Cellobiose/mannitol sugar absorption test in patients with dermatitis herpetiformis: a preliminary report

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SUMMARY
An abnormal cellobiose/mannitol ratio is present in new patients presenting with dermatitis herpetiformis and in patients who have never adhered to a strict gluten-free diet. In patients with dermatitis herpetiformis in remission on a strict gluten-free diet, small bowel absorption as measured by the cellobiose/mannitol ratio is normal. It is suggested that cellobiose/mannitol absorption is a useful screening test for the intestinal abnormality associated with dermatitis herpetiformis and failure of the test to return to normal could suggest poor dietary compliance.

INTRODUCTION
Dermatitis herpetiformis was shown to be associated with jejunal villous atrophy by Marks et al.1 and changes similar to those in coeliac disease have been found.2, 3 Although between one-third and one-fifth of dermatitis herpetiformis patients do not demonstrate jejunal villous changes,3-5 most patients show an improvement on a gluten-free diet. Tests of absorption tend to be normal or only slightly abnormal.5-7 The mucosal changes are said to be patchy,8 so that simple screening tests have not been found useful in assessing mucosal recovery and repeated jejunal biopsies may not give accurate information. A reproducible absorption test would be invaluable in the clinical management of these patients, as it would appear that clinical remission occurs only after the mucosa has returned to normal.9, 10

Abnormal sugar absorption has been shown to be a useful measure for screening jejunal function in patients with coeliac disease.11, 12 Cellobiose/mannitol absorption has been well studied with reports of clear separation between active coeliac disease and coeliac disease in remission.13 We felt that cellobiose/mannitol absorption might be a useful test in patients with dermatitis herpetiformis. Abnormal persistent defects in permeability have been demonstrated in coeliac disease and dermatitis herpetiformis patients, even if the disease is in remission and the mucosa has returned to normal using the 51 chromium-labelled...
ethylene-diamine tetra-acetate (51 Cr/EDTA) absorption test. However, in the clinical management of patients, a simple demonstration of recovery of absorptive ability is all that is required.

The present study comprises a group of patients with dermatitis herpetiformis who have been followed up for a number of years, and five patients, newly diagnosed, who have not yet started on the gluten-free diet. We measured the cellobiose/mannitol ratio, assessed the clinical response to a gluten-free diet, and looked for a correlation between the original jejunal biopsy and clinical response.

MATERIALS AND METHODS
A total of 20 patients with dermatitis herpetiformis was investigated of whom five were newly diagnosed cases (two men and three women; mean age 42 years; range 23–62 years) taking a normal diet. The remaining 15 patients (10 men and 5 women of mean age 45 years; range 19–78 years) had been on gluten-free diet treatment for a mean of eight years (range 1–13 years) at the time of the study. A jejunal biopsy had been taken before the start of gluten restriction. The diagnosis of dermatitis herpetiformis was based on the characteristic body distribution of an intensely pruritic, polymorphic and vesicular skin rash together with the demonstration by immunofluorescence of IgA deposits in the papillary dermis of clinically uninvolved skin. In a few patients presenting before the availability of IgA immunofluorescence, a classical skin rash associated with abnormal histology and a clinical response to dapsone was accepted as diagnostic of dermatitis herpetiformis.

Biopsy of the upper jejunal mucosa was carried out using a Watson capsule placed endoscopically in the second part of the duodenum and the capsule then advanced 25 cm distally from the end of the endoscope. The mucosa was examined under the dissecting microscope, following which routine microscopic sections were stained with haematoxylin and eosin. The biopsies were graded as normal, partial villous atrophy and subtotal villous atrophy. Increased intraepithelial lymphocytic infiltration in the presence of otherwise normal villi has been accepted as partial villous atrophy.

Cellobiose/mannitol absorption
A sugar solution composed of 2 gm mannitol, 5 gm cellobiose, 20 gm lactose, 20 gm sucrose, made up to 150 ml was the test solution. After an overnight fast, the patient emptied his bladder and drank the solution over a period of five minutes. All urine passed within the next five hours was collected. The amount of mannitol and cellobiose passed in the urine was measured as outlined by Strobel et al. The results were expressed in percentages and the final ratio of percentage recovery of cellobiose to percentage recovery of mannitol was calculated as the cellobiose/mannitol ratio. A cellobiose/mannitol ratio of less than 0.037 was accepted as normal.

RESULTS
The cellobiose/mannitol ratio in the five untreated dermatitis herpetiformis patients was at or above the normal range (0.037–0.19). The remaining 15 patients had been diagnosed one to 13 years previously, and cellobiose/mannitol ratio varied from 0.001–0.22 (Table I).
Cellobiose/mannitol absorption test

**TABLE I**

*Dermatitis herpetiformis: cellobiose/mannitol ratio (normal < 0.037) in five newly diagnosed (untreated), and 15 previously diagnosed patients*

| Newly diagnosed | Previously diagnosed | Never on gluten restriction |
|-----------------|----------------------|-----------------------------|
|                 | Gluten-free diet     | Stopped diet                |
| 0.037*          | 0.024                | 0.001                       | 0.220*                      |
| 0.190*          | 0.006                | 0.019                       | 0.064*                      |
| 0.064*          | 0.005                | 0.014                       | 0.011                       |
| 0.110*          | 0.002                |                             | 0.039*                      |
| 0.047*          | 0.010                |                             |                             |
|                 | 0.023                |                             |                             |
|                 | 0.031                |                             |                             |
|                 | 0.047*               |                             |                             |

*Abnormal result.

Seven of the previously treated patients had no skin symptoms and a normal cellobiose/mannitol ratio: six were on a gluten-free diet, but one who had been on a diet for a number of years had found it inconvenient and continued on dapsone (Table II). Eight previously treated patients had persistent or intermittent blistering and itch of the skin. Two had been on a strict gluten-free diet for seven years, but had stopped, and they had a normal cellobiose/mannitol ratio at the time of study. Two patients continued on a strict gluten-free diet — one of these had a normal ratio and the other who had been on a gluten-free diet for only two months, with noticeable improvement of the skin, had an abnormal ratio. Four of these 15 patients had never been on a gluten-free diet and had persisting skin problems; three of these had an abnormal ratio.

**TABLE II**

*Skin response and cellobiose/mannitol ratio*

| Cellobiose/mannitol ratio | Complete remission | Active skin disease |
|---------------------------|--------------------|---------------------|
|                           | 0.024              | 0.019               |
|                           | 0.006              | 0.014               |
|                           | 0.005              | 0.031               |
|                           | 0.002              | 0.047*              |
|                           | 0.010              | † 0.220*            |
|                           | 0.023              | † 0.064*            |
| † 0.001                   | † 0.011            | 0.039*              |

*Abnormal results.
† Patients on dapsone.
Thus, of nine patients (five new, four previously treated) not on a gluten-free diet at the time of study, eight had an abnormal cellobiose/mannitol ratio, and of 11 patients who had been or were on a strict gluten-free diet, 10 had a normal ratio. The one patient with an abnormal ratio had been on a diet for only two months.

The initial jejunal biopsy was reported as showing partial villous atrophy in all five newly diagnosed patients who were on a normal diet and in seven of the 15 previously diagnosed patients. Four of the old patients had sub-total villous atrophy and the remaining four had a normal or minimal change mucosa. Subsequent response to a gluten-free diet did not depend on the initial biopsy. Eleven patients had used dapsone 100mg daily with relief of symptoms at the onset of the disease. Three patients with poor dietary compliance continued to use it intermittently with some benefit and two out of three have an abnormal cellobiose/mannitol ratio. One patient who had been well controlled on diet has a normal ratio and continues to use dapsone, as he finds it more convenient than a strict gluten-free diet.

DISCUSSION

This study indicates a possible clinical use for the measurement of the cellobiose/mannitol ratio. The abnormal ratio in new untreated patients could be used as a screening test either prior to or instead of a jejunal biopsy. There is very good separation between patients well controlled on a gluten-free diet and new patients. Repeated tests of patients who are on a gluten-free diet could measure both dietary compliance and an improvement in jejunal mucosa. Poor dietary compliance appears to be linked to poor control of the skin condition. The actual defect in dermatitis herpetiformis is not clear but there is evidence to suggest that an abnormal leaky jejunal mucosa leads to an absorption of immune complexes which, deposited in the skin, can lead to intense pruritis. Published results tend to be confusing about the benefit of a gluten-free diet. In this study, however, it would appear that strict gluten exclusion leads to good control of dermatitis herpetiformis. The speed of response varies in that the rash responds rapidly to gluten exclusion in some patients, perhaps within a few weeks, while in other patients a gluten-free diet is necessary for many months before remission is obtained.

If jejunal 'healing' is necessary for a remission of dermatitis herpetiformis it would be interesting to follow up a group of patients with dermatitis herpetiformis taking serial measurements of the cellobiose/mannitol ratio to see if permeability has to return to normal before skin remission occurs. Our preliminary results suggest that cellobiose/mannitol absorption studies may be a good measure of jejunal healing and presumably of dietary compliance. Further investigation is necessary to find if skin improvement occurs at the same time as, or subsequent to jejunal recovery.

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