COELIAC DISEASE AND BONE HEALTH IN ADULTS

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Coeliac disease (CD) is an autoimmune disorder caused by an adverse reaction in the small intestine to dietary gluten from wheat, rye, and barley.[1] Screening studies suggest that the prevalence of CD varies from 1-2% in first world populations, but most cases (an estimated 75-90%) do not receive a clinical diagnosis.[2]

CD affects at least one in 100 people in the UK and in Europe, but only about 24% of people with the condition are clinically diagnosed.[3] In addition to gluten-induced small intestinal mucosal lesions, CD can have skin, neurological and other extra-intestinal manifestations.[4] It is associated with metabolic bone disorders including osteoporosis, osteopaenia[5] and osteomalacia.[2,6]

Osteoporosis is a skeletal disorder characterised by low bone mineral density (BMD) and micro-architectural deterioration of the skeleton,[7] with a consequent increase in bone fragility and susceptibility to fracture.[8] Primary osteoporosis occurs in the absence of an underlying disease, whilst secondary osteoporosis occurs due to the effect of certain medications, or in the presence of an underlying disease such as CD.[7] It is important to elucidate secondary causes of osteoporosis as the treatment of these patients may differ and its response to treatment may be limited if the underlying disorder is unrecognised and left untreated.[7]

Management of osteoporosis includes advice on regular physical activity, reducing smoking and alcohol consumption, ensuring a health body mass index (BMI) and calcium and vitamin D supplementation where appropriate.[9] People with CD who have successfully adopted a gluten-free diet (GFD) need to follow these basic strategies to reduce the risk of developing bone disease.[10,11] Calcium supplementation may prevent bone loss in older men and women, but there is no convincing evidence that it decreases the risk of fracture in patients with osteoporosis.[12] Drug treatments are, therefore, usually necessary and include bisphosphonates, teriparatide, raloxifene and calcitonin.[12]

Osteopenia is a condition in which BMD is lower than normal, but not low enough to be classed as osteoporosis. In some cases, it is a precursor to osteoporosis. Osteomalacia results from bone demineralisation. It is caused by vitamin D deficiency and leads to softening of the bone. The increased risk of bone fracture associated with these conditions has an important impact on a patient's activities of daily living and the ability to work.[2]

SCREENING AND DIAGNOSIS

If undiagnosed and left untreated, CD can lead to problems such as anaemia,[11] unexplained infertility problems, nutritional deficiencies,[3] osteoporosis[5,9] and osteopenia.[5] Early diagnosis and strict adherence to a gluten-free diet (GFD) are both indicated in improving BMD,[11,13,14] although some studies have shown that those with CD still have lower than average bone density despite following a strict GFD.[11]

McFarlane et al in 1995[10] noted that the largest gains in BMD were detected in the most recently diagnosed patients, suggesting that there is a reversible component to the osteopenia present at the time of diagnosis of CD and that this can be improved by treatment with

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a GFD. However, one population-based study found a similar excess risk of fractures before and after CD diagnosis and commencement of a GFD (i.e. incidence ratios five to 10 years before and after CD diagnosis were 1.8 and 2.2 respectively).[10]

A study by Valdimarsson et al in 1995[16] found that subjects without diarrhoea or weight loss had osteopenia to the same degree as subjects with these symptoms. Similarly, Molteni et al 1990[17] found no correlation between osteopenia and severity of symptoms, suggesting that screening for CD is indicated in all adult patients with osteoporosis or osteopenia.[16]

Screening for CD should be carried out in high-risk groups such as those with iron deficiency anaemia, Down's syndrome, Type 1 diabetes mellitus and osteoporosis,[15] especially in those with very low T-scores or multiple osteoporotic fractures.[18] Unfortunately, the average length of time taken for someone to be diagnosed with CD from the onset of symptoms is a staggering 13 years.[3] Clinicians must be made aware of the potential extra-intestinal manifestations of CD to avoid missed diagnoses.[18]

PREVALENCE AND COST TO NHS

Osteoporosis is a major public health problem because of its potentially severe consequences for both the patient and the healthcare system if it leads to fracture.[12] Osteoporotic fractures are associated with pain, disability and up to 30% mortality at one year.[12] The prevalence of osteoporosis amongst the CD population has been estimated to be 6%, although some studies have indicated that it may be as high as 50%.[10] NHS data indicates that the cost of treating osteoporosis in those with CD may lie somewhere between £2.3 million and £21.3 million per year.[5]

MEASUREMENT OF BMD

BMD should be measured in those at high risk of osteoporosis.[15] It can be expressed as the number of standard deviations (SD) above or below either the mean BMD for young adults (T-score) or the mean BMD for age-matched controls (Z-score).[12] BMD is usually measured using dual energy x-ray absorptiometry (DEXA), which is relatively simple and non-invasive and demonstrates a good degree of accuracy and precision (measurement error of 5-6%).[12]

The Primary Care Society for Gastroenterology (PCSG)[9] recommends that BMD be measured at the time of diagnosis and then repeated at the menopause for women, at the age of 55 years for men and at any age should a fragility fracture occur. However, the British Society of Gastroenterology (BSG)[12] advises that since there is only a small increase in fracture risk and prospective studies have demonstrated a significant improvement in BMD and calcium absorption after introduction of a GFD, DEXA should only be repeated after introduction of a GFD in the subgroups of patients in whom the risk of osteoporotic fracture is high.[12] As there is no reliable scoring system to select those most at risk, common sense suggests that patients with features such as being over 70 years of age, having had a prior osteoporotic fracture, or using corticosteroids, together with having a poor response or adherence to a GFD and a low BMI, should be considered for DEXA.[12]

MECHANISM OF METABOLIC BONE DISEASE IN CD

The exact mechanism for the association between CD and bone health is not known, but evidence from laboratory-based studies and relatively small investigations in humans supports several possibilities.[11,19] One possibility is that CD leads to dietary malabsorption and, thus, deficiency of vitamins and minerals, such as calcium and vitamin D, which are important in bone remodelling.[19] Also, patients with CD are at risk of having an inadequate intake of calcium and vitamin D.[20] Calcium and vitamin D affect bone health in a direct way by modifying bone turnover.[21] They also act indirectly by causing changes in hormone secretion and mineral absorption.[21] Calcium and vitamin D seem to have the greatest effect on risk of fracture when given in combination.[22] Other nutrients are involved in bone formation and include magnesium, phosphorus and fluoride.[23] Normal bone metabolism is supported by zinc, iron, boron, copper and manganese.[3]

THE ROLE OF CALCIUM

Parathyroid hormone (PTH) is considered the most reliable marker of inadequate calcium availability and its overproduction can be directly or indirectly linked to bone loss and several other organ disturbances.[24] In CD, a low blood calcium level can result from a poor dietary calcium intake and/or calcium malabsorption and lead to secondary hyperparathyroidism.[7] The overall effect of PTH is to raise plasma levels of calcium through osteoclast-mediated bone resorption,[25] which can lead to a reduced BMD and its associated problems.

With a deficiency in calcium leading to long-term bone problems and approximately 75% of newly diagnosed patients having some degree of bone loss, the National Osteoporosis Foundation in the United States set the recommended intake for calcium in CD at 1000mg/day (and 1,200mg/day for postmenopausal women and men >55 years), which is higher than the 700-800mg/day recommended for the general population.[20] The current guidance from the BSG[15] for adults with CD recommends at least 1,000mg of calcium per day. Calcium supplementation may be required in postmenopausal women with CD[15] and should be considered in CD patients who are avoiding calcium-rich dairy foods due to symptomatic lactose intolerance.[12]

THE ROLE OF VITAMIN D

Vitamin D comes in two main forms:

- Vitamin D3 (cholecalciferol) from sunlight and animal sources such as eggs and dairy;
- Vitamin D2 (ergocalciferol) from plant sources such as soya milk, rice milk, cheese and spreads.

After conversion to its active metabolites, vitamin D facilitates calcium absorption from the intestine and is important for a range of other metabolic processes.[26] Vitamin D deficiency is most commonly caused by insufficient exposure to the sun, but may also be due to a low dietary intake or gastrointestinal malabsorption, such as that seen in CD. Vitamin D deficiency causes a long-standing low level of calcium in the blood. The resulting hyperparathyroidism leads to bone resorption and its associated problems, as explained above.

Current guidelines recommend measurement of vitamin D levels in patients with CD and replacement where indicated.[15] The European Food Safety Authority (EFSA) have recently proposed an adequate intake of 15μg/day (600IU) for adults.[27] The Scientific Advisory Council on Nutrition (SACN) recommend an RNI for vitamin D of 10μg /day (400IU) for the UK population aged four years and above.[28] This is the amount needed by 97.5% of the population to maintain a serum 25(OH)D concentration of ≥25mmol/L when UVB sunshine exposure is minimal.[28]

Serum 25(OH)D is a measure of vitamin D status and reflects the availability of vitamin D in the body from both dietary and endogenous sources.[26] The strong inverse relationship between serum 25(OH)D and serum PTH has been used for establishing an ideal 25(OH)D lower threshold level.[24] In the UK, 25mmol/L of 25-OHD has been used as the lower threshold for vitamin D adequacy, below which there is an increased risk of rickets and osteomalacia.[29,30]

OTHER MECHANISMS

Further proposed mechanisms for the association between CD and bone health include hormone-related disorders, which may contribute to bone loss and fractures.[11] In addition to this, thyroid disease is slightly more common in those with CD and hyperthyroidism in particular may be associated with an increased risk of osteoporosis.[11] Another possibility is that an increase in the levels of inflammatory cytokines seen in patients with CD, including TNF-alpha, IL-1 and IL-6 may be responsible for an increase in bone resorption.[7,19]

CONCLUSION

CD is a multifaceted and complex autoimmune condition that can have a number of intestinal and extra-intestinal manifestations and is associated with various metabolic bone disorders. Early diagnosis and management of CD can help to improve outcomes for patients and help prevent the long-term complications of the disease, including a reduced BMD and increased risk of fracture. Clinicians should be made aware of the relationship between CD and bone health, as this may help to improve CD diagnosis rates, as well as improving the diagnosis and management of CD-related bone disorders should they be present.