited.doc).

Title: Asthma and metabolic syndrome: current knowledge and future perspectives

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Name of Journal: World Journal of Clinical Cases

ESPS Manuscript NO: 12998

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer:

Reviewer (1) Although the data described in the manuscript are generally well written, with good readability, many important and/or interesting aspects related to the complex pathophysiological mechanisms involved in asthma and metabolic syndrome are not presented or discussed in detail, and some not up-dated, impairing the novelty and innovative nature of the article.

Comment 1 (C1). Adipose derived hormones, such as adiponectin, leptin and resistin, represent molecular links between asthma and inflammation. Adipokines may have a role in the pathogenesis of allergic inflammation, and may exert pro-inflammatory activities in asthma. Adiponectin, an adipocyte-derived cytokine, is known to have anti-inflammatory effects with reduced concentrations in obese subjects and recent findings raised the intriguing possibility that adiponectin play a role in allergic inflammation. Adiponectin receptors are involved in metabolic syndrome, and AdipoR1 and AdipoR2 are also expressed in human eosinophils involved in allergic inflammation [Yamamoto R, Ueki S, Moritoki Y, Kobayashi Y, Oyamada H, Konno Y, Tamaki M, Itoga M, Takeda M, Ito W, Chihara J. Adiponectin attenuates human eosinophil adhesion and chemotaxis: implications in allergic inflammation. *J Asthma*. 2013 Oct;50(8):828-35. doi: 10.3109/02770903.2013.816725. Epub 2013 Jul 17. PubMed PMID: 23777560; Yamauchi T, Iwabu M, Okada-Iwabu M, Kadowaki T. Adiponectin receptors: a review of their structure, function and how they work. *Best Pract Res Clin Endocrinol Metab*. 2014 Jan;28(1):15-23. doi: 10.1016/j.beem.2013.09.003. Epub 2013 Sep 15. Review. PubMed PMID: 24417942]. Adipokine adiponectin is a potential protector to human bronchial epithelial cell for regulating proliferation, wound repair and apoptosis [Zhu XL, Qin XQ, Xiang Y, Tan YR, Qu XP, Liu HJ. Adipokine adiponectin is a potential protector to human bronchial epithelial cell for regulating proliferation, wound repair and apoptosis: comparison with leptin and resistin. *Peptides*. 2013 Feb;40:34-41. doi: 10.1016/j.peptides.2012.11.017. Epub 2012 Dec 5. PubMed PMID: 23220445].

R1: We acknowledge the importance of adiponectin as an anti-inflammatory cytokine. Following the suggestions of the Reviewer, we have added the relevant paragraph in the section “Pathophysiological mechanisms” of the revised version of the manuscript with related references.

C2. High resistin levels predict favourable anti-inflammatory effect of inhaled glucocorticoids suggesting that resistin may be a marker of steroid-sensitive phenotype in asthma.

R2: The role of resistin in the context of the pro-inflammatory cytokine pattern in obese asthmatics has also been discussed in the revised version of the manuscript.

C3. High leptin levels are associated with a more severe disease suggesting that the link between leptin and asthma is not restricted to obesity [Leivo-Korpela S, Lehtimäki L, Vuolteenaho K, Nieminen R, Kankaanranta H, Saarelainen S, Moilanen E. Adipokine resistin predicts anti-inflammatory effect of glucocorticoids in asthma. *J Inflamm (Lond)*. 2011 May 26;8:12. doi: 10.1186/1476-9255-8-12. PubMed PMID: 21615949; PubMed Central PMCID: PMC3117675]. Moreover, asthma in obese adults is associated with impaired macrophage/monocyte efferocytosis. Impairment of this anti-inflammatory process is associated with altered monocyte/macrophage programming, reduced glucocorticoid responsiveness, and systemic oxidative stress [Fernandez-Boyanapalli R, Goleva E, Kolakowski C, Min E, Day B, Leung DY, Riches DW, Bratton DL, Sutherland ER. Obesity impairs apoptotic cell clearance in asthma. *J Allergy Clin Immunol*. 2013 Apr;131(4):1041-7, 1047.e1-3. doi: 10.1016/j.jaci.2012.09.028. Epub 2012 Nov 13. PubMed PMID: 23154082].

R3: The contribution of leptin in the inflammatory changes in the obese and non obese asthmatics has been extensively discussed in a new paragraph included in the section “Pathophysiological mechanisms” of the revised text.

C4. Important data related to peroxisome proliferator-activated receptors (PPARs) as ligand-activated transcription factors belonging to the nuclear receptor family at the crossroads between lipid metabolism and inflammation, are not presented in the manuscript [Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPAR) and inflammation: from basic science to clinical applications. *Int J Obes Relat Metab Disord*. 2003 Dec;27 Suppl 3:S41-5. Review. PubMed PMID: 14704743; Chinetti G, Fruchart JC, Staels B. Peroxisome proliferator-activated receptors (PPARs): nuclear receptors at the crossroads between lipid metabolism and inflammation. *Inflamm Res*. 2000 Oct;49(10):497-505. Review. PubMed PMID: 11089900; Ueki S, Kato H, Takeda M, Ito W, Fujita M, Kayaba H, Chihara J. Cross-talk between arteriosclerotic diseases and allergic inflammation. *Rinsho Byori*. 2008 Dec;56(12):1107-11. Review. Japanese. PubMed PMID: 19175075]. furthermore, PPAR-gamma agonists may attenuate the upper airway allergic inflammation by induction of T_{reg} cells and inhibiting the proliferation of effector T cells [Wang W, Zhu Z, Zhu B, Ma Z. Pioglitazone attenuates allergic inflammation and induces production of regulatory T lymphocytes. *Am J Rhinol Allergy*. 2010 Nov-Dec;24(6):454-8. doi: 10.2500/ajra.2010.24.3522. PubMed PMID: 21144225; Wang W, Zhu Z, Zhu B, Ma Z. Peroxisome proliferator-activated receptor-gamma agonist induces regulatory T cells in a murine model of allergic rhinitis. *Otolaryngol Head Neck Surg*. 2011 Apr;144(4):506-13. doi: 10.1177/0194599810396133. Epub 2011 Feb 24. PubMed PMID: 21493225; Zhao Y, Huang Y, He J, Li C, Deng W, Ran X, Wang D. Rosiglitazone, a peroxisome proliferator-activated receptor- γ agonist, attenuates airway inflammation by inhibiting the proliferation of effector T cells in a murine model of neutrophilic asthma. *Immunol Lett*. 2014 Jan-Feb;157(1-2):9-15. doi: 10.1016/j.imlet.2013.11.004. Epub 2013 Nov 21. PubMed PMID: 24269293]. Thus, thiazolidinediones, oral diabetes medications that selectively activate peroxisome proliferator-activated receptor gamma, have potent anti-inflammatory properties in asthma [Rinne

ST, Feemster LC, Collins BF, Au DH, Perkins M, Bryson CL, O'Riordan TG, Liu CF. Thiazolidinediones and the risk of asthma exacerbation among patients with diabetes: a cohort study. *Allergy Asthma Clin Immunol.* 2014 Jul 3;10(1):34. doi: 10.1186/1710-1492-10-34. eCollection 2014. PubMed PMID: 25024717; PubMed Central PMCID: PMC4094895].

R4: We have addressed the topic pointed out by the Reviewer in a new paragraph in the section “Pathophysiological mechanisms” of the revised text.

C5. Some English language polishing are required. In the “Abstract”, the word “context” is used redundant in two consecutive sentences. In the „Conclusive remarks”, the “hidden asthma” seems not to be appropriate, an alternative being “airway hyperreactivity or subclinical asthma”.

R5. The text has been extensively revised. The suggested changes were made.

C6. In „References” section PubMed citation numbers for each referenced article are not provided in the reference list (PMID and DOI numbers). Moreover, some other important recent references are not presented in the manuscript [Garmendia JV, Moreno D, Garcia AH, De Sanctis JB. Metabolic syndrome and asthma. *Recent Pat Endocr Metab Immune Drug Discov.* 2014 Jan;8(1):60-6. PubMed PMID: 24397782;

Agrawal A, Prakash YS, Linneberg A. Body mass index is not a stronger predictor than the metabolic syndrome for future asthma in women. *Am J Respir Crit Care Med.* 2014 Jan 15;189(2):231-2. doi: 10.1164/rccm.201307-1333LE. PubMed PMID: 24428655;

Assad N, Qualls C, Smith LJ, Arynchyn A, Thyagarajan B, Schuyler M, Jacobs DR Jr, Sood A. Reply: body mass index is a stronger predictor than the metabolic syndrome for future asthma in women. *Am J Respir Crit Care Med.* 2014 Jan 15;189(2):232-3. doi: 10.1164/rccm.201308-1488LE. PubMed PMID: 24428656; Acay A, Erdenen F, Altunoglu E, Erman H, Muderrisoglu C, Korkmaz GG, Gelisgen R, Tabak O, Uzun H. Evaluation of serum paraoxonase and arylesterase activities in subjects with asthma and chronic obstructive lung disease. *Clin Lab.* 2013;59(11-12):1331-7. PubMed PMID: 24409668;

Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy (Cairo).* 2013;2013:627384. doi: 10.1155/2013/627384. Epub 2013 Sep 24. Review. PubMed PMID: 24204385; PubMed Central PMCID: PMC3800560; Luxon BA. Metabolomics in asthma. *Adv Exp Med Biol.* 2014;795:207-20. doi: 10.1007/978-1-4614-8603-9_13. Review. PubMed PMID: 24162911; Leishangthem GD, Mabalirajan U, Singh VP, Agrawal A, Ghosh B, Dinda AK. Ultrastructural changes of airway in murine models of allergy and diet-induced metabolic syndrome. *ISRN Allergy.* 2013 Sep 10;2013:261297. doi: 10.1155/2013/261297. eCollection 2013. PubMed PMID: 24106613; PubMed Central PMCID: PMC3782840; Periyalil HA, Gibson PG, Wood LG. Immunometabolism in obese asthmatics: are we there yet? *Nutrients.* 2013 Sep 10;5(9):3506-30. doi: 10.3390/nu5093506. Review. PubMed PMID: 24025484; PubMed Central PMCID: PMC3798918; Erkoçoğlu M, Kaya A, Ozcan C, Akan A, Vezir E, Azkur D, Kara O, Demirel F, Ginis T, Civelek E, Kocabaş CN. The effect of obesity on the level of fractional exhaled nitric oxide in children with asthma. *Int Arch Allergy Immunol.* 2013;162(2):156-62. doi: 10.1159/000351454. Epub 2013 Jul 31. PubMed PMID: 23921526; Bel EH. Another piece to the puzzle of the "obese female asthma" phenotype. *Am J Respir Crit Care Med.* 2013 Aug 1;188(3):263-4. doi: 10.1164/rccm.201306-1066ED. PubMed PMID: 23905517; Aydin M, Koca C, Ozol D, Uysal S, Yildirim Z, Kavakli HS, Yigitoglu MR. Interaction of metabolic syndrome with asthma in postmenopausal women: role of adipokines. *Inflammation.* 2013 Dec;36(6):1232-8. doi: 10.1007/s10753-013-9660-9. PubMed PMID: 23729278; Fenger RV, Gonzalez-Quintela A, Linneberg A, Husemoen LL, Thuesen BH, Aadahl M, Vidal C, Skaaby T, Sainz JC, Calvo E. The relationship of serum triglycerides, serum HDL, and obesity to the risk of

wheezing in 85,555 adults. *Respir Med*. 2013 Jun;107(6):816-24. doi: 10.1016/j.rmed.2013.02.001. Epub 2013 Mar 5. PubMed PMID: 23465506; Lucas K, Maes M. Role of the Toll Like receptor (TLR) radical cycle in chronic inflammation: possible treatments targeting the TLR4 pathway. *Mol Neurobiol*. 2013 Aug;48(1):190-204. doi: 10.1007/s12035-013-8425-7. Epub 2013 Feb 26. Review. PubMed PMID: 23436141; Sindic A. Current understanding of guanylin peptides actions. *ISRN Nephrol*. 2013 Apr 17;2013:813648. doi: 10.5402/2013/813648. eCollection 2013. Review. PubMed PMID: 24967239; PubMed Central PMCID: PMC4045495; Adamko DJ, Sykes BD, Rowe BH. The metabolomics of asthma: novel diagnostic potential. *Chest*. 2012 May;141(5):1295-302. doi: 10.1378/chest.11-2028. Review. PubMed PMID: 22553262; Pantoja-Alcantar JM, Segura-Méndez NH, Vargas-Ortega G, González-Virla BG. Association of metabolic syndrome and asthma severity. *Rev Alerg Mex*. 2012 Jan-Mar;59(1):3-8. Spanish. PubMed PMID: 24007927; Uzunlulu M, Oguz A, Gedik C, Asian G, Arik S. Is prevalence of metabolic syndrome high in patients with asthma? *Acta Clin Belg*. 2011 Jan-Feb;66(1):49-52. PubMed PMID: 21485764; McGinley B, Punjabi NM. Obesity, metabolic abnormalities, and asthma: establishing causal links. *Am J Respir Crit Care Med*. 2011 Feb 15;183(4):424-5. doi: 10.1164/rccm.201009-1525ED. PubMed PMID: 21325079; van Huisstede A, Braunstahl GJ. Obesity and asthma: co-morbidity or causal relationship? *Monaldi Arch Chest Dis*. 2010 Sep;73(3):116-23. Review. PubMed PMID: 21214041; Beuther DA. Recent insight into obesity and asthma. *Curr Opin Pulm Med*. 2010 Jan;16(1):64-70. doi: 10.1097/MCP.0b013e3283338fa7. Review. PubMed PMID: 19844182; Quek YW, Sun HL, Ng YY, Lee HS, Yang SF, Ku MS, Lu KH, Sheu JN, Lue KH. Associations of serum leptin with atopic asthma and allergic rhinitis in children. *Am J Rhinol Allergy*. 2010 Sep-Oct;24(5):354-8. doi: 10.2500/ajra.2010.24.3483. PubMed PMID: 21244735].

R6. We thank the Reviewer for providing such a comprehensive list of relevant references, some of which were already present in the original version of the manuscript. We have therefore modified the reference list by adding the PMID and DOI numbers, and have added the following references:

Garmendia JV, Moreno D, Garcia AH, De Sanctis JB. Metabolic syndrome and asthma. *Recent Pat Endocr Metab Immune Drug Discov*. 2014 Jan;8(1):60-6. PubMed PMID: 24397782;

Agrawal A, Prakash YS, Linneberg A. Body mass index is not a stronger predictor than the metabolic syndrome for future asthma in women. *Am J Respir Crit Care Med*. 2014 Jan 15;189(2):231-2. doi: 10.1164/rccm.201307-1333LE. PubMed PMID: 24428655;

Singh S, Prakash YS, Linneberg A, Agrawal A. Insulin and the lung: connecting asthma and metabolic syndrome. *J Allergy (Cairo)*. 2013;2013:627384. doi: 10.1155/2013/627384. Epub 2013 Sep 24. Review. PubMed PMID: 24204385; PubMed Central PMCID: PMC3800560

Bel EH. Another piece to the puzzle of the "obese female asthma" phenotype. *Am J Respir Crit Care Med*. 2013 Aug 1;188(3):263-4. doi: 10.1164/rccm.201306-1066ED. PubMed PMID: 23905517;

Fenger RV, Gonzalez-Quintela A, Linneberg A, Husemoen LL, Thuesen BH, Aadahl M, Vidal C, Skaaby T, Sainz JC, Calvo E. The relationship of serum triglycerides, serum HDL, and obesity to the risk of wheezing in 85,555 adults. *Respir Med*. 2013 Jun;107(6):816-24. doi: 10.1016/j.rmed.2013.02.001. Epub 2013 Mar 5. PubMed PMID: 23465506

McGinley B, Punjabi NM. Obesity, metabolic abnormalities, and asthma: establishing causal links. *Am J Respir Crit Care Med*. 2011 Feb 15;183(4):424-5. doi: 10.1164/rccm.201009-1525ED

Quek YW, Sun HL, Ng YY, Lee HS, Yang SF, Ku MS, Lu KH, Sheu JN, Lue KH. Associations of serum leptin with atopic asthma and allergic rhinitis in children. *Am J Rhinol Allergy*. 2010 Sep-Oct;24(5):354-8. doi: 10.2500/ajra.2010.24.3483. PubMed PMID: 21244735].

Reviewer (2) It's a well-written article that reviews the relationship between metabolic syndrome and asthma. It's a relatively novel research area. I just wonder the role of oxidative stress as the potential mechanisms in metabolic syndrome and asthma. Perhaps rennin-angiotensin-system also plays an important role in the pathophysiology.

We would like to thank the reviewer for his/her positive comments. As corretly pointed out, we have addressed the potential role of oxidative stress as well as the role of the rennin-angiotensin-system in the revised version of the manuscript, by inserting a new paragraph in the section "Pathophysiological mechanisms" of the revised text.

Reviewer (3) Review article on the relationship between asthma and metabolic syndrome. Topic of interest serviced properly. References are acceptably date: > 60% (56/74) of the last 5 years.

The structure of the article and its general outline is correct (Abstract, Keywords, Core tip, Introduction, Epidemiological link between asthma and metabolic syndrome, Pathophysiological mechanisms, Current and future developments and Conclusive remarks).

The relationship between asthma and obesity are properly reviewed. In this sense the other components of the metabolic syndrome (dyslipidemia, insulin resistance, hypertension and central obesity) are also evaluated. Seems that the asthma-obesity relationship is best explained by inflammatory processes related to all the factors associated with metabolic syndrome that not only with obesity.

There are no ethical problems.

TITLE: Specific, it adequately contains the primary endpoint. (Words: 9).

ABSTRACT:

Define and explain the concepts well properly structure review article.

Key words: Correct

INTRODUCTION: Clear and correct introduction. Well structured.

The DIFFERENT SECTIONS (Abstract, Keywords, Core tip, Introduction, Epidemiological link between asthma and metabolic syndrome, Pathophysiological mechanisms, Current and future developments and Conclusive remarks) are clear and well structured.

The figure is simple but summarizes the review.

The review is presented in a clear and correct form.

REFERENCES:

The references are up to date (76% of the last 5 years) in adequate numbers (74 references).

However, it strikes me that there are a number of references, with high relevance according to different databases, which have not been collected.

1.- Schumann, R. Association of metabolic syndrome and surgical factors with pulmonary adverse events, and longitudinal mortality in bariatric surgery†

- 2.- Agrawal, Anurag. Body mass index is not a stronger predictor than the metabolic syndrome for future asthma in women.
- 3.- Singh, Suchita. Insulin and the lung: connecting asthma and metabolic syndrome.
- 4.- Garmendia, Jenny V. Metabolic syndrome and asthma.
- 5.- Linderholm, Angela L. Novel Therapeutic Strategies for Adult Obese Asthmatics.
- 6.- Agrawal, Anurag. Obesity, Metabolic Syndrome, and Airway Disease: A Bioenergetic Problem?
- 7.- Assad, Tour. Reply: body mass index is a stronger predictor than the metabolic syndrome for future asthma in women.
- 8.- Perez, Miriam K. Metabolic Asthma: Is There a Link Between Obesity, Diabetes, and Asthma?

MINOR COMMENTS

Orthographic revision: It is not necessary

We thank the reviewer for his/her enthusiastic comments. We have now incorporated the suggested references in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Clinical Cases*

Sincerely yours,

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