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Editorial: a novel approach to monitor mucosal healing in coeliac disease – as simple as shifting goalposts?

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Conflict of interest: JT-D is a co-inventor of patents pertaining to the use gluten peptides in therapeutics, diagnostics and non-toxic gluten in coeliac disease. He is a shareholder of Nexpep Pty Ltd and receives consulting fees from ImmusanT, Inc.

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With the recognition that persistent villus atrophy is associated with potentially serious sequelae in our patients with coeliac disease, mucosal healing has become established as the key measure of treatment success with a gluten free diet (GFD) [1, 2]. However, an accurate and cost-effective tool to monitor healing that avoids the need for regular endoscopies remains an unmet need. IgA and IgG antibodies to transglutaminase (tTG) and deamidated gliadin peptides (DGP) reflect gluten-specific T cell activation in coeliac disease but do not directly measure intestinal inflammation. The paucity of monitoring options means that serology remains widely employed as a marker of intestinal damage even though it correlates poorly with villous atrophy. In contrast with its excellent sensitivity for disease screening, serology does not detect small amounts of gluten ingestion and the sensitivity of tTG IgA to detect persistent villous atrophy is typically less than 50% [3], although DGP antibodies may perform better [4, 5]. Normalisation of serology on a GFD does not always reflect mucosal healing [6, 7]. Novel biomarkers of intestinal damage are therefore of interest but lack specificity for coeliac disease e.g. intestinal-fatty acid binding protein, or remain in pre-clinical development e.g. metabolomic profiling [8].

Is there a simpler way? In a recent issue of *AP&T*, Fang et al. take a fresh look at tTG IgA [9]. The authors tested their clinical observation that a negative tTG IgA result (defined by their lab as < 4 U/mL) where the antibody titre was *undetectable* (< 1.2 U/mL) was more likely to be associated with mucosal healing than a negative but *detectable* tTG IgA level (1.2 – 3.9 U/mL). They retrospectively assessed the records of 402 adults with coeliac disease at the Mayo Clinic who had been on a GFD for at least 6 months and who had a negative tTG IgA level and matching small intestinal histology. They found seronegative patients with undetectable titres more often had normal duodenal histology compared to those with detectable titres (OR = 1.96). However, 51% of all patients with an undetectable titre still had intestinal damage, indicating limited value in predicting mucosal recovery. The findings suggest that serologic thresholds established for coeliac diagnosis do not apply to mucosal healing and that, possibly, a more predictive 'healing threshold' can be defined at the lower end of the tTG IgA range given a sensitive enough assay.

The technical challenges of validating a cut-off are substantial given the variation in

performance between tTG kits and the high assay variability at these low titres. More data is needed to support the clinical utility of this approach. It would be interesting to see if the DGP IgG assay has predictive value for mucosal healing at low titre, or if these observations apply in coeliac children, where tTG IgA is a better indicator of mucosal recovery than in adults [10]. The search goes on to find suitable biomarkers of healing. Novel technology, or as Fang et al. have nicely shown, innovative application of existing tests, may yet provide an answer.

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