Nutritional status in patients with dermatitis herpetiformis

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ABSTRACT Nutritional status of 86 patients with dermatitis herpetiformis (DH) was defined by anthropometric measurements and hematological and biochemical laboratory tests to establish prevalence of malabsorption and malnutrition. Anthropometric measurements in DH patients were comparable to normal control patients. Four individuals were of short stature; two had had diarrhea and failed to thrive in childhood. Abnormalities attributable to nutritional deficiency were detected in only 6 of the 86, whereas drug-associated hematological or biochemical changes were present in 36 of 55 subjects treated with dapsone or sulfapyridine. Twenty patients had hemolytic anemia or macrocytosis related to drug therapy. Only two had anemias attributable to malabsorption; one was iron deficient, the other folate deficient. Two other patients were mildly Fe deficient and two had slight folate deficiency; they lacked other stigmata of malabsorption. Drug-induced hematological and biochemical abnormalities were more common than changes that suggest nutritional disease, even though most DH patients had an enteropathy at presentation. Am J Clin Nutr 1988;48:355–60.

KEY WORDS Dermatitis herpetiformis, malabsorption, malnutrition, anthropometric measurements, drug-induced changes

Introduction

Villus atrophy is present in about three-quarters of patients with dermatitis herpetiformis (DH) (1, 2). Despite this, gastrointestinal symptoms and clinical evidence of malabsorption are infrequent in DH (3, 4), and in celiac disease symptoms suggestive of gastrointestinal disease occur in only about a half of newly presenting subjects (5, 6). Some DH patients are folate (7), iron (8), or zinc (9) deficient at presentation but in reports of large series of DH patients, nutritional problems have been encountered only occasionally (7, 10). However, mild malnutrition as judged by anthropometric measurements was recently reported to be a frequent finding in patients with celiac disease (11).

The primary objective of this study was to determine whether patients being followed up at a DH clinic are significantly at risk of developing nutritional disease and should therefore have regular monitoring of nutritional status and whether the continuing presence of villus atrophy in a jejunal biopsy is a particular risk factor. We carried out simple anthropometric measurements in a large series of subjects with DH, the majority of whom had a jejunal biopsy at the same visit. Standards for anthropometric measurements were taken from reference tables and texts but to put the results in perspective with our local population, we also took anthropometric measurements of a group of healthy individuals and two groups of patients who were expected to be malnourished (control groups).

Methods

Subjects

Eighty-six patients (29 women and 57 men) with DH were studied. All fulfilled standard criteria for diagnosis, each having granular immunoglobulin A (IgA) at the dermal papillae on direct immunofluorescence of the skin. The ages ranged between 14 and 81 y (x = 52 y). Twenty-three were receiving treatment with dapsone in doses of < 25 mg/d up to 200 mg/d and 22 were receiving sulfapyridine in doses of < 500 mg/d up to 2 g/d. Dapsone causes a hemolytic anemia (10) and sulfapyridine may also induce hemolysis, especially in individuals deficient in glucose-6-phosphate dehydrogenase (12, 13).

Procedures performed on the patients are given in Table 1. Twenty-three subjects eating a normal gluten-containing diet were studied at presentation. Sixty-two patients had had a previous jejunal biopsy: subtotal villus atrophy was present in 16, partial villus atrophy in 32, villus atrophy of uncertain severity in 2, and 12 had a normal jejunal mucosa. In the remaining patient, who had the blue rubber-bleb nevus syndrome, jejunal biopsy was contraindicated. Nine patients investigated previously were unwilling to submit to a further jejunal biopsy

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2 Reprints not available.

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TABLE 1
Procedures performed on patients

<table>
<thead>
<tr>
<th>At presentation</th>
<th>During follow-up</th>
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<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Total number</td>
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<tr>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>23</td>
</tr>
<tr>
<td>Gluten-free</td>
<td>0</td>
</tr>
<tr>
<td>Jejunal biopsy performed previously</td>
<td>0</td>
</tr>
<tr>
<td>Jejunal biopsy obtained during this assessment</td>
<td>21†</td>
</tr>
<tr>
<td>Anthropometry measurements</td>
<td>23</td>
</tr>
<tr>
<td>Blood investigations</td>
<td>23</td>
</tr>
</tbody>
</table>

* Jejunal biopsy contraindicated in one patient.
† Jejunal biopsy refused by one subject and failed in another.
‡ Twenty patients were on a normal diet; 30 were on a gluten-free diet.

and one new subject refused it. The jejunal biopsy was technically unsatisfactory in four patients (one was being studied for the first time).

Anthropometric measurements were taken on 84 DH patients and blood was drawn for hematological and biochemical determinations in all subjects. In addition, anthropometric measurements were carried out in three other groups: 57 normal volunteers (members of the hospital staff or family members visiting inpatients at the Gastro-Intestinal Unit), 44 subjects with inflammatory bowel disease, and 78 patients with malignant disease. The study was carried out in accordance with the ethical guidelines of the Ethical Committee of the Western General Hospital, Edinburgh.

Jejunal biopsy

Jejunal biopsies were performed with a Watson capsule, sampling from the jejunum at the level of Treitz' ligament. The biopsies were first examined with a dissecting microscope and were then processed for routine hematoxylin and eosin sections. Jejunal biopsies were categorized by histological appearance as normal or showing partial villus atrophy or subtotal villus atrophy.

Anthropometric measurements

Height, percentage of ideal weight for height, percentage of standard triceps skinfold thickness, and percentage of ideal arm-muscle circumference were calculated according to previously described methods (14) for 84 subjects and for the 3 groups of controls. Two nurses took the measurements; their technique was checked by duplicate testing in several dozen patients and control subjects. Each patient was weighed in a sitting chair balance (accuracy, ±0.05 kg) and 1.0 kg was subtracted from the reading to compensate for clothes. Height (accuracy, ±1 mm) was then ascertained. The triceps skinfold thickness of the nondominant arm was measured by skinfold calipers (John Bull British Indicators Ltd., England). Three measurements in duplicate were taken and the results were averaged. The arm circumference was measured at the midpoint between the olecranon and the top of the acromion. Nutritional variables were calculated by comparison with standard measurements (14). Weight was expressed as a percentage of the ideal weight for that height (for male or female). Triceps skinfold thickness was expressed as a percentage of the standard value (12.5 mm for males, 16.5 mm for females). Arm-muscle circumference was estimated by subtracting 0.314 × triceps skinfold thickness (in millimeters) from arm circumference (in centimeters) and it was expressed as a percentage of the ideal (25.3 cm for males and 23.2 cm for females).

Hematological estimations

Blood was taken for complete blood count, white cell differential count, and erythrocyte sedimentation rate (ESR) and for serum vitamin B-12, folate, and ferritin levels. Values used for normal hemoglobin were 115–165 g/L for women and 135–180 g/L for men. The vitamin B-12 and folate determinations were initially performed by a microbiological method (40 subjects) and, later, by radioimmunoassay (44 subjects). These two assays give comparable results. Any abnormalities were investigated further as necessary.

Biochemical analyses

Lithium-heparin blood samples were taken from each subject for the following determinations: plasma Na, K, chloride, urea, lactate dehydrogenase, aspartate amino-transferase, bilirubin, alkaline phosphatase, phosphate, Ca, Mg, total protein, albumin, IgA, IgG, IgM, Fe, and transferrin. Any abnormal results were investigated in further detail.

Results

Jejunal biopsy

Of the 21 newly presenting subjects on a normal diet 6 had a normal jejunal mucosa, 7 had partial villus atrophy, and 8 had subtotal villus atrophy. Twenty subjects on a normal diet, which was estimated to contain be-

TABLE 2
Previous and present jejunal histology in subjects on a normal or a gluten-free diet*

<table>
<thead>
<tr>
<th>Diet</th>
<th>Previous jejunal histology</th>
<th>Present jejunal histology</th>
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<tr>
<td></td>
<td>n</td>
<td>n</td>
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<tr>
<td>Normal (n = 20)</td>
<td>Normal</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>PVA</td>
<td>6</td>
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<td></td>
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<td></td>
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<tr>
<td>Gluten-free diet (n = 30)</td>
<td>Normal</td>
<td>1</td>
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<tr>
<td></td>
<td>PVA</td>
<td>20</td>
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* PVA = partial villus atrophy; SVA = subtotal villus atrophy; VA = villus atrophy.
† This subject was on a partially gluten-free diet for some of the time.
tween 4.5 and 40 g of gluten daily, were successfully rebiopsied (Table 2). Five had subtotal villus atrophy, six had partial villus atrophy, and nine had a normal jejunal mucosa.

Three patients previously shown to have a normal jejunal mucosa were, on this occasion, found to have partial villus atrophy. One subject on a normal diet who had previously had partial villus atrophy now had a normal biopsy; another who had previously had subtotal villus atrophy was now normal. This patient was on a gluten-free diet in the past but at the time of biopsy was only avoiding certain gluten-containing foods; her daily gluten intake was 7.8 g.

Thirty patients on a gluten-free diet were rebiopsied (Table 2). Jejunal morphology was now normal in 23 patients but 2 had subtotal villus atrophy and 5 showed partial villus atrophy. Four of the 41 subjects prescribed a gluten-free diet admitted to not adhering strictly to the diet; they took between 1 and 3 g of gluten/d.

**Height**

The height measurement was used as an index of retarded growth in childhood, accepting that in an older individual significant reduction in height could result from osteoporosis. Absolute heights for the 29 women with DH ranged from 146 to 178 cm with a median of 162 cm. For the 55 men heights ranged from 160 to 186 cm with a median of 173 cm. Four women, all of whom had subtotal villus atrophy, had heights of ≤ 150 cm. On clinical grounds there was evidence that two of the four had active celiac disease in childhood (one had a history of diarrhea, the other had old rickets) and one of these had an Fe-deficient anemia and a low arm-muscle circumference. In Figure 1 absolute heights are plotted against the results of the jejunal biopsy taken at presentation of DH (20 biopsies taken at presentation in the present study and the initial, diagnostic jejunal biopsy in the 61 patients we studied while on follow-up of their DH).

The median height for males who initially had subtotal villus atrophy was 173 cm, which is near the median of 173.8 cm for 4702 men in the general population aged 16–64 y (14). The median values for males with partial villus atrophy at presentation was, however, significantly lower than that for those presenting with normal jejunal mucosa (Mann-Whitney U test [15]; p < 0.01) but was not statistically different from that for the subtotal villus atrophy group. Females who had subtotal villus atrophy at presentation had a median height of 158 cm, which is lower than the median of 160.8 cm for the general population (16). The median heights for women presenting with partial villus atrophy or normal jejunal mucosa were similar to the values for the general population and not statistically different from the median figure for the subtotal villus atrophy group (Mann-Whitney U test).

**General nutritional status**

Ideal weight for height, triceps skinfold thickness, and arm muscle circumference were calculated as percentage of standard or ideal and the distribution of percentage values in the various patient categories is shown in Table 3. DH subjects were subdivided according to the jejunal biopsy taken for this study, and to put the results into perspective for our population values for normal controls and for two groups of nutritionally compromised patients with inflammatory bowel disease and with malignant disease are included.

Thirty-nine of the 57 normal volunteers were > 100% ideal weight for height; similarly, two-thirds of DH patients were at or above their ideal weight as were just over half of the patients with malignant disease. In contrast only 9 of 44 patients with inflammatory bowel disease reached ideal weight. The triceps skin thickness was below the 100% standard in 61% of patients with inflammatory bowel disease, in 50% of both the normal control and the malignant-disease groups, and in 52% of DH patients.

Perhaps the most discriminating method for detecting malnutrition, at least in the groups studied, was to consider subjects with an arm-muscle circumference of < 80% of the ideal. Twenty-nine percent of the inflammatory-bowel-disease group and 32% of the pa-

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**Figure 1.** Heights of 29 females (open circles) and 55 males (closed circles) with DH grouped according to the result of the jejunal biopsy at initial presentation. Bars indicate x ± SEM.
patients with malignant disease fell into this group, whereas no normal controls and only one DH patient were included.

On the basis of the anthropometric measurements only four of the DH patients were of short stature and overall anthropometric tests for general nutritional status were normal.

Hematological and biochemical abnormalities

Drug related. Eight patients had a macrocytic anemia, with hemoglobin concentrations of 108–133 g/L; in seven patients the anemia was probably related to hemolysis induced by dapsone. Thirteen other subjects had a macrocytosis without anemia, with mean corpuscular volumes between 99 and 106 fl; again, dapsone- or in some cases sulfapyridine-induced hemolysis was suspected. An additional patient had a macrocytosis without folate deficiency and was on no drugs; in our experience this is usually caused by alcohol abuse. Sulfapyridine-induced neutropenia was present in two patients (white-cell counts of 3.6 and $3.4 \times 10^3$/L), one of whom (a man) had a hemoglobin concentration of 125 g/L.

Fourteen patients had raised plasma bilirubin levels. In 11 patients these levels ranged from 16 to 25 μmol/L (normal limits are 3–14 μmol/L) and were interpreted as being related to dapsone-induced hemolysis. In three subjects hemolysis could not explain the raised bilirubin levels of 19, 34, and 38 μmol/L. Autoantibody studies were negative on these patients and the hyperbilirubinemia may be due to Gilbert’s syndrome. Plasma lactate dehydrogenase was mildly elevated in 16 subjects (ranging between 409 and 647 U/L, or between 6.8 and 10.8 μkat/L; normal range is 72–395 U/L, or 1.2–6.6 μkat/L) of whom 5 with dapsone-induced hemolysis had raised bilirubin levels. In nine others the elevation was probably related to dapsone- or, in two cases, sulfapyridine-induced hemolysis without a raised bilirubin. In another patient, a male with a slightly elevated aspartate aminotransferase, the lactate dehydrogenase of 576 U/L (9.6 μkat/L) was most likely due to a high alcohol intake, but no explanation was forthcoming in the remaining subject with a raised lactate dehydrogenase, who was on no medication and of whom other investigations were normal.

Iron. One subject, a woman aged 66 y who had subtotal villus atrophy, was Fe deficient. Her hemoglobin was 118 g/L and the red-cell indices indicated Fe deficiency. Plasma Fe was $9 \mu$mol/L (normal range 14–22 μmol/L) and the serum ferritin was low at 1 μg/L (normal range 14–150 μg/L). A low plasma Fe was present in eight other patients of whom only two had a reduced serum ferritin. These two were postmenopausal women on a gluten-free diet with normal jejunal biopsies on this occasion; they were not anemic and had no other indication of malabsorption. Their mild Fe deficiency may have been of dietary origin.

Folate. Three subjects were receiving folic acid supplements at the time of investigation, having been shown previously to be deficient. Thirteen patients had a low serum folate; of these, four had macrocytosis and three males with hemoglobin concentrations of 133, 133, and 132 g/L were anemic by definition (normal range for males 135–180 g/L), although these values were clearly borderline. Ten were on dapsone or sulfapyridine and in these patients drug-induced hemolysis was considered to be the cause of the low serum folate. Of the three patients receiving no medication one had subtotal villus atrophy, osteomalacia, and a macrocytic anemia and his serum folate of < 1 μg/L was undoubtedly caused by malab-
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Discussion

Blood abnormalities in DH patients are much more likely to be caused by drug therapy than malabsorption. This survey of 86 patients uncovered only 2 with unequivocal malabsorption and 4 with short stature, whereas 36 of the 55 on dapsone or sulfapyridine had hematological or biochemical abnormalities related to this treatment. In four other patients with an isolated low ferritin or low folate level not of clinical significance, poor dietary intake of Fe or folate was suspected. Anthropometric measurements on DH patients as a group were almost identical to normal control subjects.

As expected, patients with inflammatory bowel disease and malignant disease showed anthropometric evidence of malnutrition. About 80% of the inflammatory-bowel-disease patients and almost half of those with malignancy weighed < 100% of the ideal compared with only one-third of the normal volunteers. Triceps skin thickness was < 60% of ideal in several subjects in both the malnourished groups but the proportion with a figure < 100% of ideal was similar to the normal control subjects. However, arm muscle circumference of < 80% of ideal proved to be a useful discriminating index for malnutrition, identifying 30% of those with inflammatory bowel disease or malignancy but no normal control subjects and only one subject with DH. Although 69% of normal volunteers weighed > 100% of their ideal, only 32% had an arm-muscle circumference > 100% (the rest were 80–99% of ideal). This indicates that there is a discrepancy between an index of obesity (ideal weight) and muscle bulk (arm-muscle circumference) and underlines the need for internal controls in such studies and for continual updating of methods.

A recent anthropometric study of 18 patients with celiac disease revealed that half were below 100% of their ideal weight and one-third were below 60% of the standard triceps skin thickness (11). The authors claim that mild malnutrition was a frequent finding but no normal controls or nutritionally compromised control subjects were examined. Only one of their patients had a weight-to-height ratio < 80% and only one had an arm-muscle circumference < 80%. Malnutrition therefore may not be as common as was reported.

One DH patient had malabsorption with osteomalacia and folate deficiency but laboratory evidence of malabsorption was otherwise scant. Three subjects had Fe deficiency but only one of these was anemic. In a series of 38 DH patients Davies et al. (18) found low serum Fe in 12 but only 2 were anemic from malabsorption. None of the 14 patients reported by Brow et al. (19) was Fe deficient. When present in our subjects low serum folate levels were related to dapsone- or sulfapyridine-induced hemolysis in all but three cases. Reduced serum folate estimations were noted in between 14% (7) and 78% (20) of DH patients and have sometimes been thought to indicate malabsorption, although in the report by Fry et al. (3) the folic acid absorption test was normal in 11 of 12 subjects studied. Dapsone- or sulfapyridine-induced hemolysis resulted in a mild macrocytic anemia or in macrocytosis without anemia in 21 DH patients. The hemolytic anemia was usually mild and only rarely was it severe enough to require withdrawal of the drug.

Three patients on normal diets who had previously had normal biopsies had partial villus atrophy in the subsequent biopsy and one who had previously had partial villus atrophy subsequently had a normal mucosa. This means either that the state of the patient’s jejunum altered between normal and abnormal with time even though the diet remained the same, that the pathologist’s subjective classification of the biopsy as either normal or somewhat abnormal (partial villus atrophy) was inconsistent, or that abnormalities were present consistently but were patchy. Tests of jejunal integrity that are complementary to jejunal biopsy, such as the sugar-permeability tests, are valuable adjuncts to descriptive pathology of a tiny mucosal sample in attempting to address the question of whether or not a patchy lesion is
present and has been missed by random biopsies. Nevertheless, substantial changes in the state of the jejunal mucosa with time despite maintenance of a gluten-containing diet have been recorded. Schmitz et al (21) described three patients with unequivocal villus atrophy who, after resuming a normal diet, were shown to have normal mucosa on jejunal biopsy.

It has been our established practice for more than a decade to monitor the hematological status of patients with DH attending the clinic so that we could recognize and treat drug-associated hemolysis or dyscrasia. Although we continue to appreciate the need to recognize overt malabsorption in patients with DH who have villus atrophy, it is clear that formal screening for nutritional deficiencies is unnecessary in general and even at the time of presentation only a minority of patients have malabsorption or malnutrition. A gluten-free diet is prescribed by gastroenterologists in celiac disease to restore the jejunal mucosa to normal. In DH patients the benefit of a gluten-free diet will rarely be manifest as improvement in nutrition because nutrition is usually normal in any event. However, the gluten-free diet has the advantage of allowing dapsone or sulfapyridine to be withdrawn, thus indirectly improving the hematological status of the patient.

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References