Nutritional disturbances in Crohn's disease

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Summary

A wide range of nutritional disturbances may be found in patients with Crohn's disease. As more sophisticated tests become available to measure vitamin and trace element deficiencies, so these are being recognized as complications of Crohn's disease. It is important to recognize nutritional deficiencies at an early stage and initiate appropriate treatment. Otherwise many patients, experiencing what can be a chronic and debilitating illness, may suffer unnecessarily from the consequences of deprivation of vital nutrients.

KEY WORDS: growth disturbance, Crohn's disease, anaemia, vitamin deficiency.

Introduction

Crohn's disease is a chronic inflammatory condition of unknown aetiology that may affect any part of the gastrointestinal tract from mouth to anus. There is no effective cure, and the disease can therefore impose a substantial burden for the patient to bear and on medical, surgical and social resources. A wide range of nutritional disturbances may be found in patients with Crohn's disease and these can have significant effects on the general management of patients. Well-nourished patients may become deficient in one or more nutrients and remain otherwise in good health. However, undernourished individuals are usually at risk of multiple deficiencies and these shortfalls can complicate and add to the problems encountered in clinical practice.

Pathogenesis of malnutrition

The main mechanisms that are responsible for malnutrition in Crohn's disease are in Table 1. These may cause malnutrition either singly or in combination, and a factor that has a major part in the production of one nutritional deficiency may only play a minor role in the production of another

deficiency in the same patient. The most important causes of malnutrition are probably reduced food intake, active inflammation and enteric loss of nutrients (Dawson, 1972).

TABLE 1. Pathogenesis of malnutrition

Reduced food intake	Anorexia Fear of eating from abdominal pain
Active inflammation	Mechanisms unknown
Enteric loss of nutrients	Exudation from intestinal mucosa Interrupted entero-hepatic circulation
Malabsorption	Loss of absorptive surface from disease, resection or by-pass Stagnant loop syndrome from strictures, fistulae or surgically created blind loops
Miscellaneous	Rapid gastrointestinal transit Effects of medical therapy Effects of parenteral nutrition without trace element supplements

Weight

In their original description of regional enteritis, Crohn, Ginzburg and Oppenheimer (1932) recognized that weight loss and emaciation were common accompaniments of the disease. Several large studies have documented weight loss in 70-80% of patients, and, in some cases, this was substantial (Van Patten *et al.*, 1954; Crohn and Yarnis, 1958; Mekhjian *et al.*, 1979). However, most of these studies take no account of the patient's weight before the illness, and weight loss in a thin person may be more significant than a similar loss in an obese one. More recently the emphasis has changed and concentrated on relating weight and anthropometric measurements of muscle and subcutaneous fat to ideal standards in order to determine how far patients vary from the norm. Harries *et al.* (1982a) studied 106 unselected, consecutive outpatients with Crohn's disease who were attending a gastrointestinal clinic. Many patients

were considerably underweight and had significant reductions in muscle bulk and subcutaneous fat compared with a similar number of patients with ulcerative colitis and healthy subjects. About 20% of the Crohn's patients were below 90% of their ideal weight. Lanfranchi *et al.* (1982) found that 40% of 44 outpatients with Crohn's disease were below ideal weight. Both of these studies were carried out in patients who were not acutely ill, and emphasise that a considerable degree of undernutrition exists even in this type of patient.

Anaemia

Anaemia of varying severity may be found in 50–70% of cases who are receiving treatment predominantly in hospital (Van Patter *et al.*, 1954; Krause, Bergman and Norlen, 1971; Dyer *et al.*, 1972; Beeken, 1975). Anaemia can result from deficiency of iron, folic acid or vitamin B₁₂, or may simply be a consequence of chronic inflammation.

Iron

The prevalence of iron deficiency, as judged by hypochromia, red cell indices and serum iron, has undoubtedly been overestimated in the past. A low serum iron may be found in 50–70% of cases, usually in association with a low total iron binding capacity (TIBC) (Krause *et al.*, 1971; Eade, Cooke and Williams, 1972; Dyer *et al.*, 1972). When the TIBC is raised, this invariably reflects true iron deficiency. Bone marrow aspiration reveals absent iron stores in 25–40% of patients, unrelated to the serum iron concentration (Hoffbrand *et al.*, 1968; Thomson *et al.*, 1978). This has led some to conclude that the only certain way of diagnosing iron deficiency is by bone marrow aspiration. Recently, the serum ferritin has been found to reflect reticulo-endothelial storage iron, and is closely correlated with the amount of stainable iron in the bone marrow (Jacobs and Worwood, 1975). Levels of less than 15 µg/litre always indicate iron deficiency. However, in chronic inflammatory states, concentrations of 50 µg/litre may be associated with true iron deficiency as a result of iron shift from the red cell compartment to the storage pool (Worwood, 1980). Thomson *et al.* (1978) confirmed these findings in patients with inflammatory bowel disease. Patients who are anaemic with a serum ferritin <15 µg/litre should be treated with iron supplements. Patients whose serum ferritin is between 15 and 55 µg/litre should probably be given the benefit of the doubt and treated with iron; those with true iron deficiency should show a positive response provided the disease is not active, while those with chronic inflammation probably will not change.

Vitamin B₁₂

The prevalence of serum B₁₂ deficiency is variable, and a summary of the main published studies is in Table 2. The high incidence of B₁₂ deficiency found by Meynell and his associates (1957) may have been the result of a number of falsely low results occurring as a result of the omission of cyanide from the extraction process before the assay. Vitamin B₁₂ malabsorption occurs most commonly after ileal resection, and may be unrelated to the length of small bowel removed (Fausa, 1974). It may also occur in patients who have not undergone operation usually from disease of the terminal ileum (Dotevall and Kock, 1968). Vitamin B₁₂ malabsorption may be due to bacterial overgrowth (Beeken and Kanich, 1973) and rarely Crohn's disease of the stomach can cause a true pernicious anaemia with absence of intrinsic factor (Kraus and Schneider, 1979). All patients with Crohn's disease deserve serious consideration for vitamin B₁₂ prophylaxis, and cases which develop subacute combined degeneration of the spinal cord after ileal resection (Best, 1959) should now be events of the past.

Folic acid

The incidence of low serum and red cell folate concentrations is in Table 2. The differing incidences reflect the clinical heterogeneity of Crohn's disease; two-thirds of the patients studied by Hoffbrand *et al.* (1968) were ill, while two-thirds of the group investigated by Krause *et al.* (1971) had undergone surgical resection with no recurrence, and were presumably well. The causes of folate deficiency are undoubtedly often multifactorial; anorexia, malabsorption, disease activity and low grade drug-induced haemolysis from sulphasalazine are all important mechanisms. Elsborg and Larsen (1979) found that 67% of patients with low serum and red cell folate levels had megaloblastic changes on bone marrow examination, often in the presence of normal haemoglobin concentrations. This suggests that prophylactic folic acid therapy should be seriously considered in many patients unless regular, careful monitoring is carried out.

Vitamin B₆

Serum pyridoxal is the main form in which vitamin B₆ appears in the blood (Kelsay, Baysal and Linkswiler, 1968) and deficiency may cause a sideroblastic anaemia. Dyer (1970) found reduced serum pyridoxal levels in patients with Crohn's disease, but felt that this was a marker of active inflammation rather than true vitamin B₆ deficiency. Johansson, Allgen and Hellstrom (1973) found no evidence of vitamin B₆ deficiency, and there are no reports of

TABLE 2. Incidence of vitamin B₁₂ and folic acid deficiency in Crohn's disease. Summary of published studies

	Low B ₁₂		Low serum folate		Low red cell folate	
	No./Total No.	%	No./Total No.	%	No./Total No.	%
Meynell <i>et al.</i> 1957	26/43	60				
Dotevall and Kock, 1968	7/30	23	18/29	62	6/29	21
Hoffbrand <i>et al.</i> , 1968	3/54	6	52/64	81	7/19	37
Krause, Bergman and Norlen, 1971	37/184	20	12/150	8	7/54	13
Kyle, 1972	2/30	7	10/12	83		
Eade, Cooke and Williams, 1972	38/100	38	37/93	40		
Dyer <i>et al.</i> , 1972	11/68	16	47/66	64	13/37	35
Gerson, Cohen and Janowitz, 1973	6/46	13	8/57	14		
Beeken, 1975			7/44	15		
Elsborg and Larsen, 1979	0/30	0	16/30	52	8/30	27

The table shows the number and percentage of patients in each study with low serum B₁₂, and low serum and red cell folate levels. The total number of patients studied is also indicated.

sideroblastic anaemia occurring as a recognized complication of Crohn's disease.

Chronic inflammation

Between 30–50% of patients with anaemia have the anaemia of chronic inflammation without measurable deficiency of iron, B₁₂ or folic acid, and also associated with a normoblastic bone marrow (Dyer *et al.*, 1972; Thomson *et al.*, 1978).

Albumin

Hypoproteinaemia has been recorded in various studies with an incidence of 76% (Pimparker, Mouh-ran and Bockus, 1960), 44% (Dyer, 1970), 20% (Krause *et al.*, 1971) and 25% (Beeken, 1975). Hypoproteinaemia and oedema have been described in the absence of bowel symptoms (Cobb and Robson, 1969), a clinical situation which can cause considerable diagnostic problems.

The most important cause of hypoproteinaemia is gastrointestinal protein loss (Beeken, Busch and Sylwester, 1972), although other factors such as anorexia, malabsorption, reduced hepatic synthesis and increased catabolism from inflammation, fever or steroid administration may all contribute. Hill and his associates (1977) found that postoperative complications were more common in patients with protein malnutrition, possibly as a result of impaired immunity and poor wound healing.

Electrolytes

Sodium, potassium and chloride

Diarrhoea causes electrolyte loss and deficiencies occur if these are not replaced by increased intake or absorption. However, in Crohn's disease, anorexia is common, and water and sodium absorption may be impaired in a diseased small intestine (Atwell and Duthie, 1964). Although hyponatraemia and hypo-

chloraemia may be found in patients with active or recurrent disease (Kiefer, 1955), Beeken (1975) found low sodium concentrations in only 10% of cases.

Potassium deficiency is usually present with a low plasma concentration and sometimes occurs when the plasma potassium is normal (Cooke, 1955; Lehr *et al.*, 1982). Potassium deficiency may well account for non-specific symptoms of weakness, lassitude and depression, and correction of body potassium before surgery has been shown to reduce the complication rate and mortality (Lehr *et al.*, 1982).

Calcium

Hypocalcaemia has been reported to occur commonly in Crohn's disease (Pimparker *et al.*, 1960; Gerson, Cohen and Janowitz, 1973; Beeken, 1975). Dyer (1970), however, was the first to stress that serum calcium levels must be related to the albumin concentration. Hypocalcaemia usually occurs in association with hypoalbuminaemia, and if appropriate corrections are made, then true hypocalcaemia is relatively uncommon. Krawitt, Beeken and Janney (1976) carried out a detailed study on 31 patients and found normal serum calcium concentrations, normal absorption and normal endogenous faecal calcium excretion compared with controls.

Magnesium

As the symptoms and signs of hypomagnesaemia may be mistaken for those of hypocalcaemia, magnesium deficiency was not widely appreciated as a complication of Crohn's disease until 1970, when Gerlach, Morowitz and Kirsner described 4 patients with symptomatic hypomagnesaemia. Dependence upon serum magnesium levels for diagnosis will lead to underdiagnosis of the condition. Beeken (1975) found hypomagnesaemia in only 9 of 63 patients, but Main *et al.* (1981) using serum and urine levels together as an indicator of magnesium status found

that 15 of 17 patients admitted to hospital with severe disease were magnesium deficient. Swedish workers found clinically important magnesium deficiency in 30% of patients with intestinal resection. Diagnosis depended on muscle magnesium concentrations which were often low in the presence of normal serum levels (Hessov *et al.*, 1982).

Lipids and amino acids

Pimparker *et al.* (1960) recorded low blood cholesterol levels in 25 of 37 patients and attributed these findings to the extent of the disease and steatorrhoea. Others have found that the incidence is lower, affecting 20–30% of patients (Dyer and Dawson, 1971; Gerson *et al.*, 1973). The significance of these findings is uncertain, although serum cholesterol measurement appears to be an unreliable screening test of ileal dysfunction or hepatic disease in patients with Crohn's disease.

There is a paucity of data on amino acids in Crohn's disease. Low serum tryptophan concentrations have been reported in 40–80% of patients (Johansson *et al.*, 1973; Beeken, 1975). It was suggested that since tryptophan is a precursor of serotonin and tryptamine, the low levels might account for organic depressive states in Crohn's disease, but this association remains unproven.

Fat and carbohydrate absorption

Steatorrhoea can be found in up to 30% of patients (Dotevall and Kock, 1968; Dyer, 1970; Beeken, 1975). Both the length of diseased small bowel and the extent of surgical resection are important determinants of the degree of steatorrhoea. However, in practice the problem is often masked because of the associated anorexia and reduced fat intake (Burke, 1953). Steatorrhoea is important because it reflects not only malabsorption of fat but also malabsorption of other substances. The majority of patients studied by Pimparker *et al.* (1960) who had steatorrhoea also had hypoalbuminaemia, hypoproteinaemia and vitamin B₁₂ malabsorption.

Xylose absorption has been found to be impaired in some studies (Hertzberg, Myren and Semb, 1969; Beeken, 1975), but on the whole it is normal unless the entire jejunum and ileum are affected by the inflammatory process (Dotevall and Kock, 1968; Dyer, 1970). Lactose absorption is also generally regarded as being normal in Crohn's disease (Gudmand-Hoyer and Jarnum, 1970).

Vitamins

Vitamin B complex

Yarnis, Marshak and Crohn (1957) claimed that cutaneous signs of vitamin B deficiency were com-

mon. Pemberton and Brown (1937) described a patient who postoperatively developed a syndrome resembling wet beri-beri and responded to dietary measures including treatment with vitamin B complex. Cooke (1955) remarked, however, that he had never seen a case of obvious beri-beri with Crohn's disease, although he described two patients with severe malnutrition and skin lesions, highly suggestive of pellagra. A case of pellagra was described by Bockus (1976) and also a further report mentions an 18-year-old woman who had small and large bowel Crohn's disease (Pollack *et al.*, 1982). This latter patient had a normal thiamine and riboflavin status, and her dietary intake of tryptophan and nicotinic acid were satisfactory. The cause of pellagra was malabsorption of nicotinic acid, and the symptoms disappeared with intramuscular nicotinamide.

Vitamin C

Linaker (1979) reported the first case of scurvy in Crohn's disease with confirmatory low leucocyte ascorbic acid levels. The skin lesions rapidly resolved with oral vitamin C supplements. Nine other patients who were in remission were investigated, and ascorbic acid deficiency was found in 6 despite an adequate dietary intake. The reason for the vitamin deficiency was unclear. Malabsorption appeared unlikely and it was suggested that patients with Crohn's disease have an increased demand for ascorbic acid.

Low levels of leucocyte ascorbic acid had previously been documented (Gerson and Fabry, 1974; Hughes and Williams, 1978). Gerson related the low levels in part to a reduced intake. He also found that patients with fistulae had lower ileal and blood ascorbate concentrations than those without, and suggested that fistula formation in Crohn's disease might be related to local ascorbate deficiency. In view of these findings, the suggestions that patients should receive vitamin C supplements prophylactically do not seem unreasonable.

Vitamin A

Kiefer and Arnold (1950) described one patient with skin changes suggestive of vitamin A deficiency, and Crohn and Yarnis (1958) reported this deficiency to be moderately common. Although plasma carotene levels have been found low in over 50% of cases (Scudamore, 1961; Gerson *et al.*, 1973), low plasma vitamin A levels have been found less frequently (Camilo *et al.*, 1982). Plasma vitamin A concentrations have to be interpreted in relation to plasma protein measurements, and low levels that occur with hypoalbuminaemia do not necessarily indicate vitamin A deficiency. Main *et al.* (1982) found that when

low vitamin A levels were associated with hypoalbuminaemia, dark adaptation testing was useful in identifying those patients who required vitamin A therapy.

Vitamin D

Driscoll *et al.* (1977) found that 79% of patients with Crohn's disease had low circulating levels of 25-hydroxy-cholecalciferol (25-OHD3). This was confirmed (Compston and Creamer, 1977) and malabsorption thought to be one of the mechanisms involved, possibly as a result of interruption of the enterohepatic circulation of bile acids and vitamin D metabolites. Subsequent studies have shown that endogenous loss of 25-OHD3 also occurs in patients with Crohn's disease (Batchelor, Watson and Compston, 1982). In contrast, normal concentrations of 25-OHD3 have been found in patients with Crohn's disease (Sonnenberg *et al.*, 1977). To further study the problem, Harries *et al.* (1982b) separated patients into undernourished and well-nourished groups according to a simple anthropometric indicator. Undernourished patients had low levels of 25-OHD3 while well-nourished patients had similar values to controls. Over 50% of undernourished patients had secondary hyperparathyroidism which probably accounted for the normal concentrations of 1,25-dihydroxy-cholecalciferol which were observed.

Vitamin D metabolism is closely related to the mineralisation of bone. Cooke (1972) estimated that 5% of patients had osteomalacia, basing the diagnosis on bone biopsy and raised alkaline phosphatase levels. However, the problem was found to be more common than previously thought when a bone biopsy study on 25 patients with small bowel resection (22 with Crohn's disease) revealed osteomalacia in nine (36%) (Compston *et al.*, 1978). Bone disease could occur without clinical or biochemical abnormality, and this has since been confirmed by North American workers (Driscoll *et al.*, 1982). This raises an important problem of how to screen for the bone abnormalities. A raised alkaline phosphatase level should be a pointer to further investigations which, in the first instance, could include isoenzyme estimations (for bone or liver origins) and parathyroid hormone concentrations. Abnormalities should indicate the need for further investigation. It is probably no longer tenable to regard a raised alkaline phosphatase level simply as an indicator of hepatic dysfunction, a view put forward by Dyer and Dawson in 1972.

Vitamin K

Haemorrhagic problems have occurred in Crohn's disease as a result of vitamin K deficiency. Kiefer and Arnold (1950) mentioned one patient with intestinal

haemorrhage, and others have noted the occurrence of haematuria (Kiefer, 1955; Kalser *et al.*, 1960). Increased prothrombin times have been found in 30–50% of patients, and occur especially in the presence of steatorrhoea (Pimparker *et al.*, 1980; Scudamore, 1961; Gerson *et al.*, 1973). Malabsorption is probably the most important cause of vitamin K deficiency either from extensive disease or resection that is severe enough to interfere with bile salt absorption. Hepatic dysfunction is unlikely to be an important mechanism because most workers have claimed improvement of the prothrombin time with parenteral vitamin K.

Metals and trace elements

The investigation of zinc status has been hampered by the lack of any reliable means of assessment. Nevertheless, the recognition that zinc may be important for taste, wound healing and growth (Aggett and Harries, 1979) has raised the interesting possibility that these complications in Crohn's disease might be due to zinc deficiency.

Sandstead (1973) described an adolescent with regional enteritis who had growth retardation and biochemical evidence of zinc deficiency. Treatment with oral zinc sulphate resulted in a dramatic response in both growth and sexual maturation. This led to a number of studies investigating zinc status in Crohn's disease but, unfortunately, the results have been confusing and conflicting. Low plasma zinc levels have been reported in up to 40% of patients and often in association with impaired taste capacity (Solomons *et al.*, 1977; McClain, Soutor and Zieve, 1980; Sturniolo *et al.*, 1980; Penny *et al.*, 1983). In contrast, others have found normal plasma and urine zinc levels (Mills and Fell, 1979; Fleming *et al.*, 1983).

Studies in which dietary histories have been taken have revealed a satisfactory oral intake of zinc (McClain *et al.*, 1980; Fleming *et al.*, 1981). However, zinc absorption has been found to be considerably impaired, and this could account for zinc deficiency (McClain *et al.*, 1980; Sturniolo *et al.*, 1980). In many of the studies there was a correlation between plasma zinc and albumin, which raises the possibility that low serum zinc is simply a reflection of hypoalbuminaemia and does not necessarily indicate zinc deficiency.

The true extent of zinc deficiency remains unclear, because the incidence found by plasma zinc measurements probably overestimates the problem. The significance of low plasma zinc levels is also not known. Kirschner, Voichet and Rosenberg (1978) found low plasma zinc levels in 6 of 9 children with growth retardation, usually associated with hypoalbuminaemia. Treatment with oral zinc returned plasma zinc measurements to the normal range but

did not influence the pattern of growth. Nishi *et al.* (1980) also pointed out that low plasma zinc levels and zinc malabsorption could occur, not only in growth retarded children, but also in those with normal height and weight. However, the observation that zinc deficiency impairs the insulin response and the utilisation of glucose and amino acids provides a theoretical reason why this factor may be relevant to growth retardation (Wolman *et al.*, 1979).

Selenium deficiency has been reported anecdotally in Crohn's disease (Fell *et al.*, 1980). Penny *et al.* (1983) confirmed selenium deficiency in Crohn's disease by finding low levels of whole blood selenium and red cell glutathione peroxidase, and they attributed this to impaired nutrition. The significance of these findings is unknown, although there are epidemiological studies from China relating selenium deficiency in the population to cardiovascular disease (Editorial, 1979).

There is little information about other metals and trace elements, although Penny *et al.* (1983) found normal concentrations of plasma copper.

Growth retardation

Impaired linear growth and delayed sexual maturation may occur in 15–30% of children with Crohn's disease (McCaffery *et al.*, 1970; Burbige, Huang and Bayliss, 1975). O'Donoghue and Dawson (1977) found that stunted growth was the presenting feature in 6 of 33 children referred to hospital, and was also the most frequent physical abnormality. The mean delay in making the diagnosis of Crohn's disease was 3 years, and this was thought to be a major factor contributing to impaired growth.

Resection of diseased bowel can result in catch-up growth provided this is done before puberty and that there is no early recurrence (Block, Moossa and Simonowitz, 1977; Homer, Grand and Colodny, 1977). Steroids given in modest amounts to control the disease achieve a similar result (Tenore *et al.*, 1977).

No evidence has arisen to implicate adrenal, pituitary or hypothalamic dysfunction in the aetiology of growth retardation in Crohn's disease (Gotlin and Dubois, 1973; Tenore *et al.*, 1977). In 1978, Kirschner *et al.* put forward the important concept that caloric insufficiency superimposed on protein, mineral and vitamin deficiencies was of major importance, and that when control of the disease was established through medical or surgical therapy and when oral nutritional restitution was allowed, then growth and maturation would restart. The concept was confirmed when 7 patients with severe growth failure showed 'catch-up growth' after nutritional repletion by either the enteral or parenteral route (Kelts *et al.*, 1979).

Conclusion

Patients with Crohn's disease may have a wide range of nutritional disturbances that in their own right can cause considerable morbidity. Nutritional defects may also have more subtle effects on other systems; for example, iron and zinc deficiency may be associated with impaired immune competence (Beisel, 1982) and hypomagnesaemia may be associated with parathyroid failure (Rude, Oldham and Singer, 1976). The classical manifestations of nutritional deficiency are uncommon, but laboratory tests indicate that subclinical deficiencies are common.

On clinical grounds, it is difficult to identify the 'at risk' patient who attends the outpatient department, although those with active disease, diffuse small bowel disease and postoperative recurrence have a greater tendency to develop nutritional problems than others. In the tropics where malnutrition, especially amongst children, is prevalent, simple anthropometry has been used with good effect to identify patients at risk (Chen, Chowdhury and Huffman, 1980). These workers used the mid-arm circumference as their nutritional indicator, and preliminary studies in Crohn's disease suggest that it is valuable as a screening test to identify a group of patients who are likely to have nutritional disturbance and who would benefit from more detailed nutritional assessment (Harries *et al.*, 1982c).

Probably the most effective method of overcoming malnutrition is to treat the disease either by drug therapy or surgery as is most appropriate. Nutritional therapy, via the parenteral or enteral route, may help to improve nutrition and disease activity, although there is still a dearth of controlled clinical trials to scientifically substantiate the claims made for this form of treatment. Finally, specific nutritional defects can usually be corrected with the appropriate supplements, and this may help to improve the outlook of patients suffering from a chronic and unpredictable disease.

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