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Review Article

Hylonome

Overview of pediatric bone problems and related osteoporosis

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Abstract

Osteoporosis is a well-established clinical problem in adults. Osteoporosis in pediatrics, on the other hand, is a new and evolving area, with certain unique diagnostic and clinical challenges. Recently, there has been an increased awareness of osteoporosis in children, both as a primary problem due to genetic mutations and enzyme deficiencies, and as secondary to various diseases, medications, and lifestyle issues. In this review we discuss the common forms of osteoporosis, including candidate genes, mutations of which can lead to primary osteoporosis, the mechanisms involved in the pathogenesis of secondary bone loss, and possible ways of diagnosing, preventing, or treating these conditions. The purpose of the article is to provide a summary of our current knowledge of pediatric bone problems and to provide a basis for discussion of the most appropriate ways to detect, treat, or prevent such problems.

Keywords: Pediatric Osteoporosis, Candidate Genes, Adaptive Responses

Introduction

Osteoporosis is a well-known health problem affecting adults, especially the elderly. What is not as widely appreciated is that osteoporosis, as well as less severe forms of bone loss, also affects children. The fact that pediatricians may not recognize the risk for bone loss in children means that the bone loss will not be treated. In severe cases of bone loss, such as in osteoporosis, a child will develop fractures. With less severe but more chronic forms of bone loss a child may not reach his or her genetically-determined peak bone mass. Thus the child may be at greater risk for adult-onset osteoporosis inasmuch as he or she will enter adulthood with lower bone mass than would otherwise be expected. We begin our review with the current working definition of pediatric osteoporosis, proceed then to primary, i.e. genetic, bone loss including a section on our current understanding of candidate genes. This will be followed by a section on secondary bone loss, i.e., bone loss occurring as a result of either other health conditions or the body's response to them, and currently available methods to diagnose these problems, and, in some cases, to treat them.

Pediatric osteoporosis

Osteoporosis in children now has a different definition from that in adults. In adults, the World Health Organization definition of a bone density T score greater than 2.5 standard deviations from the peak bone mass of a young adult is still operative. If this definition were applied to children every child ever born would have osteoporosis. Therefore, in 2007 the International Society of Clinical Densitometry (ISCD) held a Pediatric Consensus Development Conference in Montreal and arrived at the current working definition of *pediatric osteoporosis*: A child is considered to be osteoporotic if he or she has a lumbar spine bone mineral density (BMD) of greater than 2 standard deviations below age and sex-related normal values and at least one fracture[1]. Therefore, in pediatrics, osteoporosis is no longer a diagnosis that can be made by bone densitometry alone. Furthermore, the term osteopenia is no longer used in pediatrics because it has neither been defined nor demonstrated to be a risk factor for fractures.

Primary bone loss

The pediatric diseases that result in the greatest loss of bone and mineral are genetic defects. The most commonly occurring

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Condition	Genetic mutation or enzyme deficiency
Osteogenesis imperfecta: Types I-IV	COL1A1, COL 1A2 mutations
Types V, VI	IFITM5, SERPINF1
Type VII	CRTAP mutations
Type VIII	Prolyl 3 hydroxylase 1 mutations
X-linked hypophosphatemic rickets	PHEX gene mutation
Homocystinuria	Cystathionine synthase deficiency
Hypophosphatasia	Tissue non-specific alkaline phosphatase deficiency
Wilson's disease	ATP7B mutation
Menkes' kinky hair syndrome	ATP7A mutation

Table 1. Common genetic diseases and mineralization deficits of primary bone loss occurring in children.

of these are shown in Table 1. They include osteogenesis imperfecta, X-linked hypophosphatemic rickets (XLH), in which mutations of the gene for type I collagen (COL1A1, *COL1A2, as well as other genetic loci*)[2] and the PHEX gene[3] respectively are the primary causes, enzymatic defects such as hypophosphatasia and homocystinuria, and disorders of copper transport, such as Wilson's disease and Menkes' kinky hair syndrome, can lead to osteoporosis or severe demineralization. This is not an exhaustive list and all of these genetic conditions are rare.

In most cases the exact mechanism of the osteoporosis is not completely defined, though it can be hypothesized that defects in type I collagen, as in osteogenesis imperfecta, fail to provide a normal matrix and mineralization cannot occur normally. This will compromise the biomechanical properties of the bone and increase susceptibility to fracture. Conditions such as XLH will result in impaired mineralization inasmuch as failure of the PHEX gene to suppress osteoblastic and osteocytic production of fibroblast growth factor (FGF)-23 results in reduced 1,25-dihydroxyvitamin D production with consequent calcium malabsorption and urinary phosphate wasting[3]. The resultant rachitic appearance also makes the bones biomechanically weaker and more subject to fracture[4]. With abnormalities in copper transport, defective cross-linking of type I collagen may be postulated[5], leading to abnormal matrix and reduced mineralization. However, details of these mechanisms are not known precisely.

Given that the exact pathogenic mechanism of osteoporosis has not been clearly established in these conditions, it is difficult to proceed with rational drug discovery to specifically address these mechanisms. In some cases, such as XLH, treatment is directed at maintaining normal circulating levels of phosphate and 1,25-dihydroxyvitamin D[3] and has resulted in successful management of this condition. However, in others, such as osteogenesis imperfecta, the use of intravenous bisphosphonates, specifically pamidronate, has been transiently successful in reducing bone pain and vertebral fracture risk in the afflicted children[6]. However, cessation of the treatment results in recurrence of bone pain and fractures[6]. Therefore, it has been hypothesized that pamidronate may have to be given until attainment of peak bone mass or even longer[6]. The actual explanation for the transient success of pamidronate in treating these patients is unclear. Perhaps by preventing resorption of even the poor quality bone made by these patients biomechanical strength is maintained at a level that significantly reduces fracture risk. However, this scenario is entirely speculative.

In other situations, such as in the copper dysmetabolism syndromes, it is unclear that the specific therapy or prevention of bone loss has begun to be addressed by appropriate investigations. Furthermore, the diseases are sufficiently rare as to make a large-scale clinical study difficult. One other caveat in the review of primary genetic disease and the pathogenesis of osteoporosis in children, is that it is unlikely that the descriptions of osteoporosis in these conditions used the current working definition of pediatric osteoporosis as many of the descriptions predated the 2007 consensus development conference[1]. It is therefore unclear if any or all of these genetic disorders meet the criteria for the current working definition of pediatric osteoporosis.

The correct diagnosis of these conditions, all of which except Wilson's disease, appear in infancy, will require the expertise of a geneticist with experience in the recognition of clinical syndromes and a proper genotypic analysis to look for the likely mutations. In some cases, candidate genes in the pathogenesis of primary osteoporosis in children have been identified. These genes are known to affect the vitamin D receptor as well as osteoblast and osteoclast function.

Candidate genes associated with primary osteoporosis in children

Genetic factors have been considered as playing an essential role in the pathogenesis of osteoporosis. Bone mineral density (BMD) has been employed most commonly as the index for defining and studying osteoporosis. Identification of candidate genes for osteoporosis remains one of the most challenging topics due to our lack of fully understanding the cause of the disease. Some of the genes have been identified as possible candidates for the regulation of bone mass; however, the mechanisms that underlie the association between given genes and osteoporosis are poorly understood. The genetic study of os-

teoporosis has been based largely on research into candidate genes relevant to bone metabolism.

Three approaches have been employed in humans: population association studies, linkage studies, and transmission disequilibrium tests (TDT)[7]. Population association studies test whether particular alleles or genotypes are associated with a higher risk or a larger trait value, usually in unrelated population samples. An association usually reflects statistical non-independence (linkage disequilibrium) of marker alleles and a functional mutation underlying the risk or variation of a trait and does not necessarily imply causality. Linkage tests whether there is a co-segregation or co-inheritance of alleles with a phenotype under study in pedigrees or affected relative pairs. Linkage refers to close physical locations of genes on one chromosome. Transmission disequilibrium tests, in families, or in discordant relative pairs, both linkage and association marker alleles with a functional mutation underlying the study trait and is significant, if and only if, both linkage and association exists. A very large number of genes have been identified as possible candidates for the regulation of bone mass. The following discussion will focus on new putative candidate genes for osteoporosis in children.

Vitamin D Receptor (VDR)

The VDR gene maps to chromosome 12q13-14 and contains at least 11 exons[8]. Vitamin D plays an important role in bone development and metabolism. Genomic action of the bioactive form of vitamin D, 1,25-dihydroxyvitamin D, is mediated through specific membrane and nuclear VDR receptors that regulate target gene expression by forming a heterodimer with retinoid X receptor[9]. Mutations in the VDR cause the syndrome of vitamin D resistant rickets, which is an autosomal recessive condition characterized by alopecia, hypocalcemia, hypophosphatemia, and severe rickets, and is resistant to treatment with vitamin D and its active metabolites[10]. The patients present in early childhood with classical features of tissue resistance to vitamin D. A number of polymorphisms in multiple candidate genes have been investigated, among which the VDR gene is the first candidate gene to be studied in relation to osteoporosis[11]. Most attention has focused on polymorphisms situated near the 3' flank of VDR. Bone density achieved in early adulthood is the major determinant of risk of osteoporotic fracture. VDR polymorphisms and bone density studies used the polymerase chain reaction and three restriction enzymes: *Apai, Bsm1,* and *Taq1*, and identified three allelic variants of the VDR gene in pre-pubertal American children. The data indicate that VDR genotype is associated with femoral and vertebral bone density[12].

Genes related to osteoblasts: Lipoprotein Receptor-related Protein 5 (LRP 5)

The canonical Wnt pathway plays a critical role in several developmental processes, including cell fate decisions, limb patterning, bone formation, and development of the central nervous system and other organs[13]. The Wnt pathway is mediated by LRP5, which forms a receptor complex with Frizzled (Fz) to activate the transcriptional activity of β-catenin, the downstream effector of the Wnt pathway[14]. LRP 5 was discovered to be an important regulator of bone mass following linkage studies in two rare human conditions, osteoporosis-pseudoglioma syndrome, which is autosomal recessive and characterized by severe early onset osteoporosis[15], and the high bone mass syndrome, that is an asymptomatic autosomal dominant disorder characterized by high bone mineral density[16]. Mutations in LRP 5 have been identified in pediatric patients with idiopathic juvenile primary osteoporosis[17]. Two mis-sense mutations, A29T and R1036Q, and one frameshift mutation, C913fs, were identified. The frameshift mutation was also seen in the proband's father and brother, both of whom had significant osteoporosis. R1036Q was observed in the proband's mother and two brothers, all of whom had osteoporosis. These results indicate that heterozygous mutations in the LRP5 gene can cause osteoporosis in both children and adults.

Osterix (Osx)

Osx is the only osteoblast-specific transcriptional factor identified so far which is required for osteoblast differentiation and bone formation. In *Osx*-null embryos, cartilage is formed normally, but the embryos completely lack bone formation[18]. The *Osx* gene is located on chromosome 15 in the mouse and on chromosome 12 in the human. *Osx* encodes a transcription factor containing three Cys2-His2 zinc-finger DNA-binding domains at its C terminal. In *Osx*-null mutant embryos, expression of type I collagen (COL1A1) in the condensed mesenchyme of the membranous skeleton and the periosteum and mesenchyme of the endochondral skeleton is severely reduced. Expressions of the osteoblast-specific markers such as osteonectin, osteopontin, and bone sialoprotein cannot be detected in these mesenchymal tissues. In E18.5 *Osx*-null embryos, osteocalcin, a late, highly specific osteoblast marker, is not expressed in endochondral and membranous skeletal elements. *Osx* is downstream from *runx2 (cbfa1)*, which is another important transcription factor required for bone formation. The observation that *Osx* inhibits the Wnt signaling pathway provides a novel concept of feedback control mechanisms involved in bone formation[19].

Recent study has indicated that genetic variants in the chromosomal region of *Osx* are associated with bone mineral density in children and adults through the primary effects on growth[20]. A genome-wide association study of BMD and related traits in 1518 children from the Avon Longitudinal Study of Parents and Children (ALSPAC) was carried out to identify genetic variants involving BMD. This research group identified associations with BMD in an area of chromosome 12 containing the *Osx* locus. A meta-analysis of these existing studies revealed strong associations between SNPs in the *Osx* region and adult lumbar spine BMD. In light of these findings, this research group genotyped a further 3692 individuals from ALSPAC who had whole body BMD and confirmed the association in children as well. Although *Osx* has been identified to be associated with osteoporosis-related phenotypes, further investigation needs to be done to determine whether *Osx* will

represent a useful diagnostic index of osteoporosis or a molecular target for therapeutic manipulation.

Osteogenesis imperfecta, as previously discussed, is a condition in which several phenotypes manifest mutations in the genes for type I collagen, COL1A1, *COL1A2, and others (Table 1)*. Using a combination of homozygosity mapping and candidate gene approaches, a homozygous single pair base deletion (c.1052delA) in the *Osx* gene has been identified in an Egyptian child with a recessive form of osteogenesis imperfecta[21]. The clinical findings in this patient include recurrent fractures, mild bone deformities, delayed tooth eruption, normal hearing, and white sclera. The frameshift caused by the c.1052delA deletion removes the last 81 amino acids of the *Osx* protein, including the third zinc-finger motif. This finding adds another locus to the spectrum of genes associated with osteogenesis imperfecta and reveals that *Osx* also plays an important role in bone development.

Noggin

The expression and function of noggin is widespread, including osteoblasts. The polypeptide noggin, encoded by the *NOG* gene, binds and inactivates members of the transforming growth factor (TGF)-β superfamily of signaling proteins, such as bone morphogenetic protein (BMP)-4. By diffusing through the extracellular matrices more efficiently than members of the TGFβ superfamily, noggin may have a principal role in creating morphogenic gradients. Noggin was discovered because of its ability to induce secondary axis formation in frog embryos[22]. Noggin is also a BMP antagonist expressed in Spermann's organizer, which induces neural tissue from dorsal ectoderm and dorsalizes lateral and ventral mesoderm. Mouse knockout experiments have demonstrated that noggin also plays a crucial role in bone development, joint formation, and neural tube fusion[23]. BMPs have been implicated in the induction of osteoblast differentiation from uncommitted progenitors during embryonic skeletogenesis. Noggin was expressed in cells of the osteoblastic lineage, and potently inhibited their differentiation into osteoblasts.

One report addressed the association between height as well as bone density in children and noggin mutations[24]. In two families with symphalangism, anthropometry, bone density and genetic analysis of *NOG* were performed and results indicated that heterozygous gene mutations in noggin are associated with tall stature in children but not necessarily in adults. The appendicular BMC and speed of sound, which, on ultrasound exam, correlates with bone density, may be low in affected children but normalizes by adulthood. In contrast, axial BMC is normal in childhood but high in adulthood.

Genes Related to Osteoclasts

The receptor activator of nuclear transcription factor KB (RANK) and its ligand (RANKL) along with another cellular moiety osteoprotegerin (OPG) have been found to be important participants in osteoclast differentiation and proliferation[25]. RANKL and OPG are members of the tumor necrosis factor (TNF) and TNF receptor superfamilies respectively , and by binding to RANK not only regulate osteoclast formation, activation and survival in normal bone modeling and remodeling, but also in several other pathologic conditions characterized by increased bone turnover. The interaction of RANK and RANKL initiates a signaling and gene expression cascade that results in differentiation and maturation of osteoclast precursor cells to active osteoclasts capable of resorbing bone. OPG acts as a decoy receptor, binding to RANKL and blocking its interaction with RANK, inhibiting osteoclast development. Mutations in the OPG and RANK genes are responsible for two hereditary forms of primary bone disorders, namely juvenile Paget's disease and early-onset Paget's disease. Identification of RANK/RANKL/OPG system as a critical mediator of the formation and activation of osteoclasts has helped us to better understand bone remodeling. Disruption of the RANK/RANKL/OPG pathway has been implicated in the pathophysiology of bone remodeling disorders including osteoporosis.

OPG

Mutations in the OPG gene can cause abnormalities in the ligand-binding properties of OPG, resulting in its inactivation and a disorder with diverse phenotypic expression[26]. Juvenile Paget's disease (JPD) is a rare autosomal recessive disorder that presents in early childhood with bone deformities, fractures, hearing deficits, and dental abnormalities of variable severity. This disorder can be due to an inactivating mutation of the OPG gene (TNFRSF11B), localized to chromosome 8q24.2[26]. Mis-sense mutations in the cysteine residues of OPG are predicted to interfere with its ligand-binding domain and are responsible for the most severe phenotype of JPD[27]. In more intermediate forms of JPD, mis-sense mutations in residues other than cysteine are present in the ligand-binding region of the *OPG* gene. In addition, an insertion-deletion in exon 5 of this gene has been associated with a milder form of the disease. All of these mutations lead to unopposed activation of RANK to varying degrees, resulting in enhanced osteoclastogenesis and consequently increased bone turnover. RANK is encoded by the TNFRSF11A gene on chromosome 18. Mutations in the RANK gene that disrupt the signal peptide region of the protein result in the lack of normal cleavage of the peptide signal and an increase in RANK-mediated signaling. These activating mutations result in three different phenotypic presentations described below[28].

Early-onset Paget's Disease of Bone (PDB2) is a heterogeneous autosomal dominant skeletal disorder characterized by bone deformities, as well as hearing deficits and dental problems. Skeletal manifestations begin in the late teen years and may progress later in life[29]. PDB2 is due to an activating mutation of the RANK gene comprised of a 27-base pair tandem duplication.

Familial expansile osteolysis is an autosomal dominant disorder that presents in early childhood to young adulthood with hearing deficit. Reduced bone density for age is a common feature and dental abnormalities are uncommon. The major skeletal finding in this disorder is osteolysis followed by bony

Adaptive responses: inflammation, stress
Malabsorption of fat-soluble vitamins and trace elements
Sarcopenia
Immobilization
Bone marrow suppression
Iatrogenic (medications)
Endocrinopathies

Table 2. Known or putative mechanisms of secondary bone loss in children.

expansion due to fat deposition rather than osteosclerosis[30]. The genetic abnormality is an activating mutation in the RANK gene linked to an 18-base pair tandem duplication. Abnormalities in conditions involving primary bone loss may be diagnosed or followed by the use of dual energy x-ray absorptiometry (DXA), otherwise known as bone densitometry.

Secondary bone loss

As previously mentioned, not all pediatric bone loss indicates osteoporosis. Milder but more protracted bone loss in children, as well as osteoporosis, can occur as a result of the body's adaptive responses to a variety of acute and chronic conditions. Some of the more common mechanisms causing secondary bone loss are listed in Table 2. The most critical characteristic of secondary bone loss is that it is silent. Its asymptomatic nature compared to the prominent presenting findings of the primary health condition prompts the pediatrician or surgeon to treat the most clearly worrisome symptoms while ignoring the asymptomatic problems. The result is that bone loss may not be detected till a fracture occurs or a bone density examination points out that the child or young adult is at serious risk for fracture.

We do not know all of the pediatric conditions that predispose to secondary bone loss but many can be inferred from the mechanisms that are involved. A partial list of conditions that have been shown to or are suspected to result in bone loss are listed in Table 3. Thus bone loss may occur as an unintended consequence of the body's response to underlying conditions. Other mechanisms may result from indirect consequences of the conditions themselves.

The two adaptive responses in question are inflammation and stress. Much of the information concerning the behavior of these responses with regard to bone loss comes from the study of bone loss following burn injury. Both adaptive responses work through the osteoblast. In the case of the inflammatory response, the cytokines interleukin (IL-) 1β and IL-6 stimulate the osteoblast to produce RANKL. As previously mentioned, RANKL stimulates the bone marrow stem cells to differentiate into osteoclasts and hence increases bone resorption. The stress response, which involves the production of large quantities of endogenous glucocorticoids and catecholamines, also initially stimulates osteoblasts to increase

Adaptive Responses: inflammation, stress
Burns[30,31,43]
Sepsis
Crohn's disease[44]
Systemic lupus erythematosus and other connective tissue disorders[45]
Arthritis[46]
Malabsorption:
Cystic fibrosis[47]
Cholestatic liver disease[48]
Celiac disease[49]
Sarcopenia:
Malnutrition, including anorexia nervosa[50]
Crohn's disease
Cystic fibrosis
Burns
Duchenne muscular dystrophy and other neuromuscular disorders[51]
Immobilization:
Spinal cord injury[52]
Traction following orthopaedic surgery
Ventilator dependence
Bone marrow suppression[53]
Cancer[54]
Radiation therapy
Marrow suppressive drugs[55]
Auto-immune marrow suppression
Medications:
Glucocorticoids
Older anti-convulsants, especially diphenylhydantoin[33]
Calciuretics/diuretics
Immunosuppressives
Endocrinopathies:
Thalassemia major
Disorders of the thyroid
Growth hormone deficiency
Hyperadrenocorticism

Table 3. Conditions in which secondary bone loss has been observed or postulated.

RANKL production and therefore bone resorption activity. We know from burn studies that the stress response will also cause osteoblast apoptosis if sustained for about two weeks[31]. At that point, urinary deoxypyridinoline, a biomarker of type I collagen breakdown, is actually decreased despite the high circulating levels of resorptive cytokines[32]. Not only do endogenous glucocorticoids cause osteoblast and probably osteocyte apoptosis, they also impair marrow stromal cell differentiation into osteoblasts[31]. Thus endogenous glucocorticoids produce a biphasic response in bone. Acutely they produce an actively resorbing bone and chronically they produce adynamic bone.

Another mechanism of bone loss involves malabsorption of nutrients, including fats, with attendant calcium and vitamin D deficiency. Malabsorption of zinc and copper, both required for normal collagen cross-linking can also occur in certain circumstances. Moreover, alkaline phosphatase, a hallmark of os-

teoblast differentiation, is a zinc-dependent enzyme. Thus inadequate zinc may lead to abnormal osteoblast function.

Sarcopenia, or muscle wasting, can also lead to bone loss by means of a reduction in skeletal loading. Similarly, immobilization or bed rest can lead to bone loss possibly by the same mechanism, but the latter is mediated by the sympathetic nervous system and the β adrenergic receptors on the osteoblast. Chemical mediators of muscle wasting may potentially affect bone loss. However, this potential mechanism remains to be evaluated. Regardless, both sarcopenia and immobilization result in reduced skeletal loading.

Suppression of normal bone marrow function by auto-immune or infiltrative diseases or by radiation therapy or drug treatment can hypothetically suppress marrow stromal cell differentiation into osteoblasts.

Various medications are also known to cause bone loss. The most notorious are the glucocorticoids. The exogenously-administered steroids act in the same manner as the endogenously-produced glucocorticoids, a result of the stress response[30]. Several studies have demonstrated that exogenous glucocorticoids can cause transiently increased bone resorption followed by osteoblastic and osteocytic apoptosis. Quite often physicians who observe bone loss in chronic inflammatory conditions cannot tell if the bone loss is related to the treatment received by the patient or to the disease process itself.

Anticonvulsants of the older type, such as diphenylhydantoin have been shown to interfere with vitamin D metabolism and possibly calcium absorption[32] in leading to high-turnover bone loss, and drugs with a marrow-suppressive effect, such as the anti-neoplastic drugs or the immunosuppressive drugs used in transplantation, especially tacrolimus, have been reported to cause bone loss[33]. However, the mechanisms by which these drugs act in this manner still lack definition. The use of diuretics, especially calciuretics such as furosemide may also lead to renal calcium wasting and possible bone loss.

Hormonal deficiencies and other endocrinopathies also play a role in bone loss, including gonadal insufficiency and growth hormone deficiency as observed in thalassemia major. All the factors that lead to a preponderance of bone resorption over formation have not, however, been identified.

Diagnosis

Unlike bone densitometry in adults, pediatric bone density interpretations are complicated. Normal values now exist in the United States and Europe for children of both sexes ages 7 years and older[34,35]. However, the current lack of adequate volumetric bone density determinations does not address the compensatory changes in bone volume that may occur secondary to bone loss in order to biomechanically compensate for the lost bone. While the appendicular skeletal volume and strength can be safely measured by peripheral quantitative computed tomography, or pQCT, no low radiation equivalent exists for the axial skeleton and the application of pQCT in clinical settings has thus far been limited. Therefore, in most institutions physicians are limited to the use of DXA with dedicated pediatric software. As determined by the 2007 ISCD Pediatric Consensus Development Conference[1], the most valuable DXA measurements used in pediatrics are lumbar spine bone mineral density (BMD) and the bone mineral content(BMC) of the total body less head (TBLH). The BMC of the head is subtracted because the skull is made of membranous bone, the properties and dynamics of which differ from cortical and trabecular bone[1]. Hip measurements are too variable during growth and total body BMD, while measured and reported, is not valuable inasmuch as different bones grow and remodel at different rates at different ages so that what essentially would be the integral of all regional BMD determinations would not provide specific information as to what part of the skeleton may be more significantly affected by a particular condition. Generally, lumbar spine BMD is used as an index of trabecular bone, while TBLH BMC is used as an index of cortical bone, as the skeleton consists of approximately 80% cortical bone and 20% trabecular bone.

Treatment

Given what we now know, how should we treat or prevent these conditions? To begin with, we must ask what therapies are currently available for children with bone loss.

With regard to genetic diseases, few specific treatments are available short of gene therapy or stem cell transplantation. Exceptions to this appear to be the use of intravenous bisphosphonates in osteogenesis imperfecta resulting in short-term benefit but with return of pain and fractures once treatment stops[6], and the use of phosphate and 1,25-dihydroxyvitamin D in XLH[3].

It should be stated from the outset that currently there are no drugs used in the treatment or prevention of bone loss in children that are approved for these purposes by the United States Food and Drug Administration. Moreover, there has been a paucity of testing of these drugs in children by the pharmaceutical industry.

The primary anti-resorptives that have been used in children are the bisphosphonates, especially intravenously-administered pamidronate. It has been used safely and with no adverse effects on growth in children with osteogenesis imperfecta[6] and it has been used safely and effectively in the first ten days following pediatric burn injury to prevent both acute[37] and chronic[38] bone loss. Otherwise, experience in pediatrics has been anecdotal.

Anabolic agents are not commonly used in children for the purpose of promoting bone density accrual or preventing bone loss. In fact, in the case of burn injury the anabolic agents available will not prevent bone loss but will, if given daily over a one year period, increase bone mineral content and bone area proportionately so that the result is a bigger and hence a biomechanically stronger bone. The anabolic agents available for use in children are two: recombinant human growth hormone (rhGH)[39], and oxandrolone[40]. Both have been used without causing either premature epiphyseal closure or virilization.

The most effective anabolic agent in adults, recombinant

human parathyroid hormone (rhPTH), is not approved for use in children. In the United States its use is expressly prohibited by the Food and Drug Administration given the experimental data in rats that demonstrated an increased incidence of osteogenic sarcoma[41], a cancer regarded as predominant in children and young adults. This current ban is in effect despite the use of PTH in larger animals not producing the same increased incidence of osteogenic sarcoma. Furthermore, rhPTH is given to children who suffer from hypoparathyroidism[42], although long-term follow-up studies have not as yet been carried out to assess the incidence of osteogenic sarcoma in this population.

So what should the proper approach be in term s of how to use these bone-active drugs in children? There are no guidelines as yet as to how to use them. We need to build consensus among pediatric caregivers as to what conditions would most benefit from which drug. However, the authors would advocate as much as possible based on existing evidence to understand the mechanisms of bone loss that are operating in as many high-risk conditions as possible. Thus, for conditions in which bone resorption is primary, treatment with an anti-resorptive agent would be the most appropriate option. For conditions in which lack of new bone formation is the predominant finding use of anabolic agents should be considered along with appropriate management of the underlying condition.

In many conditions the cause of bone loss is multifactorial. If nutritional supplements can help, for example, in malabsorption, or the inflammatory response is due to recurrent infections, as in a condition such as cystic fibrosis, then appropriate antibiotic therapy is of course indicated to address the problem. Similarly, for immobilization, either weight-bearing exercise or use of continuous vibration therapy should be considered. Clearly meeting a child's caloric and protein needs is critical when dealing with muscle wasting of malnutrition-associated diseases, and the development of newer, and hopefully safer, forms of cancer chemotherapy can hopefully spare the bone marrow as much as possible.

Finally, as mentioned earlier, the tools for the detection of bone loss and poor bone quality are not optimal. We must await more advances in technology of quantitative volumetric bone imaging as well as a more systematic pharmacokinetic testing of bone-active drugs in children.

Conclusions

In summary, children may be subject to both primary and secondary bone loss. Primary bone loss involves genetic mutations leading to fundamental defects in either collagen synthesis or in conservation of bone mineral. Secondary bone loss results from the body's response to a variety of acute and chronic conditions and could be placed in the category of unintended consequences. However, it is incumbent on the physician or surgeon providing care to the pediatric patient to maintain a working knowledge of the ways in which a child can lose bone in order to develop the means by which the bone loss may be either prevented or treated.

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