JOURNAL OF BONE AND MINERAL RESEARCH
Volume 22, Supplement 2, 2007
doi: 10.1359/JBMR.07S208

Vitamin D Insufficiency/Deficiency in Gastrointestinal Disorders

Daniel D Bikle

ABSTRACT: Vitamin D and calcium are critical for skeletal health. Their absorption from the intestine is negatively impacted by a number of gastrointestinal diseases and surgical procedures, leading to osteoporosis and/or osteomalacia. Diseases of the liver can impact the metabolism of vitamin D to its circulating form, 25(OH)D, as well as the production of carrier proteins, albumin and vitamin D–binding protein, that may alter the delivery of 25(OH)D and its active metabolite $1,25(OH)_2D$ to target tissues, including the skeleton, again leading to bone disease. The clinician evaluating a patient with apparent osteoporosis and vitamin D deficiency/insufficiency needs to consider a gastrointestinal etiology. Similarly, the clinician evaluating a patient with a gastrointestinal disorder needs to evaluate that patient for vitamin D deficiency and bone disease. Treatment involves adequate vitamin D and calcium supplementation to achieve normal serum 25(OH)D, PTH, and serum and urine calcium levels.
J Bone Miner Res 2007;22:V50–V54. doi: 10.1359/JBMR.07S208

Key words: vitamin D, calcium absorption, osteomalacia, malabsorption, bariatric surgery, liver disease

INTRODUCTION

VARIOUS GASTROINTESTINAL DISEASES and/or surgical revisions lead to bone loss by one or more of the following processes: malabsorption of vitamin D and minerals (calcium and phosphate in particular), production of inflammatory cytokines, and the use of drugs such as glucocorticoids to treat the inflammatory process. Although maintenance of adequate vitamin D and calcium nutrition is important for all diseases involving the gastrointestinal system, each disease presents its own unique issues with respect to proper management. An important problem with providing explicit recommendations for therapy, however, is the general lack of large prospective trials by which different approaches to management, in particular the use of vitamin D and its metabolites, can be judged against other treatment modalities. Furthermore, there is not total consensus on optimal vitamin D levels. Most investigators would agree that serum levels of 25(OH)D >30 ng/ml indicate vitamin D sufficiency and that serum levels of 25(OH)D <10 ng/ml indicate vitamin D deficiency. I am using the less precise term insufficiency to refer to levels of 25(OH)D between 10 and 30 ng/ml, recognizing that a level of 25(OH)D >20 ng/ml is considered sufficient by others. This review will start with a brief discussion of intestinal calcium and vitamin D absorption before turning to the specific disease entities.[1]

Calcium absorption

Absorption of calcium from the luminal contents of the intestine involves both transcellular and paracellular pathways.[2] The transcellular pathway dominates in the duodenum, and this is the pathway primarily regulated by 1,25 dihydroxyvitamin D [$1,25(OH)_2D$]. Calcium entry across the brush border membrane (BBM) occurs down a steep electrical-chemical gradient and requires no input of energy. This occurs through an epithelial specific calcium channel, transient receptor potential vanilloid 6 (TRPV6). The expression of this channel is stimulated by $1,25(OH)_2D_3$. Vesicles within the terminal web containing the calcium binding protein calbindin accumulate the calcium and shuttle it to the basolateral membrane, where it is pumped out of the cell by a CaATPase (PMCA) also induced by $1,25(OH)_2D_3$. At low calcium intakes, the transcellular pathway dominates and provides a highly efficient means of absorption. However, as calcium intake increases, nonsaturable but less efficient pathways come into play, and calcium absorption falls to ~10% of the amount ingested at calcium intakes >500 mg/d. With age, the efficiency of calcium absorption and the ability of the intestine to adapt to decreased calcium intake fall. The reason(s) for the decline in calcium absorption with age is not clear, although some reports have found a decrease in vitamin D receptors in the intestinal epithelium. Other dietary constituents alter calcium absorption. Lactose increases calcium absorption in a number of animals including humans, and lactase deficiency has been associated with an increased risk for osteoporosis. Phosphate increases fecal loss of calcium in part by increased endogenous calcium secretion. A diet rich in fiber and phytates reduces calcium absorption by chelating calcium and therefore decreases calcium balance.

Vitamin D absorption

Although the skin has the capability to produce adequate amounts of vitamin D given enough sunlight of sufficient

The author states that he has no conflicts of interest.

Department of Medicine, Veterans Affairs Medical Center, University of California, San Francisco, California, USA.

intensity, because of our indoor lifestyle, modesty with respect to amount of skin exposed, and fear of cancer leading to zealous use of sunscreens, this biological pathway does not always suffice. Thus, dietary intake and intestinal absorption of vitamin D become important especially in the winter months when the intensity of UVB from the sun is not adequate to enable cutaneous production of vitamin D.[3] Vitamin D is absorbed in the jejunum and ileum by a mechanism capable of absorbing ~75% of the vitamin D administered.[4,5] Vitamin D appears in both the portal system and lymphatics, indicating that both pathways are used, although the lymphatic route may be preferred in humans. In lymph, ~50% of vitamin D is found in the chylomicron fraction. Fatty acids reduce vitamin D absorption, but this can be reversed with the addition of bile acids.[4] The more polar metabolites 25(OH)D (calcifediol) and $1,25(OH)_2D_3$ (calcitriol) are better absorbed than vitamin D. Vitamin D metabolites undergo an enterohepatic circulation. Disruption of this process in various gastrointestinal and hepatic diseases can contribute to losses of these metabolites in the feces and/or their increased excretion in the urine as conjugated compounds.

Impact of gastrointestinal disorders

Vitamin D and/or calcium absorption could be affected by various gastrointestinal diseases for at least six reasons.[3,5,6] First, adequate intake of vitamin D and calcium is required, especially in an individual who otherwise fails to synthesize sufficient quantities of vitamin D in the skin. Milk and other dairy products are a good source of both if these products are supplemented with vitamin D. Second, vitamin D absorption requires an intact small intestine, pancreas, and liver to provide the milieu (lipase, bile acids) required for vitamin D absorption. Partial gastrectomy, chronic pancreatic insufficiency, intrinsic small bowel disease, disorders of the biliary tract, and surgical bypass procedures of the jejunum and ileum can all cause problems. Third, vitamin D that enters the body must be further metabolized to active compounds. Diseases of the liver, where the first step in bioactivation takes place, or drugs such as phenytoin, which alter this first metabolic step, lead to deficiency of the active metabolites. Fourth, the vitamin D metabolites undergo an enterohepatic circulation, being secreted in bile in conjugated form with subsequent reabsorption in the small intestine. Disruption of this pathway may contribute to vitamin D deficiency in certain diseases of the liver and small intestine. Fifth, vitamin D and its metabolites are poorly soluble in water and must be transported in blood bound to proteins, vitamin D–binding protein (DBP) and albumin, which are synthesized in the liver. Decreased synthesis of these proteins may impair the delivery of the vitamin D metabolites to the target tissues. Finally, the diseased, aging, or surgically altered intestine may fail to respond normally to the active vitamin D metabolites with respect to calcium and phosphate absorption. Treatment depends to some extent on the underlying pathophysiology, which varies for the different diseases.[7]

GASTROINTESTINAL DISEASES

Post-gastrectomy

Bone disease is quite common in patients with a history of partial or total gastrectomy, generally performed for the management of peptic ulcer disease. In some series, up to 70% of the patients develop osteopenia. Not surprisingly, the incidence of osteopenia increases with age. Widened osteoid seams have been observed in bone biopsy samples in up to 32% of patients, but most studies did not evaluate bone formation rates; therefore, the incidence or prevalence of osteomalacia is more difficult to ascertain. The increased osteoid may indicate high bone turnover resulting from secondary hyperparathyroidism rather than osteomalacia. However, fractures including pseudofractures of hip and spine are more frequent in these patients than in age-matched controls. Serum 25(OH)D levels are often reduced, but $1,25(OH)_2D_3$ levels are normal or even slightly elevated. PTH levels are generally normal but may also be increased. Urine calcium levels are generally low. The pathogenesis of the bone disease in this disorder is a bit of a puzzle. It is not at all clear that the lack of acid production by the stomach is the cause of the calcium malabsorption. The isolation of the proximal duodenum accompanied by the reduced input of pancreatic lipases and bile salts by the Billroth II procedure may account for some calcium and vitamin D malabsorption, but this has not been verified. However, the Billroth I procedure, which does not isolate the proximal duodenum from the stream of gastrointestinal contents, does not have the same impact on bone or the calcium-regulating hormones. The low 25(OH)D levels may reflect the increased catabolism of 25(OH)D as a result of secondary hyperparathyroidism and increased $1,25(OH)_2D_3$-induced CYP24A1 (24-hydroxylase) activity as much as decreased vitamin D absorption. Treatment involves sufficient vitamin D and calcium to maintain normal 25(OH)D, PTH, and urine calcium levels.

Celiac disease

Celiac disease is caused by an allergic response of the intestinal epithelium to gliadin. It can be prevented/treated by avoidance of gluten. However, this problem is frequently not diagnosed because symptoms of malabsorption such as steatorrhea may be absent. In a recent study of 89 premenopausal women being evaluated for osteoporosis, 19% were positive for IgA antibodies to gliadin, and one half of these were also positive for IgA endomysial antibodies.[8] If a gluten-free diet is started in childhood and adhered to, achieved peak bone mass is generally normal. However, a gluten-free diet initiated after childhood does not often lead to complete restoration of BMD. The bone disease is generally osteoporosis, although some studies have also found evidence for osteomalacia on bone biopsies in a small percentage of patients. Low 25(OH)D, elevated PTH, and normal to increased $1,25(OH)_2D_3$ are generally found in untreated patients as would be expected with malabsorption of calcium and vitamin D from the atrophic small intestinal epithelium. However, celiac disease is also an inflammatory process with increased cytokine levels such as interleukin

(IL)-I and IL-6. Thus, although vitamin D and calcium are important components of the therapy, normalizing the BMD is often not achieved unless the inflammatory process is corrected, which is best done with a gluten-free diet.

Inflammatory bowel syndromes

Of the two major forms of inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis, severe bone disease is more frequent with Crohn's disease, especially when it involves the small intestine, leads to partial intestinal resection, and involves treatment with glucocorticoids. These are diseases of young adults, and clinical features of bone disease are often subtle or absent. 25(OH)D levels may be normal but have been shown to be reduced in up to 65% of patients with Crohn's disease, especially in those with ileal resections. The prevalence of low 25(OH)D levels is more common in the winter and in blacks. Patients with ulcerative colitis do not show marked differences from control populations with respect to 25(OH)D levels, and in some studies, the levels of 25(OH)D do not correlate with the extent of osteopenia. Low 25(OH)D levels may be accompanied by increased PTH and increased markers of bone turnover. In a recent report, $1,25(OH)_2D_3$ levels were found to be elevated in 42% of patients with Crohn's disease, with no elevation in PTH. In that study, colonic biopsy specimens showed increased expression of CYP27B1 [25(OH)D-1α-hydroxylase] by PCR and immunohistochemistry.[9] In an interesting animal study, mice in which both IL-10 and the vitamin D receptor were deleted showed an accelerated IBD not seen with either single gene deletion model,[10] suggesting that the increase in locally produced $1,25(OH)_2D_3$ might be protective with respect to the inflammatory process. Maintaining adequate vitamin D and calcium nutrition is important for bone health. However, the inflammatory process also contributes to bone loss and needs to be addressed.

Pancreatic insufficiency

Clinically significant bone disease resulting from isolated pancreatic insufficiency is uncommon unless accompanied by a history of excess alcohol intake, cholestatic liver disease, or cystic fibrosis. Thus, low levels of 25(OH)D in patients with pancreatic insufficiency should lead to a search for other causes. For example, patients with cystic fibrosis often present with reduced BMD and fractures resulting from poor nutrition and malabsorption of calcium and vitamin D caused by abnormal small bowel function, chronic infections with elevated cytokine production, hypogonadism, use of glucocorticoids, and pancreatic insufficiency. That said, patients with pancreatic insufficiency should be monitored for adequacy of calcium and vitamin D nutrition, which should be replaced as appropriate, and provided pancreatic enzymes to facilitate absorption of fat-soluble vitamins such as vitamin D and other nutrients.

Bariatric surgery

There are two general types of gastrointestinal operations used in the management of obesity.[11] Restrictive procedures such as circumgastric banding or vertical banded gastroplasty seek to reduce the capacity of the stomach, leading to an obligatory restriction in oral intake of solids. After the initial weight loss, weight is often regained. These procedures are not expected to have much impact on bone mineral homeostasis, but this has not been well studied. Bypass procedures, on the other hand, are designed to create various levels of malabsorption and greater weight loss. There are three main bypass procedures. The jejunoileal bypass connects the jejunum to the ileum—the extent of the bypass can vary. Gastric bypass uses a Roux-en-Y anastomosis by connecting a small pouch of stomach into the transected jejunum attached to the duodenojejunal limb. The size of the gastric pouch and length of the limb can vary. Biliopancreatic diversion involves a partial gastrectomy or bypass connected to the proximal ileum/distal jejunum with reanastomosis of the duodenojejunal limb into the ileum distal to the connection with the stomach. All of these bypass procedures produce both substantial weight loss and malabsorption of vitamin D and calcium.[12] The complications of jejunoileal bypass are of sufficient severity that this procedure has declined in popularity. Up to 60% of such patients developed osteomalacia or osteoporosis as found on bone biopsy. The newer bypass procedures have received less study. However, biliopancreatic bypass seems to have a greater impact on vitamin D levels in that, in one study of 82 patients, 50% were found to have 25(OH)D levels <14 nM (5.2 ng/ml), a level commonly associated with osteomalacia on bone biopsy, and 63% had elevated PTH levels.[13] In contrast, in a smaller study of patients treated with the Roux-en-Y procedure, increased markers of bone turnover and reduced BMD were observed, but no changes in 25(OH)D or PTH were seen either in a 9-mo prospective trial or in comparison with obese controls who did not undergo the operation [25(OH)D levels were low in both groups before and after the operation].[14] Nevertheless, low 25(OH)D levels are often found in obese patients, and this should be treated with adequate calcium and vitamin D. Higher doses of vitamin D are likely to be required in those receiving bypass procedures.

HEPATIC DISEASES

Chronic cholestatic disorders

Primary biliary cirrhosis (PBC) is the most common cholestatic disorder leading to bone disease.[15] The prevalence of osteomalacia versus osteoporosis in these patients varies from series to series, with most of the osteomalacia being reported from studies in the United Kingdom where osteomalacia in the general population is more prevalent than in the United States. Bone biopsies in more recent studies generally show low turnover osteoporosis, although some patients show a high turnover form of osteoporosis, perhaps because of secondary hyperparathyroidism. However, elevated levels of PTH are not commonly seen in this disease. Biliary atresia in children, on the other hand, is often associated with frank rickets. Serum 25(OH)D levels can be normal in asymptomatic patients with PBC, but fall as the disease progresses. However, 25(OH)D levels are not a

good indicator of bone disease. Although patients with vitamin D deficiency should be improved by vitamin D supplementation, vitamin D has not proven to be useful in correcting the osteoporosis.

Chronic active hepatitis

Most of these patients are treated with glucocorticoids, so it is difficult dissociating the impact of the liver disease from that of its treatment on the bone loss observed in many of these patients. The patients tend to have low 25(OH)D similar to levels seen in PBC and alcoholic cirrhosis, but these reductions are associated with decreased levels of DBP, suggesting that their free 25(OH)D levels may be normal. Bone biopsies from 36 patients with chronic active hepatitis (CAH) showed osteopenia and not osteomalacia. The role of vitamin D therapy in this condition is not clear, although adequate levels should be maintained as would be recommended for all patients.

Viral hepatitis

Studies of the impact of viral hepatitis on the vitamin D endocrine system and on bone are limited in number and scope. Osteopenia tends to worsen as the disease progresses commensurate with the decline in 25(OH)D and increase in markers of bone resorption. IGF-I levels also decreased, correlating with the decrease in BMD. However, in a study from Brazil,[16] 25(OH)D levels were generally normal (mean value, 52 ng/ml) despite the presence of osteopenia and increased markers of bone turnover. As for CAH, the role of vitamin D in the treatment of this condition has not been well established.

Alcoholic cirrhosis

Although excessive alcohol intake is a well-established risk factor for bone disease, the role of hepatic cirrhosis in this process is not. Osteopenia is commonly observed in this population, with fractures of ribs and vertebrae seen in up to 30%, the incidence of which increases with age. Bone biopsies generally show low turnover osteoporosis, albeit with some reports of osteomalacia. 25(OH)D levels are often reduced, but in patients with cirrhosis, this reduction is associated with reduced DBP and albumin levels such that the free concentrations of 25(OH)D are normal. Similarly, the low levels of calcium often correct into the normal range when albumin levels are taken into consideration. Nevertheless, this population is prone to poor nutrition, and adequate vitamin D and calcium should be provided. However, no studies showing correction of the bone disease in these patients with such therapy have been reported.

Post–liver transplantation

Osteoporosis is a common complication in patients undergoing liver transplantation.[17,18] In part, this is because of the bone loss experienced by patients before surgery as a result of their liver disease as discussed above. However, nearly all patients suffer some bone loss after transplantation. Patients with primary biliary cirrhosis generally start with less bone, and their rate of loss tends to exceed that of patients with other forms of liver disease. Bone loss after transplantation is likely caused by the massive doses of glucocorticoids (e.g., 200 mg/d prednisolone) and immunosuppressives (e.g., cyclosporine and azathioprine) used to prevent rejection. Fractures and aseptic necrosis appear within months. The fractures tend to occur in the spine and ribs, although hip fractures are also observed. Vitamin D metabolite levels may be low before transplantation and fall further after the transplant. Although the bone loss is likely caused primarily by the immunosuppressive agents used, correction of calcium and vitamin D levels before and after the operation is important.

REFERENCES

1. Bikle DD 2001 Osteoporosis in gastrointestinal, pancreatic, and hepatic diseases. In: Marcus R, Feldman D, Kelsey J (eds.) Osteoporosis, 2nd ed. Academic Press, San Diego, CA, USA, pp. 237–258.
2. Hoenderop JGJ, Nilius B, Bindels RJM 2005 Calcium absorption across epithelia. Physiol Rev **85:**373–422.
3. Mawer EB, Davies M 2005 Vitamin D nutrition and bone disease in adults. Rev Endocr Metab Disord **2:**153–164.
4. Hollander D, Muralidhara KS, Zimmerman A 1978 Vitamin D_3 intestinal absorption in vivo: Influence of fatty acids, bile salts, and perfusate pH on absorption. Gut **19:**267–272.
5. Thompson GR, Lewis B, Booth CC 1966 Absorption of vitamin D_3-^{3}H in control subjects and patients with intestinal malabsorption. J Clin Invest **45:**94–102.
6. Bernstein CN, Leslie WD 2003 The pathophysiology of bone disease in gastrointestinal disease. Eur J Gastroenterol Hepatol **15:**857–864.
7. Von Tirpitz C, Reinshagen M 2003 Management of osteoporosis in patients with gastrointestinal diseases. Eur J Gastroenterol Hepatol **15:**869–876.
8. Armagan O, Uz T, Tascioglu F, Colak O, Oner C, Akgun Y 2005 Serological screening for celiac disease in premenopausal women with idiopathic osteoporosis. Clin Rheumatol **24:**239–243.
9. Abreu MT, Kantorovich V, Vasiliauskas EA, Gruntmanis U, Matuk R, Daigle K, Chen S, Zehnder D, Lin YC, Yang H, Hewison M, Adams JS 2004 Measurement of vitamin D levels in inflammatory bowel disease patients reveals a subset of Crohn's patients with elevated 1,25-dihydroxymitamin D and low bone mineral density. Gut **53:**1129–1136.
10. Froicu M, Weaver V, Wynn TA, McDowell MA, Welsh JE, Cantorna MT 2003 A crucial role for the vitamin D receptor in experimental inflammatory bowel diseases. Mol Endocrinol **17:**2386–2392.
11. Cannizzo F Jr, Kral JG 1998 Obesity surgery: A model of programmed undernutrition. Curr Opin Clin Nutr Metab Care **1:**363–368.
12. Carlin AM, Rao DS, Meslemani AM, Genaw JA, Parikh NH, Levy S, Bhan A, Talpos GB 2006 Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery. Surg Obes Relat Dis **2:**98–103.
13. Newbury L, Dolan K, Hatzifotis M, Low N, Fielding G 2003 Calcium and vitamin D depletion and elevated parathyroid hormone following biliopancreatic diversion. Obes Surg **13:**893–895.
14. Coates PS, Fernstrom JD, Fernstrom MH, Schauer PR, Greenspan SL 2004 Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. J Clin Endocrinol Metab **89:**1061–1065.
15. Levy C, Lindor KD 2003 Management of osteoporosis, fat-soluble vitamin deficiencies, and hyperlipidemia in primary biliary cirrhosis. Clin Liver Dis **7:**901–910.
16. Duarte MP, Farias ML, Coelho HS, Mendonca LM, Stabnov LM, Docarmod-Oliveira M, Lamy RA, Oliveira DS 2001 Cal-

cium-parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. J Gastroenterol Hepatol **16:**1022–1027.
17. Hawkins FG, Leon M, Lopez MB, Valero MA, Larrodera L, Garcia-Garcia I, Loinaz C, Moreno-Gonzalez E 1994 Bone loss and turnover in patients with liver transplantation. Hepatogastroenterology **41:**158–161.
18. Vedi S, Greer S, Skingle SJ, Garrahan NJ, Ninkovic M, Alexander GA, Compston JE 1999 Mechanism of bone loss after liver transplantation: A histomorphometric analysis. J Bone Miner Res **14:**281–287.

Address reprint requests to:
Daniel Bikle, MD, PhD
VA Medical Center
4150 Clement Street, 111N
San Francisco, CA 74129, USA
E-mail: daniel.bikle@ucsf.edu

Received in original form January 2, 2007; revised form March 9, 2007; accepted March 27, 2007.