

# General measures and gastroesophageal reflux disease

## Response to Letter to the Editor

Dear editor:

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We appreciate the interest of Doctors Ana Leguizamo, Albis Hani and Valeria Costa in our article that was recently published in the Review. (1) We also very much appreciate their comments, and below respond to them in the most cordial and respectful way.

1. *The recommendation that sleeping in left lateral decubitus position prevents gastroesophageal reflux disease (GERD).* Doctors Leguizamo and Hani base their comments on a systematic review published in 2006. (2) The most important article it reviewed was also included in our bibliography. We analyzed it in the following words, “ Khoury et al. have investigated the effect of postural management on gastroesophageal reflux. (128) They included ten patients who had been diagnosed with GERD in a study. Patients were monitored overnight with a motion sensor, and patients pH was also monitored overnight. The percentage of time pH was less than 4.0 was higher when patients were in right lateral decubitus (median 18.1, range 7.4 - 44.4) ( $p < 0.003$ ) than when patients were in left lateral decubitus (median 0.9, range 0.0 - 4.5) or prone position (median 1.4, range 0.0 to 4.5). Also, the time it took to clear esophageal acid was greater in right lateral decubitus than in the other positions. The number of reflux episodes per hour was higher in supine position than in the other positions. However, there was no assessment of GERD symptoms during the study.” In other words, this *end point* was not measured. Our comment was, “To date, there have been no randomized clinical trials that have successfully demonstrated that these measures impact patients’ GERD symptoms. For this reason, recommendation of these behaviors in the long term is difficult considering that they could significantly interfere in patients’ quality of life. (recommendation: weak level of evidence: low)” In addition, it is impossible for a patient to sleep overnight in left lateral decubitus. The authors of the publication upon which Leguizamo and Hani base their arguments, even assuming that symptoms improve (and this was not evaluated, as we emphasize), conclude the same thing: “It is a challenge to implement this life style modification in practice.”
2. *Waiting six hours after eating before lying down to prevent episodes of reflux.* With respect to this recommendation, the doctors take into account the partial results of the study by Piesman et al. which we thoroughly analyzed. (4) In our review, we also include the work of Orr et al. which had results that differed from those of Piesman. In epidemiology this type of dissimilar results are called “inconsistent results”. Both studies have methodological flaws, as we show in our work. Based on these con-

flicting results, our conclusion was that this behavior, “cannot be recommended as a therapeutic measure (weak recommendation, low level of evidence)”. In our clinical practice, we recommend that all patients with GERD not lie down until three hours after eating to avoid the risk of aspiration. This behavior relies on common sense, since we know of no study that has proven it. We recommend it because we think it does not adversely affect the quality of life of patients. That is to say, it is a recommendation based on intuition and common sense.

3. *Fatty food increases GERD symptoms and should be avoided.* To contradict our conclusion on this issue, the doctors base their opinion on a study by El-Serag et al. (6). This was an analytical study of prevalence, with healthy volunteers who are employees of a Veterans Hospital rather than a study of patients. A total of 915 people were invited to participate and were given a questionnaire. Of these, 371 (40.5%) completely answered the questionnaire. The study concluded that there is, “no statistically significant relationship between fat intake and GERD”. However, an analysis of the results and the study’s design shows that the study has methodological limitations that prohibit this conclusion. Less than half of the total sample responded to the survey which means that respondents may be different from those who did not respond. Since this was an observational study of analytical prevalence (cross-sectional), you cannot control for multiple hidden confounders. This is one of the limitations of such studies. (7) A confounding variable that could not be controlled for was obesity which is a risk factor for GERD as has been demonstrated beyond any doubt. (8) In the study by El-Serag et al. it was obviously impossible to determine whether fat consumption caused obesity nor, by the same token, was it possible to determine if this confounding variable explains an association between eating fat and GERD. The study by El-Serag et al. found an association between eating fat and GERD, but it did not demonstrate causality.

Analytical prevalence studies serve to formulate hypotheses, not to prove causality, and this is one of their disadvantages. (7) Professor El-Serag, who is an amazing gastroenterologist and epidemiologist, publicly recognizes these limitations of his study. In our article, we also took into account other publications for and against the role of fat. (9-10) On this issue there is no consistency of results. In addition, when positive associations have been found they were not always found with fat per se but with the calorie content of the diet. (11) For each of the results, pathophysiological

mechanisms are invoked as explanations giving biological plausibility. The conclusion of our article was that there is, “no evidence to support reducing dietary fat content as part of the treatment of GERD and there are no investigations that have specifically evaluated those diets.” The clinical practice guidelines of the American College of Gastroenterology (ACG) makes a similar recommendation. (12) In our practice we always prohibit fat as a habit of healthy life for all patients whether or not they suffer from GERD since fat’s high caloric content (9 kcal/g) induces obesity, etc.

4. *Chocolate induces gastroesophageal reflux symptoms and should be avoided.* The doctors came to this conclusion on the basis of an unspecified study by Dr. Castell. They consider that the recommendation is relevant because, “It is believed that chocolate’s effects are due to the percentage of methylxanthines (theobromine in particular) and their influence on cyclic adenosine monophosphate (cAMP).” Our review includes all of the main publications. We found series of cases with individuals without GERD. (13-15) Physiological analyses have shown that chocolate induces relaxations of the LES and greater exposure of the distal esophagus to acid. (13-15) However, two studies of patients with GERD found that chocolate did not increase GERD symptoms. (16, 17) The conclusion of our work was, “there are no studies that have shown that the suspension of chocolate improves GERD.” The recent ACG guide on treatment of GERD also concludes that eliminating this food has no scientific support. (12) Doctors Hani and Leguizamo believe that because theobromine relaxes the LES it should be removed from the diet. In other words, since there is a pathophysiological mechanism (biological plausibility), they deduce that elimination results in benefits for patients with GERD. However, investigations into this association have not demonstrated any benefit even if this recommendation “seems logical.”

We take this opportunity to briefly discuss some basic issues of causality and evidence-based medicine. In 1965, Austin Bradford Hill published his views on the association and causation. (18) Since then, that publication has had a significant impact on epidemiologists and researchers. The Bradford Hill criteria are as follows:

1. *Strength of association:* The magnitude of the odds ratio or relative risk, etc.
2. *Consistency:* Similar results in different populations
3. *Specificity:* A factor that specifically influences a particular outcome in a specific population. This criterion is critical, because one cause can have multiple effects

4. *Temporality*: The cause precedes the effect.
5. *Biological gradient*: The greater the exposure, the greater effect
6. *Biological plausibility*: There is a pathophysiological mechanism that can explain the result. This is the least important because knowledge of pathophysiology is always incomplete.
7. *Coherence*: A causal conclusion should not fundamentally disagree with what has already been shown.
8. *Clinical Experiment*: The ultimate evidence of causation is clinical experiment such as randomized controlled clinical trials.
9. *Analogy*: Similar factors may have similar effects.

These are the paths that a variable should approximate before it can be said to cause an effect. Not necessarily all criteria must be met, but depending on the situation, clinicians and researchers will choose the strongest criteria available to draw a cause and effect conclusion.

Doctors Leguizamo and Hani have based their controversy primarily on occasional biological plausibility and also on inconsistent results. The other criteria were absent. When in medicine we talk about published evidence, it simply means that it has been published. Evidence is not something that is incontrovertible. Hence, we have the concept of “best available evidence” or “published evidence”. The rating of evidence requires *critical reading* and minimum concepts in order to be able to assess whether the design of the publications consulted has internal validity. In other words, whether they are methodologically rigorous with variables, calculation of sample size, tracking and representative populations and whether or not they use correct statistical analyses and so on. Based on this assessment, the clinician can assess the quality of research in order to have arguments that support or contraindicate the use of a treatment or diagnostic method studied in a publication. In addition, for these results to be extrapolated, the patient the physician is treating must be similar to those included in the study that she or he has read and must not have any of the exclusion criteria of that study.

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