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Coeliac disease amongst women

Women are affected by coeliac disease twice as much as men. Moreover, it is associated with many other health issues that clinicians must be vigilant for.

The articles published in this edition of the Forum on birth complications, infertility and osteoporosis in coeliac sufferers all have one thing in common: the connection between coeliac disease and women's health. There is much interest surrounding this topic, not least because dietary treatment of coeliac disease makes it possible to prevent the occurrence of such complications. This has a positive effect on the sufferer from a medical, psychological and social point of view.

However, there are also many more connections between coeliac disease and women's health, particularly since (a) this condition affects more women than men, with a ratio of around 2:1 between female and male sufferers; (b) certain autoimmune complications, especially Hashimoto's thyroiditis, even at a young age are already more common in girls than boys; (c) some variants of coeliac disease, in particular iron-deficiency anaemia, can complicate medical problems that more commonly affect women. It may be the case – as Khashan and McCarthy claim in their excellent overview of birth complications – that there is "not yet sufficient evidence to recommend serological screening for coeliac disease at the start of pregnancy". However, a simple blood test (to identify anti-transglutaminase antibodies) could without a doubt be carried out in addition to the many other routine tests performed for pregnant women, thereby preventing at an early stage many possible problems for both the expecting mother and the unborn baby.

Summary

The topics addressed in this edition of the Forum – birth complications and osteoporosis linked to coeliac disease, combined with the more frequent occurrence of this condition in women – make coeliac disease one of the topics which are of primary interest for women, especially those of childbearing age.

PROFESSOR CARLO CATASSI

Professor of Paediatrics at the Marche Poltechnic University (Italy). President of the Italian Society for Paediatrics Gastroenterology, Hepatology and Nutrition, years 2013-2016. Coordinator of the Dr. Schär Advisory Board

Obstetric complications in women with coeliac disease

Women suffering from coeliac disease have a higher risk of complications during pregnancy, however, these may be lowered by strict adherence to a gluten free diet.

DR. ALI S KHASHAN

Department of Epidemiology and Public Health, University College Cork, Ireland and The Irish Centre for Fetal and Neonatal Translational Research (INFANT), University College Cork, Cork University Maternity Hospital, Wilton, Cork, Ireland.

DR. FERGUS MCCARTHY

Division of Women's Health KCL, Women's Health Academic Centre KHP, St Thomas's Hospital, London. United Kingdom

Coeliac disease is a gluten sensitive enteropathy which has an estimated prevalence of 1% worldwide.[1] It is widely thought that this represents the tip of the iceberg and a large proportion of coeliac disease remains undiagnosed. Coeliac disease is most commonly identified in either early childhood or in the third or fourth decades of life.

Certain ethnic groups are thought to have an increased prevalence of coeliac disease, in particular those of Celtic origin. Approximately 96% of patients with coeliac disease express the HLA molecule DQ2, whereas the remainder mostly express the less common haplotype DQ8, reflecting the pivotal role of this molecule in the pathogenesis of coeliac disease. Coeliac disease is characterised by permanent intolerance to dietary gluten. Although traditionally considered a nutritional disorder of childhood presenting with varying degrees of malabsorption and diarrhoea it is now recognised as a systemic illness with multiple clinical presentations.[2] Coeliac disease has been associated with an increased risk of many adverse pregnancy outcomes including unexplained infertility,[3] miscarriage,[3] congenital malformation,[4] preterm birth,[5] intrauterine growth restriction,[5,6] postpartum haemorrhage[7] and assisted delivery.[7] Conflicting results exist.[4,7,8]

Coeliac disease, in particular untreated coeliac disease is thought to adversely affect pregnancy via antibodies which interact with the developing placental tissue resulting in adverse pregnancy outcomes. Anti-tissue transglutaminase (tTG) immunoglobulin G antibodies have been shown to bind to human trophoblast cells in vitro resulting in impaired trophoblast function in a dose and

time dependent manner. In women with coeliac disease gluten also induces a T-cell immune response which may also contribute to adverse pregnancy outcomes. In addition, gliadin itself can activate peripheral blood T-cells resulting in elevated cytokine secretion which may affect trophoblast development.

More recently good quality large cohort studies and systematic reviews have helped clarify the degree of association between both treated and untreated coeliac disease and adverse pregnancy outcomes which has helped provide clarity in the counselling and investigations of women with adverse pregnancy outcomes. The largest population-based studies on maternal coeliac disease and adverse pregnancy outcomes used data from Sweden[9] and Denmark[5] and were published in the last decade. These studies benefited from the Medical Birth Register and Hospital Register in each country which allowed the identification of all births during the study period and whether the woman had ever been diagnosed with coeliac disease. It was possible to determine whether the mother was diagnosed with coeliac disease and whether the diagnosis took place before or after pregnancy using dates of diagnosis and pregnancy. In the population-based Swedish study including more than 2 million babies, Ludvigsson and colleagues[9] reported an association between undiagnosed maternal CD and low birthweight (OR=2.13), SGA (OR=1.62) and preterm birth (OR=1.71). Women with diagnosed CD, who were presumably treated before giving birth, had no increased risk of adverse fetal outcomes compared with non-celiac women. These findings were later replicated in a population-based Danish study including more than 1.5 million babies.[5] Women with undiagnosed coeliac disease at the time of pregnancy had a higher risk of SGA (OR=1.3), preterm birth (OR=1.33) and smaller babies with birthweight reduced by 100 grams on average compared to women with undiagnosed coeliac disease. Similar to the Swedish study women with diagnosed, and presumably treated, coeliac disease had no increased risk of adverse pregnancy outcome.

> Coeliac-specific antibodies may interact with placental tissue to cause pregnancy complications.

A recent systematic review included data from ten cohort studies which included data from over four and a half million women.[10] This systematic review demonstrated that women with coeliac disease (both treated and untreated) had a significantly higher risk of the development of preterm birth (adjusted odds ratio 1.35), intrauterine growth restriction (odds ratio 2.48), stillbirth (odds ratio 4.84), low birthweight (odds ratio 1.63), and small for gestational age defined as individualised birth centile under the tenth centile (odds ratio 4.52). No significant differences were observed in the incidence of pre-eclampsia.

Subgroup analysis was then performed to examine the association between diagnosed (and assumed treated) coeliac disease. The risk of preterm birth remained significantly higher both in the subgroup analysis of only women with diagnosed and treated coeliac disease (odds ratio 1.26) and in the subgroup analysis of only women with undiagnosed and untreated coeliac disease (odds ratio 2.50). Women with diagnosed and assumed treated coeliac disease had a significantly lower risk of having a pregnancy complicated by preterm birth, compared with women with undiagnosed and untreated coeliac disease (odds ratio 0.80).

> Undiagnosed maternal coeliac disease is associated with low birthweight and preterm birth

Adherence to a gluten-free diet significantly reduces the risk of pregnancy complications.

Data regarding the prenatal and perinatal risk factors for the development of coeliac disease in the offspring are also conflicting. However, it appears the biggest determinant of development of coeliac disease in the offspring is the presence of maternal coeliac disease.[11] The odds ratio from one mother and baby cohort of approximately one hundred thousand mother and baby pairs was approximately twelve for the development of offspring coeliac disease.

What are the risks relevant to the general obstetric population and how can these be minimised?

Overall, women with coeliac disease have an increased risk of adverse pregnancy outcomes. Treatment by means of gluten free diet ameliorates this risk. As a result women with coeliac disease should be advised to adhere to a strict gluten free diet pre-conceptually and during pregnancy to minimise any risks which may occur as a result of coeliac disease. There remains insufficient evidence, both clinically and cost effectively, to support a policy of screening healthy pregnant women for undiagnosed coeliac disease at the start of pregnancy with the aim of improving pregnancy outcomes. Similarly, there is insufficient evidence to support the screening of women with adverse pregnancy outcomes for undiagnosed coeliac disease. However, increasingly high risk groups such as those with recurrent pregnancy loss are being screened for undiagnosed coeliac disease. Non coeliac pregnant women can be reassured that maternal consumption of gluten in pregnancy does not appear to be associated with an increased risk of development of coeliac disease in the offspring.

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Gluten and female infertility

Coeliac disease is known to affect fertility in women, however less is known regarding the relationship between gluten sensitivity and fertility issues. Even in the case of negative serology, there is evidence to suggest a possible role for the gluten free diet as an adjunct therapy in some patients.

JUSTINE BOLD

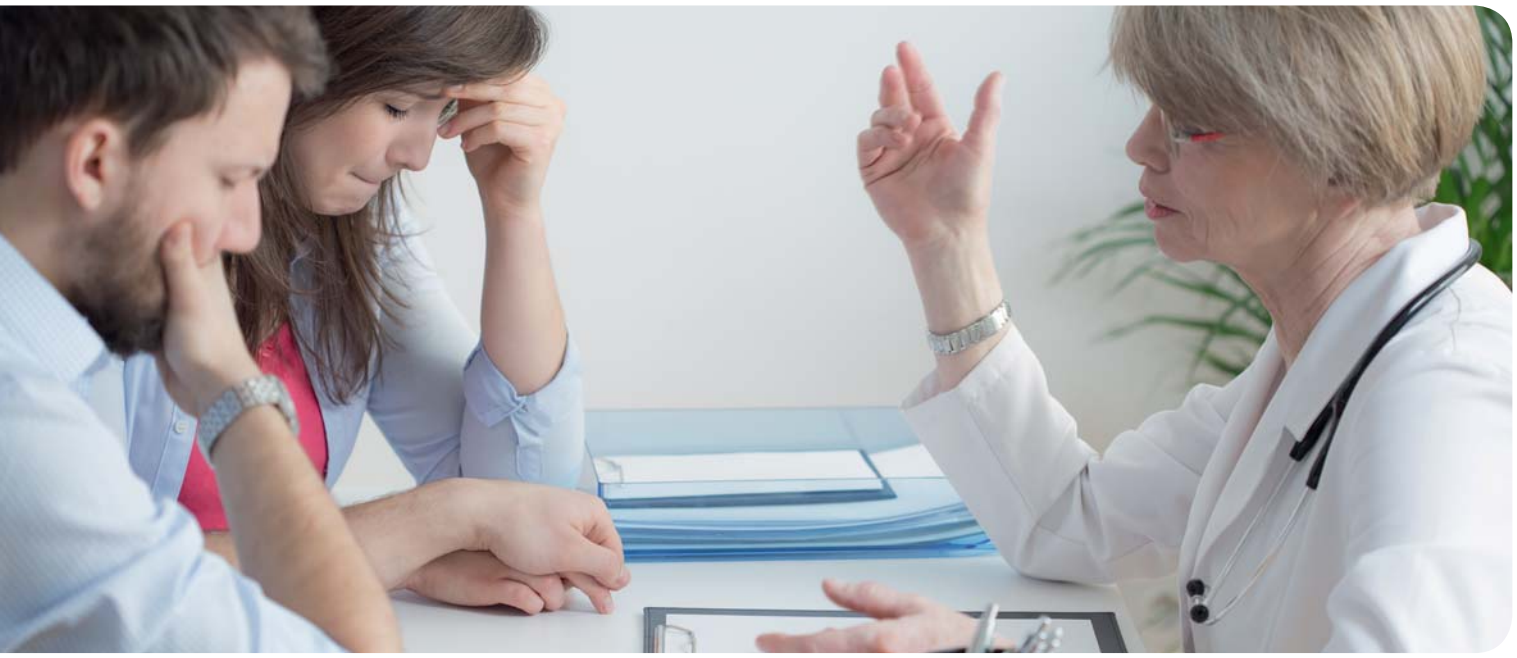
Senior Lecturer,
Institute of Health & Society,
University of Worcester

Current guidelines do not recommend routine screening of women experiencing most types of infertility for coeliac disease (CD), even though the literature documents that CD can affect fertility and many researchers make the case for screening. In women CD can delay puberty[1], cause malabsorption and many nutritional deficiencies such as zinc, B12, iron and folate[2]. These nutrients are important for conception/pregnancy and low status has been implicated in both fertility and pregnancy problems. CD is also linked to amenorrhea, premature ovarian failure and obstetric complications such as pre-term birth and low birth weight.[3] There are, however, reports of successful pregnancy outcomes for women with CD who have a history of miscarriage once a gluten free diet (GFD) has been introduced.[4] Undiagnosed and untreated coeliac disease in particular can have far reaching effects on both female fertility and pregnancy outcomes.

> The prevalence of coeliac disease is estimated to be 4 to 8 times higher in women with fertility problems than in the general population.

Reports on the prevalence of CD in women with infertility are between 4 and 8% in Europe; this is higher than the general population where it is estimated at 1%.[5] Women with unexplained fertility appear to have higher rates of CD compared to the general population.[6] In one study women with unexplained infertility had a six times higher odds of having CD than controls.[6] Given the financial cost and emotional impact of fertility treatment, health professionals working with such patients should be encouraged to screen for CD particularly in women diagnosed with infertility, especially unexplained infertility.

Whilst it is recognised that there is an association between CD and fertility problems there is little information about non-coeliac gluten



A gluten free diet may alleviate the painful symptoms of endometriosis.

sensitivity (NCGS) and infertility, though a case report on a possible association was published in 2015.[7] Interestingly, iron, folic acid, vitamin D and B12 deficiency have also been documented in NCGS.[8,9] Therefore the possibility of malabsorption of nutrients key to fertility remains a possibility in NCGS along with immunological abnormalities, which have also been reported.[7]

The literature also documents associations between CD and endometriosis.[10] Endometriosis affects around two million women in the UK[11] and is one of the leading causes of female infertility. It is also interesting that endometriosis has been reported as the primary symptom of CD when classical symptoms were absent[12] and that in many patients gastro-intestinal symptoms and irritable bowel syndrome (IBS) are frequently seen along side endometriosis[13]. It is also important to remember some patients with IBS are gluten sensitive, as the literature documents both associations between IBS and CD[14] and IBS and NCGS[15], though this area and underpinning pathogenesis are still being investigated.

A postgraduate student research project currently in progress at the University of Worcester exploring motivations of people without CD for following a GFD has ascertained many do so in an attempt to self manage symptoms. This is interesting given the widely held popular view that GFD are increasing in popularity amongst the non-coeliac patients as they are seen as fashionable. Could it be that some are self-managing women's health issues with a GFD?

There are few studies exploring the potential therapeutic effect of a GFD in supporting female health conditions such as endometriosis, however a study undertaken in Italy in

2012[16] reported that the painful symptoms of endometriosis reduced after a year on a GFD. Two-hundred-and-seven patients were studied, all were diagnosed with endometriosis and after a year, 75 per cent of the patients reported a statistically-significant reduction in painful symptoms. However, 25 per cent reported no improvement of symptoms though no patients experienced a worsening of pain. Improved scores were also reported in all patients for general health perception, vitality, mental health and social and physical functioning.

Professionals working with women diagnosed with unexplained fertility and other women's health issues such as endometriosis should assess clinical symptoms, co-morbidities and consider screening for CD, whilst being mindful that there may be no digestive symptoms present. Health professionals should, therefore, also consider NCGS when CD serology is negative and there are no indications for biopsy. Even though further research in this area is undoubtedly needed, given the emotional and financial impacts of infertility, a gluten free diet could be discussed with patients and perhaps considered as an adjunct to other treatments to address infertility or support conditions such as endometriosis.

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Osteoporosis in the coeliac population

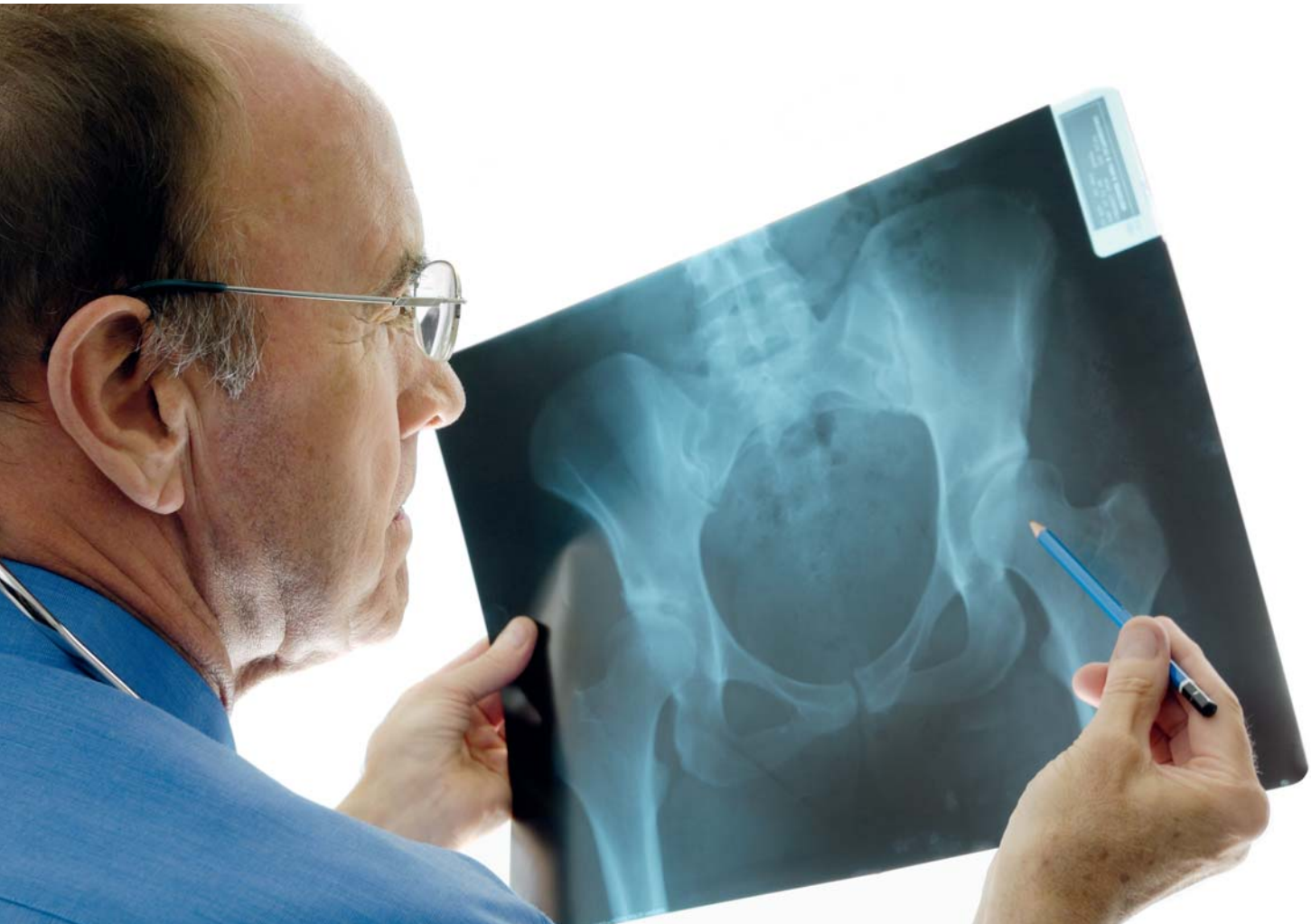
Coeliac disease increases the risk of osteoporosis due to calcium malabsorption, secondary to villous atrophy. Conversely, a calcium-enriched gluten free diet can significantly increase bone mineral density in coeliac patients.

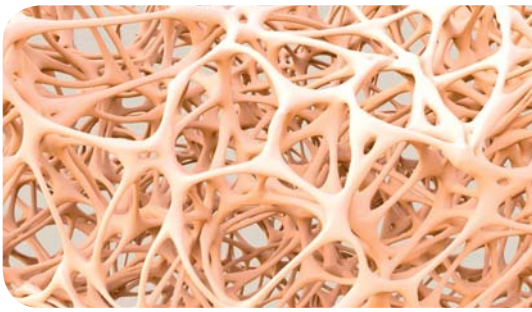
DR ALY WOODALL

Senior Lecturer – Nutrition & Dietetics, University of Chester.

Background

The impact of osteoporosis, and other bone diseases, on health and well-being is not well recognised. Currently, worldwide, osteoporosis causes in excess on 8.9 million fractures a year, this translates to 1 fracture every 3 seconds[1] and the prevalence in the UK is estimated at 3 million (Age UK; NOS, 2016). The rates of disabilities directly or indirectly associated with osteoporosis are higher than cancer[1] and once disease related fractures occur there is an 86% risk of further fracture leading to a risk of continued, and potentially escalating, risk of long term osteoporotic disability and associated co-morbidities such as chronic pain.[2] In 2010 osteoporosis was the cause of death of 43,000 Europeans[3] and the cost of treating osteoporosis in the EU in that year, including medicines management, fracture treatment and hospital stays, amounted to 37 billion euros. The burden for the population with osteoporosis was 1,180,000 lost quality adjusted life years (QALYS), this number is estimated to increase by 20% between 2010 and 2025.[3]





Aetiology

Osteoporosis occurs due to either a reduced peak bone mass or increased bone loss. Bone mass usually peaks around age 35 however a number of conditions; for example anorexia, malnutrition, Crohn's disease, coeliac disease or alcoholism can reduce the peak bone mass achieved. Increased bone loss is associated with decreased sex hormone synthesis, particularly in women, malnutrition, hyperthyroidism, and certain medications; for example anti-seizure medications, chemotherapy, proton pump inhibitors and steroids. Lifestyle can also be a factor with behaviours such as using sunscreen, smoking and lack of exercise all increasing risk of bone loss and, ultimately bone diseases such as osteoporosis.[4] Genetics, ethnicity and age are also all risk factors for osteoporosis; for example incidence of osteoporosis increasing to 1 in 3 women and 1 in 5 men over 50 and in members of the same family.[4,5] None of the factors mentioned here are mutually exclusive.

Osteoporosis and Coeliac Disease

Increased levels of low bone mineral density, osteopenia and osteoporosis have been frequently identified in people with coeliac disease when compared to the general population.[6,7,8,9] Estimates of fracture risk in the coeliac population have varied, however a recent meta analysis found a 30% increased risk of fracture at baseline in comparison to controls (95% confidence interval [CI]: 1.14, 1.50) and 69% increase in the risk of hip fracture (95% CI: 1.10, 2.59)in comparison to controls.[10] The meta analysis was, necessarily, based on observational and epidemiological studies and is therefore unable to demonstrate any causal inferences and it should also be noted that most of the subjects in the studies examined were reported to be following a gluten free diet which may impact on the results.

Potential mechanisms for changes in bone metabolism and, therefore bone health, in coeliac disease have been postulated over time. It is well established that the villous atrophy observed in coeliac disease leads to the malabsorption of many micronutrients, for example, calcium and vitamin D. Both these micronutrients have essential roles in maintaining bone health and the increased risk of osteoporosis in people with coeliac disease has been attributed to calcium malabsorption stimulating release of parathyroid hormone which increases bone turnover and leads to increased bone loss.[11] Current research is also investigating the role of increased activation of inflammatory cytokines and autoimmune factors as potential mechanisms for altered bone metabolism. Further studies are needed to fully elucidate the exact nature and balance of the mechanisms involved.

Recent studies have analysed physiological changes associated with coeliac disease in conjunction with bone health, with some interesting findings. In a largely female cohort, Garcia- Manzanares and colleagues (2012) found positive correlations between increased villous

Low bone mineral density is frequently observed in people with coeliac disease.

Calcium

atrophy and loss of bone mass on the lumbar spine.[8] In a female only population, Stein et al (2015) found significant differences in bone microarchitecture in participants with coeliac disease compared to healthy age matched controls.[9] These differences were principally found in trabecular rather than cortical bone and were associated with reduced performance in measures of skeletal strength. Stein et al (2015) also noted that despite a substantially increased calcium intake compared to the age matched controls, serum calcium levels were lower in the coeliac group.[9] This is suggestive of calcium malabsorption and consistent with long held beliefs on the mechanisms for increased osteoporosis in the coeliac population.

Further studies looking at larger groups of both male and females with coeliac disease are needed to establish the relevance and applicability of these studies to the larger coeliac population.

Diagnosis

Osteoporosis is most commonly diagnosed by using dual-energy X-ray absorptiometry (DEXA) to measure bone density. Other conventional radiotherapy techniques such as quantitative computed tomography (QCT) can also be used.[12] The measured bone mineral density is compared to standardised results from the general population using a T score; a T score of 2.5 standard deviations, or more, lower than the standard is defined as osteoporosis. The techniques for diagnosing for the coeliac population are the same as those used for the general population. Standard recommendations for the diagnosis of coeliac disease continue to be serology and duodenal biopsy; this recommendation takes into account the variability that can be found with serology and the fact that ultimately the biopsy reveals if malabsorption is present.[13] This recommendation does not apply to diagnosis in paediatric patients.[13] The biopsy, if performed, informs not only on the presence of villous atrophy of the small intestine but also on degree, usually measured using the Marsh scale[13]; a high Marsh score correlates with a high degree of villous atrophy and is associated with a high degree of malabsorption.[8,13] Repeat biopsies, when following a gluten free diet, inform on continued atrophy of the villi and likelihood of continued malabsorption.

Treatment

Current management of osteoporosis is focused on medical therapy such as bisphosphonates, hormone replacement therapy, recombinant parathyroid therapy and supplements such as calcium and calcium combined with vitamin D.

However diet and lifestyle also have a role to play in both prevention and treatment of osteoporosis, including osteoporosis in those with coeliac disease. The British Society of Gastroenterology 2014 guidelines for the management of coeliac disease emphasise the importance not only of a gluten free diet, to reduce villous atrophy, promote mucosal healing and lead to enhanced nutrient absorption, but also to ensure an adequate intake of a range of nutrients, including calcium.[13] Adequate ingestion of dietary calcium can reduce the need for calcium supplements, and some people with coeliac disease can achieve the recommended intake of 1000 mg/day from diet alone[14],

although very few achieve the previously recommended intake of 1500 mg/day[14] which is still the recommended intake for post-menopausal women and elderly men[13]. The prevalence of osteoporosis within the coeliac population emphasises the importance of a consistent and adequate calcium intake.

To conclude, current evidence suggests that preventative measures are essential for all those diagnosed or at risk of osteoporosis, whether they have coeliac disease or not. These measures include ensuring an adequate intake of a wide range of nutrients to optimise health, for example following current healthy eating advice, to maintain an active lifestyle and avoid malnutrition. For those at increased risk, for example people with coeliac disease, calcium intake should meet the 1000 mg/day recommended guidelines[13], supplements should be used if intake is insufficient from dietary sources.

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News

NEW Glutafin Fresh Seeded Loaf; PIP Code: 402-3685

Our popular seeded bread is now available as a soft and tasty fresh loaf! Based on a traditional sour dough recipe with added chia, sunflower and linseeds, Glutafin's new fresh seeded loaf is high in fibre and enriched with calcium and folic acid. It's also free from milk and wheat starch making it suitable for patients with additional intolerances. A single order contains 8 individually wrapped loaves, suitable for freezing. Glutafin Gluten Free Select Fresh Seeded Bread is ACBS approved and available to order from pharmacies now.

For full nutritional / ingredient information, visit the Glutafin website: www.glutafin.co.uk

Glutafin launch 2 great NEW High Fibre products

We're delighted to announce the launch of our latest prescription products, Glutafin Gluten Free Fibre Flakes (PIP 4014288), and Glutafin Gluten Free High Fibre Loaf (PIP 4014296).

Glutafin Gluten Free Fibre Flakes are a delicious low fat, high fibre breakfast cereal option. We've also added 9 essential vitamins and minerals, including **B vitamins, vitamin D and iron**, to provide a nutritious start to the day for coeliac patients.

Glutafin Gluten Free High Fibre Loaf has recently been voted **number 1 long life prescription bread** by an independent tasting panel. The distinct nutty flavour and lighter texture provides a traditionally-baked taste with the convenience of a long-life loaf. Based on a traditional sour-dough recipe and made with a blend of 4 flours, linseeds and sunflower seeds, it's our highest fibre loaf yet!

For full nutritional / ingredient information, visit the Glutafin website: www.glutafin.co.uk

NEW Schär Gluten-Free Breads

We're delighted to announce the launch of the **Schär Wholesome Vitality Loaf and Schär Seeded Ciabatta Rolls**, now available in Tesco stores. This extension to the Schär bread range ensures patients following a gluten-free diet have a wider selection of tasty and nutritious staple products to choose from. Both products are based on a sourdough recipe for a lighter texture and a great flavour and are:

- Gluten-free, Wheat-free and Lactose-free
- High in fibre
- Low in saturated fat
- Enriched with linseeds and sunflower seeds
- Baked with the ancient grains; millet, quinoa, sorghum and buckwheat
- Free from preservatives

Both breads are also suitable for vegans. To request your **FREE** information pack, please email: professionals@drschaer.com

Dr Schär

EDITOR
Dr Schär Institute
Dr Schär UK, Station Court, 442 Stockport Road, Thelwall, WA4 2GW
Helpline: 0800 988 8470, Email: professionals@drschaer.com
www.drschaer-institute.com

Text: zweiblick, Dr. Schär Nutrition Service
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