Kidney International, Vol. 14 (1978), pp. 355–360

Childhood renal osteodystrophy

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Chronic renal insufficiency is characterized by profound alterations in the orderly metabolic sequences which normally guarantee cellular integrity and metabolic homeostasis. Hormonal imbalances which contribute to these acquired defects include abnormal growth hormone secretory patterns, elevations in plasma aldosterone and glucagon, decreases in testosterone and thyroid hormone, and defective biological degradation of cortisol, insulin, and parathyroid hormone. These findings are often coupled with blunted end-organ responsivity to hormonal stimulation, e.g., insulin, and contribute to the disturbances in carbohydrate and lipid metabolism and to defective synthesis and catabolism of structural and enzymatic proteins. The normal kidney functions as a biological filter by regulating the excretion of a variety of substances, normally generated by either biological synthetic or degradative reactions. These products can function as metabolic "toxins" when retained by the body in sufficient quantities.

The kidney also occupies a pivotal role in the regulation of calcium, inorganic phosphate, parathyroid hormone, calcitonin, and vitamin D metabolism. Adults and children with progressive loss of renal parenchyma sustain derangements in mineral and bone metabolism with resultant osteodystrophy. Children experience abnormalities in growth and remodeling of bone as well. These changes may progress to a renal osteodystrophy characterized by growth retardation and bone pain. Hyperparathyroidism and deficiency in biological activation of vitamin D are the basic pathophysiologic mechanisms involved. The requirement of vitamin D or its biologically more active forms is increased. In this review, normal bone development is described as a basis for interpreting the pathophysiology of renal osteodystrophy in children. Because renal osteodystrophy is often termed "renal rickets" and the processes of osteodystrophy and rickets differ, the evolution of the histological changes of each are contrasted. Some of the ways renal osteodystrophy affects growth are explained by the evolution of these processes.

The unique features of childhood renal osteodystrophy relate to distinctions between the effects uremia has on the fully grown skeleton and growing bone. Understanding the development of bone is important to the understanding of bone disease and growth retardation which occurs in children with uremia.

Normal bone growth

Fetal bone development begins with clusters of mesenchymal cells which differentiate into chondroblasts or osteoblasts. When chondroid differentiation occurs, as is characteristic of long and tubular bone development, a small cartilaginous model of the adult bone is formed. This cartilage is eventually replaced by osseous tissue. Hence, the process is known as "endochondral ossification." When, on the other hand, mesenchymal cells differentiate into osteoblasts, as occurs in the flat bones, e.g., skull, osseous tissue is synthesized directly in a process known as "intramembranous" ossification.

Enchondral ossification, as occurs in long bones, is achieved by an interplay between the physical properties of the cartilaginous model and the bone which replaces it. The process first occurs in the diaphysis. It is characterized by chondrocyte hypertrophy and ingrowth of blood vessels. Simultaneously, the adjacent perichondrium differentiates into periosteum which in turn forms a collar of bone

0085-2538/78/0014-0355$01.20

about the midshaft. This bone gradually encroaches upon and replaces the diaphyseal cartilage. A similar, but not identical, process takes place at the proximal and distal ends of the bone. Chondrocyte hypertrophy and ultimate atrophy, followed by osseous encroachment, occur within ends of the cartilaginous models but do not involve differentiation of the adjacent perichondrium into periosteum. As such, a collar of cartilage surrounds these ossification centers which form the epiphyseal bone. The cartilage between the ossification center and the joint space develops into articular cartilage, while that separating the epiphyseal and diaphyseal bone forms the growth plate. This plate differentiates into four distinct zones, the development of which relates closely to longitudinal growth. Growth is achieved by interstitial expansion of the growth plate in zones juxtaposed to the epiphyseal ossification center.

Interstitial growth, a property unique in the skeleton to cartilage, implies expansion of tissue mass by replication of cells which have been incorporated into the interstices of the structure, and matrix synthesis by these internalized cells. Therefore, the epiphyseal plate can increase in mass, despite the absence of a free cartilaginous surface upon which to layer additional cartilage. As the epiphyseal cartilage ages and moves towards the metaphysis, vascular invasion of the tissue occurs, resulting in oxygenation and cell death. The most mature part of the growth plate known as the "zone of provisional calcification" is characterized by mineralization of the cartilaginous matrix and its subsequent chondroclastic resorption. Those spicules of mineralized cartilage which remain serve as a scaffolding for the deposition of bone matrix. Consequently, in normal endochondral ossification there is an integral anatomical relationship between the primary bony trabeculae and the epiphyseal growth plate. This relationship has important implications in childhood renal osteodystrophy. During normal growth, the trabeculae are actively resorbed resulting in a diaphysis composed entirely of cortical bone. Therefore, longitudinal growth is accomplished by expansion of the growth plate at the ends of the bone and resorption of the mineralized epiphyseal cartilage. The width of the epiphyseal plate remains unchanged, but it moves from the center of the long bone. When growth ceases, cartilaginous resorption exceeds formation, resulting in the gradual obliteration of the cartilaginous plate.

Intramembranous ossification, as opposed to endochondral growth, is entirely appositional. This type of bone development occurs predominantly in flat bones and, similar to its endochondral counterpart, originates with an accumulation of mesenchymal cells. In intramembranous ossification, these cells, however, differentiate directly into osteoblasts which form a spicule containing immature "woven collagen." Continued apposition and appropriate resorption results in a bone shaped similar to its adult counterpart. During the third trimester of gestation and in the first few years of life, virtually all "woven collagen" is resorbed and replaced by mature lamellar bone. Periosteal growth and modeling ceases coincidentally with epiphyseal closure.

The process of expansion of the width of long bones is considered a component of endochondral ossification. This process does not involve replacement of a cartilaginous model but occurs by matrix apposition at the periosteal surface and is more closely akin to intramembranous bone formation. When epiphyses close, periosteal bone synthesis ceases; however, periosteal bone synthesis is reactivated by diffuse or local pathological processes.

Pathogenesis of renal osteodystrophy in children

The pathogenesis of childhood renal osteodystrophy and the attendent growth retardation can be best appreciated with an understanding of the four generic morphological functions of osteoblasts and osteoclasts. These functions are *growth*, which involves the increase in skeletal mass; *modeling*, the process by which the small bones of a fetus are shaped into their adult counterpart; *remodeling*, a process intimately related to mineral homeostasis; and *repair*, the prototype of which is fracture-healing.

Growth and modeling are unique to the growing skeleton. The fact that these activities function independently is illustrated by diseases which effect one to the exclusion of the others. For example, hypopituitary dwarfism is a dysfunction of growth, while diaphyseal dysplasia or osteopetrosis may involve only modeling. If one considers the growing long bone a prototype, the functional distinction between growth and modeling becomes apparent. As longitudinal growth progresses, the metaphysis, which is characteristically a wide area of bone, must be funnelled into the diaphysis. This requires resorption and formation at specific foci necessary to sculpture the bone. If modeling fails, the bone often assumes a tubular character with little distinction between the diaphysis and metaphysis.

Remodeling, on the other hand, is a process which occurs throughout life and is abnormal in both the

uremic child and adult. The quintessential feature of this process is the cybernetic coupling between osteoblastic and osteoclastic activity [1]; i.e., where osteoclastic resorption has occurred, osteoblastic bone formation will invariably follow. Although normal remodeling leaves residual histological traces within relatively short periods of time, it does not normally effect the gross architecture of the bone. With aging, however, the site of the bone resorption exceeds that of formation. Consequently senescence is characterized by progressive loss of bone and increased propensity to skeletal fracture [2].

Although the pathogenesis and therapy of renal osteodystrophy in adults has been the subject of numerous reports and reviews [3–6], analyses of the underlying hormonal and metabolic defects which initiate and perpetuate the skeletal abnormalities in growing uremic children are relatively few. In chronic renal failure of adults or children, intestinal absorption of calcium is usually, but not always, decreased [3, 7–11] and circulating immunoreactive PTH (iPTH) levels are usually elevated [12–14]. Hypocalcemia, hyperphosphatemia, hyperphosphatasia, and acidosis also occur. In some forms of kidney disease, hypophosphatemia may be a finding in the early phases of the disease. In children, the level of circulating alkaline phosphatase may be lower for the degree of skeletal involvement, and circulating levels of calcium and phosphate bear little relationship to the growth rate or histological defects noted on bone biopsied specimens [15]. Serum iPTH may be elevated in uremic children and adults without radiologic evidence of bone disease, and it is generally elevated in over 90% of those who have detectable skeletal lesions [12, 14]. Although compensatory parathyroid overactivity (so-called secondary hyperparathyroidism) appears to be more severe in children with long-standing clinically demonstrable bone disease, plasma iPTH returns to normal much sooner following renal transplantation in children than in adults [14]. The incidence of renal osteodystrophy is greater in children and adolescents than it is in adults [16]. The growing and rapidly remodeling young skeleton has a high rate of osteoclastic activity (i.e., high "bone-turnover"), and this may make young bones more susceptible to alterations in circulating PTH, 25-OH-D_3, and 1,25$(OH)_2D_3$, which occur during the course of progressive renal insufficiency.

There are presently a limited number of recorded observations regarding the effect of end-stage renal disease on circulating 25-OH-D_3 and 1,25$(OH)_2D_3$ in children, although normal, low, or high plasma 25-OH-D_3 values have been reported for adults with renal failure [18–20] and decreased 1,25$(OH)_2D_3$ has been documented when glomerular filtration rates fall below 40 to50 ml/min [21–31]. In two 10-yr-old children, who had severe end-stage renal disease, 1-hydroylation of administered tritiated 25-OH-D_3 was easily demonstrated 8 and 21 days following successful renal homotransplantation [24]. The growing skeleton is extremely sensitive to vitamin D depletion since vitamin D (and/or its biologically active metabolites) is essential for skeletal remodeling and endochondral bone formation at epiphyseal sites.

Athough the nature of the biochemical defect(s) in the epiphyseal areas in humans is still virtually unknown, the results of experimental studies in rachitic and uremic animals may prove significant in this regard. Bone collagen maturation is defective in experimentally induced uremia [25]. Normal maturation requires hydroxylation of lysine residues (lysyl-hydroxylase) in the collagen molecule to effect proper cross-linking. An essential cofactor for the enzyme lysyl-hydroxylase is α-ketoglutarate [26], a tricarboxcylic acid (TCA) cycle intermediate. Aerobic glycolysis also is a prerequisite for normal bone matrix calcification [27, 28], and carbohydrate metabolism in the normal epiphysis is predominantly glycolytic in nature with minimal pentose shunt activity [29]. In uremic rats, there is a shift in glucose metabolism of epiphyseal cartilage from the normal glycolytic to pentose shunt pathway, resulting in defective production of α-ketoglutarate. This is corrected by feeding 25-OH-D_3 [30].

Another enzyme, lysyl-oxidase, also functions as a pivotal enzyme in the maturation of skeletal and epiphyseal collagen by catalyzing the synthesis of cross-linked aldehyde precursors, the biochemical step which immediately precedes the mineralization of collagen [31, 32]. Recent preliminary studies reveal that vitamin D and/or one of its biologically active metabolites stimulate lysyl-oxidase activity of growth cartilage obtained from either rachitic chicks or rats [33]. To date, the relationship between the maturational defect in uremic rats that shifts glucose metabolism from glycolytic to pentose shunt activity [28] and its reversibility by vitamin D treatment and the epiphyseal defects, growth retardation, and vitamin D resistance of uremic children is still uncertain and should be explored further.

Renal osteodystrophy and azotemic "rickets" are more frequent and severe in children from European and Asian communities [34, 35]. This may re-

flect the relatively lower circulating levels of 25-OH-D_3 found in normal individuals in these same geographical area [36, 37]. Where exposure to sunlight is less and vitamin D supplementation of the diet (i.e., at least 400 IU/day) is less commonly practiced, rickets may be more common. On the other hand, the incidence of radiographic osteosclerosis and osteitis fibrosa is greater in uremic children in North America [12, 38, 39].

Renal osteodystrophy is one of the causes of growth retardation in children with uremia [40]. Other factors associated with growth retardation in these children, such as acidosis, malnutrition, and hormonal factors, may also act primarily on bone (see also Lewy and VanWyk; Holliday and Chantler, this issue). Fortunately, retardation of bone growth is often accompanied by proportional retardation of bone maturation, in which case the potential for achieving catch-up growth exists [40] (see Potter and Greifer, this issue). By contrast, children whose bone age has already reached 12 yr by the time of renal transplantation rarely have significant growth thereafter [41].

Comparison in bone pathology of childhood rickets and renal osteodystrophy

Apart from those involving the epiphyseal regions, differences in bone pathology between adults and children with uremia are few. Osteosclerosis, osteoclastosis, and osteitis fibrosa are common in younger individuals [42]. Severe cancellation of the cortex occurs and results in loss of distinction between trabecular and compact bone [43]. Radiographic abnormalities in the region of the growth plate in childhood renal osteodystrophy, although occasionally presenting as those characteristically seen in nutritional rickets, may often be quite distinct. In the past, these changes have been inappropriately characterized as "rachitic," and they are believed to be histologically indistinguishable from those of nutritional rickets [44].

The histopathology of rickets due to vitamin D or phosphate deficiency centers about abnormalities of the growth plate. The characteristic features include failure of chondrocytes in the mineralization of the zone of provisional calcification or devitalized cartilage bordering on the metaphysis. As a result, the width of the growth plate increases, and its architecture becomes disarrayed. Despite this failure of mineralization, "woven collagen" is deposited on these columns, resulting in formation of primary spongiosa. Due to failure of mineralization of both the primary spongiosa and its cartilaginous cores, there is failure of modeling, and the cartilage persists within the deep metaphyseal bone. These phenomena result in the radiographic changes of a wide, overriding epiphysis with an irregular border and absence of a line of provisional calcification.

The pathology of renal osteodystrophy in children differs from that of rickets. Despite radiographic similarities, the histologic changes in the rachitic epiphysis differs from those in the uremic epiphysis or growth plate. The growth plate in uremia usually is not as thick, and in places it may be thin. Its diameter in the horizontal plane, however, generally is expanded and overrides the lateral border of the metaphysis. Full-thickness rupture of the growth plate may also occur. Histologically, the chondrocytes of the epiphyseal plate in uremia are arranged in grapelike clusters and their longitudinal orientation lost. At the junction of the growth plate and metaphysis, exuberant osteoclastic activity results from secondary hyperparathyroidism. Cartilage is reabsorbed and does not function as a lattice upon which bone can be deposited.

Hyperparathyroidism also results in metaphyseal fibrosis immediately beneath the growth plate. This failure may interfere with vascular invasion of the epiphyseal cartilage and hence development of the primary spongiosa [43]. Metaphyseal trabeculae form in a dysplastic fashion as spicules of woven osteoid within the subepiphyseal fibrous tissue. This area is radiolucent and is usually misinterpreted as representing an increase in the width of the growth plate, a finding that is characteristic for deficiency rickets. In some patients, a bony disc develops between the epiphyseal plate and metaphysis, resulting in growth arrest and a loss of the interlocking connection between the epiphyseal growth plate and metaphyseal bone. These lesions contribute to growth retardation and form a basis for the development of genu valgum, and the slipped epiphysis of the femoral head. Genu valgum and slipped epiphyses also result from erosion of bone secondary to hyperparathyroidism. Slipped epiphyses are more common in adolescents (i.e., 12 to 16 yr of age) and seem to be precipitated by pubertal growth spurt. Of note in this regard are observations documenting severe secondary hyperparathyroidism in growing children with endemic genu valgum [45].

Summary

The processes of growth and remodeling that characterize growing bone are vulnerable to the biochemical effects of uremia. These processes are affected by the alterations in vitamin D metabolism

and hyperparathyroidism that commonly occur with chronic renal insufficiency. Uremia interferes with cartilaginous developments as well. These changes, which are similar radiographically to vitamin-D-deficiency rickets, differ in their basic histological and biochemical evolution. They account for growth failure and deformity of long bones, which contribute to the short stature of children with renal insufficiency.

Acknowledgments

This work was supported in part by National Institutes of Health Grants AM11674 and AM20521.

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