Reply

To the Editor,

We appreciate to receive these constructive and valuable comments on our article about mean platelet volume (MPV) in children with asthma (1). However, some points were overlooked while reading our article. Some points could not be indicated just because our study was in 'letter to the editor' form (max. 10 references and max. 2000 words). Patients with any other chronic disease other than asthma were not included in our study. Patients with thyroid diseases are the members of this group. The effects of smoking on mean platelet volume (MPV) vary according to gender (2, 3), but Mean platelet volume was not affected in men who are smoking (2). However, there was an increase in MPV in women who are smoking (3). An acute exposure to passive smoking affected MPV according to the duration and intensity of smoke. There is a positive relationship between MPV and the duration and intensity of smoke (4). The exposure to cigarette was evaluated in patients and found no difference in our study (1). MPV increases in obese people, and a positive correlation between MPV and BMI was detected in obese patients (5, 6). So that, patients with obesity were excluded from our study. The effects of medication used for asthma (i.e., inhaled corticosteroids, montelukast, long-acting beta agonists) on MPV are not exactly known. Even so, MPV of the patients was evaluated within a minimum of 1-month period of non-medication.

The impacts of the phenotypic variance on the MPV are available for both patients and control groups. Statistical methods used in our study and the p values were defined (1). MPV values between groups were compared in these methods.

The effects of infections on MPV vary according to the severity. While MPV values increase in sepsis (7), they decrease in respiratory tract infections (8, 9). The most frequent infection seen during asthma attacks is respiratory tract infections. In our study, we detected decrease in MPV values during attack. Of our patients, 80% had high CRP values (1). As we evaluated patients without any chronic disease, we think this is due to accompanying respiratory tract infection. Reasons for the decrease in MPV during attack have been described in the Discussion section (1). In addition, a reduction of 14.6% in MPV between the patient and control groups was observed in the study of Karadag-Oncel et al. (8). In our study, MPV values during stable and exacerbated conditions of the same patients were compared (1).

The authors stated that the details of MPV measurement were not defined. The time when MPV was measured is important as there may be a time-related swelling in platelets. This is especially important when measuring with EDTA tubes (10). In our study, all blood samples were collected into EDTA tubes and were studied within an hour after the sampling.

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References

1. Dogru M, Aktas A, Ozturkmen S. Mean platelet volume increased in children with asthma. *Pediatr Allergy Immunol*. 2015. Mar 26. doi: 10.1111/pai.12381. [Epub ahead of print]
2. Arslan E, Yakar T, Yavaşoğlu I. The effect of smoking on mean platelet volume and lipid profile in young male subjects. *Anadolu Kardiyol Derg* 2008: **8**: 422–5.
3. Cho SY, You E, Lee HJ, Lee WI, Park TS. Smoking cession decreases mean platelet volume in healthy Korean populations. *Clin Lab* 2014: **60**: 1413–6.
4. Yarlioglues M, Ardic I, Dogdu O, et al. The acute effects of passive smoking on mean platelet volume in healthy volunteers. *Angiology* 2012: **63**: 353–7.
5. Coban E, Ozdogan M, Yazicioglu G, Akcit F. The mean platelet volume in patients with obesity. *Int J Clin Pract* 2005: **59**: 981–2.
6. Coban E, Yilmaz A, Sari R. The effect of weight loss on the mean platelet volume in obese patients. *Platelets* 2007: **18**: 212–6.
7. Aydemir H, Piskin N, Akduman D, Kokturk F, Aktas E. Platelet and mean platelet volume kinetics in adult patients with sepsis. *Platelets* 2012: **25**: 1–5.
8. Karadag-Oncel E, Ozsurekci Y, Kara A, Karahan S, Cengiz AB, Ceyhan M. The value of mean platelet volume in the determination of community acquired pneumonia in children. *Ital J Pediatr* 2013: **39**: 16.
9. Renshaw AA, Drago B, Toraya N, Gould EW. Respiratory syncytial virus infection is strongly correlated with decreased mean platelet volume. *Int J Infect Dis* 2013: **17**: e678–80.
10. Dastjerdi MS, Emami T, Najafian A, Amini M. Mean platelet volume measurement, EDTA or citrate? *Hematology* 2006: **11**: 317–9.

Skin testing-directed elimination diet – is 100% efficacy conceivable in eosinophilic esophagitis?

To the Editor,

As professionals largely involved in the management of patients with eosinophilic esophagitis (EoE), we have read with great interest the study by Syrigou et al. evaluating the efficacy of allergy testing-directed elimination diet in pediatric EoE (1). At first, we were puzzled by the reported 100% clinical and histological remission rate with this dietary intervention, even higher than that shown for the most restrictive and

effective elimination diets in EoE: elemental diet (90%) and empiric six-food elimination diet (SFED) (72%), according to a recent meta-analysis (2). But on a second look, the study might be riddled with several methodological flaws.

Children were arbitrarily classified to receive either intervention depending on the severity of their symptoms. GERD-like symptoms were considered 'mild' symptoms, whereas dysphagia, food bolus impaction, weight loss, and hemorrhage were considered 'severe' symptoms. This selection strategy is novel in EoE literature and clearly opens the possibility of testing different treatment strategies in different patients. Furthermore, atopic diseases, gender, and mean age of children in each group are not shown. According to IgE results (overall, IgE detection was positive in 12 of 21 cases in Group A and in 12 of 14 cases in Group B), it can be inferred patients in Group B were much more atopic. The efficacy of skin testing-guided diet is much inferior in non-atopic patients and children >8 years old.

The title of the article ignores the fact that a high proportion of patients also received concomitant treatment with topical corticosteroids during the first 5 months and then on demand. This design an additional bias that prevents accurately assess the efficacy of the proposed dietary treatment. The authors justify their protocol arguing that 'patients with more severe clinical problems were rather impossible to be cured with diet only', a statement opposed to the available evidences on this topic (2). Particularly serious is the fact that the authors attributed clinical and histological improvement to dietary elimination, while the concomitant use of steroids is ignored. Curiously, the patients who did not received corticosteroids had a twofold greater dropout rate from the study (6/21 vs. 2/14), which indirectly indicates that steroids could be the main responsible for EoE control, rather than food elimination.

However, the most striking aspect of this research is the high rate of positive results yielded by atopy patch testing (APT) with foods, contrasting with the research provided on this issue over the past decade (3–8). Because EoE is thought to be primarily non-IgE mediated, skin testing based on delayed hypersensitivity to foods through APT has been advocated (9–11). Unfortunately, interpreting APT results is subjective, prone to significant interobserver variation, and hindered by the lack of standardized extracts. APT is a non-validated technique for the study of food allergy in general, and neither is has been validated in an EoE population with the use of a control group (12–14). For these reasons, it has been repeatedly documented that the diagnostic accuracy of skin testing, especially APT, is not sufficient to support the development of dietary advancement in EoE (15).

After using the recommendations of the European Academy of Dermatology for APT in the study of eczema, it is surprising that the authors obtained sensitivity rates even better for EoE that those reported for eczema itself (16). The results from Syrigou's study completely differ from the previous experience reported on the usefulness of skin testing to guide EoE dietary treatment, which has not exceeded of a 53% efficiency in the largest series to date (7). According with the National Institute of Allergy and Infectious Diseases-sponsored guidelines for managing food allergies (17), skin test results (alone or in combination) are not diagnostic of food allergy. APTs have repeatedly shown a low sensitivity for identifying several foods, especially for cows' milk in EoE (5, 7) (the food most often involved in triggering and maintaining the disease in children and adults). Variability in negative predictive values in APT results provided by several researchers is attributable to the specific threshold they established for considering an APT result as positive (5, 7). The score results obtained by Syrigou et al. are not provided, which hampers the reproducibility of their research.

No information on eliminated foods for 1 year is provided. In addition, 72.3% of patients in this series presented sensitization to three or more allergens, which represents a huge challenge for their dietary management, as does not guarantee an adequate nutritional status of patients, and negatively impacts on the children's quality of life (18). Another criticism might be keeping children on such a restrictive diet for 1 year, when all available evidence point toward a 6- to 8-week period is enough to assess the clinical and histological efficacy of dietary intervention. In spite of this, most patients did not abandon the protocol after 1 year of follow-up.

A growing body of evidence provides insights on EoE which might represent a local disease restricted to the esophagus, with little or no systemic representation. Several facts point out in this direction, including repeated failures to identify noninvasive peripheral markers (19, 20), and the fact that the interplay in the expression of IL-5, IL-13, eotaxin-3, and eosinophils demonstrated in the esophageal mucosa has not been documented in peripheral blood (21); the association of EoE with other atopic manifestations is not universal, and patients with and without atopy show identical clinical features, pathophysiology characteristics, and therapeutic responses. The lack of agreement between skin testing results and foods triggering EoE, identified by sequential reintroduction with endoscopy and biopsy monitoring, has been described (22).

Mean cure rates for the most restrictive elimination diets in EoE (elemental diet and SFED) have been 90% and 72%. Until having a well-designed and with low risk of bias study, the breathtaking results of this paper (100%) should be taken with caution. Warning against the universal use of skin tests for management of EoE has been provided, ensuring that are restricted to the few centers where this intervention has shown some efficacy. Articles like this that seek to change well-established schemes for managing a disease should be based on solid methodological pillars and not leave any room for doubt.

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References

1. Syrigou E, Angelakopoulou A, Zande M, et al. Allergy-test-driven elimination diet is useful in children with eosinophilic esophagitis, regardless of the severity of symptoms. *Pediatr Allergy Immunol* 2015: **26**: 323–329.
2. Arias A, González-Cervera J, Tenias JM, Lucendo AJ. Efficacy of dietary interventions for inducing histologic remission in patients with eosinophilic esophagitis: a systematic review and meta-analysis. *Gastroenterology* 2014: **146**: 1639–48.
3. Liacouras CA, Spergel JM, Ruchelli E, et al. Eosinophilic esophagitis: a 10-year experience in 381 children. *Clin Gastroenterol Hepatol* 2005: **3**: 1198–206.
4. Kagalwalla AF, Amsden K, Shah A, et al. Cow's milk elimination: a novel dietary approach to treat eosinophilic esophagitis. *J Pediatr Gastroenterol Nutr* 2012: **55**: 711–6.
5. Henderson CJ, Abonia JP, King EC, et al. Comparative dietary therapy effectiveness in remission of pediatric eosinophilic esophagitis. *J Allergy Clin Immunol* 2012: **129**: 1570–8.
6. Molina-Infante J, Martin-Noguerol E, Varado-Arenas M, et al. Selective elimination diet based on skin testing has suboptimal efficacy for adult eosinophilic esophagitis. *J Allergy Clin Immunol* 2012: **130**: 1200–2.
7. Spergel JM, Brown-Whitehorn TF, Cianferoni A, et al. Identification of causative foods in children with eosinophilic esophagitis treated with an elimination diet. *J Allergy Clin Immunol* 2012: **130**: 461–7.
8. Rizo Pascual JM, De La Hoz CB, Redondo VC, et al. Allergy assessment in children with eosinophilic esophagitis. *J Investig Allergol Clin Immunol* 2011: **21**: 59–65.
9. Spergel JM, Beausoleil JL, Mascarenhas M, et al. The use of skin prick tests and patch tests to identify causative foods in eosinophilic esophagitis. *J Allergy Clin Immunol* 2002: **109**: 363–8.
10. Spergel JM, Andrews T, Brown-Whitehorn TF, et al. Treatment of eosinophilic esophagitis with specific food elimination diet directed by a combination of skin prick and patch tests. *Ann Allergy Asthma Immunol* 2005: **95**: 336–43.
11. Spergel JM, Brown-Whitehorn T, Spergel JM, Brown-Whitehorn T, Beausoleil JL, Shuker M, Liacouras CA. Predictive values for skin prick test and atopy patch test for eosinophilic esophagitis. *J Allergy Clin Immunol* 2007: **119**: 509–11.
12. Hong S. Food allergy and eosinophilic esophagitis: learning what to avoid. *Cleve Clin J Med* 2010: **77**: 51–9.
13. Heine RG, Verstege A, Mehl A, et al. Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. *Pediatr Allergy Immunol* 2006: **17**: 213–7.
14. Furuta GT, Liacouras CA, Collins MH, et al. Eosinophilic esophagitis in children and adults: a systematic review and consensus recommendations for diagnosis and treatment. *Gastroenterology* 2007: **133**: 1342–63.
15. Sicherer SH, Leung DY. Advances in allergic skin disease, anaphylaxis, and hypersensitivity reactions to foods, drugs, and insects in 2014. *J Allergy Clin Immunol* 2015: **135**: 357–67.
16. Strömberg L. Diagnostic accuracy of the atopy patch test and the skin-prick test for the diagnosis of food allergy in young children with atopic eczema/dermatitis syndrome. *Acta Paediatr* 2002: **91**: 1044–9.
17. Boyce JA, Assa'ad A, Burks AW, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored Expert Panel Report. *J Allergy Clin Immunol* 2010: **126**: 1105–18.
18. Lynch MK, Avis KT, Dimmitt RA, Goodin BR. Topical Review: Eosinophilic esophagitis in children: implications for health-related quality of life and potential avenues for future research. *J Pediatr Psychol* 2015: doi:10.1093/jpepsy/jsv032.
19. Dellon ES, Rusin S, Gebhart JH, et al. Utility of a noninvasive serum biomarker panel for diagnosis and monitoring of eosinophilic esophagitis: a prospective study. *Am J Gastroenterol* 2015: doi:10.1038/ajg.2015.57.
20. Rodríguez-Sánchez J, Gómez-Torrijos E, de-la-Santa-Belda E, et al. Effectiveness of serological markers of eosinophil activity in monitoring eosinophilic esophagitis. *Rev Esp Enferm Dig* 2013: **105**: 462–7.
21. Blanchard C, Stucke EM, Rodriguez-Jiménez N, et al. A striking local esophageal cytokine expression profile in eosinophilic esophagitis. *J Allergy Clin Immunol* 2011: **127**: 208–17.
22. Lucendo AJ, Arias Á, González-Cervera J, et al. Empiric 6-food elimination diet induced and maintained prolonged remission in patients with adult eosinophilic esophagitis: a prospective study on the food cause of the disease. *J Allergy Clin Immunol* 2013: **131**: 797–804.

Reply

To the Editor,

We thank Drs Gonzalez-Cervera et al. (1) for their comments on our recently published paper (2) and for raising an interesting debate about the exact role of skin testing-directed elimination diets in the management of eosinophilic esophagitis (EoE).

As regards treatment stratification of our patient population depending on the severity of symptoms, it must be pointed out that, although this particular classification has not been previously proposed, selection strategies – in general – are not novel in the EoE literature. For example, according to the latest guidelines of the Eosinophilic Esophagitis Working Group and the Gastroenterology Committee of ESPGHAN for the management of children and adolescents with EoE, systemic corticosteroids should be reserved only for patients with extremely severe symptoms (e.g., severe dysphagia, food impaction, dehydration, weight loss, esophageal strictures) (3). On the other hand, elimination diets and/or topical steroids – which were administered to our patient population – are both widely acceptable and recommended as first-line treatment for children with EoE (presenting with either mild or severe symptomatology). Furthermore, in the clinical setting, treatment of patients – and especially pediatric patients – is always individualized, and different patients do need different treatments.

The title of our article 'Allergy test-driven elimination diet is useful in children with eosinophilic esophagitis, regardless of the severity of symptoms' does not 'ignore the fact that a high proportion of patients also received concomitant