phosphorus or glomerular filtration rate (see Chapter 72) typifies renal phosphate wasting disorders. The diagnosis can often be made clinically but can also be confirmed using undecalcified bone biopsy after applying oral double tetracycline labeling techniques, which are used to quantitate the degree of failure of mineralization (Fig 74-1E and F).

Treatment depends on the underlying cause and may include vitamin D formulations, calcium and phosphate supplementation, and removal of the inhibitor of mineralization when possible. These diseases are gratifying to treat because the responses are often dramatic, and patients change rapidly from being chronically ill to feeling robust and healthy.

Renal Osteodystrophy

Renal osteodystrophy is a collection of moderate to severe disorders that produce bone pain, pathologic fractures, and demineralization in the setting of end-stage renal disease or dialysis. Subclinical renal osteodystrophy is common and occurs early as a result of increased levels of phosphorous and fibroblast growth factor 23 (FGF23), which cause defects in skeletal mineralization.

Secondary hyperparathyroidism also may occur as a result of defective renal production of $1,25(OH)_2d$ combined with an increased serum phosphate concentration and calcium-phosphate precipitation into soft tissues (see Chapters 72 and 73). This circumstance evokes a marked increase in PTH secretion that causes significant increases in bone turnover, demineralization, and fracture. These patients may respond dramatically to oral or parenteral replacement of $1,25(OH)_2d$ or the calcium receptor mimetic cinacalcet, or both.

Other patients with renal osteodystrophy have adequately controlled serum levels of calcium and phosphate as a result of adequate oral calcium supplementation and phosphate binders and therefore have standard PTH levels, but they have severe osteomalacia characterized by bone pain, reduced bone mineral density on DEXA or bone biopsy, and thickened osteoid seams with a mineralization defect seen on bone biopsy (see Fig. 74-1G). These patients may respond dramatically to $1,25(OH)_2d$ replacement.

Some patients with renal osteodystrophy have combinations of secondary hyperparathyroidism and osteomalacia (see Fig. 74-1G). Others have low bone turnover or aplastic bone disease. The latter terms describe patients on dialysis who have little or no osteoblastic activity, osteoid, or osteoclastic activity—the opposite of secondary hyperparathyroidism and osteomalacia. The condition may result from previous use of inhibitors of bone turnover (e.g., aluminum intoxication); from excessive treatment with $1,25(OH)_2d$ with suppression of PTH, causing low bone turnover; or from unidentified causes.

For all bone diseases, determining the cause is essential for effective treatment. Early recognition enables treatment before bone pain and fractures occur.

Genetic Diseases

Monogenic disorders that lead to reductions in bone mass are uncommon but are seen with some frequency in practices devoted to skeletal disease. The most common of these disorders is osteogenesis imperfecta, which may be very mild or very severe and may manifest in neonates or older people, depending on the mutation involved. Patients with osteogenesis imperfecta have bone fragility and deformities, and they may have involvement of collagen-containing tissues, including the tendons, skin, and eyes.

Osteogenesis imperfecta most often results from mutations in the genes for type I collagen. In contrast, hypophosphatasia results from mutations in the tissue-nonspecific alkaline phosphatase gene *(ALPL)*. These patients have demineralization, fracture, and bone pain, and they have little or no measurable serum alkaline phosphatase.

New monogenic causes of bone disease continue to appear. For example, the rare osteoporosis-pseudoglioma syndrome (i.e., severe autosomal dominant osteoporosis with blindness) results from inactivating mutations in the low-density lipoprotein receptor–related protein 5 gene *(LRP5)*. Activating mutations in this gene lead to an autosomal dominant form of very high bone mass.

Infiltrative Diseases

Patients with multiple myeloma or Waldenström's macroglobulinemia classically develop skeletal demineralization, which is also true for some patients with leukemia and marrow lymphomas (see Fig 74-1H). Other disorders associated with diffuse marrow infiltration by benign or less malignant processes can lead to diffuse osteopenia, bone pain, and fracture, and they should be considered in the evaluation of unexplained osteoporosis. Examples include hemolytic anemias such as thalassemia or sickle cell disease, sarcoidosis with diffuse marrow involvement, Gaucher's disease with lipid-laden marrow giant cells, malignant mastocytosis, and diffuse histiocytosis.

Transplantation Osteodystrophy

Patients who have undergone or are undergoing organ transplantation commonly have severe osteoporosis. In some patients, this condition is caused by treatment with immunosuppressive drugs such as glucocorticoids, tacrolimus, or cyclosporine, which are potent inhibitors of bone formation and regularly lead to reductions in bone mass.

In many patients, decreased bone mineral density exists before transplantation as a result of organ failure or its treatment. For example, those with primary biliary cirrhosis also may have osteoblast failure and calcium or vitamin D deficiency. In those with end-stage lung or cardiac disease, physical inactivity and generalized malnutrition may contribute to bone demineralization. Patients with end-stage renal disease have all of the components of renal osteodystrophy. This disorder can be expected to become increasingly common as the number of organ transplantations increases.

TREATMENT

Treatment depends on the underlying disorder. If clinically indicated, primary and tertiary hyperparathyroidism are treated with surgical resection of the affected parathyroid tissue. Osteomalacia and rickets improve when the appropriate replacement drug is administered (i.e., vitamin D, calcium, or phosphate alone or in combination) or the offending agent (e.g., anticonvulsants) is removed.