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SHORT REVIEW

Gluten tolerance; potential challenges in treatment strategies

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ABSTRACT

Tolerable gluten thresholds in gluten free products have long been debated together with issues of cross contamination of gluten free cereals during the milling process. It is well established that a totally gluten free diet is virtually impossible owing to the presence of traces of gluten. It is estimated that daily consumption of gluten from contaminated gluten free foods is in the range of 5 to 50 mg. We believe evidence is mounting that it may be possible for some coeliac patients to tolerate gluten above the limits considered permissible at threshold levels. Conversely, it seems there is evidence that some patients might have a much lower threshold for gluten. Whatever would be the individual threshold, GFD may be of benefit to any symptomatic patients even those with milder enteropathy like microscopic enteritis.

Keywords: Gluten tolerance, Coeliac disease, Gluten free diet.

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Our understanding of coeliac disease (CD) diagnosis, pathogenesis and therapy has significantly improved over the last two decades. A gluten free diet (GFD) is considered an effective therapy in most symptomatic coeliac patients (1). Dietary management is also essential in the treatment of complications like osteoporosis, anaemia and associated disorders like lactose intolerance and type I Diabetes. However, most patients with CD can tolerate small amounts of gluten in their diet (2). The highest safest level is debated and presumably differs between individuals. Therefore, the appropriateness of a life-long GFD for a some of coeliac patients is now under discussion (1, 3, 4).

The study by Errichiello et al, (5) evaluates compliance to a gluten-free diet (GFD) and explores the relationship of diet with well-being. This study has some interesting findings, suggesting that moderate amounts of gluten may be tolerated by some coeliac patients without ill effects. The study of 204 young coeliac patients in Italy, reports that 54/204 (26.5%) patients transgressed from the GFD. Of the 54 poor compliers, 14 (25.9%) were consuming 1-5 grams gluten/day and 11 (20.4%) reported consuming more than 5 grams/day. Five grams gluten/day is approximately half of the intake that might be expected in a normal diet – where gluten intake averages at 10-20 grams/day (6). Errichiello et al. report that 31/54 (57.4%) of the poor compliers were asymptomatic and that a large proportion 39/54 (73.6%) of poor compliers had negative tTG and only 14/54 (26.4%) had a positive tTG. Biopsies and histological testing were not undertaken.

Given that 54% of those in the study reported some limitation in their social lives, one has to question if it may be possible to find a way to predict individual tolerance to gluten among

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coeliac patients? It may be that some coeliac patients have a permanent tolerance to gluten at some level and that this can contribute to improved social integration and quality of life (3, 4). Perhaps a life-long GFD may not be necessary for every coeliac patient!?

Tolerable gluten thresholds in gluten free products have long been debated together with issues of cross contamination of gluten free cereals during the milling process. It is well established that a totally gluten free diet is virtually impossible owing to the presence of traces of gluten. It is estimated that daily consumption of gluten from contaminated gluten free foods is in the range of 5 to 50 mg (7). Permitted levels of gluten in gluten free foods vary in different areas of the globe. The Codex Alimentarius (World Health Organisation & UN Food and Agriculture Organization Commission) recommend ≤ 200 parts per million (ppm) of gluten is permitted in foods considered to be free of gluten (7). An intake of gluten below 10 mg/day is generally considered safe for most coeliac patients and not thought likely to cause histological abnormalities (8). Moreover, several recent studies have demonstrated that oats (which contain gluten) can be tolerated by many coeliac patients (9, 10). The prolamine gliadin in wheat constitutes 40% of the cereal; the percentages are similar for rye and barley. However, in oats, avenins constitute only 15% of the cereal (11).

We believe evidence is mounting that it may be possible for some coeliac patients to tolerate gluten above the limits considered permissible at threshold levels. Conversely, it seems there is evidence that some patients might have a much lower threshold for gluten. A GFD may be of benefit to any symptomatic patients even those with milder enteropathy like microscopic (12-15). Under current guidelines a GFD is recommended to gluten sensitive cases with villous atrophy. This policy excludes a range of symptomatic gluten sensitive cases with atypical presentation including those with small bowel Microscopic changes (Marsh 0-II). It is well known that patients with microscopic enteritis (Marsh 0-II) may also develop gluten related antibodies and minor mucosal lesions may not be apparent during routine histological analysis (16). Their appearance may precede, by months or years, the further histological progression of the disease (17, 18). The sub-microscopic changes might be due to unknown factors in CD immuno-histogenesis that lead to malabsorption syndrome much earlier than expected. It is, therefore, clear that malabsorption may occur even in patients with sub-microscopic mucosal abnormalities (12-14). This evidence would support implementing a GFD in symptomatic cases, which feature malabsorption even at microscopic stage with the absence of villous atrophy.

When presentation is atypical, it can be a challenge to identify a patient where a GFD may be of benefit. Similarly, identification of the subgroups that may need less restriction with their gluten intake could also be extremely difficult (Figure 1). There are coeliac patients for whom gluten would be detrimental, as studies show histological abnormalities with moderate (200-1000mg/day) intakes (19). There is also overwhelming evidence that a GFD might be beneficial in coeliac patients presenting with microscopic lesions (15, 20, 21). In an ideal world our aim should be to identify cases with different tolerance for gluten based on future accurate tests as gluten tolerance might be variable between different individuals (5). Hopefully by developing sensitive marker in future we may achieve the goal to lessening the degree of gluten restriction in suitable candidate and improve the quality of life in those patients with a higher threshold for gluten toxicity.

Previous studies (3, 4) and the study performed by Errichiello et al. show that some patients would tolerate even more than 5g gluten/day and still remain symptom free with negative serology.

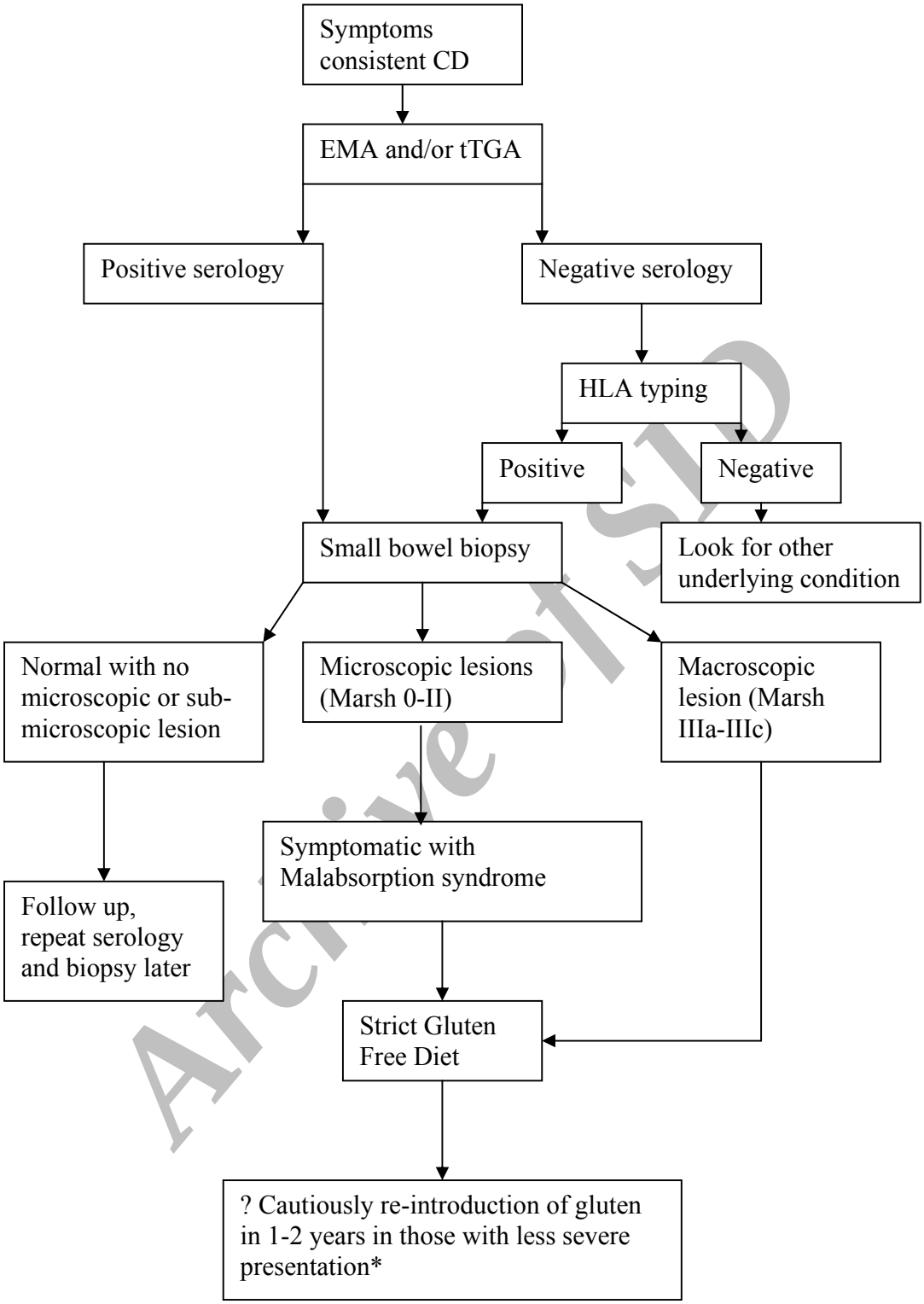

Figure 1. Gluten free diet guide. * The subgroup with a potential higher gluten tolerance need to be defined in future studies.

Unfortunately, antibody screening is not the most sensitive test for assessing intestinal mucosal recovery due to their poor correlation with histological damage (22). The antibodies are

mostly associated with severe lesions and macroscopic mucosal damage like (sub)-total villous atrophy (22, 23).

Undoubtedly, the future challenge is to sharpen the criteria in order to balance the amount of gluten restriction and gluten intake as well as qualifying the atypical subgroup where a GFD would also be appropriate. Further large-scale studies would be required to characterise the individuals with higher and lower thresholds for gluten toxicity. If a sensitive algorithm was validated in future studies, it could predict tolerance to gluten through analysis of the indicative parameters.

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