A systematic literature review on the nutritional adequacy of a typical gluten-free diet with particular reference to iron, calcium, folate and B vitamins

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Glossary of Terms

ACBS (ACBS): the Advisory Committee on Borderline Substances (ACBS) was set up to advise GPs on prescription of products that are not drugs or medical devices. The Committee is an advisory Non-Departmental Public Body (NDPB), non-statutory and UK-wide. The ACBS reviews information for applications for products to be prescribed at NHS expense.

Adaptive immune system: A system of highly specialised, systemic cells and processes that eliminate or prevent potential disease causing agents. The adaptive immune response provides the immune system with the ability to recognise and remember specific pathogens and to mount repeated responses each time the pathogen is encountered.

Addison's disease: an autoimmune disease caused by inadequate secretion of corticosteroid hormones from the adrenal glands. Symptoms include weakness, loss of energy, low blood pressure, and dark pigmentation of the skin. The disease is treated with corticosteroid therapy.

Ataxia: the shaky movements and unsteady gait that result from the brain's failure to regulate the body's posture and the strength and direction of limb movements.

Autoimmune condition: a condition where the body's own immune system attacks its own tissues. In coeliac disease the trigger for the autoimmune response is eating gluten, and as a result of this complex immune response the lining of the small bowel becomes damaged.

Bias: is a term used to describe a tendency or preference towards a particular perspective or result, especially when the tendency interferes with the ability to be impartial or objective.

Biopsy: the removal of a small piece of tissue for analysis.

Bone mineral density: A measure that is used to assess the strength of bones.

Coeliac UK: leading Charity working to improve the lives of those with coeliac disease and dermatitis herpetiformis. With 85,000 Members, it is the largest organisation of its type in the world.

Confounding factor: A variable which is related to one or more of the variables defined in a study. Confounding factors may mask an actual association or falsely demonstrate an apparent association between study variables, when in fact no real relationship exists. If confounding factors are not measured and considered, bias may result in the conclusion of the study.

Endomysial antibodies: One of the antibody blood tests that is used in screening process for coeliac disease.

Endosperm: is the nutritive tissue produced in the seeds of flowering plants. It surrounds the embryo and contains a mixture or starch, oils and protein.

Epithelium: the lining issue that covers the external surface of hollow structures (in this instance the small bowel).

Gastroenterologist: Specialist medical consultant working in the field of gastroenterology.

Haemolytic anaemia: a type of anaemia resulting from the breakdown of red blood cells.

Homocysteine: an amino acid. Raised levels of homocysteine in the blood can be associated with increased cardiovascular disease risk.

Innate immune system: provides immediate defence against infection, and comprises cells and mechanisms that defend the host from infection by other organisms, in a non-specific way. The cells of the innate immune system recognise and respond to disease in a generic way, but do not confer long-lasting specific immunity.

Infiltration: the abnormal entry of a substance into a cell or tissue.

Lamina propria: thin layer of connective tissue found below the lining of the epithelium.

LRNI (Lower Reference Nutrient Intake): the amount of a nutrient that is sufficient for only a small number of people who have low nutritional requirements (2.5%).The majority of the people in the population need more than the LRNI.

Malabsorption: when absorption of one or more substances and nutrients by the small intestine is reduced.

Marsh Classification: an accepted categorisation of mucosal damage seen in coeliac disease.

Neurological: describes medical conditions affecting the nervous system (brain, spinal cord and all peripheral nerves).

Non-Hodgkin's Lymphoma: a malignant tumour of the lymph nodes.

Odds Ratio (OR): is a measure of a given association. A value of 1.0 means there is no relationship between the variables being studied. The size of a relationship is measured by the difference (either above or below) 1.0. An OR of less than 1.0 indicates a negative association, while an OR greater than 1.0 indicated a positive relation.

Oesphageal cancer: cancer affecting the cells of the oesophagus (gullet/food pipe).

Oropharyngeal cancer: oral cancer affecting the part of the pharynx (throat) containing the tonsils.

Osteoporosis: loss of bone minerals (calcium) resulting in thin bones that are brittle and have an increase risk of fracture.

Peptide: the building block of protein (a sequence of two or more amino acids).

Primary Biliary Cirrhosis (PBC): an autoimmune disease resulting in disordered liver function tests where the bile ducts in the liver are attacked by the body's own immune system. Symptoms include extreme tiredness, poor appetite, nausea, diarrhoea, joint or bone pain. In some cases there are no symptoms.

Peripheral neuropathy: disease of the peripheral nerves causing weakness and numbness in the hands and feet.

Reference Nutrient Intake (RNI): the RNI is the amount of a nutrient that is enough to ensure that the nutritional needs of nearly all the population (97.5%) are being met.

Relative risk (RR) is the risk of developing a disease relative to exposure. Relative risk is a ratio of the probability of the disease developing in the exposed group versus a non-exposed group.

Sensitivity: is a statistical measure of the reliability of a screening test based on the proportion of people with a specific test (the higher the sensitivity the fewer false negatives).

Serological test: a test which is normally carried out on blood serum (the liquid component of blood).

Specificity: measures the proportion of people free from a disease who react negatively to the test i.e. the higher the specificity the fewer the false positives.

Sjogren's syndrome: an autoimmune disease affecting the salivary and lacrimal glands resulting in dry mouth and eyes.

Thyroid: an endocrine gland situated at the base of the neck which regulates the body's metabolic rate.

Tissue transglutaminase: an enzyme used in antibody blood test used to screen for coeliac disease.

Type 1 diabetes: an autoimmune disease where islet cells in the pancreas stop producing insulin. Those with Type 1 diabetes need to have injections of insulin to control blood glucose levels.

Villous atrophy: typical mucosal damage seen in coeliac disease.

1.0 Executive Summary

1.1 Rationale

Coeliac disease (CD) is a life-long autoimmune condition affecting 1 percent of the population in the UK.[1, 2] To date, the only effective treatment for CD is strict adherence to a gluten-free (GF) diet. A GF diet is restrictive as it involves eliminating wheat flour and its associated staple products including bread, pasta and cereals from the diet. Ranges of GF substitute foods have been developed based on GF cereals such as maize (corn) and rice.

The GF diet can be made up in a variety of different ways, but generally incorporates GF substitute products e.g. GF breads and flours in place of standard products.

In the UK, people with medically diagnosed CD may access some of their GF substitute foods on prescription. The foods on prescription are generally staples in the diet such as bread and pasta rather than foods which can be considered luxury items, such as confectionery. The GF foods that are prescribable are agreed by the Advisory Committee on Borderline Substances (ACBS).

There is no specific evidence base that compares the nutritional composition of GF substitute foods to standard products. The nutrient composition of wheat flour is covered by legislation, (The Bread and Flour Regulations, 1998)[3]; wheat flour is fortified with the minerals calcium and iron, and the B vitamins thiamin and nicotinic acid. For GF substitute products, this is not the case. GF substitute products may provide an ideal vehicle for additional nutrients to a potentially at risk group. However, the concept of fortification or enrichment of the necessary GF flours requires careful thought in terms of the perceived benefits to the consumer, health benefits to the population or a specific group of the population and marketing benefits to the food industry.

Current practices in the UK regarding addition of nutrients to GF staple foods are variable. In addition, it is necessary to consider the specific dietetic issues with regard to the GF diet including potential propensity to lower calcium intake, calcium malabsorption of the coeliac

population and other specific nutritional deficiencies such as folate deficiency, iron deficiency and B vitamin deficiency.

1.2 Aims and Objectives

The aims of this research project were:

- to produce a report which informs the Food Standard Agency (FSA) regarding the current status of evidence on the nutritional adequacy of the GF diet and its impact on nutritional status.

- to inform the FSA for future policy development and strategies to minimise any negative effect of the GF diet per se on nutritional intake for people with CD.

Due to the complexity of the composition of the GF diet, variability in consumer choice and access to GF substitute products, a range of policy options may have to be considered, if the evidence is suggestive of nutritional inadequacy.

The objectives of the project were to:

- perform a structured systematic literature review on the nutritional adequacy of a typical GF diet with particular reference to iron, calcium, folate and B vitamins by identifying, grading and reviewing the literature currently available. Both published and unpublished data are included in this review, so long as the inclusion and exclusion criteria were met.

- produce a report summarising the state of scientific evidence and with recommendations on strategies to address any issues around nutritional adequacy of a GF diet that the review has identified (including fortification of GF substitute products).

1.3 Methodology

This systematic literature review searched a series of databases, followed by hand searching of reference lists and a thorough search for unpublished research. All first authors of identified papers, established leaders in the field of CD, key professional bodies and their affiliated groups, CD related organisations and manufacturers of GF products were contacted as part of this search process. A quality assessment was carried out by two independent reviewers in order to grade the evidence. Each paper was assessed for the risk of bias by using checklists and a grading system as recommended by Scottish Intercollegiate Guidelines Network (SIGN).[4] Bias may be introduced into a study in a number of ways. Factors that were considered included sample size, method of recruitment of participants, analysis of dietary intake, inclusion and exclusion criteria, whether potential confounding factors had been addressed and likely author bias. Identifying the sources of bias is important in order to try and estimate what effect it could have on the findings of a study.

1.4 Results

There were eleven papers included in this systematic review; these consisted of ten case-control studies and one cohort. Ten of the papers were published studies and one case-control study was unpublished (it is unlikely that this work will be published until 2009). A summary of the baseline results for included studies can be found in Appendix H.

The main sources of plausible bias in the included papers were:

Recall/measurement bias: The methods used to assess dietary intake may not produce a true representation of dietary intake over the course of the study period. It is well established that, subconsciously or otherwise, self-recorded diet histories can often lead to an underreporting of nutritional intake. [5]

Ascertainment/selection bias: The details regarding the selection of participants should be stated as part of the methodology. In some studies, participants may be recruited through national associations or patient groups, so by definition are a well “motivated” group. They may therefore be more likely to adhere to the GF diet, be better informed, and may have a

balanced diet compared to those with CD who do not show a commitment to an affiliated patient organisation.

Analysis bias: This can occur if significant numbers of participants who are originally recruited to a study are not included in the analysis e.g. high drop-out rates of those failing to complete the study protocol. Although this may not necessarily be under the researchers' control, data on drop-out rates should be stated in the results.

All papers were found to have moderate or high risk of bias, meaning that that the sources of bias identified either raised some doubts about the results, or seriously weakened confidence in the results. Details on the sources of plausible bias of each paper are listed as part of the data extraction tools, which can be found in Appendix G.

Most papers concluded that individuals with CD following a GF diet had the same nutritional intake as the general population.[6,7,8,9,10,11] Where the results were found to differ between these groups, there was often no P values recorded to demonstrate statistical significance,[12,13,14,15] so it is difficult to comment on these results.

1.5 Conclusion

There is no evidence to suggest that nutritional deficiency is a significant problem in individuals diagnosed with CD and established on a GF diet. There was no firm evidence to show that those individuals following a GF diet had an inadequate intake of iron, calcium, and B vitamins.

However, these conclusions may reflect the paucity of data, rather than a genuine absence of nutritional deficiencies between conventional and GF diets.

1.6 Significance of findings

At the moment, there is not enough evidence to support fortification of GF staple substitute products although there is an argument for fortification of GF flours used in the production of

GF substitute staple products so that nutritional composition is comparable to gluten-containing staple products

More robust research is required, ensuring adequate sample sizes, to investigate further the nutritional adequacy of the GF diet in people medically diagnosed with CD.

2.0 Introduction and background

2.1 Epidemiology

Coeliac disease (CD) is a permanent autoimmune condition characterised by inflammation of the intestinal mucosa in the proximal small bowel.[16] Screening studies indicate that CD affects one percent of the UK population[1,2] making it the most prevalent small bowel disease to affect Western populations[17] and the most common cause of malabsorption in the UK. [18]

Under-diagnosis, late diagnosis and mis-diagnosis of CD are all significant problems as evidence suggests that only 1 in 8 cases are currently diagnosed.[19] Coeliac UK commissioned research project, undertaken by the Health Economics Unit, University of Oxford, found that the average time for an individual to be diagnosed with CD after initial reporting of symptoms is thirteen years.[20]

CD is a multi-system disorder that can present with non-specific symptoms that may often be overlooked. [21, 22] The symptoms of CD range from mild to severe and vary between individuals. Possible symptoms may be gut related and include bloating, nausea, constipation, diarrhoea, wind and weight loss. However, although often cited as common symptoms in CD, a study of people newly diagnosed with CD found fewer than half have symptoms of diarrhoea, and even fewer show signs of weight loss[23]. The stereotypical presentation of the underweight patient no longer applies; research has found a significant proportion of patients who are of normal weight, or overweight at diagnosis.[24]

Anaemia and associated tiredness, headaches, mouth ulcers and skin problems are also common symptoms of CD. Other associated problems include recurrent miscarriages, infertility, depression, joint or bone pain and neurological symptoms such as ataxia and peripheral neuropathy.[25]

CD affects different ethnic groups, and is common not just in Europe, but also in countries including southern Asia, the Middle East, North West and East Africa and South America.[26] Whilst the most common age for diagnosis of CD is between forty and fifty years,[27] it can

present at any age after introduction of gluten-containing cereals or later on in life. There is evidence to suggest that more women are diagnosed than men.[28]

CD is a genetic condition, and there is an increased prevalence of ten percent amongst first degree relatives and 2 percent amongst second degree relatives of those with the disease.[29]

2.2 Coeliac disease

2.2.1 Diagnosis

There is a clearly defined diagnostic process for CD. It is imperative that the treatment with a GF diet is not initiated until after diagnosis is established.

The first step is usually a blood test which measures Immunoglobulin (Ig) A class of anti-tissue transglutaminase (TTG) and/or endomysial antibody (EMA), which both have a high sensitivity and specificity of over 90 percent.[30]

Current management guidelines state that a small intestinal biopsy is mandatory to confirm diagnosis of CD both in adults[31,32] and children.[33]

In CD, immune responses to toxic proteins promote an inflammatory reaction, characterised by infiltration of the lamina propria and the epithelium with chronic inflammatory cells and villous atrophy. This response is mediated by both the innate and adaptive immune systems.[34]

The typical changes start to occur within 4–6 h of exposure to the toxic peptide.[35] Individual mucosal and clinical responses may occur; the varying degrees of mucosal changes have been classified by Marsh.[36]

Although responses may be variable and dependent on a range of factors not yet clearly identified, if gluten is reintroduced at a later stage, mucosal damage will re-occur.

2.2.2 Complications

Coeliac disease is associated with an increased risk of a number of health complications. Adherence to the GF diet can prevent and help to manage these complications.[37]

Malignancy

A study looking at a group of two-hundred and ten people with CD found an increased risk of a number of malignancies such as non-Hodgkin's lymphoma (Relative Risk 42.7), oropharyngeal cancer (Relative Risk 9.7) and oesophageal cancer (Relative Risk 12.2), although the risk of developing all types of malignancy for people with CD is reduced to that of the general population after 5 years on a GF diet.[38] The same study found that in those not deemed to be adhering to the GF diet, the risks of developing malignancy were much increased (oropharyngeal and oesophageal cancer, Relative Risk 22.7; and lymphoma Relative Risk 77.8).[37]

CD has also been associated with increased risk of Enteropathy Associated T-Cell Lymphoma (EATL) with an Odds Ratio of 19.2.[39] However more recent research from the UK looking prospectively at 5,684 person years of follow up on a GF diet found only one case of small bowel lymphoma, compared to 0.02 which would be expected, suggesting the increased risk is lower than previously thought.[40]

The development of EATL is closely associated with refractory CD, which is defined as continued villous atrophy despite following a GF diet for longer than a year.[41] The prognosis for EATL is poor; one study shows a 5 year survival rate of only 8%[42] in those with CD who developed EATL.

Osteoporosis

Untreated CD is related to a significant risk of decreased bone mineral density [43] and osteoporosis.[44] Research shows that even years after diagnosis there is an increased risk of hip fracture in those with CD (Hazard Ratio 2.1).[45] A systematic review that analysed data from published studies of a total of 20,955 people with CD, confirms a significant association between bone fractures and CD (pooled Odds Ratio 1.43).[46]

The association of CD and osteoporosis is thought to be largely related to a chronic

malabsorption of calcium as a result of mucosal damage prior to diagnosis[47] as well as a reduced dietary intake of calcium.[48] In addition, bone loss is regulated by various mediators of the immune system, so the chronic inflammatory process in CD may also play a role. [49]

Adherence to the GF diet in people with CD optimises absorption of nutrients and has been shown to minimise bone loss and can help to normalise or improve bone mass.[50] A more recent review of osteoporosis in CD provides an insight into the possible mechanisms and complexity of osteoporosis in CD.[51]

Anaemia

Anaemia is a frequent finding in those with CD, and can be the sole presenting symptom in many cases.[52]

The anaemia may be secondary to iron deficiency but may also be multi-factorial in etiology.[53] Folate deficiencies have also been identified in undiagnosed people with CD, as well as vitamin B12 deficiency.[54]

People with CD may be more at risk of nutritional deficiencies, because symptoms of intestinal damage or non-compliance are often unrecognised, resulting in associated anaemias (iron-deficiency and B-vitamin deficiency).[55]

Although these nutritional deficiencies may resolve spontaneously once a GF diet is established, due to improved absorption from mucosal healing, supplementation may be advisable in some cases.[32]This should be directed by the healthcare team and monitored and reviewed on an individual basis.

There is evidence that shows that despite good clinical response on a GF diet mucosal damage does not completely return to normal in some cases, even after many years.[56] The clinical significance of this is not known, and it may also have implications on meeting nutritional requirements on the GF diet for those with CD.

As for the general population, there is an increased recommendation for folate of 400 micrograms per day for women who are planning a pregnancy or in the first trimester of

pregnancy. Although the evidence base is limited, there may be a case for a further increase in requirements for folate pre-conceptually or during the first trimester of pregnancy in patients with CD, if there is a history of folic acid deficiency prior to diagnosis of CD.[57]

Weight gain

The main priority after diagnosis is to maintain the GF diet, to allow the mucosal damage to heal. However, following a balanced diet remains an important long term goal for people with CD to maximise heath, promote good health and prevent health problems.

Weight gain leading to obesity after diagnosis of CD is now recognised[24] and may in the long term contribute to morbidity associated with obesity. Obesity increases the risk of a number of medical conditions, including Coronary Heart Disease and Type 2 diabetes, so appropriate follow up is important to identify issues which may impact on dietary intake.

2.2.3 Associated conditions

Dermatitis Herpetiformis

Dermatitis Herpetiformis (DH) is a skin manifestation of CD, affecting 1 in 10,000 people.[58]The symptoms are red, raised patches often with blisters that burst on scratching, accompanied by severe stinging and itching. Any area of skin can be affected, although areas typically affected include elbows, knees and buttocks. The presentation of DH is characteristically symmetrical in pattern e.g. both elbows.

DH is diagnosed by a skin biopsy, which involves removing a small sample of skin (from an unaffected area) and testing for the presence of IgA antibodies.

Although people with DH may not experience typical gut symptoms, most people with DH have some degree of mucosal damage that is consistent with CD.[59] Those with DH should be referred to a gastroenterologist for follow up blood tests and small bowel biopsy investigations. However, once the GF diet has commenced, further investigations regarding diagnosis of CD may be inconclusive. It is therefore necessary to delay diet therapy until all diagnostic tests for CD have been completed.

Although the treatment for DH is a GF diet, drugs such as Dapsone may also be necessary in the short term to help alleviate symptoms. The GF diet can take as many as 4 years to be effective.[60] The lowest effective dose of medication should be used, as side effects are relatively common and can include haemolytic anaemia, nerve damage, depression and headaches. As DH is a skin manifestation of CD, those with the condition are just as susceptible to the long-term complications associated with untreated CD, including lymphoma.[61]

Autoimmune conditions

There are also disorders which share similar genetic features as CD including other autoimmune diseases such as Type 1 diabetes[62], autoimmune thyroid disease,[63]Primary Biliary Cirrhosis,[64]Sjogren's Syndrome[65] and Addison's disease.[66]

Lactose intolerance

Lactose intolerance (LI) is a secondary intolerance which can be associated with undiagnosed CD. Lactose is a type of sugar found in mammalian milk (e.g. cow, sheep, goat's milk). The enzyme (lactase) that the body produces to break down lactose is found in the jejunal mucosa. In CD, the typical mucosal damage can result in a reduction in the enzyme activity which in turn results in a failure to digest lactose.

Once established on a GF diet the mucosa heals and lactose levels and lactose digestion can be restored to normal. LI is therefore usually temporary. It can be considered as an additional problem in those experiencing continuous symptoms, once gluten related causes have been excluded.[67]

2.2.4 Treatment: The gluten-free diet

A life-long GF diet is currently the only treatment available for people with CD. A number of toxic protein fractions, found in the endosperm of certain cereals, have been identified in CD.

'Gluten' is established as a general term used to cover the alcohol-soluble prolamins; gliadins in wheat, hordeins in barley, secalins in rye. Research suggests that the alcohol insoluble

prolamins called glutenins may also have a role to play, although further research is needed to understand this better.[68]

Systematic reviews on the inclusion of oats in the GF diet have concluded that whilst most adults and children with CD can tolerate the avenins found in oats, some may be sensitive to them,[69] and that people with CD should be followed up by their healthcare team to assess tolerance to avenins.[70]

Most oat products are contaminated with wheat, rye, barley (or combination of these cereals) during processing such as milling, which makes them unsuitable for people with CD. [71]

Therefore it is essential that people with CD who can tolerate avenins choose pure, uncontaminated oats and oat products.

A GF diet requires the elimination of cereals and derived ingredients that contain toxic components (e.g. wheat flour, wheat starch, barley flour, barley malt etc). The most obvious food sources of gluten are breads, pastas, breakfast cereals, flours, pizzas, cakes, pastries and biscuits. Gluten-containing cereals may also be used as ingredients in soups, sauces, ready meals and other processed foods such as sausages.

Naturally GF foods such as rice, potatoes, corn, meat, fish, cheese, eggs, milk, fruit, vegetables and pulses, and processed foods that do not have gluten-containing cereals as an ingredient may also be consumed on a GF diet.

In the UK, people that are medically diagnosed with CD are eligible to access substitute staple products on prescription. Advisory Committee on Borderline Substances (ACBS) approved food products, on prescription are generally staples in the diet such as bread and pasta. Consistently, Coeliac UK Membership Surveys show that at least ninety percent of Members obtain GF products on prescription.[20, 72]GF substitute products may also be obtained by being purchased from supermarket ‘free from’ ranges, the internet, mail order companies and direct from the producer.

2.2.5 Nutritional requirements in coeliac disease

A GF diet should meet individual nutritional requirements and Dietary Reference Nutrient Intakes (RNIs) as per the general population.[73]

Although there may be the case for increased nutritional requirements in those with CD, currently there are no specific nutritional requirements other than recommendations for calcium.

Calcium

As diagnosis of CD commonly occurs later in life and is then associated with the concomitant diagnosis of osteoporosis, an increased calcium intake is recommended for adults (1000mg for those over eighteen years and 1200mg for postmenopausal women[74] and men over the age of fifty-five years)[75]. This compares to a calcium recommendation for the general population without CD of 700mg per day.

This is a significantly increased requirement to achieve from diet and therefore supplementation may be a necessary measure. In addition, there is no legislation currently that ensures a minimum standard composition of the flours used to produce the GF substitute products regarding calcium or iron or B vitamins as compared to standard wheat flour used in the production of bread for normal consumption. Hence GF substitute products vary in calcium content.

There is no increased requirement for calcium in children with CD. This is because there is the potential for absorption of calcium and other nutrients to normalise, in time. Children and young adults who adhere to their GF diet should be able to attain peak bone mass in their lifetime, so minimising the risk of developing osteopenia and osteoporosis in the future.[76]

2.3 Review of current literature

There are reports that GF cereals and substitute products made from them, do not contain as much iron, fibre, folate, thiamine, riboflavin and niacin compared to their gluten-containing

equivalents,[77,78]which may in turn impact on the nutritional adequacy of the GF diet.

A small study of forty-seven people with self-reported CD in the US, found that less than half (44%) of females with CD consumed the recommended amount of iron and fibre, and less than a third consumed the recommend amount of calcium. The authors conclude that based on these findings, nutrition therapy should not just centre around foods allowed/ not allowed on a GF diet, but that more emphasis should be placed on the nutritional quality of the GF diet.[15]

In the UK population, a recent study found that patients with CD consumed lower than the recommended 18g of fibre per day, a significant number failed to reach even the LRNI (Lower Reference Nutrient Intake) for calcium, and intakes of vitamin D were significantly lower in females aged 19-64 years compared to the general population. In addition, those with CD were found to obtain a significantly lower proportion of energy from fat and a significantly higher proportion of energy from protein compared to the Dietary Reference Values (DRV's).[13]

Another UK based study reports that more than one third of the fifty-four participants with CD studied had intakes of iron, copper, magnesium and folic acid which were less than the relevant reference nutrient intake (RNI). [14]

Research from Scandinavia looking at the nutritional intake of forty-nine adults with CD found that those with CD had a similar energy intake compared to controls, and also lower intakes of fibre, niacin, folate, vitamin B12 and calcium.[7] It has also been suggested, based on trends observed in homocysteine levels, that half of adult patients with CD treated with a GF diet for 8-12 years show signs of poor vitamin status.[8]

A Dutch study, looking at nutritional intakes of young adults with CD between 12-25 years of age found that fibre and iron intakes were significantly lower, and saturated fat significantly higher compared to recommended values, but these trends are consistent with that observed in the general Dutch population. The authors conclude that better medical and dietary support is necessary to prevent long-term complications and achieve satisfactory management in young people with CD. [9]

2.4 Rationale for carrying out this research

Coeliac disease is no longer considered to be a marginal condition. It is estimated that at least 600,000 people currently have the propensity to CD diagnosis in the UK.

There has been no published literature review assessing the evidence base on the nutritional adequacy of the GF diet. Therefore it is necessary to perform a systematic review which will provide a scientific approach for the assessment of the current evidence base.

There is a need to try and define more clearly the composition of the GF diet and to consider the significance to health of any differences as compared to the diet of the general population. In general terms, the most significant difference is that wheat based staples are replaced by GF substitute products. The impact on nutritional status is not clear.

It is necessary to consider the individual nutrient requirements of people with CD and compare them to those of the general population. In addition, factors including variability in consumer choice, consumption, cost and other factors affecting access to products making up the GF diet need to be taken into account when reviewing the findings and the range of options available to provide solutions.

Removing staple cereals and associated products from the diet can be restrictive and may impact on nutritional status. Ranges of GF substitute foods such as breads, flours, pasta and crackers have been developed to replace the gluten-containing staples of a normal diet. However, the nutritional composition of these products is not covered by legislation and so it may be variable and it may be different or sub-standard compared to that of normal gluten-containing staples.

In the past, in legislative terms, staple GF substitute products were classed as Foods used for Medical Purposes. [79]

However, a new EC Food Regulation on the composition of foods for those who are gluten intolerant is being developed under Foods for Particular Nutritional Uses (PARNUTS) Directive 89/398/EEC. [80]This legislation will be based on the Codex Alimentarius standard for those who are gluten intolerant. [81] Legislation used to provide guidance on the presence of allergens in foods, the EC Directive 2003/89, enables consumers with CD to select food suitable on their GF diets as it makes it mandatory for producers to list all ingredients and identify allergenic substances including gluten. [82]

In addition, individuals consume variable amounts of GF substitute products and some individuals may not consume any.[83]

Access to education on the GF diet is variable and knowledge regarding dietary management and therefore compliance may be limited, which may in turn impact on nutritional intake and status.[84]Compliance to the GF diet is also been shown to be variable, both in children[85] and adults. [86] Individuals with CD may follow quite different diets in terms of the combination and amount of foods they consume, which would then affect the dietary balance.

This research project is specifically focussing on the adequacy of the GF diet with regard to the nutrients iron, calcium, folate and B vitamins.

2.5 Aims and objectives of the project

The aims of this research project are:

- to produce a report which informs the Food Standard Agency (FSA) regarding the current status of evidence on the nutritional adequacy and impact on nutritional status of the GF diet.

- to inform the FSA for future policy development and strategies to ensure that the GF diet per se does not compromise the nutritional adequacy for people with CD.

Due to the complexity of the composition of the GF diet and variability in consumer choice and access to GF substitute products, a range of policy options may have to be considered.

The objectives of the project are to:

- perform a structured systematic literature review on the nutritional adequacy of a typical GF diet with particular reference to iron, calcium, folate and B vitamins by identifying, grading and reviewing the literature currently available.

- produce a report summarising the state of scientific evidence and with recommendations on strategies to address any issues around nutritional adequacy of a GF diet including fortification of GF substitute products that the review has identified.

3.0 Methodology

3.1 Search process

This systematic literature review used a three phase strategy to ensure that the search was thorough and reproducible. The initial phase focused on computer based electronic searching of bibliographic databases, the second phase involved hand searching reference lists of all papers identified by the electronic search for inclusion in the review, and the final phase involved using a strategy to locate and identify any unpublished research. This involved contacting all first authors of identified papers, established leaders in the field of CD, key professional bodies and their affiliated groups, CD related organisations and manufacturers of GF products. Two reviewers independently extracted data from each included study by using a data extraction form. The papers were assessed for the risk of bias (graded as low, A; moderate B or high C) by using checklists and grading system as recommended by Scottish Intercollegiate Guidelines Network (SIGN). [4] Details of study design, number of participants, study period, duration of intervention, potential confounding factors and results were assessed. Any disagreement was resolved by discussion and consensus between the two reviewers.

3.1.1 Identification of published studies

Initially a comprehensive list of key terms were produced based on the structure of the research question 'Systematic review on the nutritional adequacy of a typical GF diet with particular reference to iron, calcium, folate and B vitamins'.

Table 3.1 Explanation of key terms

Question Part	***Question term***	***Synonyms***
Population/setting	human/male/female/all ages	
Study factor	GF diet	CD, celiac disease, coeliac sprue, celiac sprue, GF, GF diet, gluten free, gluten free diet, gluten enteropathy, gluten sensitive enteropathy, gluten intolerance, gluten allergy, gluten hypersensitivity,
	Iron, calcium, folate, B vitamins	nutrients, vitamins, micronutrients, food, iron, iron absorption, calcium, calcium absorption, folic acid, B vitamins, B vitamin complex, vitamin B group
Outcome	Nutritional adequacy of the GF diet	nutritional adequacy, nutritional deficiency, nutritional screening, nutrition assessment, nutrition surveys, diet surveys, malnutrition, surveys,
Ideal design	Cohort, case-control, RCT [Also surveys, case series]	

The major electronic bibliographic databases, Medline (1950- May 2008), EMBASE (1974 – May 2008), The Cochrane Central Register of Controlled Trials (CENTRAL) – Issue 2, 2008 and CINAHL (1982 – May 2008) were used. This provided the following results:

Medline (1950-May 2008)

This search resulted in 6 hits initially. Two were excluded as duplicate reviews and 1 was irrelevant. This resulted in 3 papers.

EMBASE (1974 -May 2008)

This search resulted in ninety hits initially. Eighty-five of these were excluded, seventy-five were irrelevant, 6 were reviews, 2 were case reports, 1 was a guideline and 1 was duplicated from the Medline search. This resulted in a total of 5 papers.

The Cochrane Central Register of Controlled Trials (CENTRAL) – Issue 2, 2008

Three papers were highlighted initially, however all 3 were found to be irrelevant and so excluded.

CINAHL (1982 – May 2008)

The search resulted in 5 hits, of which all 5 were discounted, 2 were irrelevant, 1 was a review and 2 were duplicated from the initial Medline search.

Table 3.2 Summary of search for published studies

Database	**Hits**	**Excluded**	**Ordered for review**
Medline	6	3	3
EMBASE	90	85	5
Cochrane	3	3	0
CINAHL	5	5	0
Total	***104***	***96***	***8***

A more detailed summary of the search is at Appendix A.

3.1.2 Hand Searching

Those papers identified for review in Table 3.2 were analysed to ascertain whether hand searching a particular journal would be appropriate. As articles were evenly spread

throughout a range of journals and only appeared a maximum of twice in 1 journal (see Appendix B), hand searching of a specific journal was not considered necessary.

Reference lists of all papers accessed were searched. This resulted in twenty more papers being requested. Included in these papers were 2 published papers[8,9] which were not picked up in the initial search. Hopman *et al.* (2006) was not available in the databases used as it was in press. Hallert *et al.* (2002), was available from the databases used. This prompted a review of the initial search strategy. By reviewing all of the MeSH terms used in association with the Hallert *et al.* (2002) paper, the MeSH term 'nutritional status' was added into the search strategy.

Table 3.3 Summary of 2nd search for published studies

Database	**Hits**	**Excluded**	**Ordered for review**
Medline	16	7	9
EMBASE	104	98	6
Cochrane	5	5	0
CINAHL	4	4	0
Total	***129***	***114***	***15***

Although this second search provided more papers to assess suitability for inclusion in this review (fifteen compared to 8 from the first search, listed in table 3.2), no additional papers were identified as we had carried out thorough reference checking from the initial electronic search. A more detailed summary of this second search can be found in Appendix C.

3.1.3 Identification of unpublished studies

Authors of papers requested

All leading authors of the articles that have been identified in this review were contacted by email in order to ascertain whether or not they had any unpublished, current or planned research.

Key individuals

Other key individuals identified as experts in the field were contacted by email. The list of those contacted is at Appendix D. This correspondence produced 4 contacts currently involved in related research[87,88,89,90] and 1 additional published paper.[13]

It is unclear why the paper by Kinsey *et al.* (2008) was not picked up in the search. A direct search for the paper was made to ensure that there was not a gap in the search strategy. This showed that the paper was not available in any of the databases used in this review. The author was contacted and confirmed that the paper had been published, although she was unable to explain why the paper was not picked up by the search. It is possible that since it was very recently published paper, that it had not yet been added to the electronic databases.

Key institutions and organisations

Key institutions and organisations in the field of CD were also contacted. The list of those contacted can be found in Appendix D. Following this initial correspondence 2 further papers were provided.[6,91] Both papers were unpublished at the time of correspondence with the author, but were published before this systematic review had been completed. Dickey et al., 2008 was included in the final eleven papers in this review. However, Stern, 2008 was excluded as it did not meet our inclusion and exclusion criteria.

Gluten-free food manufacturers

Eleven GF manufacturers were contacted, although no information was provided. A list of manufacturers contacted can be found in Appendix D.

Data extraction process for unpublished literature

In all cases, contacts were asked to respond within 3 weeks. All those that had not responded within this time were contacted again by email. Where leading authors were not contactable or did not respond within 3 weeks, they were re-contacted and if there was still no response other listed authors contacted.

The authors of unpublished work were contacted as many times as necessary in order to ascertain adequate information with which to complete a data extraction tool. If insufficient

information was provided, authors were re-contacted at least twice in order to provide the opportunity for them to provide the necessary information.

Authors of all papers included in this review (both published and unpublished data) were contacted to clarify various areas of their research that were not clear or did not provide enough information for the researchers conducting this review to make valued judgements or comment.

Table 3.4 Details of search for unpublished data

Author	Excluded from this review	Included in this review
Alliet Ph, 2008[87]	Y	
Lovik A, 2008 [88](Untitled)	Y	
Holdoway A, 2008 (Untitled) [89]	Y	
Robins G et al., 2008 [90]		Y
Stern M., 2008 [91]	Y	
Dickey W., et al 2008 *[6]		Y

* Prior to completion of this project, Dickey., et al 2008 paper was published, so was counted in the final group of papers as a published paper. Therefore one (Robins et al, 2008) out of the eleven papers used in this review were unpublished.

As can been seen in table 3.4, a total of 6 unpublished studies were sourced. Two of the unpublished papers (Robins G et al., 2008 [90] and Dickey W., et al 2008 *[6]) met the inclusion criteria and were included in the review, 4 studies did not meet the inclusion criteria and as a result were excluded from the review.

3.1.4 Conclusion of search process

The final search was conducted in July 2008.

3.2 Summary of search

Element of search	No. requested (to be assessed for inclusion in this systematic review)		Number excluded (studies irrelevant, incomplete data etc)		Number included (in this systematic review)	
	Published	**Unpublished**	**Published**	**Unpublished**	**Published**	**Unpublished**
Electronic search (1st search)	8	-	5	-	3	-
Hand searching	20	-	15	-	5	-
Contacts(key organisations /individuals	1	6*	0	4	1	2*
Total (both published and unpublished)	35		24		**11**	

* these figures include the Dickey et al., 2008 study, which at the time of the search was unpublished, but was subsequently published prior to the completion of this project.

In total, after implementing the exclusion and inclusion criteria, eleven papers were included in this review. A full list of these papers is at Appendix E.

Papers were discounted due to the fact that there were no clear diet histories taken (n=11), no analysis of nutrients from the diet histories (n=5), it was not stated how long individuals were on the GF diet (n=1), diagnosis unclear (n=2), not enough information available from the unpublished studies (n=3) and no controls or reference values stated (n=1) and one was a review. A detailed breakdown of reasons for exclusion of papers can be found at Appendix F.

3.3 Inclusion and exclusion criteria

Inclusion criteria were made as broad as possible to ensure that a thorough review of available papers available would be made. All age ranges and both sexes have been included in the review. Randomised control trials, cohort studies, case-control retrospective studies, longitudinal surveys or case series were all included in this review, subject to meeting the inclusion and exclusion criteria. Studies published in any language were also included. Published and unpublished studies were eligible for inclusion as long as they met the inclusion and exclusion criteria.

Case reports were excluded from this review, because they provide a poor level of scientific evidence. Animal studies were also dismissed as inappropriate, since there are no accurate animal models for CD, and therefore findings from any such study would have extremely limited applications in human subjects.

Whether the authors had taken into account confounding factors (any external influences which would have a significant effect on the composition of the GF diet e.g. concomitant conditions such as diabetes, patients having limited diets due to religious/moral beliefs) were also considered carefully.

Studies were excluded if participants were diagnosed and following a GF diet for less than 6 months. If the time since diagnosis and being on the GF diet was not available (and could not be clarified following direct contact with the lead author) studies were excluded.

In addition, if medical diagnosis of CD was not confirmed by histology or participants had concomitant conditions which were likely to effect the interpretation of the results they were not included. Any studies where methodology was unclear or ambiguous (and could not be clarified following direct contact with the lead author) were excluded. Many studies initially identified were not able to be included as it was unclear whether the outcomes measured were as a consequence of following the GF diet itself, or due to the underlying CD. For this reason, we set an inclusion criterion that all patients should have been on a GF diet for at least 6 months. However, this means that an important confounding factor could not be eliminated i.e. in all eligible trials patients may have had significant involvement with dietetic services prior to assessment of nutrient intake. Whilst the focus of dietetic input is on avoiding

gluten-containing foods, inevitably the overall nutritional adequacy of the diet would also be assessed. This would have the consequence of minimising any real difference between the GF diet and a non-GF diet and would hide some of the beneficial aspects of dietetic intervention in implementing the GF diet.

Summary of Inclusion criteria

Publication type	Randomised Control Trials Cohort studies Case control studies Longitudinal surveys Case series
Type of participants	All age groups Both genders
Language	All languages
Other	Published and unpublished

Summary of Exclusion criteria

Publication type	Case reports
Type of participants	Animals Diagnosis not confirmed by histology Those diagnosed for <6 months Any concomitant conditions
Language	All languages Published and unpublished
Other	Unclear or ambiguous methodology

3.4 Data extraction

SIGN assessment checklists were used to analyse the cohort studies and case control studies. Criteria used to assess the quality of studies differed for each study type. A data extraction tool was developed by the research team specific to the protocol for the systematic review taking into account the inclusion and exclusion criteria. Copies of the data extraction forms are available at Appendix G.

3.5 Data presentation

It was decided that meta-analysis would not be possible for this review as the studies are too intrinsically different in terms of the design and population to be combined using structured statistical methodology.

4.0 Results

4.1 Summary

There were eleven papers included in this systematic review; these consisted of ten case control studies and 1 cohort. A summary of the results is at Appendix H.

Each paper that met our inclusion and inclusion criteria was assessed for the risk of bias by using checklists and grading system as recommended by Scottish Intercollegiate Guidelines Network (SIGN). [4]Factors considered included sample size, recruitment of participants, analysis of diet histories, inclusion and exclusion criteria and whether potential confounding factors had been addressed and likely author bias.

The results of this quality assessment found that 7 of the reviewed papers were deemed to have a moderate risk of bias[6,7,9,11,13,90] (where there is plausible bias in the study that raises some doubts about the results) and 4 were considered high risk [8,12,14,15](plausible bias that seriously weakens confidence in the results). No papers were considered to be at low risk of bias (where the plausible bias is unlikely to alter the interpretation of the results). In accordance with the SIGN grading system, all papers were graded as 2- : 'case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal'.[4]

The results of the quality assessment and results of the studies included in this review are addressed in more detail in the next chapter "Discussion". See also Appendix H.

Most of the papers concluded that individuals with CD following a GF diet had the same nutritional intake as the general population. [6,7,8,9,10,11]Where the results were found to differ

between these groups, there was often no P values to demonstrate statistical significance recorded [12,13,14,15] so it is difficult to comment on these results.

The unpublished work provided by Dr Gerry Robins, provides some evidence of statistical significance with regards to energy intake;[90] there was a significant increase in energy intake for female patients on a GF diet compared to the control group. However this data has been split to demonstrate the differences between females and males. No statistical data has been provided regarding the whole population group.

5.0 Discussion

5.1 Study appraisal

5.1.1 Study type

Ten of the eleven papers included in the review are case-control studies; the remaining paper is a cohort study.

5.1.2 Sample size

The sample size of the studies was generally small, which is likely to have an impact on the risk of bias. The smallest sample size was just 18, [12] the largest 111[9]and the mean sample size was 58. One of the problems with this kind of study is a high drop-out rate due to the commitment required in order to complete accurate food diaries. In addition analysing diet histories thoroughly requires a trained dietitian and is very time consuming.

5.1.3 Sourcing

Most participants were sourced from the hospital where they attended the gastroenterology clinic. [6,7,8,10,11,12,13,90]This may introduce bias as the participants are often individuals who attend clinic regularly and are motivated to comply with treatment plans and adhere to the GF diet.

The research by Hopman *et al.* (2006) sourced the 219 participants by inviting 395 members of the Dutch Coeliac Society to take part in the study. Similarly Thompson *et al.* (2005) recruited participants through national and regional CD support newsletters. These studies

use different recruitment methods and therefore potentially involve different kinds of participants compared to studies sourcing patients from clinical settings. However, members of coeliac societies may not be totally representative of the coeliac community by virtue of the commitment they exhibit. Patients that regularly attend clinics and also engage with their coeliac society may be better informed and more compliant than those who would not take an interest. McFarlane *et al.* (1995) did not state how the sample was obtained. Despite several attempts to contact the authors, and an acknowledgement of receipt of the email, the authors did not respond.

5.1.4 Confounding factors

Confounding factors varied between papers, although none of the authors explicitly considered the possibility of other dietary restrictions (e.g. lactose-free, vegetarian, weight reducing) which may affect the nutritional intake of participants. Collins *et al.* (1986) stated in the results that three of the participants that did not meet the RDA's were on a diet of low calorie or lactose-free diet. This paper also included participants in the study who had been taking gluten regularly, which is clearly likely to affect the results.

Concomitant conditions were often listed as part of the exclusion criteria, however a number of papers failed to highlight this.[12,13,15] The research paper by Hallert *et al.* (2002) included participants with other concomitant conditions as follows: thyroid (n=4), depression (n=3) and seizures (n=2). Hopman *et al.* (2006) also included 8% of participants who had associated diseases. It was considered that although it is possible that these conditions could have had an effect on dietary choices, the numbers included were considered to be unlikely to have any significant effect. In addition, as a result of the nature of these conditions previous dietetic intervention is unlikely. For this reason the Hallert *et al*. (2002) paper was still included in the review. In the study by Dickey and colleagues [6], it is possible that if any of the participants had a family history of hypercholesterolaemia or coronary heart disease, they may be more prone to higher levels of homocysteine. This was not discussed by the authors.

Other conditions which may affect health and dietary choices, such as smoking and alcohol intake should have also been considered as possible confounding factors and were not highlighted by the authors in any of the papers.

5.1.5 Exclusion and Inclusion criteria

It was not possible to ascertain the exclusion or inclusion criteria for a number of papers in the review despite, repeated author contact.[9,12,13,14]

Dickey *et al.* (2008) excluded any participants with hepatic disease, cardiovascular disease (CVD), renal disease or haematological disorders. Any individuals taking supplements containing B vitamins or drugs know to interfere with the metabolism of folate or related B vitamins were also excluded. The inclusion criteria covered all of those that were not excluded by the exclusion criteria.

Robins *et al.* (2008) included those adults with histological confirmation of CD who had been on a GF diet for a minimum of 6 months. Any individuals on a modified diet for any other reason and any which were suggestive of poor compliance regarding the GF diet were excluded. Storsrud *et al.* (2003) employed the same criteria, although individuals were required to have been on the diet for twelve months and were excluded if there were any concomitant conditions.

Grehn *et al.* (2001) only mentioned villous atrophy and concurrent dermatitis herpetiformis as reasons for exclusion. Hallert *et al.* (2002) excluded individuals who were taking a folate supplement, although this is contradicted later in the paper when it is stated that 6 individuals deemed to have poor vitamin status were on folate supplementation.

Kemppainen *et al.* (2005) had a detailed exclusion and inclusion criteria, for both the group in remission and those who were diagnosed with CD, but not yet on a GF diet. The group in remission were required to be clearly diagnosed adults, following a GF diet for longer than twelve months with normal or near normal villous architecture and without concomitant conditions. The untreated group required a clear diagnosis, partial or villous atrophy and to be free of other serious disease.

Thompson *et al.* (2005) included all people over the age of twenty years diagnosed with CD and adhering to a strict GF diet. Individuals who were pregnant or breastfeeding, not resident in the US, and provided illegible food diaries were excluded from the study. Although 1 person (2%) in the study had been on the GF diet for only 4 months, the paper was included

in this review because it was considered unlikely to affect the results and more likely to cause bias by its exclusion.

5.1.6 Non participation

Non-participation was not explained comprehensively in any of the included research papers. It may be the case that those individuals who adhere to a strict GF diet and have an interest in their health as an individual with CD may cause bias.

5.1.7 Measures

All of the research papers included food record diaries, for either three days (n=3), four days (n=5), five days (n=1) or ten days (n=1). One study[12] did not highlight how many days were recorded. Authors were contacted but no response was received. Eight papers provided serological results [6,7,8,9,11,12,14,90] and 4 of these [6,7,8,12] also carried out small bowel biopsies to assess mucosal damage.

5.1.8 Overall methodological processes of studies

Overall the methodological processes of the studies differed widely. Case-control studies rely on individual diet histories which are subjective records of the individual participants involved and have been shown to result in under reporting of actual intake.[5]

5.2 Discussion of findings

The literature review illustrates the limited evidence base available on the nutritional adequacy of the GF diet. The methodologies applied in the individual studies included in the review differ significantly from one study to another, eliminating the possibility of pooling of data and meta-analysis. This makes statistically significant comparisons and conclusions impossible.

All papers have been graded as moderate or high risk of bias, suggesting that the data available is not robust enough to draw definitive conclusions.

Hopman *et al. (*2006) did include what may be considered a reasonable sample size (n=111) and utilised a three day food diary (including one weekend day) which was analysed by computer. It also involved a thirty-four item questionnaire and serological results. However,

this paper only included participants within the age range of 12-25 years, and the sample was then sub-divided into a younger and older age group. No other paper included in this review focuses solely on this particular age group and it therefore stands alone, making it difficult to use as a comparator with any other papers.

The inclusion and exclusion criteria were not included and contact with the authors was unsuccessful, despite numerous attempts. Although there are possible causes of bias within this paper, these are highlighted by the authors in an open and thorough manner.
The results of this study, which is conducted in the Netherlands, show that the nutritional intake of young people is similar to the general population. Young people with CD showed good compliance to the diet but consumed a higher saturated fat intake and had a lower iron and fibre intake than recommended, as did their healthy peers.

The authors decided to compare results of intakes with not only the Dutch recommendations,[92] but also the American RDA's. [93, 94]The authors have not provided a rational for including the American RDA's, and there was little difference found as a result of applying these reference values.

A Finish paper by Kemppainen *et al.* (1995) also chose to make comparisons with both control groups and American RDA's. Once more the authors have not responded this reference group was chosen. Although there was no inclusion of values for statistical significance, the authors also found that the nutritional status of people with CD in remission is adequate as assessed by the blood nutrient levels.

Further to this Dickey *et al. (*2008) and Collins *et al.* (1986) found that there was no nutritional deficiency where there was no villous atrophy. Although the paper by Collins *et al.* (1986) is highly questionable in terms of validity, the use of biopsy alongside dietary analysis and serology did provide a level of more detailed comparison. However, there were obvious confounding factors as individuals were included in these studies if they were restricting dietary intake, consuming some gluten regularly and may have had concomitant conditions. In addition, these studies had low sample sizes.

Storsrud *et al.* (2003) also found that individuals with CD (with or without inclusion of oats in the diet) had a nutritionally well balanced and complete diet. It was interesting that the inclusion of oats increased intake of iron, fibre, thiamine, and zinc. This may be useful for those individuals that are found to be low in B vitamins, iron and fibre due to a poor dietary intake, particularly as it is acknowledged that breakfast cereals can be difficult to replace on a GF diet. It is important to highlight that some individuals with CD may also react to avenins found in pure oats. [69]

Some of the data provided has been misrepresented. It is unclear if this is intentional or not. Hallert *et al.* (2002) comments that whilst no mean serological results were lower than those recommended, people on a GF diet are prone to nutritional deficiency. Reported dietary intake of folate was found to be considerably lower than the Nordic Nutrition Recommendations in both cases and controls. However, mean serological folate levels were shown to be within the recommended reference range. Plasma folate levels are known to be a poor marker for folate compared to red cell folate and there was some acknowledgement by the authors, that consistency between plasma levels and dietary intakes was poor ($r<0.18$). There was also inconsistency regarding the folate supplementation, whilst the authors stated initially that any individuals taking folate supplements would be excluded, it is later discussed that 6 individuals were on folate supplementation. It is unclear if these individuals were included in the study.

The study by Grehn *et al.* (2001) and McFarlane *et al.* (1995) also demonstrated mean serology results within normal levels. The dietary analysis by Grehn *et al.* (2001) did not quite support these results as there were some lower levels of fibre, vitamin B12, niacin, calcium, phosphate and zinc. In the same way McFarlane *et al.* (1995) reported iron and folate intake to be low in a third of participants, although it is unclear if this is significant.

The research by Kinsey *et al.* (2008) and Thompson *et al.* (2005) used only dietary analysis to assess the nutritional adequacy of the GF diet. This leaves a risk of underestimation. Kinsey *et al.* (2008) found that people with CD recorded less than recommended amounts for energy, Non-starch polysaccharides (NSP), vitamin D and calcium. The outcomes from this study were difficult to understand, particularly as participants were split into groups. It is questionable why this was done and author contact has not been able to clarify the reasons.

Although the baseline results suggest that people with CD consume less than the recommended amounts of energy, NSP, vitamin D and calcium and consume excess protein, this cannot be considered conclusive. The results for energy, NSP and protein where in line with that reported of the general population. Therefore low levels of vitamin D and calcium should be considered. Kinsey *et al* comment that this may be related to lower reported intake of perceived high fat foods e.g. margarine, oily fish, dairy products. It should be noted that in most cases vitamin D would be obtained in sufficient levels from sunlight.

Thompson *et al.* (2005) found individuals with CD had a low intake of grain foods, which may result in subsequent low intakes of B vitamins and calcium. The author was contacted and it was confirmed that there was no available statistical analysis for this research. The low intake of calcium found in these studies may be of concern if the results were to be reproduced in future research.

Due to the paucity of baseline data regarding the GF diet in the UK, the Leeds Coeliac Dietary Study Group is currently undertaking a large scale study of patients on a GF diet to determine a benchmark of the UK GF diet which would be available for researchers and clinicians. The aim of the study was to quantify the nutritional content of the GF diet that its nutritional adequacy could be assessed. Preliminary data from this study, available in abstract form only (Robins et al, 2008), analysed five day food diaries of seventy participants with CD on a GF diet. They found that females with CD had a significantly higher energy intake than the general population (1912 vs 1618 kcal/day). Approximately one third of this "extra" energy intake was accounted for by non-milk extrinsic sugars (NMES). Males with CD were found not to have a significantly higher intake of energy compared to the reference population. Robins et al's data also suggests that significant numbers of patients (male and female) on a GF diet are not meeting RDAs with regards to a range of nutrients, including calcium.

5.3 Conclusions

- There is no robust evidence to show that individuals with CD adhering to a GF diet experience nutritional deficiency
- There is some evidence to show that individuals following a GF diet have a higher energy intake, which is accounted for by NMES
- The serological markers often demonstrate normal nutritional status in coeliac individuals
- There may be an association between poor nutritional status and ongoing villous atrophy
- The evidence base that is available is very limited and that which is available is generally of poor quality. This makes it difficult to draw firm conclusions in this report.

5.4 Recommendations

5.4.1 For practice

- There is not an evidence base that suggests that nutritional deficiency is a significant problem in individuals diagnosed with CD, including iron, calcium, iron and B vitamins

- There is no high level evidence that supports the statement that those diagnosed with CD have optimal nutritional status, particularly as the nutritional requirements of some individuals with CD may be increased

- At the moment, there is not enough evidence to support fortification of GF staple substitute products although there is an argument for fortification of GF flours used in the production of GF substitute staple products so that nutritional composition is comparable to gluten-containing staple products

- These statements do not imply that there are no nutritional issues for people with CD on a GF diet: because of the lack of available evidence we would still

recommend that individuals on a GF diet receive ongoing dietetic support, in order to prevent an unbalanced diet and to optimise the recovery of the gut lining and prevent nutritional deficiency as a result of ongoing villous atrophy. Any reduction in available dietetic services available to patients on a GF diet would mean these recommendations may change.

5.4.2 For research

- Further research is required, using substantial sample sizes, to investigate the nutritional content of the GF diet to assess nutritional adequacy. Although the results of this systematic review do not allow specific recommendations on study design to be made, it is evident that case-control or cohort studies that compare nutritional intake of those with CD with the general population, controls or NDNS would be most useful.

- Research which is based on dietary assessment and which compares the incidence of the defined consequence of malnutrition with a health, age, and sex matched cohort is needed.

- Research which investigates the nutritional intake and factors affecting absorption of calcium, and vitamin D in the coeliac population compared to bone status are recommended to clarify if there is a possible deficiency which may increase further the risk of osteoporosis in people with CD.

- Practical and ethical issues (primarily with regards to the need for full and proper dietetic input) will necessarily limit the quality of future trials.

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