Editorial

What are the levels of vitamin D in Crohn's disease patients?

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One of the most common extra-intestinal complications of inflammatory bowel diseases (IBD) is abnormalities in bone mineral density (BMD). The advent of technologies, such as dual energy X-ray absorptiometry, has increased our awareness, with reported prevalence rates ranging from 2-30% for osteoporosis and 40-50% for osteopenia.[1] Most studies. suggest that it is more prevalent amongst Crohn's disease (CD) patients than Ulcerative colitis (UC) patients, but not all studies agree on that. Similarly an increased risk for fractures has been attributed to CD patients (relative risk up to 1,7, but this is not seen universally). Although the aetiology of diminished BMD is not fully understood, factors such as malabsorption of fat-soluble vitamins, calcium (Ca) and other minerals, chronic inflammation of the gut, use of bone damaging medications (such as steroids), and hypogonadism seem to contribute. Obviously, patients with CD are subject to the same risk factors for osteoporosis as the general population- female sex, increasing age, white race, low weight, family history of osteoporosis, late menarche and early menopause, smoking, lack of exercise and possibly consumption of alcohol and coffee.

Vitamin D(VD) is essential for normal Ca metabolism and bone formation. The main source of VD (especially during summer) is the skin where pre-VD is generated by UV radiation, whereas in winter, food is the primary resource. Pre-VD is converted to the major circulating metabolite 25- hydroxy VD (25(OH)D in the liver and then to 1,25-dihydroxyVD($1,25(OH)_2D$) in the renal tubular epithelium integrity. This is mediated by 1-a hydroxylase, an enzyme regulated by parathyroid hormone (PTH) to maintain normal serum Ca. Therefore deficiency in VD leads to hypocalcemia, increased PTH and $1,25(OH)_2D$ resulting finally in mobilization of Ca from bones.[2] Although most clinicians (and researchers) have used a concentration of 25(OH)D of 30 nmol/l as a threshold to define VD deficiency, it seems that higher concentrations (>50 nmol/l) are necessary to maintain normal Ca metabolism.[3]

The underlying mechanisms of VD deficiency in patients with CD is multifactorial and it is thought to be primarily the result of fat-soluble vitamin malabsorption due to inflammation or previous resections. Patients with CD have been shown to lack adequate exposure to sun,[4] to have reduced dietary VD consumption,[5] to avoid dairy products and thus have inadequate Ca intake and VD (as they are supplemented with VD), and to have an abnormal enterohepatic circulation of VD. Some CD patients use drugs that inhibit absorption of VD (e.g. cholestyramine) or interfere with Ca metabolism (steroids).

Whether patients with CD are VD deficient remains controversial. Most older studies (6-10) found VD deficiency in a considerable proportion of patients. This has been attributed to the high percentage of patients with a history of a (mostly extensive) small bowel resection, and the frequent use of steroids as the main therapeutical mean. Thus recently, most patients with CD (especially those with history of enteric resection) are advised to take VD supplementation, or to increase exposure to physical or artificial (11) UV radiation.

Other studies have noted hypo-VD in a substantial proportion of patients with CD, with prevalence ranging 16-44%.[12-14] This stands true even for young patients (5-22y). [12] In general it seems to be associated with season (winter), race (African Americans), location (upper GI involvement) or small bowel resection, [13] *disease duration, CDAI score, CRP.* [15] In contrast, others have found no difference between operated and non-operated patients regarding concentration of 25 (OH)D.[13] Several papers have suggested that oral supplementation (with standard recommended dose) did not protect from

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development of hypoVD.[13,14] No difference in BMD was found between patients with normal or sub-normal values of 25(OH)D concentration.[13-16] Secondary hyperparathyroidism was seen in about 18% of patients with a history of small bowel resection, whereas it was unusual in non-operated patients.[13,14] Low BMD was found more often in patients with secondary hyperparathyroidism and it affected mostly cortical bone.[13,14] In contrast, a correlation between 25(OH)D concentration and low BMD (mostly affecting spine and hip) was seen in a study involving patients with small bowel resection, 40% of whom were VD deficient.[17] In none of the above mentioned studies did any patient have a low concentration of 1,25 (OH)2D (the active form of VD), indicating sufficient substrate for hydroxylation, even in the patients with low 25 (OH)D. Additionally, none had typical symptoms of osteomalacia (e.g. bone tenderness, or proximal muscle pain), although very few underwent a bone biopsy to exclude it. Other studies could not find hypo-VD in patients with CD, even in those with low BMD.[18-20]

An interesting aspect of the metabolism of VD was suggested in a study that included 267 patients with IBD (138 with CD). The authors noted inappropriately high levels of serum $1,25(OH)_2D$ in 42% of patients with CD compared to only 7% in UC, while PTH. and 25 (OH)D were normal. This increase in $1,25\ (OH)_2D$ was associated with low lumbar BMD and was seen mostly in patients with active disease. Intestinal epithelium expressed 1a-hydroxylase and was able thus to metabolise 25(OH)D in a manner similar to that seen in other granulomatous diseases such as sarcoidosis.[21]

REFERENCES

1. Bernstein CN, Leslie WD Leboff MS AGA technical review on osteoporosis in gastrointestinal diseases Gastroenterology 2003; 124:795-841.
2. Feldman D. Vitamin D, parathyroid hormone, and calcium: a complex regulatory network. Am J Med 1999; 107:637-639.
3. McKenna MJ, Freaney R. Secondary hyperparathyroidism in the elderly: means to defining hypovitaminosi s D. Osteoporosis Int 1998; 8 (Suppl 2):S3-6.
4. Vogelsang H, Klamert M, Resch H, et al. Dietary vitamin D intake in patients with Crohn's disease. Wien Klin Wochenschr 1995; 107/19:578-581.
5. Silvennoinen J, Lamberg-Allardt C, Karkkainen M, et al. Dietary calcium intake and its relation to bone mineral density in patients with inflammatory bowel disease. J Intern Med 1996; 240:285-292.
6. Vogelsang H, Ferenci P, Woloszczuk W, et al. Bone disease in vitamin D-deficient patients with Crohn's disease. Dig Dis Sci 1989; 34:1094-1099.
7. Harries AD, Brown R, Heatley RV, Williams LA, et al Vitamin D status in Crohn's disease: association with nutrition and disease activity. Gut 1985; 26:1197-1203.
8. Compston JE, Creamer B. Plasma levels and intestinal absorption of 25-hydroxyvitamin D in patients with small bowel resection. Gut 1977; 18:171-175.
9. Driscoll RH, Meredith SC, Sitrin M, et al Vitamin D deficiency and bone disease in patients with Crohn's disease. Gastroenterology 1982; 83:1252-1258.
10. Dibble JB, Sheridan P, Losowsky MS. A survey of vitamin D deficiency in gastrointestinal and liver disorders. Q J Med 1984; New Series LIII(209):119-134.
11. Koutkia P, Lu Z, Chen TC, Holick MF, et al. Treatment of vitamin D deficiency due to Crohn's disease with tanning bed ultraviolet B radiation. Gastroenterology. 2001; 121:1485-1488.
12. Sentongo T A, Semaeo EJ, Stettler N, et al. Vitamin D status in children, adolescents, and young adults with Crohn disease Am J Clin Nutr 2002; 76:1077-1081
13. Andreassen H, Rix M, Brot C, et al. Regulators of Calcium Homeostasis and Bone Mineral Density in Patients with Crohn's Disease Scand J Gastroenter 1998; 33:1087-1093.
14. Jahnsen J, Falch J, Aadland E, et al. Bone mineral density and bone metabolism in patients with inflammatory bowel disease Scand J Gastroenterol 2002; 37:192–199.
15. Tajika M, Matsuura A, Nakamura T, et al. Risk factors for vitamin D deficiency in patients with Crohn's disease. J Gastroenterol 2004; 39:527-533.
16. Siffledeen JS, Siminoski K, Steinhart H, et al. The frequency of vitamin D deficiency in adults with Crohn's disease. Can J Gastroenterol 2003; 1:473-478.
17. Haderslev KV, Jeppesen PB, Sorensen HA, et al. Vitamin D status and measurements of markers of bone metabolism in patients with small intestinal resection Gut 2003; 52:653-658.
18. Bernstein CN, Seeger LL, Sayre JW, et al Decreased bone density in inflammatory bowel disease is related to corticosteroid use and not to diagnosis. J Bone Miner Res 1995; 10:250-256.
19. Abitbol V, Roux C, Chaussade S, et al. Metabolic bone assessment in patients with inflammatory bowel disease. Gastroenterology 1995; 108:417-422.
20. Hessov I, Mosekilde L, Melsen F, et al. Osteopenia with normal vitamin D metabolites after small bowel resection for Crohn's disease. Scand J Gastroenterol 1984; 19:691-696.
21. Abreu M T, Kantorovich V, Vasiliauskas E A, et al Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's disease patients with elevated 1,25-dihydroxyvitamin D and low bone mineral density Gut 2004; 53:1129-1136.