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Metabolic Bone Disease in the Patient on Long-Term Parenteral Nutrition



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Metabolic bone disease is a common problem for patients who require long-term parenteral nutrition. Osteoporosis and osteomalacia, the two major forms of metabolic bone disease, may lead to bone pain, fragility fractures, limited mobility and a decrease in the quality of life. When metabolic bone disease was first recognized in long-term parenteral nutrition patients it appeared to be due to solutions contaminated with high concentrations of aluminum. Parenteral nutrition no longer contains these large amounts of aluminum; however, these patients are still at risk for the development, or worsening of, existing metabolic bone disease. The parenteral nutrition formula should allow for optimal bone health with ongoing monitoring for the presence of metabolic bone disease to identify those who require additional medication to stabilize or improve their bone health. This review will discuss many of the aspects of metabolic bone disease in patients on long-term parenteral nutrition.

INTRODUCTION

Bone is a metabolically active tissue that is continually changing in response to the physical stress placed upon the skeleton. This process, known as remodeling, is carefully regulated by parathyroid hormone (PTH) and locally active chemokines and requires adequate blood levels of vitamin D, calcium,

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magnesium and phosphorus. At a cellular level, osteoblasts are responsible for new bone deposition while osteoclasts are necessary for bone breakdown. During childhood and adolescence, bone mass gradually increases and peaks during early adulthood (~ age 30), then gradually declines as part of the aging process. However, certain disease processes accelerate mineral loss or the formation of abnormal bone that leads to an increased risk of bone fracture. Metabolic bone disease (MBD) is a term used to describe these abnormalities of bone metabolism.

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Osteoporosis and Osteomalacia

The two major forms of MBD are osteoporosis (OP) and osteomalacia (OM). Osteoporosis affects over 28 million individuals in the United States, 80% of which are women, and will lead to 1.5 million fractures each year. It occurs when there is a decrease in the total amount of bone with a normal ratio of bone osteoid (the protein matrix of bone made predominantly of collagen) to bone mineral content. Osteomalacia, which means soft bones, is characterized by defective calcification of bone osteoid and leads to a paradoxical increase in bone volume. It is usually caused by vitamin D deficiency and poor calcium absorption. Conditions that lead to MBD are outlined in Table 1. It should be noted that screening tests used to identify an individual with MBD cannot differentiate OP from OM.

Metabolic Bone Disease

MBD in long-term parenteral nutrition (PN) was first described in the early 1980's when studies from large home parenteral nutrition (HPN) programs began to report that many of their patients developed debilitating bone pain, weakness, hypercalciuria and hypercalcemia. Some of these studies described bone biopsies with increased osteoid formation, defective bone mineralization and decreased bone turnover, which is consistent with OM, while other studies found a reduction in both osteoid and bone mineralization, a picture consistent with OP (1,2). Many of the patients with OM probably had aluminum toxicity, since formulas at that time were made with amino acids derived from casein hydrolysates that contained high concentrations of aluminum. Aluminum was subsequently found in significant amounts in the plasma, urine and bone of these patients (3-5). Casein hydrolysates were eventually replaced with crystalline amino acids, which eliminated most of the aluminum in PN solutions and thus avoided the development of OM in a majority of these patients.

Today the development of MBD is still a concern in HPN patients and may be related to a number of factors including the various components of the PN solution and the conditions for which the PN is prescribed. In this paper we will discuss the prevalence of MBD in patients on long-term PN, the effect of PN on bone metabolism, and finally the evaluation and manage-

ment of these patients. We will also focus on the preparation of a PN formula that should minimize bone loss and the development of these debilitating conditions.

PARENTERAL NUTRITION-ASSOCIATED METABOLIC BONE DISEASE (PN-MBD)

Symptoms and Frequency of PN-MBD

A majority of individuals with MBD are without symptoms. The same can be said for parenteral nutrition-associated metabolic bone disease (PN-MBD). Early reports of patients with PN-MBD described an insidious onset of bone pain that was sometimes incapacitating; fractures of the spine and ribs would occur with minimal or no trauma. Blood work was typically normal, but urinary calcium losses were often found to be increased. Symptoms would usually abate when PN was discontinued.

A survey of nine centers conducted in Europe examined the prevalence of PN-MBD in patients who had been on PN for at least six months and who had a dual-energy x-ray absorptiometry scan (DXA) within the previous 12 months of the survey (6). One hundred and sixty five patients with a mean age of 52 years, who had used PN for an average of 61 months, participated in the survey. The investigators found that 84% of the participants had osteopenia (a mild form of OP) and 41.5% had OP. The frequency of MBD was not affected by the indication for PN (inflammatory bowel disease versus ischemia versus other); however, it was found to be more common in postmenopausal women. In a prospective cohort study of 88 patients receiving HPN for intestinal failure, the prevalence of OP was found to be 67% at baseline based on DXA (7). The patients with Crohn's disease who had received corticosteroids had a significantly higher prevalence of OP as well as those patients who started HPN at a younger age. The authors speculated that younger patients may have sustained the deleterious effects of malabsorption during the period that peak bone density is normally achieved, contributing to the early development of MBD.

PN Factors that Affect Bone Metabolism

The provision of an adequate diet is obviously necessary to maintain optimal bone density. It is well known that sufficient amounts of protein, energy, calcium,

Table 1
Causes of Secondary Metabolic Bone Disease

*Osteoporosis***Endocrine disease**

- Hyperthyroidism
- Hypogonadism
- Hyperparathyroidism
- Insulin dependent diabetes mellitus

Gastrointestinal disease

- Crohn's disease
- Radiation enteritis
- Short bowel syndrome
- Post-gastrectomy syndrome
- Pancreatic insufficiency

Hepatobiliary disease

- Primary biliary cirrhosis
- Sclerosing cholangitis
- Cirrhosis

Malignancy

- Chemo and radiation therapy
- Oophorectomy
- Paraneoplastic syndromes

Drugs and toxins

- Glucocorticoids
- Anticonvulsants
- Therapeutic doses of heparin
- Excess thyroxine
- Alcohol
- Tobacco

Other

- Decreased mobility

*Osteomalacia***Gastrointestinal and hepatobiliary disease**

- Crohn's disease
- Radiation enteritis
- Short bowel syndrome
- Post-gastrectomy syndrome
- Pancreatic insufficiency
- Primary biliary cirrhosis
- Sclerosing cholangitis
- Cirrhosis

Disorders of vitamin D metabolism

- Renal disease
- Liver disease
- Vitamin D dependant and resistant rickets

Drugs that inhibit bone mineralization

- Anticonvulsants
- Fluoride
- Etidronate
- Aluminum

Other unusual causes

- Renal tubular acidosis
- Hypophosphatemia
- Hypophosphatasia

Inadequate sun exposure

- Institutionalized patients
- Higher latitudes
- Excessive sun screen use
- Use of clothing that covers entire skin surface

phosphorus, magnesium, and vitamins D and K are necessary to achieve this. What is less well understood is how the provision of these and other nutrients affect bone metabolism when they are provided by the parenteral route. Several components of the PN solution have been found to effect urinary calcium excretion while others have been shown to alter bone metabolism (8). It is therefore important to understand these factors, which are listed in Table 2, so that a PN solution can be prepared to favorably affect bone mineralization.

Amino acids have been shown to cause hypercal-

ciuria by increasing renal blood flow and hence glomerular filtration rate. In a short term study comparing a dose of 1 gm/kg/d versus 2 gm/kg/d of amino acids in a PN solution, calcium loss in the urine was shown to increase from 287 mg to 455 mg per day (9). This effect is related to an associated increase in the concentration of sulfate, titratable acid and insulin in the blood. Sodium and dextrose also increase the excretion of calcium by increasing the glomerular filtration rate. Urinary calcium excretion has been shown to be positively correlated to calcium intake during

Table 2
Parenteral Nutrition Factors Associated with Metabolic Bone Disease

<i>Nutrient</i>	<i>Effect on Urinary Calcium Excretion</i>	<i>Comment</i>
Amino acids	Increased	Limit dose after nutritional repletion
Dextrose	Increased	
Sodium	Increased	Provide only enough to meet amount lost in stool and urine
Calcium	Increased	Provide enough to promote a positive balance
Phosphorus	Decreased	
Metabolic acidosis	Increased	Provide acetate to normalize serum bicarbonate
Cycled infusion	Increased	Total daily excretion the same as a 24-hour infusion
<i>Nutrient</i>	<i>Effect on Bone Metabolism</i>	<i>Comment</i>
Vitamin D	Variable	Adequate dose needed
Aluminum	Defective mineralization	High concentrations when nitrogen source was casein hydrolysates; aluminum is still present due to contaminant of additives
Magnesium	Parathyroid hormone (PTH)	PTH excretion and effect on renal response depends on adequate magnesium concentration
Acetate	Vitamin D action	Metabolic acidosis diminishes activity of vitamin D

PN. A positive calcium balance is not obtained until a certain concentration of calcium is infused. In a study of hospitalized patients on PN, positive calcium balance did not occur until a minimal dose of 15 mEq/d was provided (10). Phosphorus on the other hand has been shown to enhance renal tubular calcium resorption. In a study providing a fixed amount of calcium, a ratio of calcium to phosphorus of 1:2 was shown to lead to a positive calcium balance (11). It is therefore important to provide a proper quantity of these nutrients to avoid nutrient deficiency and excessive calcium excretion. Finally, cycling PN over a portion of the day increases the amount of calcium in the urine during infusion; however, the total daily loss of calcium is no different than if PN is infused over 24 hours (8).

Vitamin D plays an integral role in bone metabolism and is one of the principal hormonal regulators of calcium metabolism in the body. It is essential for calcium and phosphorus absorption in the intestine, calcium reabsorption in the renal tubules and normal bone mineralization. In addition to dietary sources, vitamin D is formed in the skin from exposure to sunlight (ultravi-

olet-B radiation). Vitamin D metabolism is initiated in the liver by hydroxylation to 25-hydroxyvitamin D followed by hydroxylation in the kidney to its most biologically active form 1,25-dihydroxyvitamin D. The renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D is increased by elevated concentrations of PTH that occurs when the serum concentration of calcium is below normal. This form of vitamin D increases calcium absorption in the small intestine. 1, 25-dihydroxyvitamin D also binds to specific bone cell receptor sites to induce stem cell monocytes to become mature functioning osteoclasts and stimulate osteoblast formation as part of the bone remodeling process (12).

Vitamin D status can be determined by measuring the circulating serum concentration of 25-hydroxyvitamin D. Vitamin D deficiency has been defined, by most, as a value less than 20 ng/mL. However, recent work has suggested a level of 30 ng/mL or less should be considered indicative of vitamin D deficiency (13).

Vitamin D is contained in PN and can directly affect bone metabolism. Excess vitamin D administration can
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lead to MBD. In the 1970's the dose of vitamin D used in PN solutions ranged from 400–1000 IU per day. The current dose of vitamin D is now 200 IU per day. One study even showed that some patients with MBD can benefit by removing vitamin D from the PN solution (14). At the present time, this is not a practical approach for the treatment of PN-MBD because there are no vitamin preparations that exclude vitamin D. In contrast to the deleterious effects of excess vitamin D, recent studies have documented significantly low vitamin D levels in long-term PN patients and in patients with small bowel resections (7,15). These studies also documented elevated PTH levels indicating patients had secondary hyperparathyroidism. Patients with vitamin D deficiency, despite daily multivitamin injection usage, may need oral repletion doses as there is currently no available single intravenous vitamin D source that can be added to the PN formula. Only oral supplements are available which include capsules (Drisdol® 50,000 IU [ergocalciferol], Delta-D® 400 IU [cholecalciferol] or liquid drops (Calciferol™), Drisdol® 8000 IU). However, patients with intestinal failure may not be able to fully absorb oral vitamin D and will require increased doses. Recent studies have also suggested that vitamin D₃ (cholecalciferol) may be more potent and have a longer duration of action than vitamin D₂ (ergocalciferol) (16,17). High-dose vitamin D₃ supplements (50,000 IU) are not currently available in the U.S.

Aluminum contamination can interfere with the calcification of osteoid bone resulting in OM. This was a major problem until crystalline amino acids were used to prepare PN. Current sources of aluminum contamination include calcium, acetate, phosphate, multivitamin and trace element solutions. While the total concentration is far less than the amount of aluminum found during the era of protein hydrolysates, a Federal Drug Administration mandate now requires pharmacists to report the amount of aluminum in PN solutions to physicians when the amount exceeds >4 mcg/kg/d which underscores that this problem has not yet been completely resolved (18,19).

The concentrations of magnesium and acetate need to be considered as they can indirectly affect bone metabolism. Magnesium is mostly lost in stool or ostomy effluent in patients with intestinal failure or fistulas; it must be given in sufficient quantities as it is

necessary for normal bone metabolism and has an indirect effect on the excretion of PTH and its action on the kidneys. In those patients at risk for, or those who have metabolic acidosis, adequate acetate must also be given to prevent osteoclastic activity. Acetate, the form of bicarbonate in PN solutions, may need to be increased in patients with excessive bicarbonate loss from severe diarrhea, renal insufficiency from chronic dehydration, and the release of weak phosphate and sulfate acids from the metabolism of amino acids.

Finally, a low grade inflammatory process and an altered immune response has been reported in HPN patients (20); a recent pilot study found an association between an inflammatory state, vitamin D deficiency, hyperparathyroidism and hypocalcemia (21). The inflammatory response and its relationship to MBD in HPN patients require further scrutiny.

Pre-existing Metabolic Bone Disease

Nearly every condition requiring long-term PN can predispose a patient to MBD. Patients with Crohn's disease are at risk for MBD if they experience malabsorption of calcium and vitamin D or require corticosteroids to control their disease (22). Inflamed bowel can promote bone resorption through the release of cytokines and other inflammatory mediators into the blood including tumor necrosis factor, interleukin-1 and interleukin-6 (23). Patients with cancer cachexia may not consume adequate amounts of calcium and vitamin D. Some tumors can excrete chemicals that can directly alter bone metabolism. In addition, surgery for ovarian cancer and other gynecologic tumors may result in surgical menopause in young women. There is also some experimental evidence that removing a large amount of small intestine can increase the urinary excretion of calcium (24).

Long-term PN Exposure and Bone Metabolism

While one may take the view that MBD and bone fracture is an inevitable development for patients on long-term PN, recent reports suggest that bone metabolism can be stabilized and possibly reversed to some extent in these patients. The first line of evidence is from a study that compared patients on PN for <1 year to patients on long-term PN (8). This study found the fraction of the

infused calcium excreted in the urine to be lower in the long-term group. The same investigators using a primate model of PN-MBD found that renal function gradually adapts to PN such that calcium balance became positive over time (25). One study examined changes in body composition in several patients placed on long-term PN who were severely malnourished at the start of therapy (26). These patients all had significant improvement in bone mineral content during the first three months of therapy. In a retrospective study of 88 patients on HPN, 56 patients had a second DXA performed on average of 5.5 years after their baseline study and were found to have improvement in their trabecular bone mineral density (7). In a follow-up to a report from nine HPN centers in Europe, a second DXA was performed in 65 patients on average 18 months after their initial examination (6). The mean BMD in these subjects actually improved in the lumbar spine, but was unchanged in the femoral neck. In patients with a decline in BMD, bone loss was not related to PN factors, but was negatively correlated with female gender and the initiation of HPN at an early age. Finally, in a longitudinal study of HPN patients followed for > one year, BMD was found to decline by 1% each year, a rate that was not significantly greater than that seen in age and gender matched controls who were not on HPN (27).

DIAGNOSIS, TREATMENT AND PREVENTION OF PN-MBD

Diagnosis

A thorough history, physical examination and laboratory assessment should be performed in all patients who require long-term PN. The history should include whether the patient has had a fracture with minimal or no trauma or whether there is back pain which may indicate a spinal compression fracture. Risk factors for MBD include tobacco and alcohol abuse, and a family history of OP; a thorough history is vital. A medication history should include questions about the use of vitamin and mineral supplements, estrogens, glucocorticoids, and loop diuretics (which can lead to increased urinary calcium excretion). Physical examination is often normal, but one should look for abnormal curvature of the spine, bone and spinal tenderness and signs

of endocrine disease. Initial laboratory studies should include a serum chemistry panel to exclude kidney and liver disease, a complete blood count and a thyroid-stimulating hormone to evaluate for hyperthyroidism. An intact serum PTH and 25-hydroxyvitamin D level should also be checked when there is a strong suspicion for underlying MBD or when a patient is found to have an abnormal bone mineral density study. Measurement of 1,25-dihydroxyvitamin D and a blood aluminum level should be considered if results suggest the presence of OM (as 1,25-dihydroxyvitamin D decreases in severe vitamin D deficiency).

If high bone turnover is suspected, N-telopeptide collagen, a breakdown product of bone collagen, can be measured in the blood or urine. These tests may not be readily available in all hospitals and may require sending blood or urine samples to an outside lab. A baseline DXA should be considered in most patients who will receive HPN. An exception to this would be the patient without any risk factors or conditions that result in MBD who might only need HPN for six months or less. A suggested strategy for identifying and treating these patients is outlined in Tables 3 and 4.

Bone mineral density can be assessed by several techniques including dual energy x-ray absorptiometry (DXA), single-photon absorptiometry, ultrasound, and quantitative computer tomography. DXA is currently preferred over the other methods as it is associated with the lowest level of radiation exposure (<3 mrem), it can be performed rapidly (<10 minutes), its reproducibility is excellent (1% to 2%), and the cost is relatively low. Bone mineral density for an individual is compared with a control group of gender-matched young adults. The result is expressed as a T-score where zero is equal to the mean value for the control group and deviation from this value is expressed in standard deviations (SD) above and below the mean. The World Health Organization has defined OP as a T-score of >-2.5 below the lower limit of normal. A T-score between -1.0 and -2.5 SD below normal is considered to represent osteopenia. If results are normal, then repeat measurement may be done in two-to-three years in patients on long-term PN to determine the effect of time on bone mineral content. Patients with risk factors for the development of MBD should be measured again in one year. Treatment is advised for patients with OP or a decrease in bone mass

Table 3
Identifying Patients at Risk
or with Metabolic Bone Disease

Medical History

- GI/Endocrine disorders (Table 1)
- Family history of osteoporosis
- Previous fragility fracture
- Use of tobacco or ETOH

Physical Exam

- Kyphotic thoracic spine
- Bone, joint, spine tenderness or pain
- Low body mass index
- Loss of height

Medications

- Estrogens
- Glucocorticoids
- Diuretics
- Vitamin/mineral supplements

Lab Data

- Low serum 25-OH vitamin D
- Decreased TSH
- Elevated intact PTH
- Elevated alkaline phosphatase
- Hypophosphatemia
- Hypocalciuria/Hypercalciuria
- Increased n-telopeptide collagen (blood or urine)

Other

- Abnormal DXA

of 2% to 3% per year. Finally, it should be pointed out that most individuals with a decrease in bone mineral density as measured by DXA have OP as opposed to OM. However, this test cannot discriminate between these two forms of MBD. The most precise way to diagnose OM is to perform a bone biopsy after tetracycline labeling. Since this procedure is uncomfortable and DXA is readily available, pain free and relatively inexpensive, indirect evidence is currently used to diagnose OM. Patients with OM may have hypophosphatemia, hypocalcemia, low level of 25-hydroxyvitamin D and elevated serum alkaline phosphatase (editor's note: in those patients who may have elevated alkaline phosphatase, a 5' nucleotidase can be obtained to distinguish if the origin is liver or bone). In addition, an abnormal x-ray of the chest, pelvis or hip that reveals pseudofractures may indicate OM. It is impor-

tant to recognize that OM can develop concurrently with OP as the former must be treated through repletion of vitamin D and mineral deficiencies prior to the initiation of bisphosphonates for OP.

TREATMENT AND PREVENTION

The first step in managing PN-MBD is to eliminate and/or manage secondary causes of MBD. Endocrine diseases, listed in Table 1, should be diagnosed and treated. Hormone replacement should be considered in postmenopausal women (estrogen) and men with hypogonadism (testosterone). Medical treatment for inflammatory processes such as Crohn's disease should be provided if appropriate. Tobacco containing products should be discontinued and alcohol intake should be minimized. Corticosteroids should be discontinued or tapered to the lowest possible dose. Weight bearing exercises should be encouraged to promote new bone formation.

PN should provide a sufficient amount of vitamins and minerals to maintain the integrity of bone. We provide calcium gluconate at a dose of 15 mEq each day to most of our patients on long-term PN. The dose is adjusted to keep serum values in the normal range after checking an ionized calcium. When blood values are stable we measure a 24-hour urine for calcium. If the infused dose is adequate, the urine collection results will show a normal amount of calcium in the urine (100 mg–300 mg). A low value suggests that the infused calcium is being excreted in the stool and that a higher parenteral dose is necessary to maintain normal calcium balance. Magnesium is given at a dose of 15 to 20 mEq each day; more may be needed to meet losses that occur with large volume diarrhea. A 24-hour urinary magnesium is a good way to assess if dosing is adequate because, like calcium, normal urinary losses are seen with adequate dosing and low values are seen when the body is holding on to more due to deficit, therefore, more needs to be added to the PN. Phosphate can be provided as a sodium or potassium salt, although the sodium salt has significantly less aluminum contamination. It has been suggested that calcium and phosphate be given in a ratio of 1:2. An example would be to add 15 mEq of calcium and 30 mmol of phosphorus to the PN solution each day. We also try to maintain blood lev-

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Table 4
Recommendations for the Management of Metabolic Bone Disease on Long-term Parenteral Nutrition

1. Evaluate all patients receiving long-term PN (>6 months) for MBD.
2. Monitor for physical signs of MBD: loss of height, weakness, bone, joint or back pain.
3. Provide adequate amounts of minerals in the PN solution for bone remodeling, including calcium (~15 mEq), phosphorus (~30 mmol), and magnesium (adjust amount per serum or urine levels).
4. Reduce higher protein doses to 1 gm/kg/day once nutritional and clinical status is improved.
5. Treat metabolic acidosis with adequate amounts of acetate in the PN solution to avoid calcium carbonate mobilization from bone to buffer excess acid.
6. Monitor blood studies (at least monthly) to evaluate calcium, phosphorus, magnesium, and bicarbonate levels. Maintain normal serum levels by adjusting amounts in the PN solution.
7. Monitor 25-hydroxyvitamin D levels and provide oral supplementation as needed.
8. Monitor specific biochemical markers of bone turnover for efficacy of therapeutic interventions.
9. Obtain DXA measurement for diagnosis of MBD and refer patient to endocrinologist for evaluation and pharmacologic treatment if there is low BMD (T-score below -1). Repeat DXA every 1–2 years.
10. Minimize steroid use and all medications known to cause bone resorption.
11. Promote regular weight-bearing and muscle strengthening exercise.
12. Encourage cessation of tobacco smoking and excessive alcohol intake.

els of phosphorus near the mid-range of normal. An adequate amount of acetate should be provided to avoid metabolic acidosis and to maintain serum bicarbonate near the mid-range of normal. Patients may initially require a moderately high dose of amino acids (1.5 g/kg/d), however, this dose should be reduced to a maintenance level (0.8 to 1.0 gm/kg/d) once the patient is stable. Sodium should not exceed the amount needed to meet gastrointestinal, renal and cutaneous losses. Injectable multiple vitamins provide 200 IU of vitamin D and should be given each day.

Until recently, the target action of all medications used in treating postmenopausal OP was to decrease the rate of bone resorption; these included conjugated estro-

gens, selective estrogen-receptor modulators (SERMs), calcitonin, and bisphosphonates. Recombinant parathyroid hormone (rPTH) has been approved by the FDA for the treatment of postmenopausal OP and primary or hypogonadal OP in men. rPTH is unique in that it stimulates both bone formation and resorption. The decision to use these medications should be made on an individual basis since none are approved for the treatment or prevention of PN-MBD. As previously noted, conjugated estrogens or SERMs should be considered in perimenopausal women or young, pre-menopausal women who have recently undergone bilateral salpingo-oophorectomy. A history of breast and endometrial cancer, thromboembolic disease or acute liver failure are contraindications to this therapy. Calcitonin can be used when estrogens are not appropriate or are contraindicated. Bisphosphonates are approved for the treatment and prevention of primary OP and glucocorticoid-induced bone loss. Parenteral preparations of bisphosphonates may be most appropriate for patients with short bowel syndrome and active Crohn's disease since oral forms of these medications are poorly absorbed and they can lead to ulceration of the gastrointestinal tract. There is only one small randomized placebo-controlled trial of these medications and it involves the use of intravenous clodronate in patients on long-term PN with osteopenia (28). This study showed that after one year of therapy biochemical markers of bone resorption were lower; however, bone loss was only reduced at the level of the forearm. More studies will be required to prove that these and other medications are beneficial in preventing PN-MBD.

INTESTINAL GROWTH FACTORS

Intestinal growth factors, including human growth hormone (hGH) and glucagon-like peptide-2 (GLP-2) have been studied in HPN patients for their effects on intestinal absorption as well as on bone metabolism (21). Studies using hGH in patients with intestinal failure showed improved nutrient absorption, decreased PN needs, and decreased bone loss. PN-dependent patients with intestinal failure who received hGH versus placebo in a randomized double blinded trial had significantly increased markers of bone turnover and stabilized femoral neck bone mass over a six month study period (29).

GLP-2 is an intestinotrophic hormone that promotes growth of the intestinal mucosal epithelium through stimulation of crypt cell proliferation and inhibition of enterocyte apoptosis. In a small pilot study, four HPN-dependent patients with intestinal failure treated with GLP-2, experienced a significant increase in intestinal absorption of energy and nitrogen as well as an increase in spinal and hip BMD (30). Both of these studies using intestinal growth factors attributed beneficial effects on bone health to improved intestinal absorption of calcium.

CONCLUSION

Metabolic bone disease appears to be a common problem for patients who require long-term PN. In most patients it is the result of the underlying medical condition that lead to the need for PN, or it is the primary cause of OP in and of itself. Efforts should be made to monitor patients for, and accurately diagnose, MBD to ensure that the appropriate level of intervention is undertaken. At the very least, a PN formula should be prepared that promotes a positive calcium balance and minimizes bone loss. Future research should be performed to determine the true incidence of MBD in patients on long-term PN, refine our understanding of the biologic response to PN, and develop the most optimal approach to diagnosis, prevention, and treatment of MBD in these patients. ■

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