Author's response to reviews

Title: Celiac Disease in the Mediterranean Area

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Author's response to reviews: see over
To the Editor-in-Chief:

We are pleased to re-submit to BMC Gastroenterology a paper produced by the extended MEDICEL Mediterranean Network for Celiac Disease.

We feel confident that the readers of BMC Gastroenterology will found attracting the picture of the 'Celiac Diagnostic resources' of 16 countries of the Mediterranean Basin.

The manuscript has not been published previously and is not under consideration for publication elsewhere. The manuscript is approved by all Authors.

The European Laboratory for Food Induced Diseases, from Naples, Italy, is the coordinating centre. FT, LA, RA and LG planned the study, developed the forms, run the analysis and lead the writing of the manuscript. MBH, AK, SK, GM, ZM made substantial contributions to conception and design and acquisition of data. AA, MAZ, JRB, GB, SB, SC, VD, JPH, II, DMT, ER, ST, VV, CA have been involved in drafting the manuscript and collecting data.

We modified the paper as requested by our reviewers with the point-by-point responses to the concerns.

Rachele Ciccocioppo's report:

I. The title does not allow the reader to understand what the term ‘profile’ would mean.

We modified the title.

II. The limits of a retrospective study should be discussed.

We agree. In fact we wrote that this study suffers from the objective limitation of being a retrospective study. Nevertheless we needed a cross-sectional picture of the pattern of celiac disease in the area, for which this kind of study is rapidly informative. In the same area we have already started a prospective study in order to validate the findings of this actual study.

III. The invasiveness of the perendoscopic biopsy sampling should be commented.

We focused about the fact that we shared among the 16 partners the importance of avoiding, at least in a percentage of cases, such an invasive technique.

IV. The graphics of the figures should be improved.

We modified, whenever possible, the figures in terms of quality.

We also revised the whole text in order to remove some English mistakes.

Stefano Guandalini's report:

I: Page 6: "Clinical manifestations varied greatly according to age. Infants (1–5 years) and young children (6–11 years)...". Cannot define infants subjects between 1-5 years: infants are babies below 1 year. More importantly, in Table 1 there is no differentiation of age according to presenting symptoms, while this would be an interesting data to show.
We included an extra table where we showed the distribution of symptoms according to ages.

II. Page 6, under "Biopsy". I assume T1, T2 etc. refer to the Marsh score (this is not stated in the text). If this is the case, then I would be hesitant to describe as "mild lesions" T3a.

We agree that T3a cannot be included in the mild lesions so we excluded that percentage.

III. Page 7, the title for 3.5 should be better phrased in English as "When could the biopsy be omitted?"

We modified correctly the title.

IV. Page 8: "The basic assumption that tTG antibodies predict severe mucosal damage is not confirmed". While this is indeed apparent from the authors' data, this statement that conflicts with a large body of published previous evidence to the contrary would deserve a more in-depth comment by the authors: what could be the reasons for this unexpected finding? Was a pathology revision centrally done (either on all biopsies or only on samples)? Could it be that the ELISA test for tTG was less reliably performed in some areas?

The correlation between the mucosal damage, estimated by the Marsh stages, and the level of Anti Transglutaminase antibodies has been confirmed in several relevant studies but this correlation has several weakness, due to the nature of the data. Anti Transglutaminase Antibodies, as all antibodies, do not have a normal distribution, but a logarithm distribution and Marsh stages have an ordinal distribution, not a continuous one. So the relationship between these two variables is intrinsically prone to large or very large confidence intervals, which reflect not only the nature of the variables, but also the wide polymorphism of the phenotype of the disease. The quality of serological test and the scarcity of HLA testing are the critical points that, at present, limit the chance to diagnose CD without a biopsy. Unfortunately in several of the participating referral centers, the lab experience to assay the Anti Transglutaminase is limited and performed only when financial resources are available. Some Lab produce semi-quantitative data, increasing the uncertainty of the assessment. Before that, there is one of the objective of the MEDICEL network is to support the upgrading of local diagnostic resources: hence we are now running ad hoc procedure need to standardize the methods of antibody assay and to increase the availability of HLA haplotyping by exploiting the new technologies that attempt to bring the test to the point of care.