In Reply to "Immunoglobulin E Deficiency and Autoimmune Disease"

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J Investig Allergol Clin Immunol 2023; Vol. 33(6): 509-510
doi: 10.18176/jiaci.0952

Key words: Autoimmunity. Immunoglobulin E. Hypothyroidism. Primary biliary cholangitis.

Palabras clave: Autoinmunidad. Inmunoglobulina E. Hipotiroidismo. Colangitis biliar primaria.

To the Editor:

We sincerely appreciate Dr Özdemir's interest in our work [1,2]. The objective of our study was not to investigate the significance of elevated total serum IgE levels. On the contrary, we intended to show that patients with the autoimmune disease primary biliary cholangitis (PBC) often have lower IgE levels than the general adult population in the same area. A more extensive description of IgE levels in this general population has been reported elsewhere [3], as mentioned in our article [1]. Definition of elevated total serum IgE levels in the population is subject to drawbacks, namely, its nonnormal distribution and the high frequency of atopy, which is a key determinant for total serum IgE levels. In the aforementioned general adult population of 1516 individuals (1514 evaluable), the prevalence of atopy—based on allergic sensitization revealed by skin prick test positivity to a battery of aeroallergens frequent in the area—was 21.9% [3]. Atopic individuals had much higher IgE concentrations than nonatopic individuals (median [IQR] 113 kU/L [41-274 kU/L] vs 19 kU/L [6-53 kU/L], respectively, $P<10^{-60}$) [3]. Therefore, it makes little sense to mix patients whose atopic status is unknown when trying to define reference levels for a population. The area under the receiver operating characteristic curve of total serum IgE for the diagnosis of atopy in that population was 0.796 (95%CI, 0.771-0.822), and setting the cut-off point for serum IgE at 100 kU/L would yield a sensitivity of 53.6% and specificity of 85.8% for diagnosis of atopy. An additional limitation of total IgE, as Dr Özdemir points out, is that IgE concentrations in adults may be influenced by demographic factors (IgE is higher in males), common metabolic disorders (IgE increases in relation to body mass index), and lifestyle variables (IgE is higher in smokers and in cases of excessive alcohol consumption, which is frequently associated with smoking in some populations and is a powerful determinant of IgE concentrations) [3,4]. These associations are more evident in the subgroup of nonatopic patients [3], probably because atopy per se is such a potent determinant of total IgE levels that overshadows the effect of minor factors. A major advantage of using a random sample of the population as a control group is that it confers greater representativeness than biased samples of

volunteers, blood donors, or patients with disease. In addition, a random sample can be properly phenotyped. Moreover, general populations allow the investigation of the effect of common factors, such as those mentioned above, on the analytes. The aforementioned drawbacks limit the usefulness of the isolated clinical use of total serum IgE. Given these limitations, the cut-off of 100 kU/L to define total IgE as "high" was frequently used in recent epidemiological studies [5,6], and even in reference studies aimed, as in ours, at investigating the implications of IgE deficiency [7].

Increased IgM is indeed a characteristic feature of PBC [8]. In our study, serum IgM concentrations were significantly higher in patients with PBC than in the general population [1]. This does not mean that PBC patients have hyper-IgM syndrome, a well-characterized immunodeficiency disorder [9], which was not present in any PBC patient or in the general population in the study. The distribution and factors for serum IgM concentrations in the general population have been addressed elsewhere [10]. Among PBC patients, markers of liver damage were correlated with IgM concentrations but not with IgE concentrations (the *P* value for those correlations [>0.5] is correct in all cases) [1]. Immunoglobulin concentrations were not investigated in the relatives of study participants.

In summary, we think that the interesting points raised by Dr Özdemir do not affect the fundamental conclusions of our study [1], namely, that patients with PBC, a prototype of autoimmune disease, very often have IgE deficiency, and significantly more often than the general adult population in the area. In patients from the general adult population, IgE deficiency is associated with thyroid autoimmune disease.

Funding

The study was supported by grants from the Carlos III Institute of Health (Instituto de Salud Carlos III, PI16/01404 and PI16/01395), the Spanish Network for Addictive Disorders (Red de Trastornos Adictivos, RD16/0017/0018, Spanish Ministry of Health), the Spanish Network for Preventive Activity and Health Promotion Research in Primary Care (Red de Actividades Preventivas y de Promocion de Salud en Atención Primaria, RD16/0007/0006), and the European Regional Development Funds (FEDER).

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

1. Porto-Soto A, Sopeña B, Freire M, Mosquera M, Alonso-Sampedro M, Gude F, et al. Relationship between immunoglobulin E deficiency and autoimmune Disease: The paradigm of primary biliary cholangitis. J Investig Allergol Clin Immunol. 2023;33:297-9.
2. Özdemir Ö. Immunoglobulin E Deficiency and Autoimmune Disease (Letter to the Editor). J Investig Allergol Clin Immunol. 2023;33(6):508-509.
3. Carballo I, Alonso-Sampedro M, Gonzalez-Conde E, Sanchez-Castro J, Vidal C, Gude F, et al. Factors influencing total serum IgE in adults: The role of obesity and related metabolic disorders. Int Arch Allergy Immunol. 2021;182:220-8.
4. Alvela-Suarez L, Campos J, Carballo I, Gomez-Rial J, Vidal C, Lombardero M, et al. False-positive results of serological tests for allergy in alcoholic patients. J Investig Allergol Clin Immunol. 2019;29:213-21.
5. Mora T, Sánchez-Collado I, Mullol J, Muñoz-Cano R, Ribó P, Valero A. Prevalence of atopic dermatitis in the adult population of Catalonia (Spain): a retrospective, large-scale population-based study. J Investig Allergol Clin Immunol. 2023 (in press) doi: 10.18176/jiaci.0899.
6. Domingo C, Sicras-Mainar A, Sicras-Navarro A, Sogo A, Mirapeix RM, Engroba C. Prevalence, T2-biomarkers and cost of severe asthma in the era of biologics: The BRAVO-1 study. J Investig Allergol Clin Immunol. 2023 (in press) doi: 10.18176/jiaci.0871.
7. Ferastraoaru D, Rosenstreich D. IgE deficiency and prior diagnosis of malignancy: Results of the 2005-2006 National Health and Nutrition Examination Survey. Ann Allergy Asthma Immunol. 2018;121:613-8.
8. Martin DM, Vroon DH, Nasrallah SM. Value of serum immunoglobulins in the diagnosis of liver disease. Liver. 1984;4:214-8.
9. Yazdani R, Fekrvand S, Shahkarami S, Azizi G, Moazzami B, Abolhassani H, et al. The hyper IgM syndromes: Epidemiology, pathogenesis, clinical manifestations, diagnosis and management. Clin Immunol. 2019;198:19-30.
10. Carballo I, Alonso-Sampedro M, Escribano RM, Fernandez-Merino C, Sopeña B, Vidal C, et al. Factors associated with serum IgM concentrations: a general adult population study. Scand J Clin Lab Invest. 2021;81:454-60.

Manuscript received September 26, 2023; accepted for publication October 6, 2023.

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