Format for ANSWERING REVIEWERS

April 22, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 8787-review.doc).

Title: Test-based exclusion diets in GERD patients: a randomized controlled pilot trial

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8787

The manuscript has been improved according to the suggestions of reviewers:
Reviewer **00068472**:

1) English language was attentively reviewed, and mistakes were found and corrected.
2) The Reviewer asks whether the diagnosis of GERD was made based on symptoms or endoscopic results: as clearly stated in the paper, the diagnosis was based just on symptoms, by means of a validated questionnaire (GIS). Actually, it is possible that the GIS questionnaire does not completely distinguish between GERD and other functional illnesses (but in this case a new validation study would be necessary to assess its specificity). On the other hand, in patients younger than 50 years or free from risk factors for cancer, the current guidelines for the diagnosis and treatment of GERD suggest to use a "test-and-treat" approach, without the need of an endoscopic confirmation (this is stated in the manuscript).
3) The same diagnostic doubts are expressed later on by the Reviewer: as previously underlined, our study contemplated GIS but not endoscopy, and thus the latter was not performed.
4) Regarding the definition of "non-responders" to PPI treatment, were considered non-responders the patients who experienced no improvement of symptoms after 8 weeks of PPI treatment at double dose. Regarding the concept of "partially responders" we apologize we were not so clear in the definitions. We considered partially responders the patients who experienced only slight reduction of symptoms after 4 weeks of PPI treatment or the ones who had an initial response to PPI treatment, but had relapses of symptoms during the 4 weeks of PPI treatment. Considering the usual timing of the PPI test in the diagnosis of GERD, we consider 4 weeks as a more than sufficient time to define the partial response; moreover a similar definition was used by other authors (Bytzer P et al, Aliment Pharmacol Ther 2012;36:635-43). To state this concept clearer, we modified the section "Patients" of "Materials and Methods".

5) We agree with the Reviewer that the number of involved patients is relatively low, but we consider it might be absolutely sufficient for a "pilot" study.
6) As regards to the inclusion of a Control group, it has to be underlined that half of patients enrolled received a "control diet" in the first part of the trial (1° month) thus configuring the Control group. Since they received the "true" test based diet in the second part of the study, these subjects could be compared with both subjects always treated with the "true" diet (1° and 3° month) and also with themselves after the switch (3° month).
7) As regards the possible inclusion of a group of PPI responders we do not agree with the reviewer about its possible usefulness : the study questions the possible role of a exclusion diet in GERD management, and not to compare this with the efficacy of PPI therapy.
8) We agree with the Reviewer that the results may, at least in part, be influenced by a relatively high placebo effect; we therefore revised and discussed this aspect.

Reviewer **00028194:**

1) We choose to use Leukocytotoxic test for different reasons: 1.we previously found interesting results by using this test in a retrospective evaluation (Caselli M et al. A possible role of Food Intolerance in the pathogenesis of Gastroesophageal Reflux Disease. Am J Gastroenterol 2009;104:2115-7.); 2. this test permits to test a broader panel of foods compared with IgG4 testing; 3. its cost is lower than IgG4 test's, making leukocytotoxic test more cost-effective.
2) The "true" and "control" diets were produced by specifically excluding the 5 foods giving the worse and the best responses at the leukocytotoxic test, respectively. Thus, in the "true" diet the five foods giving grade III or at least grade II reactions were excluded; on the contrary, five foods giving no reaction were randomly excluded in the "control" diet. For people having more than 5 foods giving grade III reactions, the foods to be eliminated were chosen randomly. We underline that the aim of the "control" diet was not only to provide a diet as similar as possible to the "true" diet as regards caloric, macro- and micronutrient intake, but its particular aim was to exclude from the patients' diet foods which were certainly not responsible for any leukocytotoxic reactions, as said in the text. Thus, the glucidic content of the diet was not considered; however, the patients maintained their previous alimentary habits; for example, the exclusion of grain from the diet did not imply that pasta, bread, biscuits, etc. were eliminated from the diet, but only that they had to be made with another cereal from grain (e.g. kamut). The same can be said for milk, which was substituted by soy milk or rice milk, and for every other food excluded from both "true" and "control" diets.
3) Regarding the foods more frequently eliminated from the control diets, they were soy, kiwi, honey, codfish, trout and salmon.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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