24th of August 2012

The authors would like to thank the reviewers for their specific and helpful comments.

Please find enclosed the edited manuscript in word format (file name: tack et al 2012.doc)

**Title**: Serum parameters in the spectrum of coeliac disease: beyond standard antibody testing

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The manuscript has been improved according to the suggestions of the reviewer:

**Major points**

**1.** As suggested by the reviewer, we changed the title in ´serum´ parameters as this would underline the evaluation of new parameters as opposed to the traditional serological parameters used in celiac disease.

**2.** To provide more insightin the variation and clinical relevance of the serum levels determined, we displayed the cut-off values of each ELISA-kit in the corresponding graph (dotted line in Figure 1). Furthermore, the group of CD patients with biopsy proven remission, as previously included in our study, can be considered a representative control group. Regarding the subject of age-dependency the reviewer addresses a relevant point as a minimal increase of the levels of serum cytokines has been reported in men but not woman (Young et al. Clinical and Experimental immunology 1999). In accordance with current literature, in our study the group with uncomplicated CD is indeed somewhat younger than the complicated CD group, but based on the relative small differences in age in aforementioned minimal increase we argue this is not of clinical relevance. Nevertheless, in case these parameters would be applied to various age groups, including both children and elderly, this would be a point of concern. Yet, our patients of interest represent a homogenic group regarding age, as they are almost without exception between 40-60 years of age.

We added the following sentence in the discussion: *‘Care must be taken in case our findings are extrapolated to other age groups, as it can not be excluded that normal values vary over age’*

**3.** The reviewer raised the question whether complicated CD represents merely a higher level of inflammation compared to CD, and possibly other inflammatory conditions. As we focus on ‘the spectrum of coeliac disease’, inclusion of other comparison groups is beyond the scope of this study. However, in the discussion we did place the various CD entities more in perspective with other gastrointestinal diseases, with a specific focus on Crohn’s disease. By doing so, we hope to provide more insight in our data that indeed suggests that complicated CD merely represents a more extended inflammation state. In accordance with the suggestion of the reviewers we attempted to intensify the discussion by adding relevant papers from other gastro-intestinal diseases and-or lymphomas.

For example we added the following section in the discussion: *‘Cytokine levels in comparison with other gastro-intestinal diseases: Our data suggests that complicated CD is accompanied by a higher pro-inflammatory state as compared to uncomplicated CD. To provide insight in the extend of this inflammation, it can be compared to the cytokine profile in other (small) intestinal disease, such as Crohn’s disease. Not only have elevated serum levels of IL-6 been reported in this disease, but these levels appear even higher than in complicated CD.[42] On the other hand, IL-6 and IL-8 serum levels in Helicobacter Pylori infected patients with peptic ulcer disease are not elevated.[43]*

**Minor points**

**1.** We introduced all abbreviations, corrected grammatical mistakes and added exact values to p-values.

**2.** We excluded table 2 and added p-values to the corresponding figures.

**3.** It is possible that a combination of parameters could distinguish complicated and uncomplicated coeliac disease. Probably a combination of Il-8, IL-17 and/or sCD25 may distinguish between the GFD group and the group of RDCI-II-EATL. However, the groups are to small to detect a clinical useful AUC with proper sensitivity and specificity.

**4.** With the aim to correctly analyze our data we had a statistician (VHMC) check our analysis.

We hope that our modifications render our manuscript in its current form suitable for publication in BMC gastroenterology

Yours sincerely,

On behalf of the authors,

Greetje J.Tack, MD