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Symposium on 'The challenge of translating nutrition research into public health nutrition'

Session 3: Joint Nutrition Society and Irish Nutrition and Dietetic Institute Symposium on 'Nutrition and autoimmune disease' Nutrition in Crohn's disease

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The exact aetiology of Crohn's disease remains unknown. The consensus is that the disease results from a complex interaction between genes, immunity and environmental factors. Diet is attractive, in theory, as an environmental risk factor in the aetiology of the disease. The epidemiological data, often impeded by methodological issues, have failed to confirm a direct link between pre-diet illness and the development of Crohn's disease. Once diagnosed, however, nutrition has an important role in disease management. Among the nutritional issues are malnutrition, weight loss and suboptimal nutritional status; these outcomes may be present at any stage of the disease but are likely to be overt during acute illness and hospitalisation. Malnutrition has been identified in approximately 40% of hospital admissions with Crohn's disease and is associated with higher mortality, longer hospital stays and higher healthcare costs. Patients in remission may indeed be overweight and appear to be influenced by the general population trends toward overweight and obesity. Irrespective of BMI, patients are at risk of micronutrient deficiencies. Vitamin D deficiency, for example, is common in Crohn's disease and has important implications for bone health. Moreover, newer evidence suggests that vitamin D has potential anti-inflammatory effects. Dietary approaches, in the form of enteral nutrition, have previously been shown to reduce inflammation and treat the active disease. Current guidelines now recommend that corticosteroids are more effective than enteral nutrition for treating adults. Enteral nutrition has important growth and developmental benefits and continues to be a recommended therapy for children with Crohn's disease.

Crohn's disease: Diet and disease risk: Nutritional status: Vitamin D: Nutritional therapy

Crohn's disease: background

Crohn's disease (CD) and a related condition, ulcerative colitis, are collectively referred to as inflammatory bowel disease. CD is a lifelong chronic relapsing and remitting inflammatory condition of the gastrointestinal tract. Symptoms include diarrhoea, abdominal pain, fever and fatigue. The disease is named after Dr Burrill B Crohn, who in 1932, along with his colleagues, published a landmark paper describing 'regional ileitis', which is now known as CD[1].

The incidence of CD is estimated at 6·7 cases per 100 000 annually, with a prevalence of 140 cases per 100 000 in the Western world[2]. CD may be diagnosed at any age, including childhood, but typically presents in late adolescence and early adulthood (15–30 years of age). The disease therefore affects individuals during their most active years and is associated with increased morbidity,

Abbreviation: CD, Crohn's disease.

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hospitalisation, surgery, medical and nutritional complications and high healthcare costs. For individuals with this condition it can be debilitating, resulting in poor quality of life, reduced daily functioning and the potential to cause lifelong ill health.

Given the symptoms and nature of this condition, nutritional issues are important. The present review sets out to address three key questions relating to nutrition in CD: (1) is diet a risk factor for the development of the disease; (2) what are the main nutrition-related issues in disease management; (3) are dietary approaches effective for treating active disease.

Is diet a risk factor for the development of Crohn's disease?

The exact aetiology of CD remains unknown. The consensus is that the disease results from a complex interaction between genes, immunity and environmental factors[3]. There is a known genetic component to CD; the disease runs in families and 20–25% of patients have a first-degree relative with either CD or ulcerative colitis. More recent advances in genetics show that mutations in the *NOD2/CADD15* gene, located on chromosome 16, are associated with increased susceptibility to the disease[4,5]. Cigarette smoking is one of the best-described environmental risk factors[2,6], with smokers twice as likely to develop CD as non-smokers. Several other risk factors have been proposed, including diet, socio-economic factors and childhood infections[2].

Diet is attractive, in theory, as an environmental risk factor in the aetiology of the disease. Westernised diets, typically characterised by high fat, high sugar and low fibre intakes, have been proposed as a risk factor for the development of CD[7]. The increasing incidence of the disease in countries such as Japan coincides with changes to more Westernised diets[8]. A number of case–control studies conducted in the 1970s and 1980s have identified refined sugars as a potential risk factor[9,10]; however, this finding has yet to be confirmed by large prospective studies. A larger case–control study has implicated consumption of chocolate and cola drinks as possible risk factors for the disease[11]. Overall, the data showing a relationship between sugar intake and onset of CD are inconsistent[12] and there is limited convincing evidence that high sugar intakes relate to disease onset. Similarly for fats, some studies have implicated monounsaturated and polyunsaturated fats in the development of the disease[8,13]. A hospital-based case–control study from Japan has shown that the consumption of sugars, sweeteners and confectionery as well as fats and oils (intakes of total fat, MUFA, PUFA and *n*-3 and *n*-6 fatty acids) are positively associated with CD risk[14]. Overall, the putative role of fats and sugar in the development of the disease remains inconclusive.

More recently, a Canadian study has revisited this issue of diet as a risk factor[15]. In a case–control study the dietary habits were assessed 1 year before disease onset in 130 children with CD compared with 202 controls. The findings suggested that intakes of fruit and vegetables, fish and nuts were associated with a lower risk of developing the disease in children. Data for fat intake were also reported, showing a negative association between consumption of long-chain *n*-3 fatty acids and CD, with a higher long-chain *n*-3:*n*-6 fatty acids associated with lower risks for the disease[15]. These findings, however, need to be confirmed in larger rigorously-conducted prospective studies.

There are several methodological challenges in providing supporting evidence that diet is a truly causative agent in CD. In retrospective studies it may be difficult to determine whether dietary patterns have occurred because of the disease symptoms rather than contributing to the development of the disease, bearing in mind that the onset of the disease may precede the diagnosis by a considerable time. Several methodological issues, particularly in relation to recalled dietary intakes, have been highlighted[12]. The relatively low incidence of the disease is also a challenge to studying the role of dietary factors in disease onset in large cohorts. Moreover, dietary habits may be markers for aspects of lifestyle other than diet, such as socio-economic factors, childhood factors, educational status and access to health care. For an individual with CD eating in general or eating specific foods may aggravate gastrointestinal symptoms without having a causative role in the disease.

In summary, to date, there is no conclusive evidence that pre-illness diet directly contributes to the pathogenesis of CD. There is currently no recommended diet-specific approach to reducing the risk of developing CD, over and above general healthy eating and lifestyle advice aimed at the general population. Once CD is diagnosed, however, nutrition does have an important role in the management of this chronic digestive condition.

What are the nutritional issues and challenges in CD?

There are many nutritional challenges in managing patients with CD throughout the course of their disease. These challenges include malnutrition in hospitalised patients, malabsorption, short bowel syndrome, micronutrient status[16,17], Fe-deficiency anaemia[18] and osteoporosis[19,20]. For the purposes of the present review the focus is on the contrasting nutritional issues of malnutrition and overweight in CD and on the growing problem of vitamin D insufficiency.

Malnutrition in Crohn's disease

The causes of malnutrition in CD are multiple and include poor dietary intake, impaired nutrient digestion and absorption and increased nutrient requirements (Fig. 1). Malnutrition, weight loss and suboptimal nutritional status may be present at any stage of the disease but are often overt during acute illness and hospitalisation.

A study of hospital admissions (*n* 502) has identified malnutrition in 40% of patients with inflammatory bowel disease[21]; the highest prevalence of malnutrition among patients with benign diseases. Furthermore, patients with malnutrition spend 40% longer in hospital[21]. Recently,

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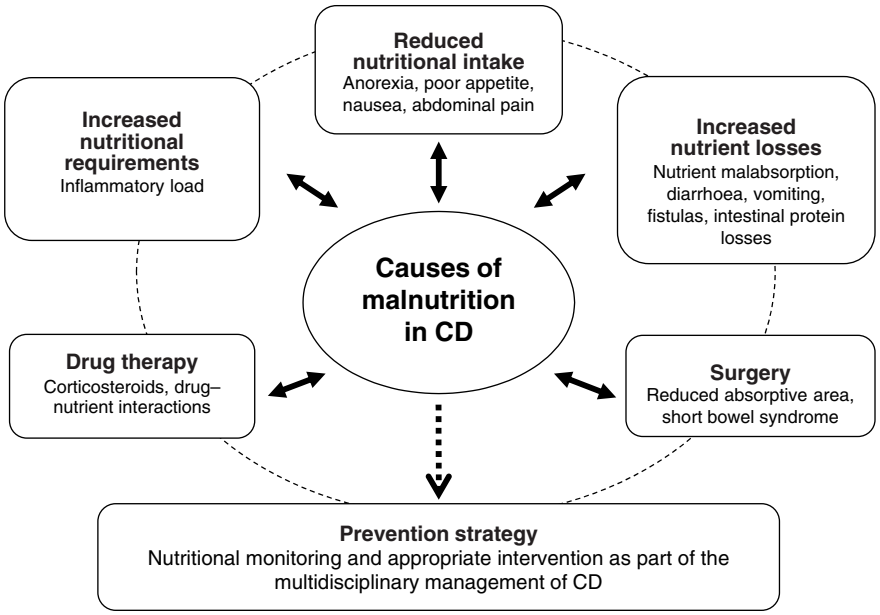

Fig. 1. Causes of malnutrition in Crohn's disease (CD).

a large study comprising >75 000 patients has highlighted a higher prevalence of protein–energy malnutrition among admissions for inflammatory bowel disease than admissions not for inflammatory bowel disease (6·1% compared with 1·8% respectively)[22]. The prevalence rates of malnutrition in this study are unusually low and are possibly underestimated because malnutrition was identified from information contained in national databases of hospital discharges rather than being measured specifically for the study. This approach is in contrast to hospital-based studies (for example, see Pirlich *et al.*[21]) in which malnutrition was measured by anthropometry and bioelectrical impedance. Nevertheless, it was found that when malnutrition is present patients have a higher mortality, longer hospital stays and higher healthcare costs[22]. In acutely-ill hospitalised patients malnutrition may be a marker of disease severity and poor prognosis. Hospitalised patients may often be malnourished on admission, which worsens while in hospital[23]. Thus, appropriate nutritional screening and intervention as part of the multidisciplinary management of CD is important.

While malnutrition during active disease or hospitalisation may be expected, the nutritional status of patients with inactive disease is less clear. Changes in lean body mass, muscle function and bone stores have been documented during remission[24–26]. Reduced hand-grip strength has been identified in patients with quiescent CD in the absence of other signs of malnutrition[27]. Also, reduced body cell mass and reduced hand-grip strength have been reported in CD in remission compared with controls[26]. Reductions in muscle function and body cell mass have, therefore, been identified in patients considered well nourished according to routine measures such as BMI, serum albumin and screening tools such as the subjective global assessment and the malnutrition universal screening tool. It would appear, however, that the emerging findings in CD among outpatients and patients in clinical remission are an increase in BMI and the presence of overweight.

Overweight: the changing shape of Crohn's disease

CD is traditionally considered to be a disease associated with weight loss and low BMI. This perception, however, appears to be changing. In a study of children with newly-diagnosed CD most of the subjects (68%) were found to have a BMI in the normal range, with 10% classed as overweight or at risk for overweight[28]. Low BMI was documented in <25% of all children at diagnosis. These findings are illustrated in Fig. 2, which compares BMI data from two cohorts of American children with inflammatory bowel disease with data from normal healthy children[28]; they suggest that overweight or obesity should not preclude a diagnosis of CD in children[28,29]. In adults the predominant form of malnutrition in patients in disease remission appears to be an excess of body fat[30]. In a preliminary study the majority of patients, even those with signs of reduced muscle function, have been found to have a BMI that is normal or above normal, with 40% classed as overweight or obese[27].

Taken together, these findings suggest that individuals with CD, at least when in remission and not hospitalised, are similar to those for the general population and are influenced by the background population trends towards overweight and obesity. There are added concerns for this phenomenon in CD. Overweight may mask other aspects of poor nutritional status such as loss of lean body mass, bone loss or micronutrient deficiencies. It has been reported that macronutrient needs of patients in disease remission are met in ≤70% of patients; micronutrient deficiencies, however, may be common and require

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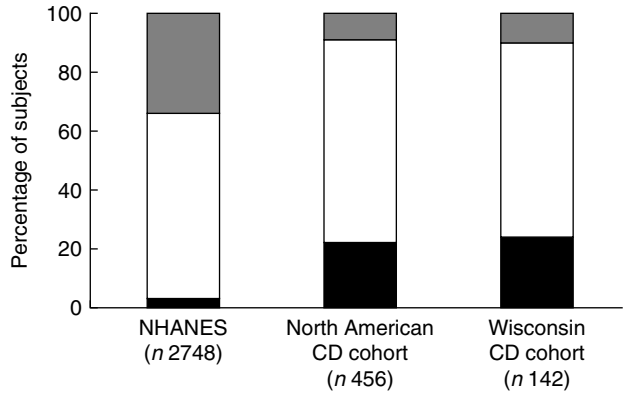

Fig. 2. Classification of BMI in 2748 US children in years 2001 and 2002, as determined by National Health and Nutrition Examination Surveys (NHANES) data (controls) and in children with newly-diagnosed Crohn's disease (CD) from the North American CD cohort (*n* 456) and the Wisconsin CD cohort (*n* 142). (▩), BMI ≥ 85th percentile (at risk of overweight or overweight); (□), BMI 5th–84th percentile (normal reference range); (■), BMI < 5th percentile (low). (Reproduced, with permission from Elsevier, from Kugathasan *et al.*[28].)

specific screening[16]. The consequences of overweight and excess body fat in the context of CD are not clear. It has been suggested that obese patients with CD are more prone to develop an active disease than matched non-obese patients with CD[31]. Furthermore, obese patients with CD require surgery sooner than non-obese patients with CD[32].

In the short term overweight among individuals with CD may reflect wellness and disease control. How overweight and excess adipose tissue interacts with a background of inflammation and contributes to relapse, comorbidity, long-term complications or disease course in CD remains to be seen. Adipose tissue, once considered to be an inert entity, is now known to produce several bioactive molecules including TNFα, which is a key pro-inflammatory cytokine in CD. Furthermore, a build up of intra-abdominal adipose tissue is a recognised feature of CD, which may contribute to intestinal inflammation[33].

Vitamin D insufficiency in Crohn's disease

Vitamin D deficiency is common in individuals with CD[34,35], with known implications for the risk of bone disease. Vitamin D stimulates bone matrix formation and maturation and promotes Ca absorption from the gut and kidney (for review, see Lanham-New[36]). The relative risk of fractures is 40% greater in patients with inflammatory bowel disease than in the general population. The prevalence of osteopenia and osteoporosis is estimated at 50% and 15% respectively[37]. Corticosteroid therapy, malabsorption, malnutrition, inflammation and hormonal and genetic factors as well as vitamin D and Ca status contribute to this increased risk of bone disease. As far back as 2000 the British Society of Gastroenterology highlighted the importance of recognising and treating vitamin D deficiency in individuals with CD and have recommended daily vitamin D supplements of 20 μg for patients taking systemic corticosteroids[19].

Individuals with CD are at most risk of vitamin D deficiency in winter[38], especially in countries of northern latitudes, because the lack of sunlight during winter months results in poor stimulation of vitamin D production in the skin. Diet alone is unlikely to maintain adequate serum vitamin D status, as few foods, apart from oily fish and fortified foods, are good sources of this vitamin. Dietary vitamin D may be further compromised for individuals with CD by poor dietary intakes and malabsorption.

Defining optimal serum 25-hydroxyvitamin D level in Crohn's disease. Serum 25-hydroxyvitamin D is the biomarker most commonly used to assess vitamin D status. The most appropriate thresholds for determining vitamin D status are an issue of debate[39–41]. The focus of this argument is on determining the optimal level for health as opposed to the minimum level to prevent deficiency and severe bone disease such as osteomalacia and rickets. Broadly speaking, a level of 40 or 50 nmol/l[39,41,42] is used to define insufficient or inadequate vitamin D status. Other researchers propose higher cut-off levels of the order of 75–80 nmol/l[40,42]. The debate about 25-hydroxyvitamin D is pertinent to CD because higher disease-specific levels may well be required to prevent bone disease in this at-risk group. Moreover, 25-hydroxyvitamin D levels that promote anti-inflammatory effects, if any, in CD have yet to be determined.

Vitamin D: possible anti-inflammatory role of vitamin D in Crohn's disease. There is growing evidence to suggest a role for vitamin D beyond its role in bone health in CD. Deficiency of vitamin D has been reported to accelerate the development of symptoms of inflammatory bowel disease in IL-10-knock-out mice[43], while dietary vitamin D and Ca have been reported to suppress experimental colitis by inhibition of the TNFα pathway[44]. Recently, anti-inflammatory effects of vitamin D on T-cells derived from patients with CD have been described[45]; in this study 1,25-dihydroxycholecalciferol was found to increase IL-10 and reduce interferon-γ production.

Vitamin D insufficiency in Crohn's disease: spectrum of a wider public health problem. The identification of vitamin D insufficiency is, of course, not isolated to CD. Indeed, numerous studies now suggest that hypovitaminosis D is widespread in adult normal populations[42,46–48]. A large cohort study of British adults has documented hypovitaminosis D in 47% of participants in winter and spring and 15% during summer and autumn. Similarly, a high prevalence (51%) of vitamin D insufficiency has been reported among healthy Irish adults, with half (51%) classed as vitamin D insufficient, rising to 58% in winter[49]. Substantial work now shows that vitamin D deficiency is common in the general population, suggesting that the high prevalence of deficiency in CD is part of a spectrum of a wider public health issue. The deficiency, however, may be more common and more severe among individuals with CD and the consequences of poor vitamin D status are likely to be considerable in terms of the added risk of bone disease and the potential role in suppressing inflammation.

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Table 1. Summary of guidelines for enteral nutrition as primary therapy in Crohn's disease

Source	Adults	Children
British Society of Gastroenterology[62]	After detailed discussion EN may be used in preference to steroids, immune modulators or surgery in any patient with active disease or for those unresponsive to mesalazine or in whom steroids are contraindicated	EN is appropriate for growth failure in children or adolescents with active small bowel CD
European Society for Clinical Nutrition and Metabolism[76]	EN is effective in the treatment of active disease. In adults, however, corticosteroids are more effective. EN as the only therapy, therefore, for acute CD is indicated mainly when treatment with corticosteroids is not feasible, e.g. because of intolerance or refusal	In children with CD the first-line therapy is considered to be EN
Japanese Society for Pediatric Gastroenterology[77]	n/a	Total EN, in the form of an elemental formula, is indicated as primary therapy for children with CD at onset as well as the active disease (other than serious illness)

EN, enteral nutrition (oral nutritional supplements or tube feeding); CD, Crohn's disease; n/a, not applicable.

Is nutrition effective in the treatment of Crohn's disease?

Adults

In the early 1970s enteral nutrition, in the form of an elemental diet, was shown to have a primary therapeutic effect in CD[50,51]. An elemental diet provides nutrients in their simplest form, i.e. protein as free amino acids, carbohydrate as glucose or short-chain maltodextrins and fat as short-chain TAG. Elemental diets were used initially to nourish patients before surgery and some of these patients with CD were found to inadvertently improve symptomatically, which suggested that the diet may have had a primary therapeutic effect[50,51]. In the 1980s the first controlled trial confirmed that an elemental diet is as effective as corticosteroids in inducing clinical remission in active CD[52]. Several subsequent studies have supported this therapeutic effect and have also shown that the less-expensive and more-palatable polymeric (whole-protein) enteral formulas are equally as effective as an elemental diet[53–55].

The therapeutic approach of enteral nutrition is based on administering the feed as the only source of nutrition either orally or by nasogastric tube for 1–2 weeks. The practicalities of this regimen for adult patients, who may have other therapeutic options, should be considered. Poor compliance typically results in poor outcome irrespective of the therapeutic agent; suggestions on overcoming the practical challenges for the use of enteral nutrition in adults with CD are detailed elsewhere[56–58].

More recent evaluation, based on meta-analyses[59,60] and a Cochrane review[61], now show that corticosteroids are more effective than enteral nutrition therapy in adults. Current guidelines mirror this finding, recommending that enteral nutrition is less effective than corticosteroids in the treatment of active CD, but that it may be considered as therapy for adults in special circumstances, e.g. where other primary therapy may not be feasible[62]. As adjunctive therapy, nutritional support is recommended for any malnourished patient with CD or for patients with difficulty maintaining normal nutritional status (Table 1). The role of nutritional therapy in the management of adult CD in the future remains uncertain[57,63,64], particularly in the era of newer therapeutic approaches such as biologic therapy that have changed the management of this disease[65]. Moreover, in adults guidelines recommend using enteral nutrition in special circumstances rather than as a generic therapy. Clearly, its role in managing malnourished patients or those at risk of malnutrition is undisputed (Table 1).

Children

In children with CD the rationale for using enteral nutrition as the primary therapy is stronger. In addition to the therapeutic effect[66], nutritional therapy has positive effects on growth and development[67,68] and may reduce the use of corticosteroids[69]. A recent meta-analysis has concluded that enteral nutrition has similar efficacy to corticosteroids in children, but has cautioned that this outcome is based on limited data[66]. A Cochrane review of strategies for growth failure in children with CD has highlighted the positive effect of enteral nutrition therapy in promoting growth[68]. In children enteral nutrition is recommended as first-line therapy for active disease, especially for those with growth failure (Table 1). As a maintenance therapy to prolong remission, enteral nutrition, in addition to normal diet, has been shown to prolong remission and improve linear growth in children who have achieved remission by exclusive enteral nutrition[70].

Mode of action

The mechanisms underlying the therapeutic response to enteral nutrition remain unclear. There is evidence that enteral nutrition therapy promotes mucosal healing and down regulates mucosal pro-inflammatory cytokines[71,72]. Low antigenic load (absence of whole protein) was initially proposed to contribute to the therapeutic effect, but it is now known, however, that whole-protein enteral feeds are as effective as the amino acid-based elemental diets[73]. Other theories[74] relate to the provision of fatty acids[75],

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changes in gut flora and changes in intestinal permeability. Better understanding of the biological mechanisms underlying a therapeutic response, as well as the phenotypic and genotypic factors that predict this response, may allow more innovative approaches to diet therapy in the future.

In summary, enteral nutrition arguably offers a safe mode of delivery of potentially immune-modifying substrates directly to the gastrointestinal mucosa. Its role, however, as primary therapy for CD in adults remains uncertain in the light of pharmacological advances, such as biologic therapy, that have changed the management of this disease. Judged in the context of the best evidence and consensus guidelines, enteral nutrition is shown to be less effective than corticosteroids in adults but is an effective and important first-line therapy for children.

Conclusion

Diet is attractive, in theory, as an environmental risk factor in the aetiology of CD. Currently, there is no conclusive evidence, however, that pre-illness diet is a risk factor for development of this disease. How Westernised diets and environmental factors contribute to the pathogenesis of this disease remain active areas of research interest. Once CD is diagnosed, nutrition has an important role in disease management; in particular, the prevention and treatment of malnutrition is a key clinical priority throughout all stages of this disease. While individuals with CD have disease-specific nutritional needs, they appear to be influenced also by the wider-population health issues such as vitamin D deficiency and overweight. Vitamin D deficiency is common in CD and has important implications for bone health. While CD is traditionally associated with weight loss, the emerging picture suggests that overweight may be common, particularly in patients in clinical remission.

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