Reviewer's report

Title: Efficacy of dietary prebiotic supplementation on advanced glycation, insulin resistance and inflammatory biomarkers in adults with pre-diabetes: a study protocol for a double-blind placebo-controlled randomised crossover clinical trial

Version: 3
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Reviewer: Marie-José Butel

Reviewer's report:

1- General comments

The announced aim of the study is to investigate the effect of a prebiotic dietary supplement on gut microbiota and advanced glycation endproducts (AGEs) accumulation in adults diagnosed with prediabetes. The background of such study stemmed from epidemiological studies which showed that elevated plasma carboxymethyllysine (CML) – the major AGE – are at increased risk of all cause and especially cardiovascular mortality. Reducing circulating AGEs could therefore improve the metabolic health of individuals at risk for the development of type 2 diabetes. Prebiotics which are known for their microbiota modulation capacities, in particular in increasing lactic acid bacteria, have been shown to be able to counteract several metabolic alterations linked to obesity, including hyperglycemia, inflammation, and hepatic steatosis. Hence, appropriate human intervention studies with prebiotic dietary supplement are of interest to confirm the relevance of such supplementation.

However, some comments must be addressed to the proposed clinical trial.

2- Major compulsory revisions

The authors chose to design a cross-over trial. Regarding this trial, the advantage is to minimize the intravariability within patients of the effect of the treatment. Two points must be raised. First, the hypothesis is that prebiotic supplementation will lead to improvement in biomarkers of cardiovascular disease risk through a mechanism which can be modifications in microbiota profile. However, does a two-week wash-out period long enough to be sure that microbiota return to its initial profile, without any resilience, for the group beginning by prebiotic intervention? It should be useful to plan blood, urine, and particularly stool analyses at the beginning of the second period of intervention.

Second, the sample size seems to be low. It is calculated based only on the objective to detect a reduction of CML concentration (p7) although the announced objective is to investigate the effect of prebiotic on gut microbiota and AGE accumulation (p6). Morover, in the abstract methylglyoxal levels differences between treatments is noted as primary outcomes, but it is not included in the sample size calculation. If regarding CML levels and reduction objective, the sample size calculation appears correct; regarding gut microbiota, this sample size appears too low to take into account the diversity of the gut microbiota.
Moreover, the authors plan to analyze only bifidobacteria and lactobacilli populations although publications involved also other bacterial groups in metabolic disorders (recently reviewed by Delzenne et al, Br J Nutr, 2013, 109:S81-S85). To assess the announced aim, the authors should include other PCR to detect the major bacterial groups, including those suggested to be involved in metabolic disorders and those suggested by the authors to be involved in AGE metabolism (p5). Finally, to validate their choice concerning the primers used, they must give the references of the primers used.

The aim of the study should be therefore reconsidered. To my point of view, it is very interesting to complete biochemical dosages with appropriate microbiota determination.

As far as exclusion criteria are concerned, how long before the inclusion visit the patients should they had not taken antibiotics of pre/probiotics supplements? Otherwise, will guidelines for eating be given taking into account that numerous foodstuffs contain pre- and/or probiotics?

3- Minor essential revisions

Could the authors explain why the prebiotic intake should be given with a gradually increased dose over ten days until the target dose is reached? Is it usual in prebiotic supplementation clinical trials (to my knowledge…no, but I did not check this point).

Currently, it is better to use the term “microbiota” instead of “microflora”.

4-Other points

Except the points rose above, this clinical trial follows the recommendations for a randomized trial including inclusion and exclusion criteria definitions, randomization allocation, and blinding.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

I declare that I have no competing interests