

To The Editor, World Journal of Gastroenterology

Response to Reviewers' comments

We thank the reviewers for their comments and provide our responses below. Where necessary, changes have been made to the manuscript according to the remarks of the editor.

### **Reviewer 1**

You have prepared an article devoted to the urgent problem of clinical medicine. The material is presented logically and correctly. Selected methods are adequate to the research problems and the aim. I recommend the article for publication.

*Authors' response:* Thank you for your comments.

### **Reviewer 2**

In this manuscript, the authors tried to evaluate the effect of dietary fiber on the presence of gastroesophageal reflux, esophageal acidity, lower esophageal sphincter pressure and clinical manifestations of non-erosive gastroesophageal reflux disease (NERD) in patients with low dietary fiber intake. The study was uniquely designed and the results were very interesting. Limitations of this study were also stated. However, some more questions were raised as follows:

1) NERD is a multifactorial disease, so NERD patients are not suitable for this acid-reflux study.

*Authors' response:* Thank you for your comment. We absolutely agree with the reviewer that GERD is a multifactorial disease. Beside acid reflux, among these factors are impaired esophageal motility, increased number of transient lower esophageal sphincter relaxations and delayed gastric emptying. According to the stated aim and chosen methods our study was mainly dedicated to GERD symptoms and esophageal motility parameters rather to acid reflux per se.

2) In this study, intake of dietary fibers resulted in increasing of LES minimal resting pressure, decrease in number of acid, weakly-acid and total refluxes and it was associated with as twice as low frequency of heartburn and GERD-Q score in patients with NERD. Which mechanisms?

*Authors' response:* Supposed mechanism of action of dietary fibers (psyllium) may be related to their ability to bind nitric oxide contained in food and diminish its negative influence on LES pressure (Karamanolis G, Tack J, 2006; Terry P et al, 2001). Another mechanism may be explained by increased gut motility and as a result by the increase of gastric emptying. Moreover, some studies suggest that dietary fibers may also decrease acidity of gastric content, make the number of gastroesophageal refluxes lower and reduce their damaging ability (Harju E, 1984). Though the exact data are not known, the results, obtained in our study, may also be explained by the mechanisms mentioned above.

### Reviewer 3

To Authors, The article entitled " Fiber-enriched diet helps to control symptoms and improves esophageal motility in NERD" was reviewed. This article needs minor revisions; 1. Abbreviation could not be stated at the title ( NERD), please write the whole name

*Authors' response:* Thank you for your comments. The abbreviation was used to meet journal's criteria. The necessary corrections were made (title page).

2. All abbreviations written in the text should be evaluated and explanation of them should be written when first using (e.g.GSAS-ds score). This should be done at the tables also and explanations should be added below the tables (M±SD = Mean or median ?).

*Authors' response:* The manuscript was re-checked for the presence of previously unexplained abbreviations and necessary corrections were made. According to 'Guidelines for manuscript preparation and submission\_clinical trials study' (page 8) statistical data are expressed as mean±SD. The explanations of the abbreviations were added to the footnotes of the tables 1 and 2 (manuscript pages 5, 12, 17, 18, 19).

### Reviewer 4

This paper is proposing an evaluation of increased fiber intake to improve clinical and laboratory outcome (mainly esophageal motility) of NERD patients. The results are not clear-cut however, and there several drawbacks.

It is not clear to me why the authors choose NERD patients instead of clearly diagnosed GERD patients. The outcome of NERD patients after antireflux therapy is more unpredictable and intricate and this will make any evaluation more tricky.

*Authors' response:* Thank you for your comments. There are some facts that influenced our decision to choose NERD as a studied group. Epidemiological and cross-sectional studies showed that decreased dietary fiber consumption is associated with higher risks of gastroesophageal reflux disease symptoms (El-Serag HB et al 2005, Nilsson M et al, 2004). The 2010 Dietary Guidelines for Americans addressed the concern that most people consume inadequate amounts of dietary fiber, and thus recommendations were to choose foods that provide more fiber (Dahl WJ, Stewart ML, 2015). Some mechanisms of action of dietary fibers mentioned in the reply to the comment of reviewer 2 may suggest that they may add some additional effect to the treatment of GERD patients. The treatment of GERD patients, especially with reflux esophagitis, is clearly established: long-term profound acid suppression (with PPIs) or antireflux surgery. NERD patients more often respond to life-style modification and dietary interventions (Genwal workshop on GERD, Statement 7, J Dent et al, 1999). Due to that we supposed that NERD patients would be the adequate group for evaluation of the role of dietary fibers in GERD. We'd like to point that diagnosis of NERD was clearly confirmed by negative endoscopy, presence of

pathological acid reflux and association of symptoms with reflux (positive SI, SSI, SAP) by 24-hrs pH-impedance studies. Therefore, we had highly selected, clearly diagnosed group of reflux-disease patients in which other reasons of symptoms (irritable esophagus, reflux-like dyspepsia *etc*) were excluded. To avoid misunderstanding we added some explanations to the manuscript (page 7).

Obviously, to identify a satisfactory number of NERD patients is also difficult and this can explain the low number of patients reported in the paper, which indeed affects the results. The authors should explain the reason for their choice. As said above, the number of patients is relatively low to extrapolate any conclusion, especially in such a debatable issue.

*Authors' response:* It was found that up to 70% of GERD patients have non-erosive form of the disease (E. Savarino et al, 2016; El-Serag HB et al, 2014, Vakil N et al, 2006). Or at least 50% according to Genwal workshop on GERD, Statement 23 (J Dent et al, 1999). Therefore, it is easy to find such patients, but is more difficult to confirm that they really have NERD. In our study it was confirmed by negative endoscopy, presence of pathological acid reflux and association of symptoms with reflux (positive SI, SSI, SAP) by 24-hrs pH-impedance studies.

The study described in the manuscript is a pilot one, in which we tried to find out whether the consumption of dietary fibers is associated with decrease of NERD symptoms and changes in esophageal motility and number of refluxes or not. For these purposes we needed to repeat examinations with the use of high resolution esophageal manometry and esophageal pH-impedance and follow strict inclusion criteria prohibiting wide spectrum of medications. However, it was easy to calculate statistical power and the correspondent sample size using, for example, the data showed in the table 2. As for the GERD-Q score, 80% power is reached when the sample size consists of only 9 patients. Therefore, the number of patients was sufficient to demonstrate the significant differences in those parameters which we planned to study. Improvements were made to the text (pages 7, 8).

Several references are coming from Russian literature, which does not mean that they are unreliable, but certainly the reader would be more confident with results or conclusions coming from papers published in high-impact gastroenterological journals. An example is the validation of the "dietary questionnaire".

*Authors' response:* It is recommended that any questionnaires for the evaluation of patients' diet should be on the native language of the interviewed subject and contain information about the products that the subjects usually use, which is quite different from country to country. It is hardly possible that the data of local validation studies could be interesting for high-impact gastroenterological journals. Therefore, it is not surprising that these results were published in the Russian journals.

Accordingly, even in the discussion it is well outlined how different are the fiber intake guidelines between Russian and US population, a difference that can have some influence in the methods and can raise some questions about the reliability of the conclusions.

*Authors' response:* It is well known that different countries have own recommended nutrients daily allowances which usually depend on dietary habits, climate and so on. But it is not quite clear how recommended daily allowances may affect study results. We'd like to point that the aim of the present study was to evaluate whether the increase of amount of dietary fiber consumed is associated with NERD symptoms, change in esophageal motility and pattern of gastroesophageal reflux. As it was mentioned in the discussion, Russian recommended daily allowances for the dietary fiber consumption are lower compared to that coming from the US. The choice of the dose was caused by several factors and first of all by ethical consideration (so that not to exceed local recommended daily allowance, higher doses of dietary fiber consumption would be associated with unjustified risk of side effects). According to the comment we added a note to the discussion and study highlights (pages 13, 15).

Psyllium was taken into consideration for this trial to enrich the amount of fiber. However, it would be nice to compare the ingested amount of different types of fibers instead of Psyllium only, whose influence on esophageal motility is indeed still unknown, how it was outlined by the authors.

*Authors' response:* We absolutely agree with the comment. It is not yet clear what kind of dietary fiber (soluble, insoluble, and of which chemical structure) may have greater impact on the studied parameters, as well as the amount of them necessary to reach the expected effect. The choice of psyllium as a mean of dietary intervention was caused by the fact that Mucofalk is the only dietary fiber approved as a drug in Russia. The amount of dietary fiber in the drug is controlled in contrast to food supplements where the quantity of psyllium may somewhat differ. According to the aim of the study we needed guaranteed amount of dietary fiber consumed to be sure in the results. And of course, it would be interesting to compare the effects of different dietary fibers and especially in the studies with cross-over design. We added comment to the discussion and study highlights (pages 12-13, 15)

Patients included in the study had previous responses to PPI or anti H2 therapy. Considering how less powerful are anti H2 drugs in the treatment of GERD, this raises the question about how the patient populations was homogeneous (patients responding to anti H2 have usually a less severe disease).

*Authors' response:* We agree with the reviewer that groups of GERD patients are usually non-homogenous from the point of the response to any type of treatment. Early studies showed that approximately 1/3 of NERD patients responses good on H<sub>2</sub> histamine receptors blockers. It was suggested effective to initiate

treatment of NERD with H<sub>2</sub>-histamine receptor blockers (Reynolds JC, 1995), though their use in maintenance (i.e. long-term) treatment was not that effective as with PPIs (Vigneri S et al, 1995; J Dent et al, 1999). In our study it was necessary to evaluate the response in the group of patients selected by the diagnosis, not by the response. Previous response of patients to any antisecretory therapy combining with the results of negative endoscopy, presence of pathological acid reflux and association of symptoms with reflux (positive SI, SSI, SAP) by 24-hrs pH-impedance studies confirmed that these patients had NERD, but not any functional diseases. The effect of the response to dietary fiber was not linear also taking into account obtained values of SD's. Text improvements were made according to the comment (page 7).

The comparison of the results of the paper with those of Sun XH (ref.42) does not seem correct. Actually, while fatty meals were responsible in that paper of increased numbers of reflux episodes and increased percent of time with pH< 4, in the present study no significant changes in the mean esophageal pH and proportion of time with pH<4 in the lower esophagus were found during the study. Absence of symptoms and improved GERD Q score decrease cannot be considered totally reliable in the evaluation of patients, that should be as much as possible objective, i.e. by evaluation of acid exposure in esophageal mucosa. In this paper the exposure to acid was not significantly changed after dietary fiber enrichment, therefore raising some doubts about its effectiveness. Moreover, the number of Transient Esophageal Relaxations, a well-known important factor in the genesis of GERD, were not significantly influenced by the use of fibers.

*Authors' response:* There is a lack of interventional studies on the discussed matter. Usually it is necessary to compare the obtained results with the available data in the discussion. All the mentioned trials were different by study design and the methods used. In the study by Sun XF (by the way only 8 subjects were enrolled) it was shown that symptoms as well as acidification of the esophagus depended on not one but at least two factors. We could not study TLESRs due to another method used. But our results may suggest that not only acid exposure time, but the number of reflux episodes may be important for triggering NERD symptoms.

In the methods is written: "No PPIs, H<sub>2</sub>-histamine receptors blockers and prokinetics were allowed during the study. Antacid use was allowed when needed." However, antacid use may affect the results. Did the patient use alginate in case of esophageal burning? In this case the number of patients and the amount should be specified.

*Authors' response:* We agree with the reviewer that some of the antacids could affect data of symptoms, motility or esophageal acid exposure. Therefore, alginates were not allowed during the study. Actually, it was recommended to avoid concomitant medication when possible, and in case of heartburn to use Rutacid (the preparation of hydrotalcite). According to the source data only 2 patients used antacid during the study. We added this important information to the manuscript (pages 8, 10).

In conclusion, the hypothesis of the paper that fiber intake may have an influence on esophageal motility and NERD management is not clearly and strongly supported by the paper. Likely the role of fibers is overemphasized.

*Authors' response:* There was not the aim of the study to generalize the results on the recommended course of GERD treatment. We tried to evaluate the effect of the single dietary factor on esophageal motility and NERD symptoms in well-defined group of patients. It is necessary to support the results in larger, prospective studies. The improvements were made to the article text, conclusions and study highlights according to the comment (pages 12, 13, 14).

The number of patients is low for such types of studies.

*Authors' response:* We agree with the reviewer that the greater the number of patients enrolled to the study, the more accurate results obtained. The need for larger studies is mentioned in the discussion. Power analysis suggest that the number of enrolled patients is sufficient for the study purposes. Text was modified per comment (see pages 13, 14, 15).

English style could be improved.

*Authors' response:* According to the journal's requirement and per reviewer request the manuscript was sent to the language agency for the evaluation and polishing.

My feeling is that the paper should have major revisions.

*Authors' response:* We are grateful to all reviewers for the comments and suggestions. In accordance to them several improvements were made to the text of the manuscript.

On behalf of the authors  
Sergey Morozov, MD, PhD