EDITORIAL

Too much stress for enterocytes in celiac disease? On the way to better control of treatment outcome

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Celiac disease (CD) is a systemic immune-mediated disorder triggered by gluten intake in genetically predisposed individuals.[1] Gluten-free diet (GFD) is the cornerstone of CD treatment and is highly efficacious in inducing and maintaining clinical remission. However, GFD with life-long elimination of wheat, rye, and barley has dramatic consequences for the patient's everyday life. Adherence to GFD is variable,[2] and current guidelines strongly support a follow-up, particularly in the first year after diagnosis to assess diet adherence and disease activity. This includes assessment of clinical symptoms, dietary review, serological assessment, and, in some cases, follow-up biopsies.[3] Although GFD is highly efficacious regarding clinical and serological disease remission, with the latter being used for assessment of GFD adherence in particular, there is a significant mismatch between clinical and serological disease activity on one side, and histological disease activity on the other. Dickey et al[4] demonstrated that more than 80% of patients with persistent villous atrophy had normal levels of serological markers. In general, the rates of mucosal healing under GFD are reported to be only 57% to 76%.[3] However, whether follow-up endoscopies are needed for every patient remains an issue of ongoing debate. Current guidelines recommend routine follow-up biopsies only in patients with clinical nonresponse or increased risk of lymphoma (or both). However, there certainly is an unmet need for noninvasive markers being in between serological and endoscopic disease evaluation.

In this issue of the *Polish Archives of Internal Medicine* (*Pol Arch Intern Med*), Piątek-Guziewicz et al[5] pursue an approach of implementing the previously studied oxidative imbalance as a marker for CD activity. They demonstrated that not only oxidative stress measured by fasting serum nitride oxide (NO) levels is significantly elevated in active disease compared with controls, but that also several antioxidants show decreased serum levels. Furthermore, NO is elevated and antioxidants (vitamin E, glutathione perodixase) are decreased—to a smaller extent—in dietary-controlled celiac patients. NO even shows a significant correlation with intestinal mucosal damage, although this correlation is low.

Piątek-Guziewicz et al[5] are by far not the first to focus on the NO pathway. It has been known for years that colonic NO synthesis is increased in active ulcerative colitis.[6,7] Toxicity and inflammation can lead to increased transcription of pro-inflammatory cytokines and enzymes including inducible NO synthase (iNOS, expressed in enterocytes), which in turn leads to higher NO levels promoting oxidative stress.[8] In CD, adult patients have been shown to have higher iNOS activity, which was partly corrected by GFD.[9] Spencer et al[10] further showed that plasma NO end products fell rapidly after introduction of GFD and were related to histological disease grade. The novelty presented in the study by Piątek-Guziewicz et al[5] is that even in adult patients with nonclassic symptoms, the oxidative imbalance can be used to differentiate patients with active CD from those without CD and, to some extent, from treated CD patients. Moreover, the authors showed that other markers of oxidative imbalance such as elevated uric acid might also be applied. The fact that there is ongoing oxidative imbalance in treated patients compared with controls raises several questions: did patients simply not adhere to GFD? Or is an ongoing oxidative imbalance an indicator of noncontrolled mucosal damage? Is there any clinical impact of patients with normal serology and absence of symptoms, but oxidative imbalance?

Given the correlation of increased NO with mucosal damage and the known gap between clinical, serological, and histological disease activity,

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NO may indeed be a more reliable surrogate than any clinically applied serological marker. However, NO and antioxidants should be tested as diagnostic and follow-up markers, respectively, and compared to the gold standard (biopsy) in more detail in order to allow the receiver operating characteristic curve analysis and calculation of positive and negative predictive values. This, however, was beyond the scope of this study.

Nonetheless, the reported results have to be interpreted with caution, because the study is purely descriptive, and it therefore remains unclear whether the oxidative imbalance is a contributor to the disease or a simple result of it. If it is "the chicken or the egg", it has to be studied in experimental models. Furthermore, the study was certainly underpowered to detect smaller differences between treated CD patients and controls, and the cross-sectional design instead of a long-term follow-up with several serum samples over time in every patient is a clear limitation, since there might have been significant interindividual variation.

The question remains why we have to care about ongoing mucosal damage despite clinical and serological remission? Well, because there is still the possibility of CD complications. However, data on this are conflicting: persistent mucosal disease activity is not associated with overall mortality.[11] Nonetheless, the lack of mucosal healing might be a risk factor for autoimmune disease, pregnancy, and lymphoma.[3] The latter has been shown to be significantly associated with persistent villous atrophy.[12]

Due to the lack of a marker in between serology and endoscopy, and given the fact that the latter is not cost-efficient in the context of the low number of patients with CD complications, guidelines still recommend assessment of clinical and serological disease activity as the first step and reserve endoscopy for a selected subset of patients only. Nonetheless, recommended follow-up assessments are underused. We have recently shown that less than 70% of CD patients had a follow-up serology within 1 year after their diagnosis. Although the rate was higher when patients were followed by a gastroenterologist, a significant proportion of the specialists did not adhere to the current guidelines.[2] So, while better noninvasive markers are needed, physicians—general specialists and gastroenterologists in particular—should be aware of the importance of a follow-up management in patients with CD. Regarding the unmet need of surrogates in between serology and endoscopy, NO and other indicators of oxidative imbalance may close an important gap some day. We are not there yet; however, the results of the study by Piątek-Guziewicz et al[5] are a further piece in this complex puzzle.

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