

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Intestinal barrier function in obesity with or without metabolic syndrome: A systematic review protocol
AUTHORS	Bona, Mariana; Torres, Carlos Henrique; Lima, Severina; Lima, Aldo; Maciel, Bruna

VERSION 1 – REVIEW

REVIEWER	Joost Rutten Radboud University Medical Hospital Department of Internal Medicine Section of Vascular Medicine Nijmegen, the Netherlands
REVIEW RETURNED	01-Oct-2020

GENERAL COMMENTS	<p>Thank you for the opportunity to review the paper of Bona et al. Intestinal barrier function in obese patients with or without metabolic syndrome: A systematic review protocol. The manuscript describes a protocol to perform a systematic review of human studies investigating the intestinal barrier function in various populations. A relevant topic as described in the introduction. The systematic review might provide insight in the various methodologies used to assess the intestinal barrier function in humans</p> <p>Major points In the supplement the authors provide the PRISMA-P guideline. These guidelines ask authors to extensively report the methodology used to perform a systematic review. I would like to ask the authors to report in advance the methodology as asked in the PRISMA guidelines. For instance, report the PICO, time frame. As this paper focusses on intestinal barrier function, and specific methodologies are mentioned for measurement of intestinal barrier function, provide more background information on the specific diagnostic tests that will be the focus of the review. How will the authors assess the risk of bias due to selective publication? Statistics are only briefly described. I would suggest to provide a more rigorous overview of the statistical methodology that will be applied to assess the quantitative data of this systematic review. For instance which variables are being used as outcome parameters in the systematic review. How will the authors investigate the effect of differences between populations of different studies on their outcome parameter</p> <p>Minor point In the abstract it is stated " The aim of this paper was to describe a systematic review protocol with studies that determine the relationship between the intestinal barrier function, in obese patients</p>
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	with or without metabolic syndrome." Which relationship is being meant between intestinal barrier function and .. ?
REVIEWER	João R. Araújo Nova Medical School, Universidade Nova Lisboa, Portugal
REVIEW RETURNED	03-Dec-2020
GENERAL COMMENTS	Although the upcoming systematic review is of unquestionable relevance, the reviewer considers that there is not enough scientific interest and novelty in publishing such an ordinary and already widely used methodology to perform this kind of systematic review.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Dr. Joost H. W. Rutten, Radboud Universiteit

Comments to the Author:

Thank you for the opportunity to review the paper of Bona et al. Intestinal barrier function in obese patients with or without metabolic syndrome: A systematic review protocol. The manuscript describes a protocol to perform a systematic review of human studies investigating the intestinal barrier function in various populations. A relevant topic as described in the introduction. The systematic review might provide insight in the various methodologies used to assess the intestinal barrier function in humans.

R- We thank the reviewer for the kind revision and nice comments on our manuscript. All suggestions were thoroughly addressed, and we hope this version is better suitable for publication.

Major points

In the supplement the authors provide the PRISMA-P guideline. These guidelines ask authors to extensively report the methodology used to perform a systematic review. I would like to ask the authors to report in advance the methodology as asked in the PRISMA guidelines. For instance, report the PICO, time frame.

*R- We thank the reviewer for the suggestion. In this systematic review, observational studies will be addressed, so the traditional PICO (population, intervention, comparator and outcomes) format for systematic reviews does not align with the question relating to our study (Moola et al *Int J Evid Based Healthc* 2015; 13: 163-169). Thus, attending to the reviewer's suggestion, we included the population and variables that will be studied, time frame and better explained the study's question. The 'reporting checklist for protocol of a systematic review', based on PRISMA-P guidelines was used to ensure all the needed information was included as a step for submission at BMJ open.*

As this paper focusses on intestinal barrier function, and specific methodologies are mentioned for measurement of intestinal barrier function, provide more background information on the specific diagnostic tests that will be the focus of the review.

R- We thank the reviewer for the suggestion. This information was added in section "introduction" (highlighted in the text).

How will the authors assess the risk of bias due to selective publication? Statistics are only briefly described. I would suggest to provide a more rigorous overview of the statistical methodology that will be applied to assess the quantitative data of this systematic review. For instance which variables are

being used as outcome parameters in the systematic review. How will the authors investigate the effect of differences between populations of different studies on their outcome parameter.

R- We thank the reviewer for these observations and we revised the text in the methodology section, considering this is a systematic review protocol with narrative synthesis of association studies aiming to investigate if obesity with or without metabolic syndrome is associated with an altered intestinal barrier function. Because of the differences in the factors controlled for in multivariable analyses, reporting with lack of details in the association studies (Moola et al *Int J Evid Based Healthc* 2015; 13: 163-169) and possible small number of human studies, this review will not be a meta-analysis. Therefore, there will be no assessment of quantitative data.

Two reviewers will independently conduct sensitive search for eligible studies, through the electronic databases PubMed Database, Embase Database, Cochrane Library, Scopus, Web of Science (WOS) and Science Direct. In order to reflect the latest data, a search of the literature from the last 15 years (2006 to 2021) will be performed. Articles will be imported into Mendeley reference manager (1.19.4), and duplicates will be deleted. Initial screening of studies will be based on the information in their title, keywords and abstracts, following the eligibility criteria. When the reviewers disagree, the article will be re-evaluated and, if the disagreement persists, a third reviewer will make a final decision.

We also revised the sections "2.6 Methodological quality assessment" and "2.7 Data analysis and synthesis" adding the following information, as suggested by the reviewer:

Assessment of methodological quality and risk of bias in the studies with case-control design will be performed using the adapted Newcastle-Ottawa Scale, in which studies that receive at least five stars (maximum of eight) will be classified as good quality studies. Two independent reviewers will assess the methodological quality of eligible studies. These independent reviewers will score the selected studies, and a third reviewer will resolve any disagreement.

The systematic review will describe the relevant information of the included studies. Essential information on characteristics, methods, results, and quality scores of included studies will be registered. Following this, a narrative synthesis will be conducted.

Firstly, in the narrative review, the number of studies to be included in the synthesis will be reported, and the characteristics of each study will be described as well the location, kind, and study population. Secondly, the narrative synthesis will report and discuss the methods used to evaluate intestinal permeability and the relevant data. The quality of the methods used will be discussed based on the related and observed study limitations. Finally, the observation of altered intestinal barrier function in patients with obesity added or not to metabolic syndrome will be explored, and similarities and differences of findings will be reported.

The best-evidence synthesis will be guaranteed, and the risk of bias due to selective publication will be controlled by following the steps described above and assessing the quality of the evidence by the GRADE framework, regarding the association between intestinal barrier function alteration and patients with obesity added or not to metabolic syndrome. GRADE ranks the evidence as high (when there is strong certainty that the association is close to the estimated); moderate (when there is moderate certainty in the estimated association); low (when certainty in association is limited); and very low (when certainty in the association estimate is very limited owing to a significant degree of uncertainty in the findings) (Guyatt et al 2008).

Minor point

In the abstract it is stated " The aim of this paper was to describe a systematic review protocol with studies that determine the relationship between the intestinal barrier function, in obese patients with

or without metabolic syndrome." Which relationship is being meant between intestinal barrier function and .. ?

R- This was revised to "This study aims to describe a systematic review protocol investigating if obesity with or without metabolic syndrome is associated with an altered intestinal barrier function".

Reviewer: 2

Dr. João Ricardo Araújo, Universidade Nova de Lisboa

Comments to the Author:

Although the upcoming systematic review is of unquestionable relevance, the reviewer considers that there is not enough scientific interest and novelty in publishing such an ordinary and already widely used methodology to perform this kind of systematic review.

R- Evidence supports a causal pathway between diet, gut microbiota, intestinal barrier function, and metabolic dysfunction (Khoshbin, Camilleri, 2020). Animal models have shown that communication between the gut-adipose tissue and the gut-brain is essential for maintaining energy balance, and this communication is impaired during obesity and type 2 diabetes (Geurts et al., 2017). In this context, metabolic endotoxemia, characterized by an increase in lipopolysaccharides (LPS) in plasma, was identified as one of the main factors that lead to the development of metabolic inflammation and insulin resistance. Increasing evidence supports that the intestinal microflora is responsible for the development of a low-grade inflammation that generates dysfunctions in the intestinal barrier, increases its permeability, and allows a consequent endotoxemia (Cani et al., 2009; Cani et al., 2012).

Although these findings are well delineated for animal models, few studies in humans have been performed (Portune et al., 2017).

A study compared two groups of women with and without obesity, assessing intestinal permeability by urinary L/M ratio. Although both sugars' urinary excretions were higher in women with obesity, a statistically significant difference in the L/M ratio was not found between the studied groups. Nevertheless, a higher L/M ratio was associated with higher homeostatic model assessment (HOMA), insulin and LDL/HDL concentrations, and lower HDL concentrations (Teixeira et al., 2012). Thus, the intestinal barrier function might be associated with obesity and metabolic syndrome.

Because of the differences in the factors controlled for in multivariable analyses, reporting with lack of details in the association studies (Moola et al. Int J Evid Based Healthc 2015; 13: 163-169) and possible small number of human studies, this review will not be a meta-analysis.

The introduction was revised, including the studies cited above and methodology reviewed to meet all the existing guidances for systematic reviews thoroughly.