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Leading article

Bone mineral density in coeliac disease

Most gastroenterologists are familiar with coeliac disease presenting with problems of calcium malabsorption. Hypocalcaemia, increases in alkaline phosphatase activities and parathyroid hormone values, and presumed or biopsy proved osteomalacia are all well recognised and respond eventually to gluten withdrawal.[1] Treatment reduces the loss of villous cells in the proximal intestine, which are those that absorb calcium actively, and lowers the amount of unabsorbed fatty acids which bind calcium in the intestinal lumen. Once serum calcium and alkaline phosphatase values have returned to normal, and patients are asymptomatic and accustomed to their gluten free diets, can calcium and bone disease be forgotten? Recent work suggests it cannot.

Bone mineral density is now easily measured by dual energy *x* ray absorptiometry (DXA). This relatively cheap, low radiation method rapidly produces precise and accurate results of bone density at selected sites such as the lumbar spine and femoral neck.[2] These individual values are compared with a large reference database adjusted for age, sex, weight, and ethnic origin, and results can then be expressed in terms of the mean and standard deviation value for that population. DXA will thus detect low bone density, that is osteopenia, which means that steps can be taken to prevent further bone loss and the development of clinical osteoporosis. Osteoporosis is an increasing problem as the population ages, and lost bone is not easily replaced, so resources are best directed to the early detection of osteopenia and prevention of further bone loss in those most at risk.[3,4] Patients with coeliac disease should probably now be screened for osteopenia.

Two groups recently presented preliminary DXA data on treated, asymptomatic adults with coeliac disease.[5,6] Both showed that about 40% of patients had bone mineral density values more than 1 SD below the standardised population mean. This is more than twice the proportion expected (16%), and represents a greater yield of osteopenic subjects than in screening studies of most other 'high risk' groups. It was not possible to predict clinically those with osteopenic bones; factors such as age at diagnosis, length of disease, lapses from gluten free diet, menopausal status, and milk intake were all unhelpful.

These results confirm and extend the earlier studies in coeliac disease that used less precise methods of measuring bone density. In treated adults, spine and forearm bone mineral content, measured respectively by dual and single photon absorptiometry, was significantly reduced, with mean levels 7 to 13% lower than normal.[7] However, no difference was found in forearm mineral density in teenagers who had been treated for at least 10 years.[8] Untreated patients, not surprisingly, have reduced bone mineralisation, and this was not corrected after one year's treatment with a gluten free diet.[9] A recent study that looked at the problem from the other side, found that the incidence of unsuspected, asymptomatic coeliac disease was nearly 10 fold higher than expected in patients with clinical osteoporosis who were screened with IgA antibodies to gliadin, and if a positive result was found underwent small bowel biopsy.[10]

What are the mechanisms that lead to osteopenia in coeliac disease? The most obvious is that the immunological disease continues with low activity, reducing the total absorptive surface area and the number of mature duodenal villous cells, thus impairing the absorption of calcium. Calcium malabsorption causes secondary hyperparathyroidism which leads to loss of bone mineral; a similar mechanism is thought to be a major problem in senile osteoporosis.[11] Malabsorption of vitamin D (calciferol) is probably of less importance.[12] Most ambulatory subjects will synthesise sufficient vitamin D in the skin with moderate sun exposure, but in the elderly or housebound, dietary sources are required. It is important to recognise that stores of vitamin D (usually determined as serum 25-hydroxyvitamin D) will be metabolised more rapidly when the parathyroid hormone concentration is raised[13] and greater amounts of vitamin D are then needed to maintain serum concentrations. Nevertheless, in the absence of renal disease, serum concentrations of the active metabolite, 1,25-dihydroxycholecalciferol (calcitriol) are usually maintained, even with a gross reduction in serum 25-hydroxyvitamin D.[14]

At the cellular level, the vitamin D receptor has been shown in intestinal biopsy specimens from patients with active coeliac disease,[15] but there is some evidence of relative resistance to its action. One study[16] measured values of immunoreactive calcium binding protein, the vitamin D-dependent protein now known as calbindin-D9k in biopsy specimens. In active coeliac disease it was almost undetectable, but surprisingly, in patients in remission with no other evidence of villous atrophy, median levels were still only 26% of the control group. Now that human calbindin-D9k has been cloned,[17] it will be possible to study the transcriptional control and regulation of expression of this key protein in humans. Another calcium binding protein, calmodulin, does not change to account for the calcium malabsorption.[18]

Other factors could contribute to the reduced bone mineral density in some patients. Associated lactose intolerance may have reduced the lifelong intake of milk, the major dietary source of calcium. Osteoporosis seems to be more common in populations with reduced calcium intake, and the peak bone mass achieved in early adulthood can be influenced by dietary calcium.[19] Amenorrhoea, induced by low body weight or athletic training, can lower bone mineralisation, as will an early menopause. Moderate exercise can help maintain bone density and in the elderly will also help prevent the falls which often lead to the fractures. Smoking and coffee intake have been associated with osteopenia, but there is no evidence to suggest that coeliac patients as a group are different in these respects from the general population.[3] Unlike patients with inflammatory bowel disease, who also should be assessed by bone densitometry,[20] steroid treatment and bowel resection will not usually be contributing factors.

When osteopenia has been detected, what are the implications? Osteoporotic fractures are almost twice as likely with each SD decrease in the value of bone density below the mean.[21] Treatment should first be aimed at preventing further bone demineralisation. Clearly, adherence to a gluten free diet needs reviewing, possibly with further biopsy. Endomysial, reticulin or gliadin antibodies may help assess

compliance to the diet. Hormone replacement treatment is the most effective means of delaying the major loss of bone mineral in women, and should be strongly advocated for as long as possible. As many coeliacs were diagnosed as children between 1950 and 1960, when the cause and treatment of the disease were first appreciated, perimenopausal screening and subsequent hormone replacement are now becoming topical.

Dietary calcium supplements, while controversial in the general population with osteopenia,[22 23] are rational in coeliac disease. Studies have indicated that large amounts of dietary calcium (up to 1·5 g/day) may be needed to maintain the calcium balance in postmenopausal women,[24] and as diets frequently contain less than 400 mg of calcium, supplementation with 500 to 1000 mg of elemental calcium is advisable. In healthy women with low dietary calcium intake who were more than six years past the menopause, supplementation with 500 mg elemental calcium was shown to reduce bone loss in a prospective, randomised, double-blind study.[25] Dietary calcium can be easily assessed to establish those most in need of supplements, bearing in mind that the net calcium absorbed also depends on the absorptive efficiency. Fractional calcium absorption varies widely, even in apparently healthy women,[26] but the value of routine determinations is not yet known.

While there are differences in bioavailability of calcium from various formulations depending on how the preparation disperses, which calcium salt is given is of little practical importance so long as sufficient is taken for long enough. In coeliac disease, the use of gluten as a binder must be excluded, but most of the currently prescribed and 'over the counter' calcium citrate or carbonate preparations are satisfactory. Potent vitamin D metabolites or pharmacological doses are not needed if the calcium intake is adequate, but physiological vitamin D supplementation (that is, ergocalciferol 10 or 20 μg/day) may be necessary, particularly in the elderly in winter. Clinical osteoporosis, in coeliac disease patients, as in the general population, may need more aggressive therapy with calcitonin or bisphosphonates; these and other aspects of prevention and treatment in osteoporosis have been reviewed recently.[4]

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