

Extending the Debate on Poor Response to Hepatitis B Virus Vaccination in Children With Celiac Disease: Which Question Remains?

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Dear Editor,

A poorer response to hepatitis B vaccination, in coeliac subjects, compared to healthy subjects, has been largely debated. Almost all authors postulated that human leukocyte antigen (HLA) genotype DQ2, found in 90 - 95% of coeliac patients, could represent the main cause in determining the impaired antibody response to recombinant HBV vaccine (1), as well as observed also in healthy not responder subjects.

However it has been supposed that gluten intake could represent the main factor in influencing a poorer response to vaccine, since in several studies, it has been observed that the percentage of responders in patients compliant with a gluten free diet (GFD) was similar to healthy subjects (2, 3). Since type I diabetes (T1DM) and coeliac disease (CD) have the same genetic background, given by the HLA molecules that have also been identified as haplotypes associated with unresponsiveness to hepatitis B virus (HBV) vaccination (DR3 and DR4 for T1DM, DQ2 and DQ8 for CD), we firstly compared three different groups of patients, corresponding to T1DM, CD and DMT1-CD, that had in common the same HLA haplotypes, to establish the weight of specific haplotypes of HLA and/or gluten that could favor a poorer response to HBV vaccine.

In 30 children suffering from both CD and DMT1, vaccinated by the administration of three doses of vaccine (Engerix-B, Glaxo Smith Kline, London, United Kingdom) at the age of 3, 5 and 11 months of life, according to the national vaccination schedule, we discovered 16 (53.3%) non-responders. This percentage was similar to a previ-

ous study on 60 coeliac patients (4), although not significantly higher, compared to a previous study on 100 diabetics (5) (Table 1).

As the mean age and the anti-HBs antibodies titers was similar between coeliacs and coeliacs/diabetics, we consider that the presence of T1DM and its HLA haplotype seems to not decrease anti-HBs antibodies production and percentage of responders. The open question is: what is the role of gluten in this matter?

Comparing the T1DM/CD and T1DM, in which both groups had a similar HLA haplotype, we found a higher non-significant percentage of non-responders in T1DM/CD than in T1DM (53.3% vs. 38.2%), although the first group even had a significantly lower mean age ($P < 0.0001$), which usually is associated to a higher titer of anti HBs antibodies ($P < 0.02$) and a higher percentage of responders, as we also found in our study (Table 1). The question still remains open: what is the role of gluten in this matter?

First of all, we observed that the percentage of non-responders is higher in T1DM/CD patients, compared with diabetics (53.3% vs. 38.2%). However, if we compare the first group with coeliacs, the percentage of non-responders is similar (53.3% vs. 50%). As the genetic substrate of HLA haplotypes, in the two diseases, is the same, this comparison indirectly confirms that gluten certainly represents a second variable, which favors a further decrease of efficacy to HBV vaccine, beyond the HLA system.

As written in 1890 by in the chapter "The Science of Deduction" of the book "The Sign of Four, eliminate all other factors and the one which remains must be the truth (6)."

Table 1. Characteristics of Patients With Type 1 Diabetes Mellitus, Celiac Disease and Associated Type 1 Diabetes Mellitus/Coeliac Disease ^a

	DMT1 ⁴ (n = 100)	CD ⁵ (n = 60)	DMT1/CD (n = 30)	P Value
Age years mean (SD) ^b	13.6 (4.9)	8.6 (4.5)	6 (4.2)	< 0.0001
Anti HBs mean (SD) ^b	58 (112.9)	216.1 (315.8)	143 (299.2)	< 0.02
Non responders/Responders (%) ^c	46/64 (38.2)	30/30 (50)	16/14 (53.3)	> 0.02

^a Abbreviations: CD, Coeliac Disease; DMT1, Type 1 Diabetes Mellitus; ns, not significant.

^b Mann-Whitney U test.

^c Fisher's exact test.

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