Concepts of Osteomalacia in 1979

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Osteomalacia is normally the most rewarding of the various metabolic disease of bone to diagnose and treat. The histologic criteria for the diagnosis of osteomalacia have been refined in recent years, and together with newly acquired information concerning vitamin D metabolism have improved our understanding of the condition. New causes of osteomalacia continue to be described.

The pathogenesis of osteomalacia continues to be debated. When the serum calcium and phosphate product is reduced as a result of vitamin D deficiency, intestinal malabsorption, or renal tubular abnormality, an insufficient concentration of mineral is present for deposition at the mineralizing front of the preosseous matrix. On histologic examination this is characterized by an increase in unmineralized and poorly mineralized osteoid—the morphologic hallmark of osteomalacia. Whether vitamin D enhance the healing of osteomalacia only through its effect of increasing serum concentrations of calcium and phosphorus, or by an additional direct effect at the mineralization front is still unsettled. It may well be that both actions are important and complement each other in the normal mineralization process. The administration of vitamin D metabolites result in a much sharper and better defined demarcation at the mineralization front when used in the treatment of osteomalacia than when calcium and phosphorus are given without vitamin D. This suggests a local tissue role for vitamin D in the mineralization process, perhaps enhancing osteoblast function directly.

Phosphate depletion and hypophosphatemia are more critical than calcium deficiency in the pathogenesis of osteomalacia. Systemic acidosis as observed for instance, after ureterosigmoidostomy may be associated with severe osteomalacia, even when the serum concentrations of calcium and phosphorus are normal, and there is no reason for vitamin D deficiency. This suggests that altered pH alone can impair normal mineralization of bone. Other factors such as altered concentrations of trace metals, inhibitors of mineralization, and critical enzymes need additional investigation. In addition, intrinsic metabolic defects in the osteoblasts and maturing osteoid, may theoretically result in defective mineralization. Currently, it is not possible to ascribe a specific histologic feature or bone remodeling abnormality to a specific etiologic factor in osteomalacia.

The symptomatology of osteomalacia is not specific and can be misleading. Many patients with osteomalacia have been improperly diagnosed for years with such diagnoses as arthritis, lumber disc disease, and muscular rheumatism. Bone pain oc-
occurs more commonly in the pelvis and lower extremities and is aggravated by weight bearing. Severe skeletal deformities, with or without fracture, may occur in softend osteomalacic bone that may be tender to firm pressure. In contrast, in patients with osteoporosis fractures usually occur before the appearance of bending deformities. Patients with osteoporosis are often asymptomatic between acute fractures, while osteomalacic patients usually have continuing skeletal disability and pain. The skeletal discomfort of osteitis fibrosis is more like that of osteoporosis, in that pain-free intervals may be interspersed between acute episodes of skeletal disability which may occur following pathologic fractures. There are exceptions to all generalities regarding pain patterns in patients with metabolic bone disease. The patient's tolerance to pain, motivation, and medical sophistication often make interpretation of skeletal discomfort most difficult in the patient with metabolic bone disease.

True muscle weakness is present in some patients with osteomalacia and is to be differentiated from the pseud-weakness that results when muscle action on bone causes pain and limits full use of muscle strength. Proximal muscle weakness in osteomalacia may simulate the weakness that is observed in muscular dystrophy and polymyositis. In most instances the muscle weakness observed in osteomalacia responds promptly to the administration of vitamin D or phosphate supplements.

The biochemical changes in osteomalacia are not specific and may be misleading. They depend primarily upon the underlying etiology of the osteomalacia. Hypophosphatemia is usually a more obvious and helpful sign than is hypocalcemia. Secondary hyperparathyroidism occurs commonly in osteomalacia and may accentuate the hypophosphatemia while restoring serum calcium levels towards normal. An increased serum alkaline phosphatase does not always correlate directly with the severity of the osteomalacia and occasionally may be only slightly elevated, even in advanced disease. In the presence of vitami D deficiency and intestinal malabsorption, urinary calcium is usually low but may be increased in the presence of systemic acidosis or renal tubular abnormality. Measurement of the vitamin D in the serum may be helpful in differentiating various etiologies in osteomalacia. In vitamin D deficiency serum concentration of vitamin D itself as well as the subsequent vitamin D metabolites are decreased. In liver disease or enzyme induction resulting from anticonvulsants, serum levels of 25-(OH)D$_3$ and 1,25(OH)$_2$D$_3$ are depressed. In renal failure and vitamin D dependency with impaired 1-hydroxylation, only decreased serum concentration of 1,25(OH)$_2$D$_3$ are observed. In renal failure, serum 25-(OH)D$_2$ may also be reduced if anorexia and vomiting lead to impaired nutrition.

Skeletal roentgenograms in osteomalacia may appear entirely normal or demonstrate only a nonspecific reduction in bone mineral content. Reduced bone mineral content may better be demonstrated by the more sensitive photon beam absorptiometry. However, demonstration of a reduced bone mineral content by any method is nonspecific reduction in bone mineral content. Reduced bone mineral content may better be demonstrated by the more sensitive photon beam absorptiometry. However, demonstration of a reduced bone mineral content by any method is nonspecific. Study of a bone biopsy specimen by histologic method is needed to delineate the underlying cause for the skeletal demineralization. Occasionally the trabecular pattern in osteomalacia as observed of skeletal roentgenograms is coarsened, and subperiosteal resorption of secondary hyperparathyroidism may be visualized. If osteomalacia is suspected, a careful search should be made for the characteristic Loo-
ser zone or pseudofracture. This is a transverse radiolucency of bone with varying degrees of callus formation. The typical Looser zone is almost pathognomonic of osteomalacia and may occur even before there is apparent reduction in bone mineral content. A technetium bone scan may show evidence of increased uptake of the isotope at the site of a Looser zone before its presence can be detected on skeletal roentgenograms.

A definitive diagnosis of osteomalacia can be established only by the interpretation of a properly prepared and stained bone biopsy specimen. At Henry Ford Hospital it is customary to study bone removed from the iliac crest after the administration of a double tetracyclenic bone-label. The specimen is fixed in polymethacrylate, cut with a Jung microtome and stained with Goldner's and Villanueva's osteochrome stain. It is then examined under light and fluorescent microscopy. The extent of osteoid can be measured by 1) determining the percent of bone surfaces covered by osteoid; 2) the number of osteoid seams observed in a given area of bone, and 3) the width of the osteoid seams. Normally all three indices are increased in osteomalacia. At present, different histologic criteria are used in various laboratories throughout the world for the diagnosis of osteomalacia. Histomorphic standards for the diagnosis of osteomalacia should be agreed upon by an international conference of authorities in the field. This would help prevent some of the current confusion apparent in the literature regarding diagnosis. In osteomalacia, osteoblasts are usually fewer in number and abnormal in structure. This suggests that osteomalacia is a disease of impaired osteoblast function. Whether this is due to a basic defect in osteoblast function or is secondary to reduced concentrations of mineral and vitamin D metabolites is not certain. Probably the latter leads to the former.

Bone remodeling dynamics studied with the aid of a double tetracycline bone-label enhances our understanding of the osteomalacic process. Normally, about 80–90% of the total osteoid seam surface shows fixation of administered tetracycline (identified by its fluorescence). Both mineral and tetracycline are deposited in osteoid, at the site of an active mineralizing front. Deposition of both are impaired in osteomalacia. With the aid of a double tetracycline bone-label, the amount of bone mineralized per unit time can be measured. This is normally about one micron per day. In osteomalacia, it is reduced because both matrix synthesis and mineralization are decreased. Mineral apposition may be depressed to a greater degree than matrix synthesis. This "uncoupling" leads to osteoid seams that are wider than normal. Utilization of the double tetracycline bone-label helps to exclude high turn-over bone states such as occurs in hyperthyroidism and hyperparathyroidism. Histologically at the tissue level these conditions may be confused with osteomalacia. Increased amounts of osteoid as observed histologically occur in both high turn-over bone as well as in osteomalacia. In osteomalacia the osteoid is increased because newly formed osteoid is not properly mineralized. The life span of the osteoid seam is thereby increased. This leads to an accumulation of osteoid over bone surfaces and to an increase in both the number and width of the osteoid seams observed microscopically. In high turnover bone states the numbers of osteoid seams in a given area are also increased, but the seam width is usually normal. Seam number is increased because new seams are being initiated at a faster rate than normal, as a result of the actions of increased concentrations of thyroid and parathyroid hormones (i.e., increased activation frequency). A mineralization defect is usually not present in high turn-over
bone conditions, so that newly formed osteoid is normally mineralized. As a result an increase in the number of osteoid seams is observed at the tissue level, but the seam width and the percent of seams labeled with tetracycline are usually normal.

Since secondary hyperparathyroidism commonly occurs in most osteomalacic states, histologic evidence of increased bone resorption may also be evident on histologic examination. In addition, many patients with osteomalacia have underlying osteopenia, so the number and size of the individual bone trabeculae as well as cortical thickness may be reduced.

Once the clinical diagnosis of osteomalacia is confirmed, a search is undertaken for a specific etiology. In some instances this can be a most challenging and difficult task.

Osteomalacia due to dietary deficiency of vitamin D although reduced in prevalence continues to be observed. It is seen primarily in a setting of poverty or ignorance and especially may occur in food faddists. Elderly patients in nursing homes are prime candidates for nutritional osteomalacia, where it may masquerade as involutional osteoporosis. An absence of exposure to sunlight will reduce the synthesis of vitamin D in the skin from 7-dehydrocholesterol and may further reduce vitamin D stores in susceptible individuals.

Intestinal malabsorption is the leading cause of osteomalacia in most nutritionally advanced countries. This may occur following gastric resection, intrinsic small bowel disease or resection, various forms of biliary tract disease, and occasionally associated with pancreatic insufficiency. The reduced absorption of vitamin D, as well as calcium and phosphorus, are thought to be etiologic factors. Since 25(OH)D₃ is excreted in the bile and then reabsorbed in the small intestine, the stage is set for an additional deficit in the availability of this vitamin D metabolite in malabsorption states. Additional study is needed to define the extent and nature of the bone mineralizing defect in patients with hepato-cellular damage as observed in chronic hepatitis and cirrhosis. Both osteomalacia and osteoporosis may occur in these circumstances.

Much recent attention has been centered on disturbances in bone and mineral metabolism that occur after the administration of anticonvulsants and other agents that cause enzyme induction in the liver. As a result of enzyme induction in the liver, inactive metabolites of both vitamin D and 25(OH)D₃ are formed. This, in conjunction with suboptimal dietary intake of vitamin D present in some institutions caring for epileptics, leads to osteomalacia in susceptible individuals. The prevalence of osteomalacia in patients receiving long-term anticonvulsant therapy is quite variable. Nevertheless, prophylactic vitamin D (50 μg or 2,000 i. U./daily) should probably be administered to these individuals.

Impaired 1-hydroxylation of 25(OH)D₃ in the kidney is a frequent cause of osteomalacia. In most cases this is due to the destruction of renal cortex in patients with various forms of chronic renal disease. The resulting hypocalcemia is also the stimulus for secondary hyperparathyroidism and its additional deleterious effects on the skeleton. The combination of a mineralization defect and the effects of a surfeit of parathyroid hormone are the main factors in the skeletal disability observed in patients with renal osteodystrophy.

Vitamin D dependency (pseudo-vitamin D deficiency) is a rare autosomal disorder resulting from a congenital deficiency of 25(OH)D₃ 1-hydroxylase in the renal cortex. The resulting clinical picture of rickets and osteomalacia is similar to that observed in vitamin D deficiency. However, continuous pharmacologic rather than physiologic doses of vitamin D and
25(OH)D₃ are needed for adequate treatment. However, as expected from the nature of the metabolic error, treatment is successful with the administration of physiologic doses of the 1, 25(OH)₂D₃ metabolite.

It is an interesting fact that phosphate rather than calcium depletion is more likely to result in osteomalacia. The reasons for this are not entirely clear, although theory of mineralization ascribes primary importance to the initial binding of phosphate by collagen. Phosphate deficiency may develop in a variety of ways. A reduced serum phosphate concentration results from decreased intestinal absorption secondary to small bowel disease or to therapeutically administered phosphate-binding antacids. A variety of diseases may lead to a defect in renal tubular function resulting in hypophosphatemia and a tissue depletion of phosphate. There may be a singular defect in renal tubular transport of phosphate or there may be additional defects in the transport of glucose, aminoacids, and hydrogen ion. These renal tubular defects may result from a hereditary inborn error of metabolism or be acquired as a result of drug toxicity, heavy metal poisoning or paraproteinemias.

All patients with osteomalacia and persistent hypophosphatemia should be surveyed carefully for the presence of tumors that may play a role in etiology. Removal of certain mesenchymal tumors of blood vessels as well as giant cell tumors of the bone may reverse severe intractable osteomalacia in some patients. Certain available evidence suggests that these tumors may synthesize a phosphaturic substance that results in hypophosphatemic osteomalacia. Other evidence suggests that in some cases the tumor may in some way cause inhibition of 1, 25(OH)₂D₃ synthesis which in turn can be corrected by treatment with this metabolite. Perhaps different mechanisms for the osteomalacia are present in such patients. The prevalence of such tumor-osteomalacia is not known. The tumors may be quite small and difficult to detect. However, a careful search should be made, since removal of an incriminating tumor results in a gratifying correction of the hypophosphatemia and improvement in the osteomalacia.

Some drugs appear to interfere with mineral deposition at the mineralization front in osteoid which results in leading to osteomalacia. The administration of di-phosphonates as may be given for treatment of Paget's disease or sodium fluoride as used in the treatment of osteoporosis may both result in the accumulation of osteoid over the trabecular surfaces of bone. Sodium fluoride may accelerate matrix formation as well, which theoretically would increase the width of the osteoid seams even to a greater degree.

Most of the varieties of osteomalacia mentioned so far result from a generalized disturbance in mineral or vitamin D metabolism. There is evidence that local disturbance in mineral or vitamin D metabolism. There is evidence that local tissue abnormalities without a generalized defect in mineral metabolism may also lead to defective mineralization of the preossseous matrix. In the rare form of fibrogenesis imperfecta ossium, a disruption of the normal polarization of collagen fibers is apparent. This seems to interfere with normal mineralization and results in the histomorphic changes of osteomalacia.

The rare form of axial osteomalacia involves only the axial and not the appendicular skeleton. Here, there is normal polarization of the collagen fibers but still an abnormal acculation of unmineralized matrix. A generalized disturbance in mineral metabolism does not appear to be present. Such patients as yet have not been investigated for a possible disturbance in vitamin D metabolism, but there are no biochemical findings to suggest this possibility.
The role of alkaline phosphatase in the mineralization process is not certain. Nevertheless, the marked reduction of alkaline phosphatase seen in the inborn error of metabolism known as hypophosphatasia results in a mineralization defect compatible with osteomalacia. Most evidence suggests that alkaline phosphatase normally destroys organic phosphate compounds that act as inhibitors of mineralization. Its absence would then allow a local accumulation of such compounds that might interfere with the normal mineralization of osteoid.

New varieties and cause of osteomalacia continue to be described. Careful application of new bone histomorphic and remodeling techniques in conjunction with recent new knowledge of vitamin D metabolism will undoubtedly extend the list of mechanisms and causes of osteomalacia. As yet, it is not possible to ascribe a specific defect in mineralization of osteoid to a specific etiologic factor in any variety of osteomalacia. This will be a goal for the future. At present the defect in bone remodeling dynamics and mineralization appear to be the same in all currently recognized forms of osteomalacia, irrespective of etiology. Perhaps one day an isolated defect in mineral or vitamin D metabolism will be pinpointed to interrupt a specific stage of the mineralization process. In conjunction with knowledge gained by the new rapid advances in the pharmacology of vitamin D, it may then be possible to administer a single vitamin D metabolite to correct a singular defect in the mineralization sequence of preosseous matrix.

General References