

# Intestinal lactase, sucrase, and alkaline phosphatase in 373 patients with coeliac disease

JG O'GRADY, FM STEVENS, R KEANE, EM CRYAN, B EGAN-MITCHELL, B McNICHOLL, CF McCARTHY, PF FOTTRELL

*From the Departments of Medicine, Paediatrics, and Biochemistry, Regional Hospital and University College, Galway, Ireland*

**SUMMARY** Lactase, sucrase, and alkaline phosphatase activities were measured in 833 peroral small intestinal biopsies from 373 patients with coeliac disease. Enzyme activities decreased with increasing degrees of mucosal damage. Enzyme activities in mucosae of patients with coeliac disease in remission were lower than in control groups matched for age, sex, and site of biopsy. Enzyme activities were measured in 81 patients when the mucosa was severely damaged and later when considerable improvement had occurred. Lactase activity remained low in 13% of patients under the age of 18 and in 33% of those over 18 years. Sucrase activity usually improved with histological recovery, but alkaline phosphatase activity tended to remain depressed in patients in whom lactase activity failed to improve.

Activities of small intestinal brush border enzymes such as lactase, sucrase, and alkaline phosphatase are reduced in patients with untreated coeliac disease but recover again during remission.<sup>1-6</sup> It has been suggested that the measurement of such enzymes may be used as a quantitative index of improvement of the small intestinal mucosa.<sup>3</sup> The rates of recovery of the aforementioned enzymes vary: sucrase activity recovers more rapidly than lactase, which may remain severely depressed for many years especially in older patients.<sup>4</sup> We have previously described the influence of age, sex, and site of intestinal biopsy on enzyme activity in control subjects.<sup>7</sup> This paper investigates the importance of these factors in a large group of patients with coeliac disease with due regard to the histological state of the intestinal mucosa. We also present an analysis of data from 81 patients where mucosal enzyme activity was examined in severely damaged mucosae and subsequently when the mucosae had improved considerably with the withdrawal of gluten from the diet.

## Material and methods

A total of 833 small intestinal biopsies were studied in 373 coeliac patients (218 female, 155 male) over 10 years. In all cases coeliac disease was diagnosed

on the basis of severe small bowel mucosal damage with histological or clinical improvement, or both, on a gluten free diet. Patients' ages ranged from 1 to 78 years, and 230 of the patients were under the age of 18 when first studied. Enzyme data are presented on biopsies from 157 patients originally on normal diets and subsequently on gluten free diets, 126 patients on gluten free diets only, and 90 patients on normal diets only. The patients were divided into three age groups: 0 to 18 years, 19 to 45 years, and 45+ years.

Small intestinal biopsies were obtained and processed as previously described.<sup>7</sup> Biopsies were obtained from the proximal duodenum (site A) in 40 cases, distal duodenum (site B) in 533 cases, and jejunum (site C) in 240 cases and were graded histologically on a scale of 0-3 as described by McNicholl and Egan.<sup>8</sup> Briefly these gradings are: grade 0/1 = normal or minor abnormalities, grade 2 = moderate mucosal damage, and grade 3 = severe mucosal damage. Sucrase, lactase, alkaline phosphatase, and protein were measured as described previously.<sup>7</sup>

## Results

The data for the groupings based on histological grade, site of biopsy, and age of patient are presented as sample means with the upper and lower limits of activity found for each group. In all

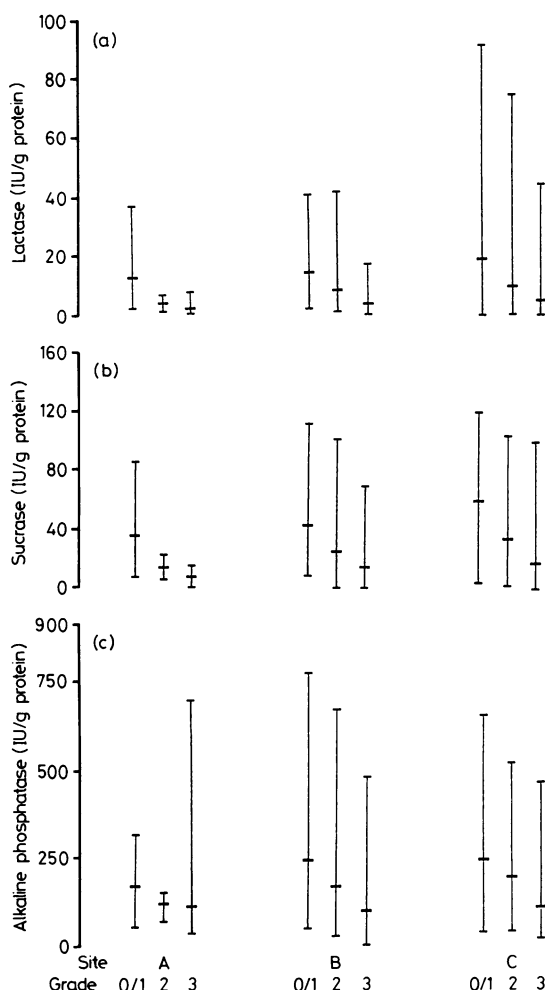


Fig. 1 Means and ranges of activities found for (a) lactase, (b) sucrase, and (c) alkaline phosphatase for each histological grade at the three sites of biopsy.

instances the distribution of results is not Gaussian but is positively skewed. The results of paired enzyme studies (grade 0/1 and grade 3 biopsies from the same patient) are presented as individual data points. In all instances where comparative analysis of enzyme activity was carried out the minimum number in any group was 15. The statistical tests used were the Mann-Whitney U test, paired *t* test, and  $\chi^2$  test.

#### GRADE AND SITE OF BIOPSY (Fig. 1)

At each of the three sites of biopsy enzyme activity decreased with increasing degrees of mucosal damage ( $p < 0.001$ ). Enzyme activities in biopsies from site A were considerably lower than those from sites

B and C with the exception of alkaline phosphatase in grade 3 biopsies. Both lactase and sucrase had significantly higher activities in site C than in site B in grade 0/1 biopsies ( $p < 0.05$ ). Alkaline phosphatase activity in the aforementioned sites did not differ significantly. In grade 3 biopsies enzyme activities did not differ between sites B and C.

#### AGE OF PATIENTS

Enzyme activities in the three age groups outlined above were compared in biopsies matched for histological grade and site of origin. Lactase activities were higher in patients under the age of 18 with grade 0/1 biopsies than in their older counterparts ( $p < 0.01$ ). No such difference was found for sucrase or alkaline phosphatase activities. Age did not significantly influence enzyme activity in grade 2 or grade 3 biopsies.

#### COMPARISON WITH CONTROL POPULATIONS

The details of intestinal enzyme activity in 477 subjects without coeliac disease, which form the basis for this comparison, were described previously.<sup>7</sup> Unlike the normal controls, disaccharidase activity in patients with coeliac disease did not fluctuate in the 0–18 age group and no sex differences were found. Enzyme activities in grade 0/1 coeliac biopsies were lower than those in controls matched for age, sex, and site of biopsy. This was most striking with lactase activity, which rarely reached the mean value found in control groups even in patients under the age of 18 with grade 0 biopsies. Sucrase activity in grade 0/1 coeliac biopsies approached control values to a greater extent than lactase, while alkaline phosphatase activity was closest to control values.

#### PAIRED STUDIES (Fig. 2)

In 81 patients (age range 1–76 years) enzyme activities were available for both grade 0/1 and grade 3 biopsies from comparable sites. The mean duration between biopsies was 3.9 years with a range of one to 10 years. These patients were divided into two groups: 45 patients who were under the age of 18 years at the time of both biopsies and 36 patients who were 18 or over at the time of one or both biopsies. Enzyme activity increased considerably in most patients with histological recovery ( $p < 0.001$  in both age groups for all enzymes). Persistently low lactase activity (less than 10 IU/g protein), was found in six children (13.3%) and 12 adults (33.3%) despite good morphological recovery of the mucosa ( $p < 0.01$ ). In 14 of these 18 patients there was a significant increase in sucrase activity, but in 13 patients alkaline phosphatase activity remained low in parallel with the lactase activity. No case of persistently low sucrase activity

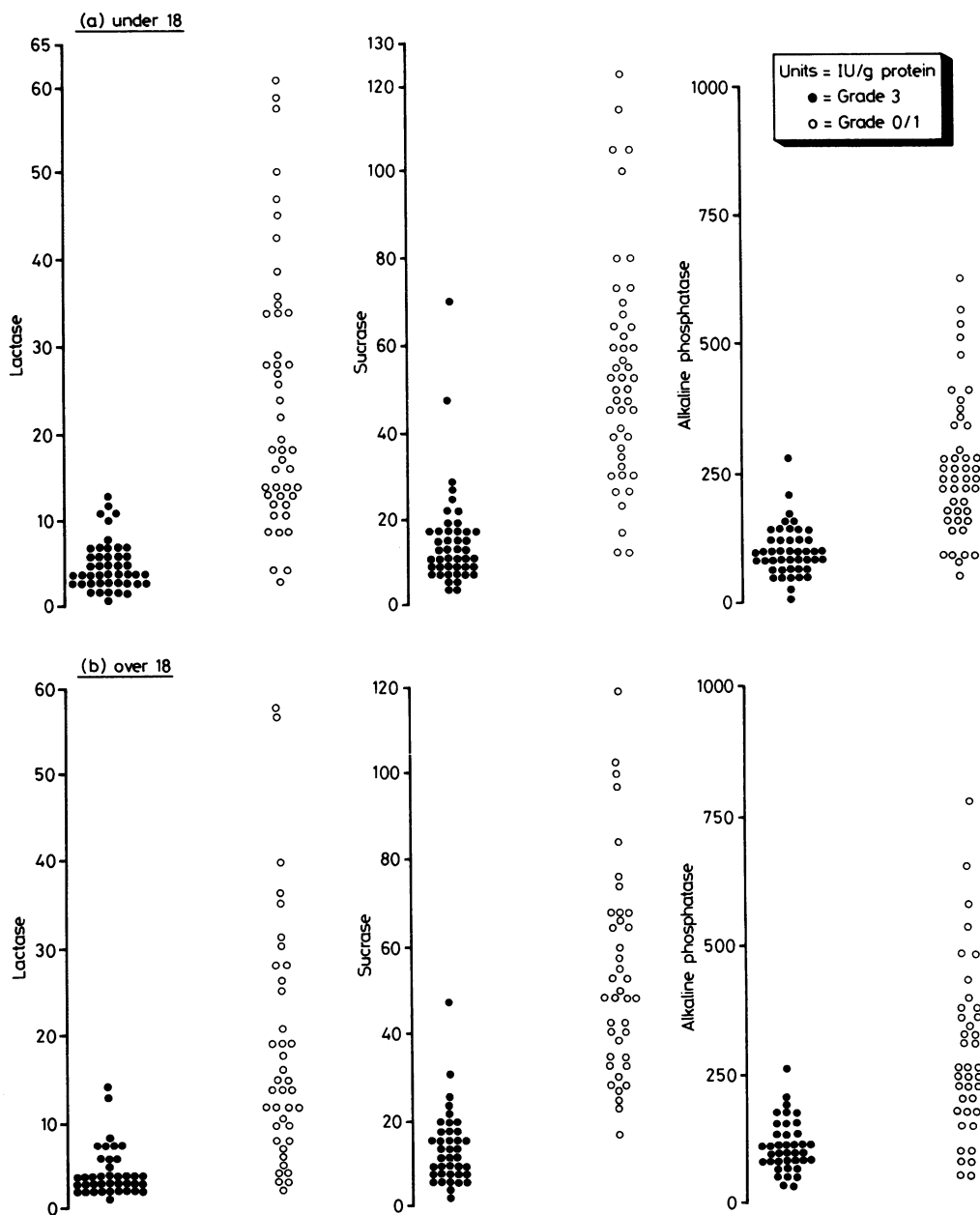


Fig. 2 Enzyme activities in grade 0/1 and grade 3 biopsies in (a) 45 patients under the age of 18 and (b) 36 patients over the age of 18.

in isolation was found. The degree of change in alkaline phosphatase activity was less than for either of the disaccharidases. The mean duration on a gluten free diet for these 18 patients was 4.4 years compared with 3.7 years for the remaining patients

(not significant). The major histocompatibility antigen B8 was present in 75.5% and 76.5% respectively of those with and without improvement in lactase activity when the small bowel mucosa improved histologically.

## Discussion

This study of small intestinal brush border enzyme activity in a large number of patients with coeliac disease illustrates the advantages and some disadvantages of using these enzymes as quantitative assessments of mucosal damage in coeliac disease. As expected enzyme activities were lowest in patients with severe mucosal damage and highest in those with normal mucosae. Patients with grade 2 biopsies showed intermediate values. Although lactase is the most sensitive indicator of mucosal damage, its activity in patients with coeliac disease in remission was less than in controls and it remained very low in a significant number of patients despite good morphological improvement in the mucosa. The importance of persistently low lactase activities in patients with coeliac disease in remission is unclear. It is not related to the duration of treatment with a gluten free diet or to the presence of the HLA-B8 antigen. It may indicate incomplete regeneration of the mucosa, especially in adults, but it is unlikely to be due to a specific defect in lactase as alkaline phosphatase activity remained low in parallel with lactase in most of these patients.

Sucrase activity is the best indicator of mucosal response to a gluten free diet. It increased significantly in most patients including the majority of those whose lactase activities remained depressed. The extent of change in alkaline phosphatase activity with progressive damage to the mucosa is less than for the two disaccharidases, but it has the advantage that its activity in mucosae in remission approximates the closest to the activity found in control populations.

The influence of age, sex, and site of biopsy on enzyme activities was much less important than in control subjects. In general, for biopsies taken from the distal duodenum or proximal jejunum the histological grade of the biopsy is the single most

important influence on enzyme activities. There are, however, some pitfalls in interpreting enzyme activities in patients with coeliac disease owing to the persistence of low lactase and alkaline phosphatase activities in some patients after the mucosa has improved histologically. In addition, the wide range of values found for enzyme activities within the various subgroups tends to limit the value of these measurements in individual patients.

We thank the Medical Research Council of Ireland and the Wellcome Trust for generous grants.

## References

- Malis F, Lojda Z, Fric P, Jodl J. Disaccharidases in coeliac disease and mucoviscidosis. *Digestion* 1972;5:40-8.
- Arthur AB. Intestinal disaccharidase deficiency in children with coeliac disease. *Arch Dis Child* 1966;41:519-24.
- Campbell BC, Cowen AE, McGeary HM, Gaffney TJ. Mucosal enzyme activity as a quantitative index of early functional improvement in the management of coeliac disease and other small intestinal diseases. *Aust NZ J Med* 1972;3:220-7.
- Pena AS, Truelove SC, Whitehead R. Disaccharidase activity and jejunal morphology in coeliac disease. *Q J Med* 1972;164:457-71.
- Peters TJ, Heath JR, Wansbrough-Jones MH, Doe WF. Enzyme activities and properties of lysosomes and brush borders in jejunal biopsies from control subjects and patients with coeliac disease. *Clin Sci Mol Med* 1975;48:259-67.
- McNicholl B, Egan-Mitchell B, Stevens FM, et al. Mucosal recovery in treated childhood coeliac disease. *J Pediatr* 1976;89:418-24.
- Keane R, O'Grady JG, Sheil J, et al. Intestinal lactase sucrase and alkaline phosphatase in relation to age, sex and site of intestinal biopsy in 477 Irish subjects. *J Clin Pathol* 1983;36:74-7.
- McNicholl B, Egan-Mitchell B. Jejunal biopsy in coeliac disease. *Clin Pediatr* 1968;7:544-52.

Requests for reprints to: Dr JG O'Grady, Department of Medicine, Regional Hospital, Galway, Ireland.