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1.0 General Reference

1. Ablin, D. S. "**Osteogenesis Imperfecta: a Review.**" *Can Assoc Radiol J* 49, no. 2 (1998): 110-23.
The wide spectra of the clinical features, classification, genetics and imaging features of osteogenesis imperfecta (OI) are discussed, especially in the context of distinguishing the condition from child abuse. A broad general knowledge of the clinical and genetic aspects of the disease, as well as the imaging features of OI, is required for radiologists to knowledgeably provide the proper diagnosis and to participate responsibly in a team approach with geneticists, clinicians, lawyers and child protection services. There are 4 major types of OI, ranging from mild to severe. The diagnosis is made from clinical, genetic and radiographic features. The complications of OI and the use of bone mineral density measurements, collagen analysis and prenatal ultrasonography are presented. Their clinical relevance to the diagnosis of OI are discussed. Skin biopsy for collagen analysis may be needed to aid in the diagnosis in confusing or mild cases. It is

important to distinguish OI from child abuse in order to protect an abused child or to avoid an improper accusation of child abuse in a child with obvious OI.

2. Byers, P. H. "**Osteogenesis Imperfecta: Perspectives and Opportunities.**" *Curr Opin Pediatr* 12, no. 6 (2000): 603-9.

The last 2 years have seen additions proposed to the very limited armamentarium of treatments for osteogenesis imperfecta. These include the use of bisphosphonates to decrease bone resorption, growth hormone to augment growth and collagen production, and bone marrow transplantation to create chimeras at the level of the collagen production unit in bone. Although there are optimistic proponents for each strategy, the lack of well-controlled studies and the absence of clearly defined objectives for therapy hinder clear assessment.

3. Kocher, M. S. , and F. Shapiro. "**Osteogenesis Imperfecta.**" *J Am Acad Orthop Surg* 6, no. 4 (1998): 225-36.

Osteogenesis imperfecta (OI) is a genetically determined disorder of connective tissue characterized by bone fragility. The disease state encompasses a phenotypically and genotypically heterogeneous group of inherited disorders that result from mutations in the genes that code for type I collagen. The disorder is manifest in tissues in which the principal matrix protein is type I collagen (mainly bone, dentin, sclerae, and ligaments). Musculoskeletal manifestations are variable in severity along a continuum ranging from perinatal lethal forms with crumpled bones to moderate forms with deformity and propensity to fracture to clinically silent forms with subtle osteopenia and no deformity. The differential diagnosis includes other entities with multiple fractures, deformities, and osteopenia. Classification is based on the timing of fractures or on multiple clinical, genetic, and radiologic features. Molecular genetic studies have identified more than 150 mutations of the COL1A1 and COL1A2 genes, which encode for type I procollagen. Various systemic treatments have been attempted; however, these interventions have been ineffective or inconclusive or are still experimental. Gene therapy has the potential to increase the synthesis of type I collagen in mild variants and to correct mutations in severe variants, but there are a great number of technical difficulties to overcome. The goals of treatment of OI are to maximize function, minimize deformity and disability, maintain comfort, achieve relative independence in activities of daily living, and enhance social integration. Attainment of these goals requires a team approach to tailor treatment needs to the severity of the disease and the age of the patient. Nonoperative management is the mainstay of orthopaedic treatment, with the goals of preventing and treating fractures and enhancing locomotion. Operative intervention is indicated for recurrent fractures or deformity that impairs function.

4. McAllion, S. J., and C. R. Paterson. "**Causes of Death in Osteogenesis Imperfecta.**" *J Clin Pathol* 49, no. 8 (1996): 627-30.

AIMS: To determine the causes of death in patients with osteogenesis imperfecta, excluding infants with the perinatal lethal form (type II). METHODS: Seventy nine patients with known osteogenesis imperfecta were identified, 37 of whom had been seen clinically in life. Causes of death were identified from death certificates, postmortem reports, medical records, hospital consultants, relatives, and the Brittle Bone Society's records. RESULTS: Patients with the milder types of osteogenesis imperfecta, I and IV, often had a normal lifespan and died of unrelated illnesses such as

myocardial infarction and malignancy. In some of these patients and in many patients with the more severe type III disease, it was clear that osteogenesis imperfecta contributed significantly to death, almost certainly to many of the respiratory deaths and to deaths from cardiac failure due to kyphoscoliosis. Osteogenesis imperfecta also caused six deaths, directly or indirectly, due to basilar invagination of the skull. Osteogenesis imperfecta may have contributed to deaths from intracranial bleeding. Apparently minor traumatic incidents may have disastrous consequences in patients with this disorder. CONCLUSIONS: Prompt care for respiratory infections and prevention of trauma in patients with osteogenesis imperfecta is essential.

5. Petersen, K., and W. E. Wetzel. **"Recent Findings in Classification of Osteogenesis Imperfecta by Means of Existing Dental Symptoms."** *ASDC J Dent Child* 65, no. 5 (1998): 305-9, 354.

The findings are based on a clinical investigation conducted on forty-nine patients suffering from osteogenesis imperfecta (OI), as well as on a questionnaire study in which 117 osteogenesis imperfecta-affected persons or their parents were involved. The survey established pathological tooth discolorations as well as tooth abrasions. Dentinogenesis imperfecta (DI) was more frequently found in primary teeth than in permanent teeth. There were no gender-specific differences. Radiological abnormalities were found in both, abraded and/or discolored teeth, as well as in clinically normal appearing teeth. In most cases there were club-shaped extensions of the pulp chambers and obliterations of the root canals. The probability that dentinogenesis imperfecta occurs as an accompanying symptom of osteogenesis imperfecta was not dependent on the degree of skeletal severity. The self-assignment according to A and B forms of osteogenesis imperfecta types I and IV in accordance with the presence/absence of dental symptoms was contradictory, since the literature was based on varying classifications.

6. Primorac, D., D. W. Rowe, M. Mottes, I. Barisic, D. Anticevic, S. Mirandola, M. Gomez Lira, I. Kalajzic, V. Kusec, and F. H. Glorieux. **"Osteogenesis Imperfecta at the Beginning of Bone and Joint Decade."** *Croat Med J* 42, no. 4 (2001): 393-415. Osteogenesis imperfecta (OI), or brittle bone disease, is a heritable disorder characterized by increased bone fragility. Four different types of the disease are commonly distinguished, ranging from a mild condition (type I) to a lethal one (type II). Types III and IV are the severe forms surviving the neonatal period. In most cases, there is a reduction in the production of normal type I collagen or the synthesis of abnormal collagen as a result of mutations in the type I collagen genes. These classic forms of OI are described in this review. There are instances, however, where alterations in bone matrix components, other than type I collagen, are the basic abnormalities of the OI. Recently, three such discrete types have been identified by histomorphometric evaluation (types V and VI) and linkage analysis (Rhizomelic OI). They provide evidence for the as yet poorly understood complexity of the phenotype-genotype correlation in OI. We also discuss bisphosphonates treatment as well as fracture management and surgical correction of deformities observed in the patients with OI. However, ultimately, strengthening bone in OI will involve steps to correct the underlying genetic mutations that are responsible for this disorder. Thus, we also describe different genetic therapeutic approaches that have been tested either on OI cells or on available OI murine models.

7. Prockop, D. J. **"What Holds Us Together? Why Do Some of Us Fall Apart? What Can We Do About It?"** *Matrix Biol* 16, no. 9 (1998): 519-28.

One of the intriguing questions about complex organisms is, What holds them together? One of the principal answers is the tough, fibrous material known as collagen. A related question is, How is collagen made? The biosynthesis of the protein has several unusual features. One is the extensive use of the principle of spontaneous self-assembly seen in the formation of crystals. The three polypeptide chains of the protein fold into a triple-helical conformation by a process that begins with the formation of a small nucleus of triple helix at the C-terminus of the molecule and then propagation of the nucleus in a zipper-like fashion. Also, the self-assembly of the collagen monomers into fibrils is an entropy driven, crystallization-like process. Why do some of them fall apart? Mutations that alter the expression or primary structure of collagen are the predominant causes of severe skeletal defects such as osteogenesis imperfecta and chondrodysplasias. Mutations that have milder effects on the synthesis or structure of the protein are found in a subset of patients with more common diseases such as osteoporosis and early onset osteoarthritis. What can we do about the defects in collagen? Recent results have emphasized the importance of earlier observations that bone marrow contains a small subset of cells that are progenitors of osteoblasts, chondroblasts and several other types of nonhematopoietic cells. After systemic infusion into irradiated mice, the infused cells slowly replace a small fraction of the cells in bone, cartilage, lung and several other tissues. Therefore, the results suggest that the cells, known as mesenchymal stem cells or marrow stromal cells, can be used for both cell and gene therapy of diseases in which bone, cartilage and other connective tissues fall apart.

8. Vetter, U., B. Maierhofer, M. Muller, D. Lang, W. M. Teller, R. Brenner, D. Frohneberg, and O. Worsdorfer. **"Osteogenesis Imperfecta in Childhood: Cardiac and Renal Manifestations."** *Eur J Pediatr* 149, no. 3 (1989): 184-7.

We examined 58 children aged 1-16 years with various forms of osteogenesis imperfecta (OI). Congenital cardiac malformations were diagnosed in 4 children (valvular aortic stenosis, 2 with atrial septal defect II, Fallot Tetralogy). Two additional children developed holosystolic mitral valve prolapse and regurgitation. Children suffering from a severe clinical course (type III according to the Sillence classification) showed aortic root dilatation (28%) and increased septal (40%) and posterior left ventricular wall thickening (68%) on initial evaluation. All three parameters were significantly correlated to body surface area. Kidney stones and renal papillary calcifications were detected in 4 children. Cardiovascular abnormalities and nephrolithiasis may be important extraskelatal manifestations of childhood OI.

2.0 Genetics and Diagnosis

1. Berge, L. N., V. Marton, L. Tranebjaerg, M. S. Kearney, T. Kiserud, and P. Oian. **"Prenatal Diagnosis of Osteogenesis Imperfecta."** *Acta Obstet Gynecol Scand* 74, no. 4 (1995): 321-3.

The lethal perinatal types (II A-C) of osteogenesis imperfecta are reported to occur in approximately 1:55000 births. We here present three cases in three unrelated families, diagnosed by antenatal ultrasound within one year. A reliable diagnosis of the lethal perinatal type of osteogenesis imperfecta can be made by ultrasound examination

during the second trimester, by identification of fractures of the long bones. The compression of the fetal head by the ultrasound probe and the low echogeneity of the cranium, should raise the suspicion of skeletal dysplasia, but is not diagnostic for osteogenesis imperfecta. The diagnosis is confirmed by postmortem examination including radiography and biochemical studies of cultivated fibroblasts from the fetus. Although rare, this lethal condition should be recognized when an ultrasound examination is performed, to prevent unnecessary obstetric intervention. In families with a previously affected fetus, prenatal diagnosis by first trimester transvaginal ultrasound investigation or chorionic villus sampling should be discussed.

2. Blumsohn, A., S. J. McAllion, and C. R. Paterson. "**Excess Paternal Age in Apparently Sporadic Osteogenesis Imperfecta.**" *Am J Med Genet* 100, no. 4 (2001): 280-6.

The objective of this study was to examine whether parental age is associated with the occurrence of apparently sporadic osteogenesis imperfecta (OI). We compared parental age and the joint distribution of maternal and paternal age with expected distributions based on statutory birth records for each year and location of birth. The study included patients with OI based in the United Kingdom. The study was restricted to cases born in England, Wales, and Scotland between 1961 and 1998. Subgroup analysis was by clinical type [Sillence et al., 1979: *J Med Genet* 16:101-116] and apparent mode of inheritance based on pedigree analysis. Of 730 eligible cases, 357 were apparently sporadic. The mean age of fathers at birth of children with apparently sporadic OI was 0.87 years greater than expected ($P = 0.010$; 95% confidence interval = 0.21 to 1.54 years). The relative risk was 1.62 for fathers in the highest quintile of paternal age compared with fathers in the lowest quintile. The magnitude of the paternal age excess did not differ significantly between Sillence types (analysis of variance $P = 0.534$). In sporadic cases, paternal age was 0.51 years greater than expected, given maternal age, year, and location of birth ($P = 0.033$). In contrast, in familial cases, there was no significant paternal age excess, and paternal age was not significantly different from that expected given maternal age. Increased paternal age is a significant risk factor for sporadic OI. This effect is not accounted for by increasing maternal age. The magnitude of the paternal age excess is small in comparison with that in some other autosomal dominant disorders.

3. Cohn, D. H., B. J. Starman, B. Blumberg, and P. H. Byers. "**Recurrence of Lethal Osteogenesis Imperfecta Due to Parental Mosaicism for a Dominant Mutation in a Human Type I Collagen Gene (COL1A1).**" *Am J Hum Genet* 46, no. 3 (1990): 591-601.

We have determined that two infants with perinatal lethal osteogenesis imperfecta in one family had the same new dominant point mutation. Although not detected in his dermal fibroblast DNA, the mutation was detected in somatic DNA from the father's hair root bulbs and lymphocytes. The mutation was also detected in the father's sperm, demonstrating that mosaicism in the father's germ line explains recurrence. The presence of both germ-line and somatic mosaicism indicates that the mutation occurred prior to segregation of the germ-line and somatic cell progenitors. About one in eight sperm carry the mutation, which implies that at least four progenitor cells populate the germ line in human males. The observation that the mosaic individual is clinically normal suggests that genetic diseases can have both qualitative and quantitative components.

4. De Vos, A., K. Sermon, H. Van de Velde, H. Joris, M. Vandervorst, W. Lissens, A. De Paepe, I. Liebaers, and A. Van Steirteghem. "**Two Pregnancies After Preimplantation Genetic Diagnosis for Osteogenesis Imperfecta Type I and Type IV.**" *Hum Genet* 106, no. 6 (2000): 605-13.

Osteogenesis imperfecta (OI) is an autosomal dominant genetic disorder characterized by the presence of brittle bones and decreased bone mass (osteopenia), as a result of mutations in the genes that encode the chains of type I collagen, the major protein of bone. The clinical features of the disease range from death in the perinatal period to normal life span with minimal increase in fractures. The present report describes two polymerase chain reaction (PCR)-based assays allowing preimplantation genetic diagnosis (PGD) on the one hand for OI type I, the mildest form, and on the other hand for OI type IV, which is intermediate in severity between OI type I and OI type III. In the couple referred for PGD for OI type I, the female partner carried a 1-bp deletion in exon 43 of the COL1A1 gene, resulting in a premature stop codon in exon 46. The synthesis of too little type I procollagen results from such a non-functional or COL1A1 null allele. In the other couple, referred for PGD for OI type IV, the male partner carried a G to A substitution in exon 19 of the COL1A2 gene, which results in an abnormal gene product due to an alphaGly247 (GGT) to Ser (AGT) substitution (G247S). Both mutations result in the loss of a specific restriction enzyme recognition site and can therefore be detected by PCR amplification followed by restriction fragment analysis. PCR amplification of genomic DNA of the parents-to-be with one of the two primers fluorescently labelled, followed by automated laser fluorescence (ALF) gel electrophoresis of the amplified and restricted fragments, allowed a distinction between the healthy and affected genotypes. PCR on single Epstein-Barr-virus (EBV)-transformed lymphoblasts resulted in acceptable amplification efficiencies (87% and 85% for OI type I and OI type IV respectively) and the allele drop-out (ADO) rate was assessed at 11.5% and 11.1% for OI type I and OI type IV respectively. With research blastomeres, 100% amplification rates were obtained and no contamination was observed in the blank controls, which validated the tests for clinical application. Embryos obtained after intracytoplasmic sperm injection (ICSI) were evaluated for the presence of the normal genotype of the non-affected parent. For OI type I, two frozen-thawed ICSI-PGD cycles and two fresh ICSI-PGD cycles were carried out for the same couple. The transfer of two unaffected embryos in the last cycle resulted in a twin pregnancy. A twin pregnancy was also achieved in one clinical ICSI-PGD cycle for OI type IV.

5. Glorieux, F. H., F. Rauch, H. Plotkin, L. Ward, R. Travers, P. Roughley, L. Lalic, D. F. Glorieux, F. Fassier, and N. J. Bishop. "**Type V Osteogenesis Imperfecta: a New Form of Brittle Bone Disease.**" *J Bone Miner Res* 15, no. 9 (2000): 1650-8.

Osteogenesis imperfecta (OI) is commonly subdivided into four clinical types. Among these, OI type IV clearly represents a heterogeneous group of disorders. Here we describe 7 OI patients (3 girls), who would typically be classified as having OI type IV but who can be distinguished from other type IV patients. We propose to call this disease entity OI type V. These children had a history of moderate to severe increased fragility of long bones and vertebral bodies. Four patients had experienced at least one episode of hyperplastic callus formation. The family history was positive for OI in 3 patients, with an autosomal dominant pattern of inheritance. All type V patients had limitations in the range of pronation/supination in one or both forearms, associated with

a radiologically apparent calcification of the interosseous membrane. Three patients had anterior dislocation of the radial head. A radiodense metaphyseal band immediately adjacent to the growth plate was a constant feature in growing patients. Lumbar spine bone mineral density was low and similar to age-matched patients with OI type IV. None of the type V patients presented blue sclerae or dentinogenesis imperfecta, but ligamentous laxity was similar to that in patients with OI type IV. Levels of biochemical markers of bone metabolism generally were within the reference range, but serum alkaline phosphatase and urinary collagen type I N-telopeptide excretion increased markedly during periods of active hyperplastic callus formation. Qualitative histology of iliac biopsy specimens showed that lamellae were arranged in an irregular fashion or had a meshlike appearance. Quantitative histomorphometry revealed decreased amounts of cortical and cancellous bone, like in OI type IV. However, in contrast to OI type IV, parameters that reflect remodeling activation on cancellous bone were mostly normal in OI type V, while parameters reflecting bone formation processes in individual remodeling sites were clearly decreased. Mutation screening of the coding regions and exon/intron boundaries of both collagen type I genes did not reveal any mutations affecting glycine codons or splice sites. In conclusion, OI type V is a new form of autosomal dominant OI, which does not appear to be associated with collagen type I mutations. The genetic defect underlying this disease remains to be elucidated.

6. Glorieux, F. H., L. M. Ward, F. Rauch, L. Lalic, P. J. Roughley, and R. Travers. **"Osteogenesis Imperfecta Type VI: a Form of Brittle Bone Disease With a Mineralization Defect."** *J Bone Miner Res* 17, no. 1 (2002): 30-8.

Osteogenesis imperfecta (OI) is a heritable disease of bone in which the hallmark is bone fragility. Usually, the disorder is divided into four groups on clinical grounds. We previously described a group of patients initially classified with OI type IV who had a discrete phenotype including hyperplastic callus formation without evidence of mutations in type I collagen. We called that disease entity OI type V. In this study, we describe another group of 8 patients initially diagnosed with OI type IV who share unique, common characteristics. We propose to name this disorder "OI type VI." Fractures were first documented between 4 and 18 months of age. Patients with OI type VI sustained more frequent fractures than patients with OI type IV. Sclerae were white or faintly blue and dentinogenesis imperfecta was uniformly absent. All patients had vertebral compression fractures. No patients showed radiological signs of rickets. Lumbar spine areal bone mineral density (aBMD) was low and similar to age-matched patients with OI type IV. Serum alkaline phosphatase levels were elevated compared with age-matched patients with type IV OI (409 +/- 145 U/liter vs. 295 +/- 95 U/liter; $p < 0.03$ by t-test). Other biochemical parameters of bone and mineral metabolism were within the reference range. Mutation screening of the coding regions and exon/intron boundaries of both collagen type I genes did not reveal any mutations, and type I collagen protein analyses were normal. Qualitative histology of iliac crest bone biopsy specimens showed an absence of the birefringent pattern of normal lamellar bone under polarized light, often with a "fish-scale" pattern. Quantitative histomorphometry revealed thin cortices, hyperosteoidosis, and a prolonged mineralization lag time in the presence of a decreased mineral apposition rate. We conclude that type VI OI is a moderate to severe form of brittle bone disease with accumulation of osteoid due to a mineralization defect, in the absence of a disturbance of mineral metabolism. The underlying genetic defect remains to be elucidated.

7. Jensen, B. L. , and A. M. Lund. **"Osteogenesis Imperfecta: Clinical, Cephalometric, and Biochemical Investigations of OI Types I, III, and IV."** *J Craniofac Genet Dev Biol* 17, no. 3 (1997): 121-32.

The aim of the study was to analyze craniofacial development in 54 patients with osteogenesis imperfecta (OI), who were classified into OI types I, III, and IV according to clinical criteria, and to relate the findings to the abnormalities in collagen I production. In 33 patients, analysis of radioactively labelled procollagen was performed. Cephalometric radiographs, facial photographs, and CT-scans (a single case) were analyzed and mean facial diagrams for lateral and frontal films were produced based on registration of 221 reference points. Radiographs of 102 male and 51 female Danish students served as control material. In OI type I, size of the skull and jaws was generally slightly reduced, but morphology was within normal limits. In OI type IV and especially type III more severe abnormalities were found; the cranial base was flattened, the maxilla posteriorly inclined, and nearly all size-measurements were reduced. In OI type III the sagittal jaw relations were reduced and a mandibular overjet recorded. Three OI type I patients, whose fibroblasts produced structurally abnormal collagen I, had the stature and several features in the craniofacial region, which corresponded to those recorded for the OI type IV group. Also, in three OI type IV patients whose fibroblasts produced a reduced amount of normal collagen I, craniofacial morphology showed several features resembling type I patients. We conclude that structural abnormalities of collagen I generally give rise to more severe alterations of the craniofacial features than a quantitative defect of collagen I. OI type I patients are only slightly affected in their craniofacial region, while patients with OI type IV and especially type III are moderately to severely affected. The combined cephalometric and biochemical findings suggest that future classification of patients with osteogenesis imperfecta should be based on biochemical/molecular and radiological analyses in combination with clinical criteria rather than on clinical features alone.

8. Lund, A. M., A. C. Nicholls, M. Schwartz, and F. Skovby. **"Parental Mosaicism and Autosomal Dominant Mutations Causing Structural Abnormalities of Collagen I Are Frequent in Families With Osteogenesis Imperfecta Type III/IV."** *Acta Paediatr* 86, no. 7 (1997): 711-8.

Protein-chemical and molecular studies were conducted on all osteogenesis imperfecta (OI) type III/IV patients referred to our hospital during the last 15 y. Of a total of 16 OI type III/IV patients studied, 15 patients were heterozygous for a mutation in one of the two genes coding for collagen I, COL1A1 or COL1A2. Cultured fibroblasts from these 15 patients produced both normal and abnormal collagen I molecules, pointing to a dominant-negative effect of the mutation. Nine mutations had not been described previously. Parental mosaicism was demonstrated in three families. In the 16th child the causative mutation was not found. In conclusion, OI type III/IV in most patients of Western European ancestry is caused by dominant mutations in the genes for collagen I, and recurrence of OI is caused in most cases by parental gonadal mosaicism.

9. Lund, A. M., M. Schwartz, and F. Skovby. **"Genetic Counselling and Prenatal Diagnosis of Osteogenesis Imperfecta Caused by Paternal Mosaicism."** *Prenat Diagn* 16, no. 11 (1996): 1032-8.

In a family with recurrent osteogenesis imperfecta (OI) caused by paternal mosaicism, prenatal diagnosis was made using restriction enzyme analysis for a mutation in

COL1A2. Parental mosaicism is important to consider in genetic counselling for OI. Prenatal diagnosis of OI is available currently by means of collagen or gene analyses in the first trimester or by ultrasonography in the second trimester.

10. Moore, M. S. , C. M. Minch, R. W. Kruse, H. T. Harcke, L. Jacobson, and A. Taylor. "**The Role of Dual Energy X-Ray Absorptiometry in Aiding the Diagnosis of Pediatric Osteogenesis Imperfecta.**" *Am J Orthop* 27, no. 12 (1998): 797-801.

The role of dual energy x-ray absorptiometry (DEXA) in the evaluation of the pediatric patient with multiple fractures has not been well established. We retrospectively examined the medical records of 45 patients who had presented to our institution with multiple fractures of unknown cause, who were not known to have osteogenesis imperfecta, and who had obtained DEXA as part of their evaluation. Of these, 26 patients had sufficient clinical data for inclusion in this study. Patients underwent DEXA of the anteroposterior spine and whole body. A z score was calculated to normalize the DEXA values for age. The diagnosis of osteogenesis imperfecta was correlated with the outcome of each DEXA scan to assess the validity of DEXA as a diagnostic tool. The DEXA of the anteroposterior spine had the highest sensitivity at 91.7%, while DEXA of the whole body had the highest specificity at 100.0%. Decreased bone mineral density may be associated with osteogenesis imperfecta, and DEXA is helpful in detecting low bone mineral density that may be missed on plain radiographs of children with milder forms of osteogenesis imperfecta.

11. Pepin, M., M. Atkinson, B. J. Starman, and P. H. Byers. "**Strategies and Outcomes of Prenatal Diagnosis for Osteogenesis Imperfecta: a Review of Biochemical and Molecular Studies Completed in 129 Pregnancies.**" *Prenat Diagn* 17, no. 6 (1997): 559-70.

We completed prenatal diagnostic studies from 129 pregnancies at risk for osteogenesis imperfecta (OI). Studies in 107 pregnancies were completed by analysis of collagen synthesized by cells cultured from chorionic villus biopsies and the remaining 22 used direct mutation identification or analysis of polymorphic restriction sites in the COL1A1 gene of type I collagen. The vast majority of studies (n = 113) were obtained to identify fetuses with OI type II (the perinatal lethal form) and some fetuses affected with OI type III or IV (the deforming varieties). Of the 50 couples who had had one previous affected pregnancy with the lethal form of OI, one had a second affected pregnancy, a rate of 2 per cent. Two of the seven unaffected couples (28 per cent) who had had two previous affected pregnancies with OI type II had a third affected pregnancy; none of the three with two previous pregnancies with OI type III had a third. Pregnancies at risk for OI type I could not be ascertained reliably by biochemical analysis of cultured CVS cells but were identified by direct analysis of the causative mutation or the use of linked markers in families. All prenatal diagnostic studies were undertaken only after earlier diagnostic studies (biochemical or molecular) had been completed on the proband, a necessary strategy for accurate results. In all pregnancies at risk for OI type II, OI type III, and OI type IV studied with biochemical strategies and in pregnancies at risk for OI type I studied with molecular techniques, there were neither false-negative nor false-positive results. Diagnostic information can be obtained within 20-30 days of biopsy using biochemical techniques and within 10-14 days when molecular strategies are used.

12. Silience, D. O., K. K. Barlow, W. G. Cole, S. Dietrich, A. P. Garber, and D. L. Rimoin. **"Osteogenesis Imperfecta Type III. Delineation of the Phenotype With Reference to Genetic Heterogeneity."** *Am J Med Genet* 23, no. 3 (1986): 821-32.

The existence of a rare form of osteogenesis imperfecta, OI type III, has been postulated. This is characterized by autosomal recessive inheritance with neonatal manifestations of bone fragility or deformability. It is usually nonlethal. Studies of some 345 pedigrees of OI in the last 8 years confirm that patients falling into this group are rare. They should be distinguished as a special group within the group of OI subjects with a progressively deforming OI phenotype delineated in previous publications [Silience et al, 1979a, b]. The OI type III phenotype does not necessarily equate with progressively deforming OI, and probably only a proportion of cases with severe deformity and normal sclerae have OI type III. On the other hand, distinction between these patients and those with a milder form of perinatally lethal OI type II might be difficult. Whereas the natural history of skeletal deformity and fractures in patients with OI type III has certain similarities, variable severity between families indicates that OI type III is likely to be genetically heterogeneous.
13. Silience, D. O., K. K. Barlow, A. P. Garber, J. G. Hall, and D. L. Rimoin. **"Osteogenesis Imperfecta Type II Delineation of the Phenotype With Reference to Genetic Heterogeneity."** *Am J Med Genet* 17, no. 2 (1984): 407-23.

A group of fetuses with a perinatally lethal variety of osteogenesis imperfecta (O.I. type II) is characterized by short limbs, and clinical and roentgenological evidence of severe osseous fragility and defective ossification. Forty-eight cases were reviewed and can be subdivided into 3 groups on the basis of small but probably significant differences in clinical and radiographic findings. Group A (38 cases): short, broad, "crumpled" long bones, angulation of tibiae and continuously beaded ribs. Group B (6 cases): short, broad, crumpled femora, angulation of tibiae but normal ribs or ribs with incomplete beading. Group C (4 cases): long, thin, inadequately modelled, rectangular long bones with multiple fractures and thin beaded ribs. Consistency of findings within sibships suggests the groups reflect genetic heterogeneity. An increased frequency of parental consanguinity, sib occurrence with normal parents, and normal mean paternal age at birth, suggest that most cases of O.I. type II represent autosomal recessive traits. Some previously reported cases and the biochemical findings in one case suggest still further genetic heterogeneity.
14. Silience, D. O., A. Senn, and D. M. Danks. **"Genetic Heterogeneity in Osteogenesis Imperfecta."** *J Med Genet* 16, no. 2 (1979): 101-16.

An epidemiological and genetical study of osteogenesis imperfecta (OI) in Victoria, Australia confirmed that there are at least four distinct syndromes at present called OI. The largest group of patients showed autosomal dominant inheritance of osteoporosis leading to fractures and distinctly blue sclerae. A large proportion of adults had presenile deafness or a family history of presenile conductive hearing loss. A second group, who comprised the majority of newborns with neonatal fractures, all died before or soon after birth. These had characteristic broad, crumpled femora and beaded ribs in skeletal x-rays. Autosomal recessive inheritance was likely for some, if not all, of these cases. A third group, two thirds of whom had fractures at birth, showed severe progressive deformity of limbs and spine. The density of scleral blueness appeared less than that seen in the first group of patients and approximated that seen in normal

children and adults. Moreover, the blueness appeared to decrease with age. All patients in this group were sporadic cases. The mode of inheritance was not resolved by the study, but it is likely that the group is heterogeneous with both dominant and recessive genotypes responsible for the syndrome. The fourth group of patients showed dominant inheritance of osteoporosis leading to fractures, with variable deformity of long bones, but normal sclerae.

15. Steiner, R. D., M. Pepin, and P. H. Byers. "**Studies of Collagen Synthesis and Structure in the Differentiation of Child Abuse From Osteogenesis Imperfecta.**" *J Pediatr* 128, no. 4 (1996): 542-7.

OBJECTIVE: To determine whether analysis of collagen synthesized by dermal fibroblasts could identify children with osteogenesis imperfecta (OI) among those suspected to have been abused. **METHODS:** We reviewed biochemical studies and clinical findings for all children who were referred to us to distinguish OI from abuse during a 4-year period. **RESULTS:** Cells from 6 of 48 children tested to distinguish OI from abuse had biochemical evidence of OI. In five of the six children with abnormal results on collagen studies, clinical signs of OI in addition to fractures were present on examination by a physician familiar with the condition. In those five cases, the diagnosis of OI was strongly suspected. **CONCLUSIONS:** OI can be diagnosed by biochemical studies in some cases of suspected abuse, but clinical evaluation by experienced physicians is usually sufficient to do so. When diagnostic uncertainty persists in cases of suspected child abuse, biochemical studies may be a useful adjunct, but routine biopsy for children suspected to have been abused is unwarranted.

16. Thompson, E. M. "**Non-Invasive Prenatal Diagnosis of Osteogenesis Imperfecta.**" *Am J Med Genet* 45, no. 2 (1993): 201-6.

The main mode of non-invasive prenatal diagnosis of osteogenesis imperfecta (OI) is fetal imaging, either by radiography or detailed ultrasonography. Radiography is more of historical interest and ultrasonography is in practice virtually exclusively used for non-invasive second trimester diagnosis of OI. Both methods have also been reported later in pregnancy when diagnosis allows the most appropriate method of delivery to be planned. For example, a caesarean section can be avoided if the fetus is shown to have a form of OI associated with limited survival. Ultrasonography is useful mainly for prenatal diagnosis of the severe forms of OI, especially the perinatally lethal forms (Sillence type II) and to a lesser extent for the severe progressively deforming forms (Sillence types III and III/IV). For the milder varieties of OI (Sillence types I and IV), many cases will be missed by scans. Invasive methods of prenatal diagnosis of OI (principally chorion villous sampling) are used for families with the milder dominant forms of OI and in severe forms of OI in which the actual biochemical or molecular defect in type I collagen is known. Many cases of type II OI and a few of type III have now been reported which were detected by scans before 20 weeks gestation, the earliest being at 15 weeks, for type IIA OI. These include cases not only at genetic risk but also sporadic cases in which scans were done either routinely or for obstetric indications. The ultrasonic abnormalities which are found include reduced echogenicity, multiple fractures, and deformity of the long bones, ribs and skull.

17. Tongsong, T. , C. Wanapirak, and S. Sirianguk. "**Prenatal Diagnosis of Osteogenesis Imperfecta Type II.**" *Int J Gynaecol Obstet* 61, no. 1 (1998): 33-8.

OBJECTIVE: To characterize the prenatal sonographic features of osteogenesis imperfecta (OI) type II. DESIGN: Descriptive (case series). SETTING: Department of Obstetrics and Gynecology, Faculty of Medicine, Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University. SUBJECTS: Six fetuses with prenatal diagnosis of OI were evaluated. RESULTS: Six fetuses were prenatally diagnosed as OI type II in five mothers without familial history of the disease. One mother had two consecutive pregnancies complicated with this condition. The first five cases were classified as OI type IIA, while the last one was OI type IIB. All of subtype A exhibited typical triad of bone shortening, diffuse hypomineralization and multiple fractures of long bones including beaded ribs whereas the subtype B showed shortening of only femurs, normal bone echodensity and isolated fractures of long bones. The postnatal radiography and autopsy confirmed the prenatal diagnosis in all cases. Other findings may occasionally be found, including polyhydramnios, oligohydramnios, hydrop fetalis and small for gestational age. CONCLUSION: The triad of bone shortening, decreased bone density and numerous fractures including beaded ribs permits a confident diagnosis of OI type IIA. Furthermore, sonographic features may differentiate the subtype of OI type II, depending on degree of bone shortening and echodensity.

3.0 Basic Science

3.1 Bone

1. Boyde, A., R. Travers, F. H. Glorieux, and S. J. Jones. "**The Mineralization Density of Iliac Crest Bone From Children With Osteogenesis Imperfecta.**" *Calcif Tissue Int* 64, no. 3 (1999): 185-90.

We studied iliac crest biopsy cores taken from young individuals with osteogenesis imperfecta of several types, and from age-matched normals; the same samples had been used in prior studies using conventional light microscopic histomorphometric procedures. The PMMA blocks were micro-milled to a fine finish, carbon coated, and imaged using backscattered electrons (BSE) in an automated digital scanning electron microscope (SEM). For comparison of BSE signal levels between samples, microscope operation parameters were standardized by reference to halogenated dimethacrylate standards, and recording data from stereological arrays of 512*512 nonoverlapping pixels at 3.5 micrometer separation. All OI types showed higher average mineralization densities than age- and site-matched normals. This is interpreted as the result of the failure in matrix assembly, such that it has a higher water volume fraction available for mineral deposition. Added to the net deficit in bone quantity, the predicted higher stiffness of the more mineralized bone will account for much of the observed 'brittleness' that characterizes this class of genetic disease. The mean mineralization density, which was higher in types III, IV, and V than in type I, appears to be correlated with disease severity.

2. Camacho, N. P., L. Hou, T. R. Toledano, W. A. Ilg, C. F. Brayton, C. L. Raggio, L. Root, and A. L. Boskey. **"The Material Basis for Reduced Mechanical Properties in Oim Mice Bones."** *J Bone Miner Res* 14, no. 2 (1999): 264-72.

Osteogenesis imperfecta (OI), a heritable disease caused by molecular defects in type I collagen, is characterized by skeletal deformities and brittle bones. The heterozygous and homozygous oim mice (oim/+ and oim/oim) exhibit mild and severe OI phenotypes, respectively, serving as controlled animal models of this disease. In the current study, bone geometry, mechanics, and material properties of 1-year-old mice were evaluated to determine factors that influence the severity of phenotype in OI. The oim/oim mice exhibited significantly smaller body size, femur length, and moment of area compared with oim/+ and wild-type (+/+) controls. The oim/oim femur mechanical properties of failure torque and stiffness were 40% and 30%, respectively, of the +/+ values, and 53% and 36% of the oim/+ values. Collagen content was reduced by 20% in the oim/oim compared with +/+ bone and tended to be intermediate to these values for the oim/+. Mineral content was not significantly different between the oim/oim and +/+ bones. However, the oim/oim ash content was significantly reduced compared with that of the oim/+. Mineral carbonate content was reduced by 23% in the oim/oim bone compared with controls. Mineral crystallinity was reduced in the oim/oim and oim/+ bone compared with controls. Overall, for the majority of parameters examined (geometrical, mechanical, and material), the oim/+ values were intermediate to those of the oim/oim and +/+, a finding that parallels the phenotypes of the mice. This provides evidence that specific material properties, such as mineral crystallinity and collagen content, are indicative and possibly predictive of bone fragility in this mouse model, and by analogy in human OI.

3. Cassella, J. P., P. J. Barrie, N. Garrington, and S. Y. Ali. **"A Fourier Transform Infrared Spectroscopic and Solid-State NMR Study of Bone Mineral in Osteogenesis Imperfecta."** *J Bone Miner Metab* 18, no. 5 (2000): 291-6.

Fourier transform infrared spectroscopy and ³¹P solid-state nuclear magnetic resonance spectroscopy were used to determine if any structural or compositional differences in osteogenesis imperfecta (OI) bone mineral could be detected that might help to explain the bone fragility observed in this disease. A previous study by Cassella et al. used an electron probe X-ray microanalytical technique to compare the calcium to phosphorus (Ca/P) molar ratios in normal bone and bone from patients with OI. It was demonstrated that bone from OI patients had a lower Ca/P molar ratio. This study demonstrated that OI bone mineral had a general hydroxyapatite structure and that isomorphous substitutions in the carbanapatite lattice could account for the low Ca/P molar ratio.

4. Cassella, J. P., T. C. Stamp, and S. Y. Ali. **"A Morphological and Ultrastructural Study of Bone in Osteogenesis Imperfecta."** *Calcif Tissue Int* 58, no. 3 (1996): 155-65.

A morphological and electron microscopic study of bone from patients with osteogenesis imperfecta (OI) has been performed. Bone from OI patients from various anatomical sites has been compared with that from normal, age-, site-, and sex-matched controls. The morphology of OI bone appeared variable among patients and sites of bone examined. Immature woven bone and a poor lamellar pattern were the significant morphological features and demonstrated that OI could not be characterized on the basis of a single histological pattern. At the ultrastructural level, a number of previously unreported features were evident. Abnormal collagen fibers and an altered mineral

composition were found in many OI patients, however, the panoramic heterogeneity between clinical types and indeed within a single clinical type made it difficult to classify OI in this manner. The presence of intermitochondrial inclusions containing calcium and phosphorus and the presence of a stromal calcification in the bone in some OI patients suggested an abnormal mineral formation. Qualitatively, no obvious difference in the number of osteoblasts or osteoclasts was observed. The morphology and ultrastructure of OI bone were good indicators of the disease and serve a role in assessing the progress of a patient through diagnosis and treatment. This report presents new ultrastructural findings in collagen and in mineral formation in OI compared with normal human bone.

5. Cepollaro, C. , S. Gonnelli, C. Pondrelli, A. Montagnani, S. Martini, D. Bruni, and C. Gennari. "**Osteogenesis Imperfecta: Bone Turnover, Bone Density, and Ultrasound Parameters.**" *Calcif Tissue Int* 65, no. 2 (1999): 129-32.
We studied 21 patients (11 men and 10 women) with osteogenesis imperfecta (OI) and 21 age- and sex-matched controls. In all patients we measured serum levels of total alkaline phosphatase (ALP), type I procollagen carboxy-terminal propeptide (PICP), osteocalcin (BGP), urinary excretion of hydroxyproline (HOP/Cr), and pyridinoline crosslinks (Pyr/Cr). Bone mineral density was measured at the distal radius (BMD-R) and at the lumbar spine (BMD-LS) by dual X-ray absorptiometry (DXA). Ultrasound parameters were also performed at the calcaneus with the Achilles device and at the phalanges with DBM Sonic 1200. A significant reduction ($P < 0.001$) in BMD and in ultrasound parameters was found in OI patients compared with normals. PICP was significantly reduced in the OI patients compared with controls ($P < 0.001$); other markers of bone turnover were higher in OI than in controls, but the difference did not reach the statistical significance. A significant correlation ($P < 0.05$) was found between PICP and BMD at the lumbar spine and between PICP and ultrasound parameters at the calcaneus. On the basis of our data, we conclude that patients with OI show low values of BMD and ultrasound parameters; therefore in these patients, not only is bone mass disturbed but also bone quality. The reduced levels of PICP in OI patients confirm that most OI patients have defects in collagen I biosynthesis. These defects may contribute to the fragility of OI bone by interfering with complete mineralization and/or normal tissue structure. PICP may be considered a useful marker in the clinical management of OI.

6. Fedarko, N. S., M. Moerike, R. Brenner, P. G. Robey, and U. Vetter. "**Extracellular Matrix Formation by Osteoblasts From Patients With Osteogenesis Imperfecta.**" *J Bone Miner Res* 7, no. 8 (1992): 921-30.
Extracellular matrix proteins synthesized by bone cells isolated from 16 patients with different forms of osteogenesis imperfecta (OI) were analyzed in vitro. Specific components of the extracellular matrix by OI and age-matched cultures were investigated by steady-state radiolabeling followed by quantitation of label into specific proteins and comparison of OI cultures to those of age-matched controls. The in vitro proliferation of OI bone cells was found to be lower than that of control cells. In seven patients, abnormalities of the alpha 1(I) and/or alpha 2(I) chains of type I collagen were detected by gel electrophoresis. In two of these patients, the mutations in the COL1A1 and COL1A2 genes have been previously identified. Although the amount of total protein synthesized by the cells in culture was the same for OI bone cells and age-

matched control cells, OI bone cells showed a significantly reduced synthesis of not only collagen but also other bone matrix glycoproteins. The synthesis of osteonectin (SPARC/BM40) and three proteoglycans [a large chondroitin sulfate proteoglycan, biglycan (PGI), and decorin (PGII)] was found to be decreased in OI cells. The reduction was most pronounced at the developmental age at which these macromolecules reach maximal levels during normal development.

7. Jones, S. J., F. H. Glorieux, R. Travers, and A. Boyde. **"The Microscopic Structure of Bone in Normal Children and Patients With Osteogenesis Imperfecta: a Survey Using Backscattered Electron Imaging."** *Calcif Tissue Int* 64, no. 1 (1999): 8-17. The microstructure of iliac crest biopsies from normal children or from those afflicted with osteogenesis imperfecta (OI) has not previously been studied to determine the tissue histology in the context of the degree of mineralization. The material in this study comprised 112 iliac crest biopsies from children aged 1.9-22.9 years. Fifty-eight were reference biopsies taken from children with no bone disease and the remainder were biopsies from children diagnosed as having OI (23 were Type I, 8 Type III, 18 Type IV, and 5 Type V). The specimens, which had been embedded in polymethylmethacrylate (PMMA), were micromilled and carbon coated to permit backscattered electron imaging. Reference biopsies from very young children often contained densely mineralized cartilage, and evidence of rapid cortical drift. Circumferential lamellae became a prominent feature after the toddler stage, and active remodeling and slower cortical drift continued through childhood. The biopsies from older teenagers and young adults were indistinguishable. Occasional mineralized osteocyte lacunae were detected in even the youngest children. Bone from children with OI Type I often appeared normal in microstructure and amount, but in some there was a dearth of bone and an abundance of osteocytes. Compared with age-matched controls, cortical and trabecular bone from children with OI Types III and IV were markedly sparse and very cellular, and primary osteonal systems continued to be formed later than expected. A distinguishing feature of the bone from OI Type V patients was the failure of patches of bone to mineralize, especially adjoining a reversal line. Packets of bone tissue exhibiting either considerably higher than normal or deficient mineralization would contribute to the characteristic trait of mechanical weakness.
8. McCarthy, E. F., K. Earnest, K. Rossiter, and J. Shapiro. **"Bone Histomorphometry in Adults With Type IA Osteogenesis Imperfecta."** *Clin Orthop*, no. 336 (1997):254-62. A histologic and histomorphometric analysis was performed on undecalcified bone from 8 adult patients, ages 34 to 64 years, with Type IA osteogenesis imperfecta. Complete histomorphometric data, including static and dynamic parameters of bone remodeling, could be generated on 6 patients, and partial data were obtained from the other 2 patients. Findings in some patients of reduced eroded surfaces and reduced osteoid surfaces suggested low bone turnover. Other findings included normal or slightly reduced labeled surfaces, slightly reduced bone formation rate, decreased cortical thickness, and decreased bone volume. Histologic examination results showed lamellar bone with mature cortical Haversian systems. Trabeculae showed qualitatively normal connectedness despite low trabecular volume. The finding of normal or reduced bone turnover in adults with Type IA osteogenesis imperfecta has not been reported. Earlier histomorphometric studies, performed without correlation with a specific age or phenotype, indicated high bone turnover. The present study suggests that future

research should correlate histopathologic changes with specific phenotypes. The finding of normal or slightly reduced bone turnover in Type IA osteogenesis imperfecta may have important therapeutic implications for this phenotype.

9. Pereira, R. F., E. L. Hume, K. W. Halford, and D. J. Prockop. "**Bone Fragility in Transgenic Mice Expressing a Mutated Gene for Type I Procollagen (COL1A1) Parallels the Age-Dependent Phenotype of Human Osteogenesis Imperfecta.**" *J Bone Miner Res* 10, no. 12 (1995): 1837-43.

An inbred strain of transgenic mice that expressed a mutated gene for type I procollagen and that developed spontaneous fractures was used to study the effects of age on the phenotype of fragile bones. The mutated gene has been shown to cause depletion of type I collagen in the transgenic mice because it generated shortened pro alpha 1(I) chains that bound to and produced degradation of normal pro alpha 1(I) chains synthesized from the endogenous mouse COL1A1 gene. For this study, femurs from transgenic mice ranging in age from 0.5-24 months were examined. The results demonstrated that the level of expression of the transgene was independent of age. Femurs from the transgenic mice were more fragile than controls at 0.5 and 1.5 months, they were biomechanically normal at 6 months, and then they were more fragile at 24 months. The normal biomechanical properties of the bones from the transgenic mice at 6 months were accompanied by periosteal thickening of the bones together with an increase in the collagen content that was not associated with a proportional increase in mineral content. The results indicated that the effects of age, mechanical stress, and hormonal action produced a biological compensation for the mutated gene by either increasing collagen synthesis of bone, decreasing collagen degradation, or both. The biological compensation was apparently lost by 24 months when the outer diameters of the femurs were again less than in controls, the cortical thickness was about the same as in controls, and both the collagen and mineral contents were less than controls. The results demonstrated that bone fragility in the transgenic mice paralleled the age-dependent phenotype of human osteogenesis imperfecta. Therefore the transgenic mice appeared to be useful models for osteogenesis imperfecta. They also may be useful models for some forms of osteoporosis.

10. Rauch, F., R. Travers, A. M. Parfitt, and F. H. Glorieux. "**Static and Dynamic Bone Histomorphometry in Children With Osteogenesis Imperfecta.**" *Bone* 26, no. 6 (2000): 581-9.

Osteogenesis imperfecta (OI) is a genetic disorder characterized by increased bone fragility and low bone mass. Four clinical types are commonly distinguished. Schematically, type I is the mildest phenotype, type II is usually lethal, type III is the most severe form compatible with postnatal survival, and type IV is moderately severe. Although mutations affecting collagen type I are responsible for the disease in most patients, the mechanisms by which the genetic defects cause abnormal bone development have not been well characterized. Therefore, we evaluated quantitative static and dynamic histomorphometric parameters in tetracycline-labeled iliac bone biopsies from 70 children, aged 1.5 to 13.5 years, with OI types I (n = 32), III (n = 11), and IV (n = 27). Results were compared with those of 27 age-matched controls without metabolic bone disease. Biopsy core width, cortical width, and cancellous bone volume were clearly decreased in all OI types. Decreased cancellous bone volume was due to a 41%-57% reduction in trabecular number and a 15%-27% lower trabecular thickness.

Regression analyses revealed that trabecular number did not vary with age in either controls or OI patients, indicating that no trabecular loss occurred. The annual increase in trabecular thickness was 5.8 microm in controls and 3.6 microm in type I OI, whereas no trabecular thickening was evident in type III and IV OI. Wall thickness, which reflects the amount of bone formed during a remodeling cycle, was decreased by 14% in a subgroup of 17 type I OI patients, but was not determined in the other OI types. The remodeling balance was less positive in type I OI than in controls, and probably close to zero in types III and IV. Surface-based parameters of bone remodeling were increased in all OI types, indicating increased recruitment of remodeling units. No defect in matrix mineralization was found. In conclusion, there was evidence of defects in all three mechanisms, which normally lead to an increase in bone mass during childhood; that is, modeling of external bone size and shape, production of secondary trabeculae by endochondral ossification, and thickening of secondary trabeculae by remodeling. Thus, OI might be regarded as a disease in which a single genetic defect in the osteoblast interferes with multiple mechanisms that normally ensure adaptation of the skeleton to the increasing mechanical needs during growth.

11. Sarathchandra, P., M. V. Kayser, and S. Y. Ali. "**Abnormal Mineral Composition of Osteogenesis Imperfecta Bone As Determined by Electron Probe X-Ray Microanalysis on Conventional and Cryosections.**" *Calcif Tissue Int* 65, no. 1 (1999): 11-5.

Osteogenesis imperfecta (OI) is a genetic disorder of the connective tissue characterized by frequent bone fractures. The cause of bone fragility is still unknown even though substantial work on collagen has been done. We measured the calcium to phosphorus ratio (Ca/P) of bone mineral from 35 OI bone samples and 25 age- and site-matched control specimens, using electron probe X-ray microanalysis in the transmission electron microscope. Ultra-thin cryosections and conventionally prepared resin sections were used. Cryo-ultramicrotomy avoids any possible artifactual demineralization that may occur in conventional aqueous media. The Ca/P ratio obtained by these two methods was compared and there was no statistical difference between them. The results were differentiated according to the clinical types of OI for the first time. The Ca/P ratio of OI bone mineral was lower than normal in both resin and cryosections, and mirrored the severity of the disease. OI type II had the lowest ratio (Ca/P = 1.49) compared with normal age- and site-matched controls (Ca/P = 1.69). This abnormal mineral composition in OI type II could be a contributory factor to bone fragility in OI bone.

12. Sarathchandra, P., F. M. Pope, M. V. Kayser, and S. Y. Ali. "**A Light and Electron Microscopic Study of Osteogenesis Imperfecta Bone Samples, With Reference to Collagen Chemistry and Clinical Phenotype.**" *J Pathol* 192, no. 3 (2000): 385-95.
A detailed morphological study was carried out using light and electron microscopy on 36 bone specimens from patients suffering from osteogenesis imperfecta (OI) and 20 age- and site-matched control bone specimens. The findings were grouped into the clinical types of OI according to the Sillence classification. The morphological and ultrastructural alterations observed in OI bone correlate well with clinical severity. Thus, OI type I, the mildest type, showed the least abnormalities in bone ultrastructure. OI type IV closely resembled type I, with only minor abnormalities in the bone cells and osteoid. OI type III showed abnormalities in the structure and distribution of osteoid

collagen fibrils, whilst OI type II, the lethal form, revealed many varied abnormalities such as thin cortical bone, sparse trabecular bone, increased numbers of osteoclasts and osteocytes, thin osteoid with thin collagen fibrils, and patchy mineralization.

3.2 Collagen

1. Bank, R. A., J. M. Tekoppele, G. J. Janus, M. H. Wassen, H. E. Pruijs, H. A. Van der Sluijs, and R. J. Sakkers. **"Pyridinium Cross-Links in Bone of Patients With Osteogenesis Imperfecta: Evidence of a Normal Intrafibrillar Collagen Packing."** *J Bone Miner Res* 15, no. 7 (2000): 1330-6.

The brittleness of bone in patients with osteogenesis imperfecta (OI) has been attributed to an aberrant collagen network. However, the role of collagen in the loss of tissue integrity has not been well established. To gain an insight into the biochemistry and structure of the collagen network, the cross-links hydroxylysylpyridinoline (HP) and lysylpyridinoline (LP) and the level of triple helical hydroxylysine (Hyl) were determined in bone of OI patients (types I, III, and IV) as well as controls. The amount of triple helical Hyl was increased in all patients. LP levels in OI were not significantly different; in contrast, the amount of HP (and as a consequence the HP/LP ratio and the total pyridinoline level) was significantly increased. There was no relationship between the sum of pyridinolines and the amount of triple helical Hyl, indicating that lysyl hydroxylation of the triple helix and the telopeptides are under separate control. Cross-linking is the result of a specific three-dimensional arrangement of collagens within the fibril; only molecules that are correctly aligned are able to form cross-links. Inasmuch as the total amount of pyridinoline cross-links in OI bone is similar to control bone, the packing geometry of intrafibrillar collagen molecules is not disturbed in OI. Consequently, the brittleness of bone is not caused by a disorganized intrafibrillar collagen packing and/or loss of cross-links. This is an unexpected finding, because mutant collagen molecules with a random distribution within the fibril are expected to result in disruptions of the alignment of neighboring collagen molecules. Pepsin digestion of OI bone revealed that collagen located at the surface of the fibril had lower cross-link levels compared with collagen located at the inside of the fibril, indicating that mutant molecules are not distributed randomly within the fibril but are located preferentially at the surface of the fibril.

2. Bateman, J. F., and S. B. Golub. **"Deposition and Selective Degradation of Structurally-Abnormal Type I Collagen in a Collagen Matrix Produced by Osteogenesis Imperfecta Fibroblasts in Vitro."** *Matrix Biol* 14, no. 3 (1994): 251-62.

Collagen matrix deposition and turnover were studied in skin fibroblasts from a control and from a patient with lethal perinatal osteogenesis imperfecta (OI) identified as a Gly667 to Arg substitution in the alpha 1(I) chain. A culture system where ascorbic acid was included to stimulate collagen matrix formation over extended culture periods was used. Serial extraction of the control cell collagen matrix confirmed that a substantial mature crosslinked collagen matrix was formed in the control fibroblast cell layer. In contrast, total collagen deposition by the OI fibroblasts was poor, with the quantity of collagen deposited only about a quarter of that of the control cells. Detailed analysis of the OI fibroblast matrix revealed that the mutant collagen chains were incorporated into

the collagenous matrix. These data indicate that, when grown with ascorbate in long-term culture, OI fibroblasts reproduced the abnormal matrix deposition pattern of OI tissues in vivo. The overall dramatic reduction in collagen matrix formation was not accounted for by reduced collagen production, since during the period of matrix deposition (days 8-12) the rate of production by the OI cells was only slightly less than that of the control cells. The incorporation of the newly-synthesized OI collagen into the matrix was less efficient than in control cells, reflecting the cooperative nature of matrix deposition. The fate of this mutant collagen containing the Gly to Arg charge-change was followed in the matrix by a pulse-chase experiment and two-dimensional electrophoresis. These data demonstrated that the mutant incorporated into the matrix was unstable, with the proportion of mutant declining during the chase. The deposition of the mutant monomers into a pool more accessible to proteolytic degradation indicated that the mutant and normal collagens did not copolymerize to form collagen fibers of even collagen distribution, but rather the mutant collagen was either enriched on the exposed surfaces of mixed-composition fibers, or was unable to form copolymers efficiently and polymerized into mutant-only fibrillar assemblies more prone to proteolytic attack.

3. Beck, K., V. C. Chan, N. Shenoy, A. Kirkpatrick, J. A. Ramshaw, and B. Brodsky. **"Destabilization of Osteogenesis Imperfecta Collagen-Like Model Peptides Correlates With the Identity of the Residue Replacing Glycine."** *Proc Natl Acad Sci U S A* 97, no. 8 (2000): 4273-8.
Mutations resulting in replacement of one obligate Gly residue within the repeating (Gly-Xaa-Yaa)(n) triplet pattern of the collagen type I triple helix are the major cause of osteogenesis imperfecta (OI). Phenotypes of OI involve fragile bones and range from mild to perinatal lethal. In this study, host-guest triple-helical peptides of the form acetyl-(Gly-Pro-Hyp)(3)-Zaa-Pro-Hyp-(Gly-Pro-Hyp)(4)-Gly-Gly-amide are used to isolate the influence of the residue replacing Gly on triple-helix stability, with Zaa = Gly, Ala, Arg, Asp, Glu, Cys, Ser, or Val. Any substitution for Zaa = Gly (melting temperature, T(m) = 45 degrees C) results in a dramatic destabilization of the triple helix. For Ala and Ser, T(m) decreases to approximately 10 degrees C, and for the Arg-, Val-, Glu-, and Asp-containing peptides, T(m) < 0 degrees C. A Gly --> Cys replacement results in T(m) < 0 degrees C under reducing conditions but shows a broad transition (T(m) approximately 19 degrees C) in an oxidizing environment. Addition of trimethylamine N-oxide increases T(m) by approximately 5 degrees C per 1 M trimethylamine N-oxide, resulting in stable triple-helix formation for all peptides and allowing comparison of relative stabilities. The order of disruption of different Gly replacements in these peptides can be represented as Ala <= Ser < CPO(red) < Arg < Val < Glu <= Asp. The rank of destabilization of substitutions for Gly in these Gly-Pro-Hyp-rich homotrimeric peptides shows a significant correlation with the severity of natural OI mutations in the alpha1 chain of type I collagen.
4. Cabral, W. A. , E. J. Chernoff, and J. C. Marini. **"G76E Substitution in Type I Collagen Is the First Nonlethal Glutamic Acid Substitution in the Alpha1(I) Chain and Alters Folding of the N-Terminal End of the Helix."** *Mol Genet Metab* 72, no. 4 (2001): 326-35.
The majority of osteogenesis imperfecta (OI) is caused by substitutions for glycine residues in the two alpha chains of type I collagen. Since only 4% of possible nucleotide

changes in type I collagen glycine codons would result in a glutamic acid substitution, these are predicted to be infrequent. Only one glutamic acid substitution in type I collagen has been fully reported. We describe here the clinical, biochemical, and molecular characterization of a girl with severe type III OI caused by a G76E substitution in COL1A1. This is the first delineation of a glutamic acid substitution in the alpha1(I) chain causing nonlethal osteogenesis imperfecta. The proband's fibroblast type I collagen chains and cyanogen bromide peptides were electrophoretically normal, while osteoblast collagen was slightly overmodified. This suggested a mutation near the N-terminal end of the collagen helix. A mismatch was detected by RNA:DNA hybrid analysis in cDNA coding for 106 amino acids at the N-terminal end of the helical region. Subclones of both alleles were sequenced and revealed a G --> A (c.761G > A) mutation causing an alpha1(I) G76E substitution in one allele. The presence of the mutation in the proband's leukocyte gDNA, and its absence in parental gDNA, was confirmed by Tsp509I digestion. The glutamic acid substitution alters the folding of the mutant collagen helices. Pericellular processing of type I collagen by the proband's fibroblasts yielded an earlier appearance of the pC-alpha1(I) form and of mature alpha chains as compared to control cell processing. Also, the presence of the glutamic acid substitution apparently exposes the adjacent Arg75 residue in the alpha1 chain. Trypsin digestion of proband fibroblast collagen resulted in shortened alpha1 chains, as confirmed by CNBr analysis. In addition, the Tm for mutant helices from fibroblasts and osteoblasts was decreased 2-4 degrees C versus controls, demonstrating a decrease in helix stability. These findings increase our understanding of the disruptive effect of glutamic acid substitutions in collagen. Copyright 2001 Academic Press.

5. Cabral, W. A. , A. Fertala, L. K. Green, J. Korkko, A. Forlino, and J. C. Marini. **"Procollagen With Skipping of Alpha 1(I) Exon 41 Has Lower Binding Affinity for Alpha 1(I) C-Telopeptide, Impaired in Vitro Fibrillogenesis, and Altered Fibril Morphology."** *J Biol Chem* 277, no. 6 (2002): 4215-22.

Previous in vitro data on type I collagen self-assembly into fibrils suggested that the amino acid 776-796 region of the alpha1(I) chain is crucial for fibril formation because it serves as the recognition site for the telopeptide of a docking collagen monomer. We used a natural collagen mutation with a deletion of amino acids 766-801 to confirm the importance of this region for collagen fibril formation. The proband has type III osteogenesis imperfecta and is heterozygous for a COL1A1 IVS 41 A(+4) --> C substitution. The intronic mutation causes splicing of exon 41, confirmed by sequencing of normal and shorter reverse transcriptase-PCR products. Reverse transcriptase-PCR using RNA from proband dermal fibroblasts and clonal cell lines showed the mutant cDNA was about 15% of total alpha1(I) cDNA. The mutant transcript is translated; structurally abnormal alpha chains are demonstrated in the cell layer of proband fibroblasts by SDS-urea-PAGE. The proportion of mutant chains in the secreted procollagen was determined to be 10% by resistance to digestion with MMP-1, since chains lacking exon 41 are missing the vertebral collagenase cleavage site. Secreted proband collagen was used for analysis of kinetics of binding of alpha1(I) C-telopeptide using an optical biosensor. Telopeptide had slower association and faster dissociation from proband than from normal collagen. Purified proband pC-collagen was used to study fibril formation. The presence of the mutant molecules decreases the rate of fibril formation. The fibrils formed in the presence of 10-15% mutant molecules have strikingly increased length compared with normal collagen, but are well organized, as

demonstrated by D-periodicity. These results suggest that some collagen molecules containing the mutant chain are incorporated into fibrils and that the absence of the telopeptide binding region from even a small portion of the monomers interferes with fibril growth. Both abnormal fibrils and slower remodeling may contribute to the severe phenotype.

6. Dawson, P. A. , and J. C. Marini. "**Hammerhead Ribozymes Selectively Suppress Mutant Type I Collagen mRNA in Osteogenesis Imperfecta Fibroblasts.**" *Nucleic Acids Res* 28, no. 20 (2000): 4013-20.

Ribozymes are a promising agent for the gene therapy of dominant negative genetic disorders by allele-specific mRNA suppression. To test allele-specific mRNA suppression in cells, we used fibroblasts from a patient with osteogenesis imperfecta (OI). These cells contain a mutation in one alpha1(I) collagen allele which both causes the skeletal disorder and generates a novel ribozyme cleavage site. In a preliminary in vitro assay, ribozymes cleaved mutant RNA substrate whereas normal substrate was left intact. For the studies in cell culture we generated cell lines stably expressing active (AR) and inactive (IR) ribozymes targeted to mutant alpha1(I) collagen mRNA. Quantitative competitive RT-PCR analyses of type I collagen mRNA, normalized to beta-actin expression levels, revealed that the level of mutant alpha1(I) collagen mRNA was significantly decreased by approximately 50% in cells expressing AR. Normal alpha1(I) collagen mRNA showed no significant reduction when AR or IR was expressed from the pHbetaAPr-1-neo vector and a small (10-20%) but significant reduction when either ribozyme was expressed from the pCI.neo vector. In clonal lines derived from cells expressing AR the level of ribozyme expression correlated with the extent of reduction in the mutant:normal alpha1(I) mRNA ratio, ranging from 0.33 to 0.96. Stable expression of active ribozyme did not affect cell viability, as assessed by growth rates. Ribozyme cleavage of mutant mRNA results in a reduction in mutant type I collagen protein, as demonstrated by SDS-urea-PAGE. This is the first report of ribozymes causing specific suppression of an endogenous mutant mRNA in cells derived from a patient with a dominant negative genetic disorder.

7. Forlino, A., D. R. Keene, K. Schmidt, and J. C. Marini. "**An Alpha2(I) Glycine to Aspartate Substitution Is Responsible for the Presence of a Kink in Type I Collagen in a Lethal Case of Osteogenesis Imperfecta.**" *Matrix Biol* 17, no. 8-9 (1998): 575-84.

Type I collagen synthesized by cultured skin fibroblasts was analyzed biochemically and molecularly to characterize the defect in a patient affected by lethal Osteogenesis Imperfecta. The SDS-Urea-PAGE of procollagen and collagen revealed a broad alpha1(I) band, a normal alpha2(I) and another alpha2(I) band migrating equidistant between alpha1 and alpha2. When synthesized in the presence of alpha,alpha'-dipyridyl, an inhibitor of prolyl and lysyl hydroxylation, procollagen and collagen of media and cell layers contained both normal and slower alpha2(I), but only normal alpha1(I). The persistence of the two forms of alpha2(I) chains suggested a mutation in a COL1A2 gene. CNBr cleavage of collagen yielded overmodified alpha1(I) CB3 and CB7 peptides and delayed migration of the alpha2(I) CB3-5 peptide. A delayed CB3-5 was also found after alpha,alpha'-dipyridyl treatment. These data localized the mutation between aa 353 and 551 in alpha2(I) (CB3-5). Sequencing the subcloned alleles in this region revealed a G-->A transition at nt 1671 in one allele, changing Gly 421 to Asp in

an alpha2(I) chain. The mutation was demonstrated to occur on the paternally derived allele, using a common C-->A polymorphism at alpha2(I) nt 1585 and by the presence of a rare variant, Arg618-->Gln (Phillips et al., 1990), in the paternal genomic DNA and the proband's mutant allele. Procollagen processing was normal. The Tm of the slow alpha2(I) collagen was 2 degrees C lower than the control, indicating decreased triple helix stability. Mutant collagen was incorporated in the extracellular matrix deposited by cultured fibroblasts. The dramatic delay in alpha2(I) electrophoretic mobility must be induced by the Gly-->Asp substitution, since the Arg-->Gln variant causes only mild electrophoretic delay. Substantial delay in gel mobility even in the absence of overmodification suggested the presence of a kink in the mutated alpha2(I) chains. Rotary shadowing electron microscopy of secreted fibroblast procollagen confirmed the presence of a kink in the region of the helix containing the glycine substitution. The kinking of the collagen helix occurs in the absence of dimer formation. Kinking may interfere with normal helix folding, as well as with the interactions of collagen fibrils with the collagenous and non-collagenous extracellular matrix proteins.

8. Johnson, C., D. Primorac, M. McKinstry, J. McNeil, D. Rowe, and J. B. Lawrence. **"Tracking COL1A1 RNA in Osteogenesis Imperfecta. Splice-Defective Transcripts Initiate Transport From the Gene but Are Retained Within the SC35 Domain."** *J Cell Biol* 150, no. 3 (2000): 417-32.

This study illuminates the intra-nuclear fate of COL1A1 RNA in osteogenesis imperfecta (OI) Type I. Patient fibroblasts were shown to carry a heterozygous defect in splicing of intron 26, blocking mRNA export. Both the normal and mutant allele associated with a nuclear RNA track, a localized accumulation of posttranscriptional RNA emanating to one side of the gene. Both tracks had slightly elongated or globular morphology, but mutant tracks were cytologically distinct in that they lacked the normal polar distribution of intron 26. Normal COL1A1 RNA tracks distribute throughout an SC-35 domain, from the gene at the periphery. Normally, almost all 50 COL1A1 introns are spliced at or adjacent to the gene, before mRNA transits thru the domain. Normal COL1A1 transcripts may undergo maturation needed for export within the domain such as removal of a slow-splicing intron (shown for intron 24), after which they may disperse. Splice-defective transcripts still distribute thru the SC-35 domain, moving approximately 1-3 micrometer from the gene. However, microfluorimetric analyses demonstrate mutant transcripts accumulate to abnormal levels within the track and domain. Hence, mutant transcripts initiate transport from the gene, but are impeded in exit from the SC-35 domain. This identifies a previously undefined step in mRNA export, involving movement through an SC-35 domain. A model is presented in which maturation and release for export of COL1A1 mRNA is linked to rapid cycling of metabolic complexes within the splicing factor domain, adjacent to the gene. This paradigm may apply to SC-35 domains more generally, which we suggest may be nucleated at sites of high demand and comprise factors being actively used to facilitate expression of associated loci.

9. Kivirikko, K. I. **"Collagens and Their Abnormalities in a Wide Spectrum of Diseases."** *Ann Med* 25, no. 2 (1993): 113-26.

Collagens are a family of extracellular matrix proteins that play a dominant role in maintaining the structural integrity of various tissues. Nineteen collagen types containing altogether more than 30 distinct polypeptide chains have now been

identified, and their genes have been found to be dispersed among at least 12 chromosomes. Mutations in collagen genes or deficiencies in the activities of specific post-translational enzymes of collagen synthesis have been characterized in many heritable disorders such as osteogenesis imperfecta, several chondrodysplasias, several subtypes of the Ehlers-Danlos syndrome, the X-linked Alport syndrome and dystrophic forms of epidermolysis bullosa. In addition, collagen mutations have been found in certain common diseases, namely osteoporosis, osteoarthritis and aortic aneurysms, and it is now evident that subsets of patients with these diseases have defects in types I, II or III collagen, respectively, as a predisposing factor. Mutations have so far been identified in only six of the more than 30 collagen genes, and thus research into collagen defects is only in its early stages. Transgenic mice have been shown to offer an excellent tool for investigating the consequences of mutations in collagen genes and identifying additional diseases caused by collagen defects. Excessive collagen accumulation also poses a common problem in medicine, leading to fibrosis with impairment of the normal functioning of the affected tissue. This has prompted attempts to develop drugs which inhibit collagen synthesis. Prolyl 4-hydroxylase would seem a particularly suitable target for antifibrotic therapy, and several compounds are now known that inhibit this enzyme. In particular, derivatives of pyridine 2,4-dicarboxylate have been shown to inhibit hepatic collagen accumulation in rats with two models of liver fibrosis.

10. Kuivaniemi, H., G. Tromp, and D. J. Prockop. "**Mutations in Fibrillar Collagens (Types I, II, III, and XI), Fibril-Associated Collagen (Type IX), and Network-Forming Collagen (Type X) Cause a Spectrum of Diseases of Bone, Cartilage, and Blood Vessels.**" *Hum Mutat* 9, no. 4 (1997): 300-15.

This review summarizes the data on 278 different mutations found to date in the genes for types I, II, III, IX, X, and XI collagens from 317 apparently unrelated patients. A majority (217 mutations; 78% of the total) of the mutations are single-base and either change the codon of a critical amino acid (63%), or lead to abnormal RNA splicing (13%). Most of the amino acid substitutions are those of a bulkier amino acid for the obligatory glycine of the repeating-Gly-X-Y-sequence of the collagen triple helix (155; 56%). Altogether, 26 different mutations (9.4% of the mutations) occur in more than one unrelated individual. The 65 patients in whom the 26 mutations were characterized constitute almost one-fifth (20.5%) of the 317 patients analyzed. The mutations in types I, II, III, IX, X, and XI collagens cause a wide spectrum of diseases of bone, cartilage, and blood vessels, including osteogenesis imperfecta, a variety of chondrodysplasias, types IV and VII of the Ehlers-Danlos syndrome, and, rarely, some forms of osteoporosis, osteoarthritis, and familial aneurysms.

11. Lund, A. M., M. Hansen, G. Kollerup, A. Juul, B. Teisner, and F. Skovby. "**Collagen-Derived Markers of Bone Metabolism in Osteogenesis Imperfecta.**" *Acta Paediatr* 87, no. 11 (1998): 1131-7.

Markers of bone formation [C-terminal and N-terminal propeptides of procollagen I (PICP, PINP), osteocalcin and alkaline phosphatase] and bone resorption [C-terminal cross-linked telopeptide of collagen I (ICTP) and hydroxypyridinium cross-links, pyridinoline (Pyr) and deoxypyridinoline (Dpyr)] were measured in 78 osteogenesis imperfecta (OI) patients to investigate bone metabolism in vivo and relate marker concentrations to phenotype and in vitro collagen I defects, as shown by sodium

dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE). PICP and PINP were generally low, and the serum levels were lower in all children and adults with mild OI and a quantitative collagen defect than in patients with severe OI and a qualitative collagen I defect. ICTP, Pyr and Dpyr were generally normal or reduced, but elevated in severely affected adults with a qualitative collagen I defect. The in vivo findings correlated with in vitro results of collagen I SDS-PAGE. Bone turnover is reduced in OI children and mildly affected OI adults, whereas bone resorption is elevated in severely affected adults. These findings may prove helpful for diagnosis and decision-making regarding therapy in OI.

12. Marini, J. C., M. B. Lewis, Q. Wang, K. J. Chen, and B. M. Orrison. **"Serine for Glycine Substitutions in Type I Collagen in Two Cases of Type IV Osteogenesis Imperfecta (OI). Additional Evidence for a Regional Model of OI Pathophysiology."** *J Biol Chem* 268, no. 4 (1993): 2667-73.

Serine for glycine substitutions in type I collagen have been described in seven cases of lethal type II osteogenesis imperfecta (OI), and six cases of nonlethal OI. We describe here two cases of moderately severe type IV OI with serine substitutions at alpha 1(I) Gly352 and alpha 2(I) Gly922, respectively. In both cases, G-->A point mutations were detected by RNase A cleavage of RNA/RNA and RNA/DNA hybrids. These cases extend the location for serine substitutions producing the moderately severe OI phenotype to the alpha 2(I) chain and the amino-terminal end of the alpha 1(I) chain. Their location supports a regional model of OI pathophysiology for serine substitutions. The proband with alpha 2(I) Gly922-->Ser has both normal and overmodified forms of both type I collagen chains. The overmodified form has delayed migration of all CNBr peptides. Helix thermal stability is decreased 4 degrees C. The fibroblast collagen protein and RNA of her unaffected parents are normal. However, the father was demonstrated to be a mosaic carrier using leukocyte DNA. The fibroblasts of the proband whose serine substitution is at alpha 1(I) Gly352 synthesize type I procollagen chains with delayed electrophoretic migration; normally migrating forms are difficult to detect. Only alpha 1(I) CB 8 displayed delayed migration. Helix thermal stability is reduced 2 degrees C. Parental genomic DNA was normal.

13. Misof, K., W. J. Landis, K. Klaushofer, and P. Fratzl. **"Collagen From the Osteogenesis Imperfecta Mouse Model (Oim) Shows Reduced Resistance Against Tensile Stress."** *J Clin Invest* 100, no. 1 (1997): 40-5.

Osteogenesis imperfecta (OI) is a disease attributable to any of a large number of possible mutations of type I collagen. The disease is clinically characterized in part by highly brittle bone, the cause of this feature being unknown. Recently a mouse model of OI, designated as osteogenesis imperfecta murine (oim), and having a well defined genetic mutation, has been studied and found to contain mineral crystals different in their alignment with respect to collagen and in their size. These observations are consistent with those reported in human OI and the unusual crystal alignment and size undoubtedly contribute to the reduced mechanical properties of OI bone. While the mineral has been investigated, no information is available on the tensile properties of oim collagen. In this study, the mechanical properties of tendon collagen under tension have been examined for homozygous (oim/oim), heterozygous (+/oim), and control (+/+) mice under native wet conditions. The ultimate stress and strain found for oim/oim collagen were only about half the values for control mice. Assuming that

prestrained collagen molecules carry most of the tensile load in normal bone while the mineral confers rigidity and compression stability, the reported results suggest that the brittleness of OI bone in the mouse model may be related to a dramatic reduction of the ultimate tensile strain of the collagen.

14. Raff, M. L., W. J. Craigen, L. T. Smith, D. R. Keene, and P. H. Byers. "**Partial COL1A2 Gene Duplication Produces Features of Osteogenesis Imperfecta and Ehlers-Danlos Syndrome Type VII.**" *Hum Genet* 106, no. 1 (2000): 19-28.

Type I collagen is the most abundant structural protein in the mammalian body. It exists as a heterotrimer of two subunits in the form $[\alpha 1(I)]_2\alpha 2(I)$. Pathogenic mutations in COL1A1 and COL1A2, the genes that encode the two subunits, cause a range of phenotypes including mild to lethal forms of osteogenesis imperfecta and a restricted set of Ehlers-Danlos syndrome phenotypes. Lethal mutations usually result from missense mutations that disrupt the normal triple helical structure of the molecule. Multi-exon duplication or deletion in type I collagen genes has rarely been observed and has generally resulted in a lethal or severe phenotype. We report a partial duplication in the COL1A2 gene that causes a relatively mild phenotype, despite the addition of 477 amino acids to the triple helical domain of the pro $\alpha 2(I)$ chain. The abnormal molecule is synthesized and secreted by cultured dermal fibroblasts in a normal fashion. Electron microscopy of dermal tissue reveals small but otherwise near normal collagen fibrils. The gene duplication occurred by mitotic sister chromatid exchange in the mother who is mosaic for the duplication allele. Examination of the abnormal sequence suggests a means by which the duplicated molecule could be processed and properly incorporated into mature collagen fibrils.

15. Sarafova, A. P., H. Choi, A. Forlino, A. Gajko, W. A. Cabral, L. Tosi, C. M. Reing, and J. C. Marini. "**Three Novel Type I Collagen Mutations in Osteogenesis Imperfecta Type IV Probands Are Associated With Discrepancies Between Electrophoretic Migration of Osteoblast and Fibroblast Collagen.**" *Hum Mutat* 11, no. 5 (1998): 395-403.

In three cases of type IV osteogenesis imperfecta (OI), we identified unique point mutations in type I collagen $\alpha 1(I)$ cDNA. In two cases, the appearance of dimers indicated the presence of cysteine substitutions in the $\alpha 1(I)$ protein chain. Cyanogen bromide digestion localized these cross-links to CB8 and 3, respectively. In the third case, the overmodification pattern of the CNBr peptides was compatible with a substitution in the aa 123-402 region of either type I collagen chain. We identified a unique point mutation in each proband, which resulted in substitutions for glycine residues in a 300-aa region of the $\alpha 1(I)$ helix, specifically, Gly to Ala at codon 220 (GGT-->GCT), Gly to Cys at codon 349 (GGT-->TGT) and Gly to Cys at codon 523 (GGT-->TGT). We compared each proband's fibroblast and osteoblast collagen directly, as well as with fibroblast and osteoblast controls. For all cases, the OI osteoblast collagen was more electrophoretically delayed than OI fibroblast collagen. In the patient with G349C, OI fibroblast and osteoblast collagen synthesized in the presence of α, α' -dipyridyl co-migrated on gels, demonstrating that the electrophoretic discrepancy resulted from differences in post-translational modification. Melting temperature curves for stability of the collagen helix yielded an identical T_m for control fibroblast and osteoblast collagen (41.2 degrees C). By contrast, for collagen with the gly349-->cys substitution, the T_m of the fibroblast collagen was 1 degree C lower than

the Tm of the osteoblast collagen. These data indicate that the metabolism of mutant collagen might be cell-specific and has significant implications for understanding the phenotype/genotype correlations and the pathophysiology of OI.

16. Sarathchandra, P., F. M. Pope, and S. Y. Ali. "**Morphometric Analysis of Type I Collagen Fibrils in the Osteoid of Osteogenesis Imperfecta.**" *Calcif Tissue Int* 65, no. 5 (1999): 390-5.

Electron microscopy and morphometric measurements of bone osteoid collagen diameter from 42 osteogenesis imperfecta (OI) patients and 25 age- and site-matched controls were carried out. Although the mean diameter did not correlate well with the severity of the disease, it related well with the clinical types and revealed collagen fibrils of reduced diameter in the osteoid of all OI types. Thus, OI type II (the severest type) demonstrated the smallest diameter (45 nm), followed by OI type I (the mildest form) with a mean diameter of 57 nm. The diameter obtained for type III (67 nm) and type IV (64 nm) was lower than the normal control mean diameter (73 nm) but did not show a statistical difference. The thinner fibrils observed in OI bone may be unable to provide nucleating and scaffolding sites for mineral propagation and may play a role in the fragility of bone in this disease.

17. Slayton, R. L., S. P. Deschenes, and M. C. Willing. "**Nonsense Mutations in the COL1A1 Gene Preferentially Reduce Nuclear Levels of mRNA but Not hnRNA in Osteogenesis Imperfecta Type I Cell Strains.**" *Matrix Biol* 19, no. 1 (2000): 1-9.

Osteogenesis imperfecta (OI) is a heterogeneous disorder of type I collagen resulting in varying degrees of severity. The mildest form of OI (Type I) is associated with bone fragility, normal or near normal stature and blue sclerae. All forms of OI are the result of mutations in COL1A1 or COL1A2, the genes that encode the proalpha1(I) and proalpha2(I) chains of type I collagen, respectively. Mutations identified in patients with OI type I lead to premature termination codons and allele-specific reductions of nuclear mRNA (termed nonsense-mediated mRNA decay or NMD), resulting in a COL1A1 null allele. In mammals, this process primarily effects RNA that co-purifies with the nuclear fraction of the cell. Using a semi-quantitative RT-PCR assay, we compare the relative amounts of normal and mutant transcripts in unprocessed hnRNA and mature mRNA isolated from the nuclear fraction of cells from 11 OI type I individuals with previously identified mutations distributed throughout the COL1A1 gene. While we detect about equal amounts of normal and mutant hnRNA from each cell strain, there is preferential reduction in the relative amount of mutant mRNA when compared to normal; only the cell strain with a mutation in the last exon escapes the major effects of NMD. Our data indicate that NMD targets mRNA rather than hnRNA for degradation, and that this occurs either during or after splicing but prior to cytoplasmic translation.

3.3 Other Basic Science

1. Cole, W. G. "**The Nicholas Andry Award-1996. The Molecular Pathology of Osteogenesis Imperfecta.**" *Clin Orthop*, no. 343 (1997): 235-48.

A systematic analysis of the molecular pathology of osteogenesis imperfecta was undertaken in 200 cases. The findings indicate that molecular defects of Type I collagen are the major cause of this disease. The mild form of osteogenesis imperfecta is caused by quantitative anomalies of Type I collagen. The other forms of the disease, which are more severe, are caused by quantitative and qualitative anomalies of Type I collagen. The mutant Type I collagen molecules are secreted poorly and are susceptible to intracellular and extracellular degradation with loss of normal and mutant collagen chains. The mutant molecules severely impair the formation of the extracellular matrix causing an abnormal architecture of dermis and bone. The molecular pathology was correlated with the clinical, radiologic, and pathologic features. As a result, the clinical classification was expanded and a new biochemical classification of osteogenesis imperfecta was developed.

2. Fedarko, N. S., P. D'Avis, C. R. Frazier, M. J. Burrill, V. Fergusson, M. Tayback, P. D. Sponseller, and J. R. Shapiro. "**Cell Proliferation of Human Fibroblasts and Osteoblasts in Osteogenesis Imperfecta: Influence of Age.**" *J Bone Miner Res* 10, no. 11 (1995): 1705-12.

Clinical studies indicate that as a group, osteogenesis imperfecta (OI) subjects are shorter than age- and sex-matched controls. Not only somatic growth, but also cellular growth appears to be impaired, and these may be related to defects in extracellular matrix common to this disorder. We have investigated the growth characteristics of dermal fibroblasts and trabecular osteoblasts isolated from patients with OI and control subjects of various ages. Cell growth curves and cell doubling times were determined by measuring cell number using crystal violet dye binding. Growth curves were modeled by a modified logistic function, the three parameters of which are markers for biologically relevant growth parameters: the plateau value or upper asymptote, which reflects the maximum cell density upon confluence; the maximal growth rate (microM); and the lag time. Both normal human fibroblasts and osteoblasts showed an age-dependent decrease in microM. Normal fibroblasts exhibited no age-dependence to their upper asymptote or lag time. Fibroblasts derived from patients with OI did not have significantly different upper asymptote values microM, or lag times when compared with normal fibroblasts. Normal osteoblasts had a decrease in upper asymptote, decrease in microM, but a relatively constant lag time with increasing age. In contrast, OI osteoblast microM was decreased relative to that of normal subjects. For osteoblasts from OI patients, decreased microM appeared unrelated to the age of the subject, whereas OI fibroblasts did exhibit an age-dependent decrease in microM. The percentage of collagenase-digestible protein (a measure of collagen synthesis) produced by normal human fibroblasts correlated well with microM. Treating normal human osteoblasts with the proline analogue 3,4-dehydroproline, which destabilizes collagen triple helix formation and alters collagen synthesis, secretion, and turnover, also decreased microM. A dose response to varying concentrations of 3,4-dehydroproline was observed for normal human bone cell microM. These data suggest a link between type I collagen synthesis and cellular proliferation.

3. Forlino, A., F. D. Porter, E. J. Lee, H. Westphal, and J. C. Marini. **"Use of the Cre/Lox Recombination System to Develop a Non-Lethal Knock-in Murine Model for Osteogenesis Imperfecta With an Alpha1(I) G349C Substitution. Variability in Phenotype in BrtlIV Mice."** *J Biol Chem* 274, no. 53 (1999): 37923-31.

We utilized the Cre/lox recombination system to develop the first knock-in murine model for osteogenesis imperfecta (OI). The moderately severe OI phenotype was obtained from an alpha1(I) Gly(349) --> Cys substitution in type I collagen, reproducing the mutation in a type IV OI child. We introduced four single nucleotide (nt) changes into murine colla1 exon 23: the disease causing G-->T transversion (nt 1546), an adjacent G-->T change (nt 1551) to generate a GUC ribozyme cleavage site, and two transversions (nt 1567 C-->A and nt 1569 C-->G) to cause a Leu --> Met substitution. We also introduced a 3.2-kilobase pair transcription/translation stop cassette in intron 22, flanked by directly repeating lox recombination sites. After homologous recombination in ES cells, two male chimeras were obtained. Chimeras were mated with transgenic females expressing Cre recombinase to remove the stop cassette from a portion of the progeny's cells. To generate mice with full expression of the Gly(349) --> Cys mutation, these offspring were then mated with wild-type females. Skeletal staining and bone histology of the F2 revealed a classical OI phenotype with deformity, fragility, osteoporosis and disorganized trabecular structure. We designate these mice BrtlIV (Brittle IV). BrtlIV mice have phenotypic variability ranging from perinatal lethality to long term survival with reproductive success. The phenotypic variability is not associated with differences in expression levels of the mutant allele in total RNA derived from tissue extracts. Expression of the mutant protein is also equivalent in different phenotypes. Thus, these mice are an excellent model for delineation of the modifying factors postulated to affect human OI phenotypes. In addition, we generated knock-in mice carrying an "intronic" inclusion by mating chimeras with wild-type females. Alternative splicing involving the stop cassette results in retention of non-collagenous sequences. These mice reproduce the lethal phenotype of similar human mutations and are designated BrtIII.

4. Gebken, J., R. Brenner, A. Feydt, H. Notbohm, J. Brinckmann, P. K. Muller, and B. Batge. **"Increased Cell Surface Expression of Receptors for Transforming Growth Factor-Beta on Osteoblasts From Patients With Osteogenesis Imperfecta."** *Pathobiology* 68, no. 3 (2000): 106-12.

Osteogenesis imperfecta (OI) is a heritable connective tissue disorder usually characterized by either a reduction in the production of normal collagen I or the synthesis of abnormal collagen. The variability in the clinical phenotype is not in each case sufficiently explained by the underlying mutation in the collagen I genes. Also, biochemical differences between mutant collagen from different tissues suggest additional regulatory mechanisms possibly involved in matrix deposition and maturation, two processes in which transforming growth factor-beta (TGF-beta) plays an important role. We, therefore, studied the cell surface expression and functional properties of TGF-beta receptors I, II and III on osteoblasts from a group of OI patients compared to healthy controls. Receptor number and affinity were determined by Scatchard analysis of binding data and TGF-beta receptor II gene expression was assessed by RT-PCR. Ligand-induced downregulation of TGF-beta receptors was analyzed to demonstrate the dynamic response to exogenous stimuli. All experiments were performed in parallel in human osteoblastic cells from OI patients and from age-

matched controls. TGF-beta receptors I, II and III (betaglycan) were present on osteoblasts from both healthy donors and OI patients. The receptor numbers were significantly higher (29,000 per cell) on OI osteoblasts than on age-matched control osteoblasts (12,000 per cell) in spite of similar steady state levels for TGF-beta receptor II mRNA in OI and control cells. Furthermore, receptor affinity was not significantly different in OI osteoblasts (181 vs. 177 nM(-1)), and the receptor number did not depend on the culture substrate. With respect to dynamic adaption, ligand-induced downregulation of TGF-beta receptors was reduced in OI osteoblasts. In conclusion, the human osteoblastic cells from patients with OI investigated all have an elevated number of cell surface receptors for TGF-beta, without any evidence for a transcriptional regulation of TGF-beta receptor II. On the functional level, there is some evidence for an impaired adaptive behavior of receptor presentation, whereas receptor affinity is unchanged.

5. Korkko, J., L. Ala-Kokko, A. De Paepe, L. Nuytinck, J. Earley, and D. J. Prockop. **"Analysis of the COL1A1 and COL1A2 Genes by PCR Amplification and Scanning by Conformation-Sensitive Gel Electrophoresis Identifies Only COL1A1 Mutations in 15 Patients With Osteogenesis Imperfecta Type I: Identification of Common Sequences of Null-Allele Mutations."** *Am J Hum Genet* 62, no. 1 (1998): 98-110. Although >90% of patients with osteogenesis imperfecta (OI) have been estimated to have mutations in the COL1A1 and COL1A2 genes for type I procollagen, mutations have been difficult to detect in all patients with the mildest forms of the disease (i.e., type I). In this study, we first searched for mutations in type I procollagen by analyses of protein and mRNA in fibroblasts from 10 patients with mild OI; no evidence of a mutation was found in 2 of the patients by the protein analyses, and no evidence of a mutation was found in 5 of the patients by the RNA analyses. We then searched for mutations in the original 10 patients and in 5 additional patients with mild OI, by analysis of genomic DNA. To assay the genomic DNA, we established a consensus sequence for the first 12 kb of the COL1A1 gene and for 30 kb of new sequences of the 38-kb COL1A2 gene. The sequences were then used to develop primers for PCR for the 103 exons and exon boundaries of the two genes. The PCR products were first scanned for heteroduplexes by conformation-sensitive gel electrophoresis, and then products containing heteroduplexes were sequenced. The results detected disease-causing mutations in 13 of the 15 patients and detected two additional probable disease-causing mutations in the remaining 2 patients. Analysis of the data developed in this study and elsewhere revealed common sequences for mutations causing null alleles.
6. Nuytinck, L., C. Coppin, and A. De Paepe. **"A Four Base Pair Insertion Polymorphism in the 3' Untranslated Region of the COL1A1 Gene Is Highly Informative for Null-Allele Testing in Patients With Osteogenesis Imperfecta Type I."** *Matrix Biol* 16, no. 6 (1998): 349-52. In patients with osteogenesis imperfecta (OI) type I, a decrease in synthesis of type I collagen is usually observed as a result of a COL1A1 null allele. Testing for COL1A1 null alleles can be done using polymorphic markers in the coding region of the COL1A1 gene. Until now, only one marker for polymorphism in the 3' untranslated region (3' UTR) of the COL1A1 gene has been available. We have identified a 4 bp insertion in the 3' UTR of the COL1A1 gene localized downstream of the MnlI RFLP

and used both markers in combination for the analysis of patients with OI type I. In a total of 50 patients, 28 showed heterozygosity for one of the two markers; 14 of them were shown to have a COL1A1 null allele.

7. Pereira, R. F., M. D. O'Hara, A. V. Laptev, K. W. Halford, M. D. Pollard, R. Class, D. Simon, K. Livezey, and D. J. Prockop. "**Marrow Stromal Cells As a Source of Progenitor Cells for Nonhematopoietic Tissues in Transgenic Mice With a Phenotype of Osteogenesis Imperfecta.**" *Proc Natl Acad Sci U S A* 95, no. 3 (1998): 1142-7.

Marrow stromal cells from wild-type mice were infused into transgenic mice that had a phenotype of fragile bones resembling osteogenesis imperfecta because they expressed a human minigene for type I collagen. In mice that were irradiated with potentially lethal levels (700 cGy) or sublethal levels (350 cGy), DNA from the donor marrow stromal cells was detected consistently in marrow, bone, cartilage, and lung either 1 or 2.5 mo after the infusions. The DNA also was detected but less frequently in the spleen, brain, and skin. There was a small but statistically significant increase in both collagen content and mineral content of bone 1 mo after the infusion. Similar results were obtained with infusion of relatively large amounts of wild-type whole marrow cells into the transgenic mice. In experiments in which male marrow stromal cells were infused into a female osteogenesis imperfecta-transgenic mouse, fluorescence in situ hybridization assays for the Y chromosome indicated that, after 2.5 mo, donor male cells accounted for 4-19% of the fibroblasts or fibroblast-like cells obtained in primary cultures of the lung, calvaria, cartilage, long bone, tail, and skin. In a parallel experiment in which whole marrow cells from a male mouse were infused into a female immunodeficient rag-2 mouse, donor male cells accounted for 4-6% of the fibroblasts or fibroblast-like cells in primary cultures. The results support previous suggestions that marrow stromal cells or related cells in marrow serve as a source for continual renewal of cells in a number of nonhematopoietic tissues.

8. Willing, M. C., C. J. Pruchno, and P. H. Byers. "**Molecular Heterogeneity in Osteogenesis Imperfecta Type I.**" *Am J Med Genet* 45, no. 2 (1993): 223-7.

Osteogenesis imperfecta (OI) type I is characterized by bone fragility without significant deformity, osteopenia, normal stature, blue sclerae, and autosomal dominant inheritance. Dermal fibroblasts from most affected individuals produce about half the expected amount of type I collagen, suggesting that the OI type I phenotype results from a variety of mutations which alter the apparent expression of either COL1A1 or COL1A2, the genes encoding the chains of type I collagen. Short-pulse labeling of dermal fibroblasts with [³H]proline from affected individuals in 19 families indicates that most have alterations in the expected 2:1 synthetic ratio of pro alpha 1(I): pro alpha 2(I), with most having decreased production of pro alpha 1(I). Ratios of COL1A1:COL1A2 mRNA from these individuals, using slot-blot hybridization, indicate that they fall into different groups, but that most have decreased COL1A1 mRNA levels, compared with controls. These data suggest that most of our OI I families have COL1A1 mutations. Copy number and size of the COL1A1 gene by restriction endonuclease analysis of genomic DNA from affected individuals are normal in the families examined. We have identified one 3 generation family in which all affected members have one normal COL1A1 allele and another with a 5 base-pair deletion near the 3' end of the gene. The deletion creates a shift in the translational

reading-frame and predicts the synthesis of an elongated pro alpha 1(I) chain. In a second family, a father and a son have a single exon deletion that results from a splicing mutation. Chemical cleavage analysis of amplified cDNA from affected individuals in different regions of the COL1A1 gene, including the promoter, suggests that several individuals have point mutations within the coding region of the gene, while one individual may have a small deletion within the alpha 1(I) carboxyl-terminal propeptide region. Our data provide evidence for significant molecular heterogeneity within the OI type I phenotype and indicate that a variety of mutations can result in decreased synthesis of type I collagen.

9. Zhuang, J., G. Tromp, H. Kuivaniemi, S. Castells, M. Bugge, and D. J. Prockop. "**Direct Sequencing of PCR Products Derived From cDNAs for the Pro Alpha 1 and Pro Alpha 2 Chains of Type I Procollagen As a Screening Method to Detect Mutations in Patients With Osteogenesis Imperfecta.**" *Hum Mutat* 7, no. 2 (1996): 89-99.
More than 150 mutations in the genes for type I procollagen have been found in unrelated patients with osteogenesis imperfecta (OI), but mutations have been difficult to define in many patients with the mildest forms of the disease. Here, we have used robotically automated sequencing of the cDNAs for type I procollagen to screen for mutations in 12 patients suspected of having nonlethal OI (types I, III, and IV). Single base mutations that changed codons for obligate glycine residues were found in seven of the patients. Altogether, we analyzed 4,379 bp of sequences of both alleles of the pro alpha 1 (I) collagen (8,758 bp of allelic sequences) and 4,200 bp of sequences of both alleles of the pro alpha 2(I) collagen (8,400 bp of allelic) from each patient.

4.0 Clinical Manifestations

4.1 Callus

1. Dobrocky, I., G. Seidl, and F. Grill. "**MRI and CT Features of Hyperplastic Callus in Osteogenesis Imperfecta Tarda.**" *Eur Radiol* 9, no. 4 (1999): 665-8.
We describe the MRI and CT findings of hyperplastic callus formation simulating a tumour of pelvis in patient with osteogenesis imperfecta tarda. Possible differential diagnoses and the impact of different imaging techniques on the correct diagnosis are discussed.
2. Nakamura, K., T. Kurokawa, A. Nagano, and T. Umeyama. "**Familial Occurrence of Hyperplastic Callus in Osteogenesis Imperfecta.**" *Arch Orthop Trauma Surg* 116, no. 8 (1997): 500-3.
There is a hypothesis that hyperplastic callus (HC) in osteogenesis imperfecta (OI) is not merely a rare complication but could actually be inherited, although this idea has not yet been investigated. We described two cases, a mother and son, with mild OI, normal scleral colour and no dentinogenesis imperfecta, who repeatedly had HC in their femur. Familial occurrence of HC was found in 13 cases in 5 families among 21 cases in 7 families with a familial background of OI in the literature (including this report). This is higher than the reported incidence of HC, 1.5% (5 cases of 333), and the mode of transmission is concomitant with autosomal dominant inheritance in all these

families. Since a review of 47 cases in the literature shows that HC occurs independently of scleral colour and the degree of bone fragility, it may be an additional criterion for subdivision within each type of the Sillence classification.

3. Rieker, O., K. F. Kreitner, and A. Karbowski. "**Hyperplastic Callus Formation in Osteogenesis Imperfecta: CT and MRI Findings.**" *Eur Radiol* 8, no. 7 (1998): 1137-9.

Hyperplastic callus formation is a noteworthy condition in patients with osteogenesis imperfecta because it often mimicks osteosarcoma on radiography. The findings of CT and MRI in hyperplastic callus formation have not been reported. In the presented case, MRI demonstrated contrast enhancement and edema of the surrounding soft tissue, consistent with benign as well as malignant disease. Computed tomography showed a calcified rim of the lesion which may be a useful feature to rule out osteosarcoma in this condition.

4. Smith, R. "**Hyperplastic Callus and Osteogenesis Imperfecta.**" *Lancet* 357, no. 9252 (2001): 248-9.

4.2 Cardiovascular System

1. Almassi, G. H., G. R. Hughes, and J. Bartlett. "**Combined Valve Replacement and Coronary Bypass Grafting in Osteogenesis Imperfecta.**" *Ann Thorac Surg* 60, no. 5 (1995): 1395-7.

Open cardiac procedures in osteogenesis imperfecta have been associated with a high mortality rate. A patient with osteogenesis imperfecta underwent successful aortic valve replacement and coronary artery bypass grafting along with closure of a patent foramen ovale in preparation for a planned hip replacement. [See related comment: Cusimano, R. J. "Repeat Cardiac Operation in a Patient with Osteogenesis Imperfecta." *Ann Thorac Surg* 61, no. 4 (April 1996): 1294.]

2. Hortop, J., P. Tsiouras, J. A. Hanley, B. J. Maron, and J. R. Shapiro. "**Cardiovascular Involvement in Osteogenesis Imperfecta.**" *Circulation* 73, no. 1 (1986): 54-61.

While aortic root dilatation and valvular dysfunction have been well-documented in osteogenesis imperfecta (OI), the nature and extent of cardiovascular involvement in OI have not been clearly delineated. A clinical and echocardiographic survey involving 109 individuals with various nonlethal OI syndromes from 66 separate families was undertaken. Clinically discernible valvular dysfunction was encountered in only four of the 109 individuals (aortic regurgitation in two, aortic stenosis in one, and mitral valve prolapse in one), none of whom were related. Aortic root dilatation was recognized echocardiographically in eight (12.1%) of 66 individuals comprising a subset of the sample in which each family was represented by a single individual. The extent of the aortic root dilatation was mild (the largest dimension measuring 4.3 cm) and was unrelated to the age of the individual. Dilatation was seen in each of the different OI syndromes but was strikingly segregated within certain families (p less than .001). In the same subset of 66 individuals, mitral valve prolapse was encountered in two or 6.9% of the 29 individuals aged 15 years or greater in whom adequate studies were obtained. This observed frequency was not different from that seen in a normal adult

population. Aortic root dilatation appears to represent a distinct phenotypic trait in patients with OI that is nonprogressive and occurs in about 12% of affected individuals. Whether mitral valve prolapse should be considered as a part of the cardiovascular phenotype in OI, or alternately segregates as an independent autosomal dominant trait has yet to be determined.

3. Isotalo, P. A., M. M. Guindi, P. Bedard, M. P. Brais, and J. P. Veinot. "**Aortic Dissection: a Rare Complication of Osteogenesis Imperfecta.**" *Can J Cardiol* 15, no. 10 (1999): 1139-42.

Osteogenesis imperfecta (OI) is an inherited connective tissue disorder, a group that includes Ehlers-Danlos syndrome, Marfan's syndrome and pseudoxanthoma elasticum. OI is a heterogeneous disease of collagen I biosynthesis characterized by variable clinical phenotypes, including skeletal and cardiovascular manifestations. A 65-year-old man with OI who had extensive prior successful cardiac valve surgeries is described. He survived for 18 years after his initial valve surgery, but died of multiorgan failure and sepsis after repair of a spontaneous type A aortic dissection. This is the fourth reported case of aortic dissection secondary to OI and illustrates the extensive cardiovascular pathology associated with OI. Aggressive management of arterial dissection risk factors, such as systemic arterial hypertension, is advocated for patients with OI.

4. Izzat, M. B., S. Wan, I. Y. Wan, K. S. Khaw, and A. P. Yim. "**Ministernotomy for Aortic Valve Replacement in a Patient With Osteogenesis Imperfecta.**" *Ann Thorac Surg* 67, no. 4 (1999): 1171-3.

Open heart operations in patients with osteogenesis imperfecta are associated with increased morbidity and mortality resulting from tissue friability and bone brittleness. We used a ministernotomy approach for aortic valve replacement in a patient with osteogenesis imperfecta, with clear benefits and a satisfactory outcome.

5. Wong, R. S., F. M. Follis, B. K. Shively, and J. A. Wernly. "**Osteogenesis Imperfecta and Cardiovascular Diseases.**" *Ann Thorac Surg* 60, no. 5 (1995): 1439-43.

Aortic and mitral valvular insufficiency in patients with osteogenesis imperfecta result from an underlying defect in connective tissue formation. The surgical cases reported in the literature have included mechanical and bioprosthetic valve replacement as well as attempts at repair and reconstruction. Despite complications related to bleeding and tissue friability, acceptable results have been obtained. In this report, we describe aortic regurgitation secondary to osteogenesis imperfecta treated with homograft replacement. The unique cardiovascular complications of osteogenesis imperfecta and the available therapeutic options are discussed in light of the literature review. [See related comment: "Repeat Cardiac Operation in a Patient with Osteogenesis Imperfecta." *Ann Thorac Surg* 61, no 4 (April 1996): 1294.]

6. Zegdi, R., N. D'Attellis, P. Fornes, J. F. Fuzellier, J. P. Carteaux, J. N. Fabiani, and A. Carpentier. "**Aortic Valve Surgery in Osteogenesis Imperfecta: Report of Two Cases and Review of the Literature.**" *J Heart Valve Dis* 7, no. 5 (1998): 510-4.

Aortic insufficiency is a well known but uncommon valvular dysfunction in patients with osteogenesis imperfecta. In such cases, aortic valve surgery has rarely been performed, and carries a high risk of perioperative complications. We report two

patients with osteogenesis imperfecta, who underwent elective successful aortic valve replacement. The surgical problems encountered in this connective tissue disorder are also reviewed.

4.3 Dental

1. Bell, R. B., and R. P. White Jr. "**Osteogenesis Imperfecta and Orthognathic Surgery: Case Report With Long-Term Follow-Up.**" *Int J Adult Orthodon Orthognath Surg* 15, no. 3 (2000): 171-8.

Osteogenesis imperfecta (OI) is the product of the abnormal synthesis and/or production of Type I collagen. Successful surgical management of extremity and spinal skeletal problems secondary to OI is documented in the orthopedic literature. Reports of successful facial skeletal surgery in all types of OI are encouraging. The purpose of this paper is to report on the long-term results of an orthognathic surgery patient successfully treated to correct a severe dentofacial deformity. The patient underwent an uncomplicated Le Fort I osteotomy with homologous interpositional bone grafts to advance and inferiorly reposition the maxilla. Clinically, the patient appeared to heal without difficulty, and a stable Class I skeletal and dental relationship was achieved. Nine years after surgery, the patient has a Class I occlusion, with maintenance of his facial height and skeletal relationship. Craniomaxillofacial surgery can be predictably performed in patients with OI as long as the surgeon maintains strict adherence to proper surgical technique and bears in mind the deficiencies of bone density and other possible medical complications.

2. Lindau, B., W. Dietz, T. Lundgren, K. Storhaug, and J. G. Noren. "**Discrimination of Morphological Findings in Dentine From Osteogenesis Imperfecta Patients Using Combinations of Polarized Light Microscopy, Microradiography and Scanning Electron Microscopy.**" *Int J Paediatr Dent* 9, no. 4 (1999): 253-61.

OBJECTIVES: The aim of this study was to investigate the morphological appearance of dentine in teeth from individuals with osteogenesis imperfecta type I, III and IV using different histological techniques, and to correlate morphological findings to different types of osteogenesis imperfecta. SAMPLE AND METHODS: Extracted or exfoliated primary and permanent teeth were collected from 15 patients with the osteogenesis imperfecta diagnoses I, III or IV, with or without the additional diagnosis dentinogenesis imperfecta. Ground and decalcified sections were prepared from the teeth. Histomorphological studies of the dentine were performed utilizing light and polarized light microscopy, microradiography and scanning electron microscopy. RESULTS: Characteristic findings were irregular tubules, remnants of capillary inclusions and obliterated pulps. All types of osteogenesis imperfecta exhibited similar types of dentine aberrations, but patients with type III or IV had a higher frequency of aberrations when compared to type I. CONCLUSIONS: The combination of either polarized light microscopy or micro-radiography, together with scanning electron microscopy, gave the most amount of morphological information from dentine samples. In addition, aberrations in dentine structure were more clearly observable. Light microscopy was not critical for the analyses.

3. Lindau, B. M. , W. Dietz, I. Hoyer, T. Lundgren, K. Storhaug, and J. G. Noren. **"Morphology of Dental Enamel and Dentine-Enamel Junction in Osteogenesis Imperfecta."** *Int J Paediatr Dent* 9, no. 1 (1999): 13-21.
OBJECTIVES: The aim of this study was to examine the morphology of primary and permanent human enamel, and the dentine-enamel junction, in individuals with osteogenesis imperfecta (OI) type I, III and IV in undecalcified sections using polarized light microscopy, microradiography and scanning electron microscopy (SEM), and to relate the findings to the type of OI. SAMPLE AND METHODS: Extracted or exfoliated teeth from 15 patients representing the OI types I, III and IV (12 primary teeth from seven patients, and 11 permanent teeth from eight patients). Ten primary and nine permanent teeth from normal healthy patients served as controls. The teeth were serially cut longitudinally in a bucco-lingual direction and contact microradiographs were made. The sections were examined in polarized light. Sections of primary and permanent teeth were examined by means of SEM. RESULTS: This study shows that the permanent enamel from patients with OI exhibits few structural changes. No relationships were found between enamel morphology and the types of OI (I, III, IV). Primary enamel appeared to be slightly more irregularly mineralized, especially in cases with the additional diagnosis dentinogenesis imperfecta. The major findings were deviations in association with the dentine-enamel junction, and locally a lower degree of mineralization. CONCLUSIONS: The mesodermal disease OI might also be manifested in ectodermal enamel, probably because of suboptimal mesenchymal-ectodermal interactions during amelogenesis.

4. Lund, A. M., B. L. Jensen, L. A. Nielsen, and F. Skovby. **"Dental Manifestations of Osteogenesis Imperfecta and Abnormalities of Collagen I Metabolism."** *J Craniofac Genet Dev Biol* 18, no. 1 (1998): 30-7.
The in vitro protein-chemical features and the molecular background of osteogenesis imperfecta (OI), a heritable disorder of collagen I metabolism, have been elucidated in recent years. The aim of our study was to find the prevalence of dentinogenesis imperfecta (DI) and other dental anomalies in 88 patients with OI, to compare clinical with radiologic abnormalities, and to correlate these clinical/radiologic findings with the results of gel electrophoresis and molecular studies of collagen I. Twenty-eight percent of OI patients had DI. Most patients with DI had radiologic abnormalities, but some patients had radiologic signs compatible with DI, but no clinical signs of DI. OI type I patients with DI were more severely affected by OI than those without DI. In OI type III and IV, in contrast, there was no difference in overall severity between patients with and without DI. DI was not associated with any particular molecular aberration in any OI type. If defining DI from the presence of both clinical and radiologic signs, collagen I produced by cultured fibroblasts was qualitatively abnormal from all OI patients with DI. Some OI patients had dental abnormalities not resembling DI. A qualitative collagen abnormality could not be found in any of these patients. Denticles, i.e., calcifications within the pulpal cavity, were found more frequently in OI patients than in control subjects.

5. Lygidakis, N. A., R. Smith, and C. J. Oulis. "**Scanning Electron Microscopy of Teeth in Osteogenesis Imperfecta Type I.**" *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 81, no. 5 (1996): 567-72.

Opalescent teeth from five patients and nonopalescent teeth from six patients with osteogenesis imperfecta type I were examined with the scanning electron microscope and their appearances compared with those of teeth from normal persons. In opalescent teeth the main findings were a reduction in the number and variation in the size of the dentinal tubules that were irregularly embedded within the disturbed dentinal matrix and an abnormally smooth enamel-dentinal junction. Similar less marked dentinal abnormalities were found in the nonopalescent teeth from three patients. No abnormality was found in the enamel in any of the teeth examined. These findings suggest that in osteogenesis imperfecta teeth that appear normal may have defective dentine. This relevant to the current clinical classification of the disorder into subgroups according to the clinical presence or absence of affected teeth.

6. Mahoney, E. K., R. P. Widmer, and D. O. Sillence. "**Opalescent Dentine in Two Affected Siblings.**" *N Z Dent J* 97, no. 427 (2001): 15-8.

This report describes the dental findings and management of siblings in a family in which three generations had been affected by osteogenesis imperfecta Type IV with opalescent dentine. Hereditary opalescent dentine, or opalescent teeth, is a pathologic dental condition characterised by a disturbance of dentine formation that occurs concurrently with osteogenesis imperfecta. Osteogenesis imperfecta is a genetically heterogenous group of systemic disorders of the connective tissue. The two siblings affected with opalescent dentine were treated under general anaesthesia, and included stainless steel crowns, extractions, and strip crowns on primary teeth. These reports highlight that appropriate treatment of the dentition of young patients with opalescent dentine should be carried out early in the primary dentition, and that this initial treatment can have long-term benefits in the mixed and permanent dentitions.

7. O'Connell, A. C., and J. C. Marini. "**Evaluation of Oral Problems in an Osteogenesis Imperfecta Population.**" *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 87, no. 2 (1999): 189-96.

OBJECTIVE: The incidence of craniofacial and dental anomalies in children with the more severe nonlethal forms of osteogenesis imperfecta was evaluated. **STUDY DESIGN:** The study evaluated 40 children (age range, 1-17.5 years) with types III and IV osteogenesis imperfecta. In each case, the dentition was evaluated for the presence of dentinogenesis imperfecta, attrition, and caries, as well as for radiographic appearance, dental development, and malocclusion. **RESULTS:** The incidence of dentinogenesis imperfecta was greater than 80% in the primary dentition. Clinically, the color of the dentition was of predictive value in appropriate management of the primary dentition. Tooth discoloration and attrition did not occur to the same extent in the permanent dentition as in the primary dentition in either group. Class III dental malocclusion occurred in 70% to 80% of this osteogenesis imperfecta population, with a high incidence of anterior and posterior cross bites and open bites. A delay in dental development was observed in 21% of patients type III osteogenesis imperfecta, whereas accelerated development was noted in 23% of the patients with type IV. In addition, ectopic eruption occurred in 13 patients. **CONCLUSIONS:** In addition to dentinogenesis imperfecta, significant oral problems occur in types III and IV

osteogenesis imperfecta. Other features that impact the dental management of this population are highlighted.

4.4 Hearing

1. Dieler, R., J. Muller, and J. Helms. "**Stapes Surgery in Osteogenesis Imperfecta Patients.**" *Eur Arch Otorhinolaryngol* 254, no. 3 (1997): 120-7.

Osteogenesis imperfecta (OI), or the Van der Hoeve-de Kleyn syndrome, is a heterogeneous group of connective tissue disorders. The key features in this disease are bone fragility with a tendency to spontaneous fractures and deformations. The classical triad of symptoms involves a conductive and/or sensorineural hearing impairment together with a tendency to spontaneous bone fractures and blue sclerae. Between January 1988 and December 1994, ear surgery was performed on eight ears of six OI patients who presented with mixed hearing loss preoperatively. Pathological changes observed in the middle ear were atrophy and/or fractures of the stapedial crura in combination with thickening and fixation of the stapes footplate. Partial stapedectomy was performed in seven cases and a neo-window was created in the promontory of one patient when an overhanging facial canal obscured visualization of the oval window niche. Pre- and postoperative bone conduction thresholds did not differ in any of the patients. Postoperatively, mean values of the air-bone gap in the main speech frequency range were below 10 dB. Functional results following stapes surgery in patients with otosclerosis during the same time interval (n = 857) did not differ significantly. These data indicate that stapes surgery in OI patients can be performed with the same functional predictability as in otosclerosis patients, even though the underlying etiology is considerably different.

2. Ferekidis, E. , P. Stavroulaki, I. Vossinakis, J. Yiotakis, L. Manolopoulos, and G. Adamopoulos. "**Stapedotomy in Osteogenesis Imperfecta Patients.**" *J Laryngol Otol* 114, no. 6 (2000): 424-8.

Osteogenesis imperfecta (OI) is a connective tissue disorder characterized by osseous fragility, blue sclerae and hearing loss. In order to assess the impact of stapedotomy on improving hearing on OI, a retrospective, one-group, pre-test-post-test design was used to compare the pre-operative and post-operative audiograms of nine OI patients, treated with stapedotomy for their mixed hearing loss. Operative findings included fixation or thickening of the stapes footplate with normal superstructure configuration and hypervascularization of the promontory mucosa. Immediate post-operative results showed a significant improvement ($p < 0.05$) from 250-4000 Hz in air conduction and from 250-2000 Hz in bone conduction. A significant closure of the air-bone gap between 250-2000 Hz was also achieved ($p < 0.05$). The long-term results remained satisfactory with a mean threshold shift of 8 dB HL and an almost unchanged air-bone gap. These satisfactory results and the lack of complications make stapedotomy an appealing method for the management of OI-associated hearing loss.

3. Garretsen, A. J., C. W. Cremers, and P. L. Huygen. "**Hearing Loss (in Nonoperated Ears) in Relation to Age in Osteogenesis Imperfecta Type I.**" *Ann Otol Rhinol Laryngol* 106, no. 7 Pt 1 (1997): 575-82.

Hearing loss was studied in relation to age in nonoperated ears in a group of 142 subjects with autosomal dominant osteogenesis imperfecta type I, which was compared to that in a random subsample of 70 subjects. In the n = 142 group, particularly below the age of 30 years, considerable selection (ie, for ear surgery) had occurred on hearing loss. The hearing threshold increased gradually with age. A hearing loss of greater than 30 dB (Fletcher index) was observed for 51% of the subjects older than 20 years and younger than 60 years. The median hearing loss progressed from the 10th to the 45th years of life with an average annual threshold increase (ATI) of 1 dB/y (0.5 to 4 kHz) up to 1.7 dB/y (8 kHz). Sensorineural loss accounted for 0.6 dB/y ATI at 0.5 to 4 kHz and 1.3 dB/y ATI at 8 kHz; conductive loss accounted for 0.4 dB/y ATI at all frequencies.
4. Kuurila, K., R. Grenman, R. Johansson, and I. Kaitila. "**Hearing Loss in Children With Osteogenesis Imperfecta.**" *Eur J Pediatr* 159, no. 7 (2000): 515-9.

Osteogenesis imperfecta (OI) is a genetic disorder of connective tissue. Progressive hearing loss is one of the principal symptoms of OI, affecting about 50% of adult patients. Hearing loss may also occur in childhood and results in additional disability in education and psychosocial adaptation and aggravates the physical handicap. This can be avoided by appropriate otological and audiological treatment. In a nationwide search, 254 Finnish patients with OI were identified indicating a prevalence of 4.9/100,000. Of the 60 children, 45 aged between 4 and 16 years accepting to participate the study on hearing, were evaluated by a questionnaire and clinical audiometry. Hearing loss was defined as pure tone average (PTA0.5-2 kHz) more than 20 dB hearing level (HL). A clinical geneticist determined the type of OI among the 45 patients. Two sporadic OI cases with conductive hearing loss were ascertained (4.4%): An 11-year-old girl with type IV OI with a PTA0.5-2 kHz of 35/40 dB HL and a 15-year-old boy with type IV OI with a PTA0.5-2 kHz of 27/18 dB HL. In addition, a 6-year-old girl with familial OI type I had either a congenital sensorineural deafness or early progressive deafness with PTA0.5-2 kHz of 97/103 dB HL, probably of unrelated aetiology. CONCLUSION: Hearing loss in children with osteogenesis imperfecta is less frequent than generally suspected. Nevertheless, it is recommended that audiometry is performed in children with osteogenesis imperfecta even without symptoms of hearing loss at the age of 10 years, and repeated every 3 years thereafter.
5. Paterson, C. R., E. A. Monk, and S. J. McAllion. "**How Common Is Hearing Impairment in Osteogenesis Imperfecta?**" *J Laryngol Otol* 115, no. 4 (2001): 280-2.

Hearing impairment has long been recognized as a common feature in osteogenesis imperfecta. The figures in some publications could be taken to imply that, with increasing age, the proportion of osteogenesis imperfecta patients with hearing impairment approaches 100 per cent. The incidence of hearing loss in a large survey of 1394 patients with osteogenesis imperfecta was examined. It was found that the most common age of onset was in the second, third and fourth decades of life. At the age of 50 approximately 50 per cent of the patients had symptoms of hearing impairment; over the next 20 years there was little further increase. Differences were shown between patients with different clinical types of osteogenesis imperfecta as delineated in the

Sillence classification; hearing loss was significantly less common in the type IV disease than in the type I disorder. Among the 29 families with osteogenesis imperfecta type IA there were distinct differences in the likelihood of hearing loss. These findings provide insights which will be valuable in giving patients advice on the likelihood of developing hearing loss in the future.

6. Pedersen, U. "**Hearing Loss in Patients With Osteogenesis Imperfecta. A Clinical and Audiological Study of 201 Patients.**" *Scand Audiol* 13, no. 2 (1984): 67-74.
Clinical otological features, hearing status and middle ear function in 201 patients with osteogenesis imperfecta are presented. The study covered 76% of the expected total number of patients with osteogenesis imperfecta in Denmark. 78% of the patients exhibited an autosomal dominant inheritance pattern with an almost 100% penetrance. In 39% of the ears examined, a conductive or mixed hearing loss was found. Sensorineural hearing loss or anacusis was seen in 11% of the ears. In most cases the onset of hearing impairment was noted in the second or third decade and progressing with increasing age, especially after the age of 60. Tympanometry and acoustic reflex measurements suggested that the cause of conductive or mixed hearing loss was stapedial fixation and in a few cases ossicular discontinuity due to aplasia or fracture of the stapedial crura. Findings during stapedectomy in 32 patients confirmed these assumptions.
7. Szilvassy, J. , J. Jori, J. Czigner, F. Toth, Z. Szilvassy, and J. G. Kiss. "**Cochlear Implantation in Osteogenesis Imperfecta.**" *Acta Otorhinolaryngol Belg* 52, no. 3 (1998): 253-6.
A case is reported in which a Nucleus 22 channel intracochlear implant was applied to a Hungarian woman (age 50 yr) with profound deafness associated with osteogenesis imperfecta. Successful intracochlear insertion of the 22 electrodes resulted in a 70 dB hearing improvement at frequencies 250-2000 HZ. Nevertheless, a characteristic facial twitching appeared upon activation of electrodes 9-13. Inactivation of these electrodes abolished the non-acoustic nerve excitation with preservation of acoustic performance. Osteogenesis imperfecta may involve a state of risk for non-acoustic nerve activation in cochlear implant patients possibly resulting from a reduced impedance to current spread by abnormal bone tissue. This, however can be overcome by simple programming manoeuvres.
8. Verstreken, M., J. Claes, and P. H. Van de Heyning. "**Osteogenesis Imperfecta and Hearing Loss.**" *Acta Otorhinolaryngol Belg* 50, no. 2 (1996): 91-8.
A review of the literature of osteogenesis imperfecta (OI) and hearing loss in the last century is given. This includes the first association in 1912 by Adair-Dighton of OI with hearing loss, the triad of VAN DER HOEVE and DE KLEYN and different clinical and audiometric studies and classifications of the disease. A case report of a 14 year old patient is also included. The genetics of OI and the complexity in correlating genetics with clinical classifications is elucidated. Finally, the findings reported after middle ear surgery, the results of surgery and comparisons with otosclerosis are reviewed.

4.5 Neurology

1. Charnas, L. R., and J. C. Marini. "**Communicating Hydrocephalus, Basilar Invagination, and Other Neurologic Features in Osteogenesis Imperfecta.**" *Neurology* 43, no. 12 (1993): 2603-8.

Osteogenesis imperfecta (OI) is anecdotally associated with macrocephaly, hydrocephalus, basilar invagination, and cerebral atrophy, but the frequency and the spectrum of neurologic features of this condition are poorly defined. We report our experience with 76 patients with OI seen at NIH. Neuroimaging studies demonstrated sulcal prominence and ventriculomegaly consistent with communicating hydrocephalus in 17 patients. Eight individuals with severe OI types displayed basilar invagination, causing brainstem compression in three patients. Head circumference growth showed abnormal kinetics with percentile crossing after fontanelle closure in 13 patients, and absolute macrocephaly was present in 11 patients. Additional neurologic complications included skull fracture (10 individuals); seizure disorders (five); transient, unexplained long tract signs (three); and spinal compression and pontine, cervical, and thoracic syringohydromyelia (one patient each). The clinically important neurologic complications appear to be brainstem compression from basilar invagination, skull fracture, and seizure disorders. Neurologic evaluation should be part of a team approach in the management of patients with severe OI types.

2. Emery, S. C., N. C. Karpinski, L. Hansen, and E. Masliah. "**Abnormalities in Central Nervous System Development in Osteogenesis Imperfecta Type II.**" *Pediatr Dev Pathol* 2, no. 2 (1999): 124-30.

Osteogenesis imperfecta (OI) type II is a perinatally lethal condition resulting from mutations in type I collagen genes. In addition to characteristic skeletal anomalies, OI type II has recently been shown to be associated with neuropathological alterations, specifically perivenous microcalcifications, and impaired neuroblast migration. In light of these findings, and because type I collagen promotes neuritic maturation both in vitro and in vivo, we sought to determine if additional central nervous system (CNS) developmental anomalies could be found in previously autopsied OI type II cases, and if specific abnormalities correlate with OI subtypes. We retrospectively studied brains of nine patients diagnosed with OI. Of these, seven were OI type II: five were OI type IIA, one was type IIB, and one was type IIC. One OI type I specimen and one OI type III brain were included for comparison, as well as five controls. The IIC brain showed hippocampal malrotation, agyria, abnormal neuronal lamination, diffuse hemorrhage, and periventricular leukomalacia (PVL). The IIB brain had white matter gliosis, PVL, and perivascular calcifications, but was normally developed. Of the five type IIA brains, two showed migrational defects with coexisting PVL and gliosis, two were normally developed with similar white matter injuries, and one was grossly normal. These findings support the contention that collagen mutations might negatively impact CNS development.

3. Hayes, M., G. Parker, J. Ell, and D. Sillence. "**Basilar Impression Complicating Osteogenesis Imperfecta Type IV: the Clinical and Neuroradiological Findings in Four Cases.**" *J Neurol Neurosurg Psychiatry* 66, no. 3 (1999): 357-64.

OBJECTIVES: To describe the clinical and neuroradiological features of basilar impression in patients with osteogenesis imperfecta type IV. METHODS: Four patients

with basilar impression were ascertained in a population study of osteogenesis imperfecta. All four had detailed clinical and neuroradiological examination with both CT and MRI of the craniocervical junction and posterior fossa structures. RESULTS: All four showed significant compression of the posterior fossa structures and surgical decompression was performed with relief of symptoms. CONCLUSION: Symptoms of cough headache and trigeminal neuralgia occurring in patients with osteogenesis imperfecta are indications for detailed clinical and neuroradiological investigation to document basilar impression.

4. Sawin, P. D., and A. H. Menezes. "**Basilar Invagination in Osteogenesis Imperfecta and Related Osteochondrodysplasias: Medical and Surgical Management.**" *J Neurosurg* 86, no. 6 (1997): 950-60.

Osteogenesis imperfecta (OI) is a heritable disorder of bone development caused by defective collagen synthesis. Basilar invagination is an uncommon but devastating complication of this disease. The authors present a comprehensive strategy for management of craniovertebral anomalies associated with OI and related osteochondrodysplasias. Twenty-five patients with congenital osteochondrodysplasias (18 OI, four Hajdu-Cheney syndrome, and three spondyloepiphyseal dysplasia) and basilar invagination were evaluated between 1985 and 1995. The male/female ratio in this cohort was 1:1. The mean age at presentation was 11.9 years (range 13 months-20 years). Fourteen patients (56%) presented during adolescence (11-15 years of age). Symptoms and signs included headache (76%), lower cranial nerve dysfunction (68%), hyperreflexia (56%), quadriparesis (48%), ataxia (32%), nystagmus (28%), and scoliosis (20%). Four patients (16%) were asymptomatic. Seven (28%) had undergone previous posterior fossa decompression; one had also undergone ventral decompression. Imaging findings included basilar invagination (100%), ventral brainstem compression (84%), hydrocephalus (32%), hindbrain herniation (28%), and syringomyelia/syringobulbia (16%). Patients with hydrocephalus underwent ventricular shunt placement. Reducible basilar invagination (40%) was treated with posterior fossa decompression and occipitocervical fusion. Those with irreducible ventral compression (60%) underwent transoral-transpalatopharyngeal decompression followed by occipitocervical fusion. All patients improved initially. However, basilar invagination progressed radiographically in 80% (symptomatic in 24%) despite successful fusion. Prolonged external orthotic immobilization with the modified Minerva brace afforded symptomatic improvement and arrested progression of the deformity. The mean follow-up period was 5.9 years (range 1.1-10.5 years). Ventral brainstem compression in OI should be treated with ventral decompression, followed by occipitocervical fusion with contoured loop instrumentation to prevent further squamooccipital infolding. Despite fusion, however, basilar invagination tends to progress. Prolonged immobilization (particularly during adolescence) may stabilize symptoms and halt further invagination. This study represents the largest series to date addressing craniovertebral anomalies in OI and related congenital bone softening disorders.

4.6 Renal Function

1. Chines, A., A. Boniface, W. McAlister, and M. Whyte. "**Hypercalciuria in Osteogenesis Imperfecta: a Follow-Up Study to Assess Renal Effects.**" *Bone* 16, no. 3 (1995): 333-9.

In 1991, we reported that hypercalciuria is a common finding in our pediatric patient population with osteogenesis imperfecta (OI) (17 of 47 = 36%). Here, we prospectively screened 12 of these hypercalciuric children, on average 4 years subsequent to the discovery of elevated urine calcium levels, for adverse effects on renal function. Despite an ad libitum decrease since initial investigation of about 30% in their previously normal dietary calcium intake (adjusted for body weight), 8 of the 12 patients remained hypercalciuric (urine calcium/creatinine > 0.62 mmol/mmol). We found, once again, that urinary calcium levels significantly correlated with the severity of the skeletal disease as assessed by z-score for height ($r = -0.75$, $p = 0.005$). Evaluation of kidney function, however, revealed: (i) normal routine urinalysis in all but 1 subject who had transient microscopic hematuria; (ii) unremarkable concentrating ability determined by fasting urine osmolality; (iii) normal creatinine clearance, and (iv) unremarkable ultrasonography to measure renal size and to screen for nephrocalcinosis or nephrolithiasis. Although no significant renal compromise was detected with these studies in our hypercalciuric pediatric OI patients, investigation of affected adults, especially those severely affected, will be important to assess whether this is a long-term problem and if adverse effects on the kidneys do develop.

2. Venugopala, D., S. Babu, M. P. Korath, and K. Jagadeesan. "**Renal Stone Disease As Extra Skeletal Manifestation of Osteogenesis Imperfecta.**" *J Assoc Physicians India* 48, no. 10 (2000): 1027-8.
3. Williams, C. J., R. A. Smith, R. J. Ball, and H. Wilkinson. "**Hypercalcaemia in Osteogenesis Imperfecta Treated With Pamidronate.**" *Arch Dis Child* 76, no. 2 (1997): 169-70.

The response to the bisphosphonate, pamidronate, is reported in a child with osteogenesis imperfecta who had recurrent symptomatic hypercalcaemia after immobilisation following fractures. Oral clodronate was effective in the prevention of immobilisation hypercalcaemia in the same child. The bisphosphonates may have other roles in osteogenesis imperfecta by decreasing bone turnover. [See related comment : Shaw, N. J. "Bisphosphonates in Osteogenesis Imperfecta." *Arch Dis Child* 77, no. 1 (July 1997): 92-3.]

4.7 Spine

1. Engelbert, R. H., W. J. Gerver, L. J. Breslau-Siderius, Y. van der Graaf, H. E. Pruijs, J. M. van Doorne, F. A. Beemer, and P. J. Helders. "**Spinal Complications in Osteogenesis Imperfecta: 47 Patients 1-16 Years of Age.**" *Acta Orthop Scand* 69, no. 3 (1998): 283-6.

We examined in a cross-sectional study, 47 children (mean age 7.7 (1-16) years) with osteogenesis imperfecta (OI) to find the prevalence of spinal deformities and to correlate these observations with anthropometry. The associations between

dentinogenesis imperfecta, joint hypermobility and spinal deformities were also studied. Disproportion in stature in OI type I and type IV was mainly caused by spinal involvement, as evidenced by a greater decrease in body height than in leg length. In OI type I, the decrease in sitting height was mainly caused by platyspondyly, whereas in OI types III and IV, it was also caused by progressive scoliosis and kyphosis. Scoliosis was present in 22 children, and pathological kyphosis in 18, mainly in the severe OI types. Basilar impression was observed in 10 children, mainly in type III. Children with dentinogenesis imperfecta seemed to be prone to develop scoliosis, pathological kyphosis and basilar impression. Children with generalized joint hypermobility were less prone to develop scoliosis and basilar impression. Our observations may contribute to a better understanding of the risk factors for progressive spinal deformities in OI.

2. Ishikawa, S., S. J. Kumar, H. E. Takahashi, and M. Homma. **"Vertebral Body Shape As a Predictor of Spinal Deformity in Osteogenesis Imperfecta."** *J Bone Joint Surg Am* 78, no. 2 (1996): 212-9.

We analyzed forty-four patients who had osteogenesis imperfecta, in order to determine the prevalence of spinal deformities. At the time of the most recent follow-up scoliosis was present in thirty patients (68 per cent) and kyphosis, in eighteen (41 per cent). According to the classification system of Falvo et al., scoliosis progressed rapidly with growth in twelve of fifteen patients who had the congenita type of osteogenesis imperfecta and in four of thirteen who had the tarda-I type. Curves that progressed before puberty did not always continue to progress after cessation of growth. Lateral roentgenograms made at the initial examination revealed four types of vertebral body deformities: biconcave, flattened, wedged, and unclassifiable vertebrae: Biconcave vertebrae were seen characteristically in patients who had the congenita type of osteogenesis imperfecta. The presence of six biconcave vertebrae or more before puberty indicated that severe scoliosis (more than 50 degrees) was likely to develop. Biconcave vertebrae did not appear to affect the severity of kyphosis. The other types of vertebral deformities were not useful for predicting progression of spinal deformity.

3. Janus, G. J., G. Finidori, R. H. Engelbert, M. Pouliquen, and J. E. Pruijs. **"Operative Treatment of Severe Scoliosis in Osteogenesis Imperfecta: Results of 20 Patients After Halo Traction and Posterior Spondylodesis With Instrumentation."** *Eur Spine J* 9, no. 6 (2000): 486-91.

Correction and stabilisation of the scoliotic spine in osteogenesis imperfecta is difficult. The optimal technique has yet to be determined, since no large series in which a single procedure has been carried out by a single surgeon using a single protocol has yet been described. The charts of 20 patients with osteogenesis imperfecta who had undergone halo gravity traction (HGT) and a posterior spondylodesis with Cotrel-Dubousset (n = 18) or Harrington (n = 2) instrumentation were reviewed. No correction was made at the time of the surgical spondylodesis. The average follow-up was 4.8 years (range 2-10.5 years). The preoperative traction improved the Cobb angle of the scoliosis by 32% (from a mean of 78.5 degrees to a mean of 53.3 degrees) and improved the kyphosis by 24% (from a mean of 56.0 degrees to mean of 42.5 degrees). This correction deteriorated slightly at final follow-up, for both the scoliosis and the kyphosis (mean 57.6 degrees and 44.4 degrees respectively). Few complications were encountered during the HGT period. In 16 cases no complications occurred during the follow-up period. Ambulation and functional ability were upgraded for 7 of 20 patients.

4. Livesley, P. J., and P. J. Webb. "**Spinal Fusion in Situ in Osteogenesis Imperfecta.**" *Int Orthop* 20, no. 1 (1996): 43-6.

Osteogenesis imperfecta in its most severe forms has a devastating effect on the peripheral and central skeleton, and patients are unable to walk. Spinal deformity is common and causes difficulty in sitting, pain and potentially life-threatening complications. Instrumented spinal fusion might be considered the treatment of choice, but the bone may be too weak to sustain the implants and autogenous bone graft is poor in quantity and quality. We present the preliminary results of a technique of fusion without instrumentation and using Keil bone graft in 5 patients with severe osteogenesis imperfecta. The curve was stabilised and back pain relieved.

5. Reinus, W. R. , W. H. McAlister, F. Schranck, A. Chines, and M. P. Whyte. "**Differing Lumbar Vertebral Mineralization Rates in Ambulatory Pediatric Patients With Osteogenesis Imperfecta.**" *Calcif Tissue Int* 62, no. 1 (1998): 17-20.

The purpose of this study was to evaluate serial changes in bone mineral density (BMD) of the lumbar spine in individual children and adolescents with untreated osteogenesis imperfecta (OI) using dual X-ray absorptiometry (DXA). Twenty-seven pediatric patients with OI who had no historical or radiographic evidence of lumbar fracture, required no assistive device for mobility, and were taking no medications known to affect skeletal mineralization during the study period comprised the investigational group. Absolute BMD and age- and gender-matched BMD (Z-scores) were assessed relative to standard parameters of growth (height, weight, age, height adjusted for age and gender and body surface area) and severity of disease (lifetime fracture rate). The spinal mineralization rate (SMR) between examinations for 15 patients with more than one measurement (n = 20 intervals) was expressed as the magnitude of the change in BMD Z-score per year. Both BMD and BMD Z-score were closely correlated with height, height Z-score, weight and body surface area and were inversely related to fracture rate (P < 0.001 for all comparisons). BMD was also highly correlated with patient age (P < 0.001). Stepwise regression analysis showed that together height Z-score and lifetime fracture rate improved the prediction of BMD Z-score (r = 0.71; P < 0.001). SMRs ranged from -0.5 to 3.5. The average change in SMR between sequential measurements was 168% for the five children who had more than two DXA examinations. Linear regression showed a significant negative correlation between SMR and height Z-score (r = -0.79, P < 0.001). We conclude that vertebral body size is a critical determinant of BMD and BMD Z-score in OI because DXA results are expressed per unit area, not per unit volume. Pediatric patients with OI mineralize their lumbar vertebrae at rates similar to healthy children but tend to lag behind in overall mineralization. The rate of mineralization at any age appears to be related to the patient's height (adjusted for age- and gender-matched controls) and inversely related to the patient's lifetime rate of fractures. Our data suggest that vertebral mineralization in children with OI is related primarily to rapid increases in vertebral volume and only secondarily to increases in vertebral mineral density.

6. Widmann, R. F., F. D. Bitan, F. J. Laplaza, S. W. Burke , M. F. DiMaio, and R. Schneider. "**Spinal Deformity, Pulmonary Compromise, and Quality of Life in Osteogenesis Imperfecta.**" *Spine* 24, no. 16 (1999): 1673-8.

STUDY DESIGN: A cross-sectional radiologic and clinical study of patients with osteogenesis imperfecta. OBJECTIVES: To determine whether pulmonary compromise

is more closely correlated with scoliosis, kyphosis, or chest wall deformity in the population with osteogenesis imperfecta, and to assess the impact of spinal deformity, chest wall deformity, and pulmonary function on quality of life. SUMMARY OF BACKGROUND DATA: The incidence of scoliosis in osteogenesis imperfecta is between 39% and 80%. Up to 60% of patients with osteogenesis imperfecta have significant chest wall deformities. Pulmonary compromise is the leading cause of death in adults with osteogenesis imperfecta. METHODS: Fifteen patients with osteogenesis imperfecta between the ages of 20 and 45 were evaluated with sitting or standing anteroposterior and lateral radiographs of the entire spine, pulmonary function testing, and a validated health self-assessment questionnaire (Short Form-36). Radiographs were evaluated for thoracic scoliosis, thoracic kyphosis, and chest wall deformity. Correlation analysis was performed. RESULTS: Thoracic scoliosis was strongly correlated with decreased predicted vital capacity ($r = -0.76$). Significant diminution in vital capacity below 50% occurred at a curve magnitude of 60 degrees. Kyphosis and chest wall deformity were not predictive of decreased pulmonary function. Physical health (PCS) was closely correlated with predicted vital capacity ($r = 0.65$; $P < 0.01$) and with scoliosis ($r = -0.52$; $P < 0.05$). CONCLUSIONS: Thoracic scoliosis of more than 60 degrees has severe adverse effects on pulmonary function in those with osteogenesis imperfecta. This finding may partly explain the increased pulmonary morbidity noted in adult patients with osteogenesis imperfecta and scoliosis compared with that in the general population.

4.8 Other Clinical Manifestations

1. Cubert, R., E. Y. Cheng, S. Mack, M. G. Pepin, and P. H. Byers. "**Osteogenesis Imperfecta: Mode of Delivery and Neonatal Outcome.**" *Obstet Gynecol* 97, no. 1 (2001): 66-9.

OBJECTIVE: To evaluate the pregnancy characteristics, methods of delivery, and neonatal outcomes of fetuses affected by osteogenesis imperfecta. METHODS: We reviewed medical records of 1016 individuals whose cells were sent to the University of Washington Collagen Diagnostic Laboratory between 1987 and 1994 for confirmation of diagnoses of osteogenesis imperfecta. Information and neonatal records were available for 167 of those pregnancies. From those we identified method(s) of prenatal detection, delivery method, and neonatal complications, including survival and acquisition of new fractures, and related them to type of delivery. RESULTS: The cesarean delivery rate was 54%, most of them (53%) for nonvertex presentation and fewer than 15% because of an antenatal diagnoses of osteogenesis imperfecta. There was an unusually high rate of breech presentation at term (37%). In infants with nonlethal forms of osteogenesis imperfecta, 24 of 59 (40%) delivered by cesarean and 17 of 53 (32%) delivered vaginally had new fractures ($\chi^2 = .89$; $P = .3$). Among 55 infants with the most severe form, 24 of 31 delivered by cesarean and 21 of 24 delivered vaginally died within 2 weeks of birth. CONCLUSION: Cesarean delivery did not decrease fracture rates at birth in infants with nonlethal forms of osteogenesis imperfecta nor did it prolong survival for those with lethal forms. Prenatal diagnosis did not influence mode of delivery in most instances. Most cesarean deliveries were done for usual obstetric indications.

2. Lee, J. H., J. G. Gamble, R. E. Moore, and L. A. Rinsky. **"Gastrointestinal Problems in Patients Who Have Type-III Osteogenesis Imperfecta."** *J Bone Joint Surg Am* 77, no. 9 (1995): 1352-6.

We performed a study of forty-three patients who had type-III osteogenesis imperfecta. Our purpose was to determine the frequency and severity of abdominal problems and the relationship between these problems and pelvic deformity. Twelve patients had had recurrent episodes of abdominal pain. Eleven of them had a history of chronic constipation, and five had been treated for fecal impaction. Radiographs had been made for ten of these patients, and eight of them had radiographic evidence of pelvic deformity with severe acetabular protrusion. Chronic constipation and recurrent abdominal pain are more frequent in patients who have osteogenesis imperfecta and acetabular protrusion than in those who do not have protrusion. These patients may benefit from early attention to a bowel program and referral to a gastrointestinal specialist.
3. Mietz, H., L. Kasner, and W. R. Green. **"Histopathologic and Electron-Microscopic Features of Corneal and Scleral Collagen Fibers in Osteogenesis Imperfecta Type III."** *Graefes Arch Clin Exp Ophthalmol* 235, no. 7 (1997): 405-10.

BACKGROUND: This report describes the histopathologic and electron-microscopic features of an eye from a patient with osteogenesis imperfecta type III. In particular, the diameters of corneal stromal and scleral collagen fibers were determined. METHODS: The eyes of an 18-year-old white male with osteogenesis imperfecta type III were examined by light and electron microscopy and the pathological features were compared with an age-matched control eye. RESULTS: The cornea was clear. The sclera had a blue color and was moderately thinned, especially at the equator. Light microscopy revealed absence of Bowman's layer. Transmission electron microscopy confirmed complete absence of Bowman's layer without evidence of scarring or inflammation. The collagen fibers of the corneal stromal lamellae were about 25% narrower than in the control, but the cornea was otherwise unremarkable ultrastructurally. The collagen fibers of the sclera were approximately 50% narrower than in the control and were much more uniform in size. Prominent portions of elastic fibers, which are usually only present in a small number in the inner portion of the sclera, were present throughout the sclera. CONCLUSION: We propose that it is the uniformity of the scleral collagen fibers which gives the sclera translucence, producing the blue color often observed clinically in osteogenesis imperfecta. Absence of Bowman's layer of the cornea did not interfere with the stability of the cornea in this case. This appears to be the first published pathological examination of the eye in osteogenesis imperfecta type III.
4. Ogilvie-Harris, D. J., and R. Khazim. **"Tendon and Ligament Injuries in Adults With Osteogenesis Imperfecta."** *J Bone Joint Surg Br* 77, no. 1 (1995): 155-6.

Osteogenesis imperfecta is a genetically and clinically heterogenous disorder of bone and connective tissue, characterised by osteoporosis, fragile bones, hyperextensible joints, dentinogenesis imperfecta, bluish sclera and adult-onset hearing loss. Although the main defect is in the production of type-I collagen, there have been few reports of injuries to tendons and ligaments in such patients in the English literature. Three case studies are presented.

5. Silience, D., B. Butler, M. Latham, and K. Barlow. "**Natural History of Blue Sclerae in Osteogenesis Imperfecta.**" *Am J Med Genet* 45, no. 2 (1993): 183-6. Scleral hue is an important sign which distinguishes 2 broad groupings of patients, those with and those without blue sclerae with nonlethal osteogenesis imperfecta (OI). Individuals with OI type I have distinctly blue sclerae which remain intensely blue throughout life. In OI type III and OI type IV the sclerae may also be blue at birth and during infancy, but the intensity fades with time such that these individuals have sclerae of normal hue by adolescence and adult life.
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5.0 Treatments

5.1 Medical Management

1. Adami, S., D. Gatti, F. Colapietro, E. Fracassi, V. Braga, M. Rossini, and L. Tato. "**Intravenous Neridronate in Adults With Osteogenesis Imperfecta.**" *J Bone Miner Res* 18, no. 1 (2003): 126-30.
Osteogenesis imperfecta (OI) is a heritable disease of connective tissue, characterized by increased bone fragility. Bisphosphonates currently seems to be the most promising therapy, at least in children. We tested IV neridronate, an amino-bisphosphonate structurally similar to alendronate and pamidronate in adults with OI. Twenty-three men and 23 premenopausal women with OI were randomized to either iv neridronate (100 mg infused intravenously for 30 minutes every 3 months) or no treatment with a ratio of 2 to 1. Control patients were given the same bisphosphonate therapy at the end of the first year. Clinical evaluation included bone densitometry measurements using dual energy X-ray absorptiometry (DXA), fasting serum and urinary biochemistry every 6 months, and radiographs of the spine taken at baseline and after 12 and 24 months of follow-up. Spine and hip bone mineral density rose by 3.0 +/- 4.6% (SD) and by 4.3 +/- 3.9%, respectively, within the first 12 months of treatment, whereas small insignificant changes were observed in the control group. During the second year of follow-up, additional 3.91% and 1.49% increases were observed at the spine and hip, respectively. Markers of skeletal turnover significantly fell during neridronate treatment. Fracture incidence during neridronate treatment was significantly lower than before therapy and compared with controls. Neridronate iv infusions, administered quarterly, significantly increase bone mineral density and lowered the risk of clinical fracture in adults with OI. Bisphosphonate therapy seems to provide clinical benefits, not only to children with OI, but also to adult patients.
2. Antoniazzi, F., F. Bertoldo, M. Mottes, M. Valli, S. Sirpresi, G. Zamboni, R. Valentini, and L. Tato. "**Growth Hormone Treatment in Osteogenesis Imperfecta With Quantitative Defect of Type I Collagen Synthesis.**" *J Pediatr* 129, no. 3 (1996): 432-9.
OBJECTIVES: We studied growth rate, bone density, and bone metabolism in patients affected by type I osteogenesis imperfecta (OI) with quantitative defect in type I collagen synthesis during treatment with human growth hormone (hGH), being aware of its collagen-stimulating synthesis activity in vitro. STUDY DESIGN: Fourteen patients (6 boys; ages 4.8 to 10.8 years) were studied. Any structural alteration in the collagen chains was excluded, and reduced production of structurally normal type I

collagen (increase in type III/type I collagen; reduction in the messenger ribonucleic acid alpha 1 (I)/ alpha 2 (I) ratio) was demonstrated. The patients were divided into two groups comparable in sex, age, height, and clinical severity of OI; seven patients (three boys) were treated for 12 months with hGH at a dosage of 0.2 mg/kg per week (0.6 IU/kg per week), in six injections subcutaneously, and seven were followed as control subjects. Auxologic data were measured every 3 months, and bone age was determined at the start, after 1 year of treatment, and 1 year after its completion. Every 3 months, serum insulin-like growth factor type I, osteocalcin, carboxyterminal propeptide of type I procollagen, alkaline phosphatase, calcium, and phosphorus levels and urinary hydroxyproline and calcium levels were determined. Bone mass measurements were carried out at the start of the study in all patients and repeated after 12 months in treated patients at the lumbar spine by dual-energy x-ray absorptiometry and by anteroposterior (second, third, and fourth lumbar vertebrae) and lateral (third lumbar vertebra) scan. Results were expressed as areal (anteroposterior and lateral) bone density (in milligrams per square centimeter) and as calculated true density (in milligrams per cubic centimeter). RESULTS: After 12 months, linear growth velocity in treated patients increased significantly in comparison with the pretreatment period (from 3.57 +/- 0.55 to 6.04 +/- 0.69 cm/yr; $p < 0.05$) and with the untreated group ($p < 0.05$). Bone age did not advance faster than chronologic age. The fracture index per year was low before treatment, and during therapy no patient had any fractures. Serum osteocalcin levels were statistically lower than in control subjects before treatment and increased significantly after 12 months (3.3 +/- 1.0 vs 2.1 +/- 0.9 nmol/L; $p < 0.05$). Serum levels of carboxyterminal propeptide of type I procollagen were significantly lower than normal values before treatment (164.6 +/- 46.7 vs 310.3 +/- 97.6 ng/ml; $p < 0.05$) and rose, but not significantly, during and after treatment. Before therapy, patients with OI had significantly lower lumbar anteroposterior, lateral, and calculated true bone density than the normal population of the same sex compared for both age and height. After hGH treatment, bone density increased significantly in the lumbar spine, in anteroposterior and lateral scans (+2.6 +/- 2.5% and +9.8% +/- 14.0%, respectively; $p < 0.05$). CONCLUSIONS: From our results, we conclude that hGH treatment in moderate OI does not increase the fracture risk in treated patients in the short term, significantly increases the rate of linear growth velocity, and increases bone turnover and mineral content in trabecular bone at the lumbar spine.

3. Antoniazzi, F., M. Mottes, P. Frascini, P. C. Brunelli, and L. Tato. "**Osteogenesis Imperfecta: Practical Treatment Guidelines.**" *Paediatr Drugs* 2, no. 6 (2000): 465-88. Osteogenesis imperfecta (OI), an inherited connective tissue disorder of remarkable clinical variability, is caused by a quantitative or qualitative defect in collagen synthesis and is characterised by bone fragility. The number of fractures and deformities, and the age at which they begin greatly influence the prognosis and the achievement of walking and autonomy. A multidisciplinary team approach is essential for diagnosis, for communication with patient and parents, and to tailor treatment needs to the severity of the disease and the age of the patient. Three types of treatment are available: nonsurgical management (physical therapy, rehabilitation, bracing and splinting), surgery (intramedullary rod positioning, spinal and basilar impression surgery), and drugs to increase the strength of bone and decrease the number of fractures. An aggressive rehabilitative approach is indicated to optimise functional ability and walking capacity; appropriately timed surgery to insert intramedullary rods provides improved function of

extremities. Despite a high rate of complications, intramedullary telescopic roding has proven to be the most successful method for preventing and correcting fractures and deformities of long bones, improving walking capability and leading to successful rehabilitation of even severely affected patients. Surgery may be required in patients with progressive spinal deformity and in those with symptomatic basilar impression. Hearing function, dentinogenesis imperfecta, cardiac and respiratory function, and neurological changes must be monitored. The causal defect of the disease cannot be corrected with medical treatment and, currently, only symptomatic therapy is available. In recent years growth hormone (GH) and bisphosphonate agents have been used in OI therapy. GH is beneficial in patients with moderate forms of OI, showing a positive effect on bone turnover, bone mineral density and height velocity rate. Bisphosphonates have proved beneficial in children with severe OI, increasing bone mineral density and reducing the fracture rate and pain with no adverse effects reported. These data require confirmation in double-blind controlled studies; however, bisphosphonates have markedly improved morbidity in patients with OI. Future developments in genetic therapy may be directed towards either replacing cells carrying the mutant gene with normal cells or silencing the mutant allele using antisense suppression therapy, thus transforming a biochemically severe form of OI into a mild form.

4. Chevrel, G., and P. J. Meunier. "**Osteogenesis Imperfecta: Lifelong Management Is Imperative and Feasible.**" *Joint Bone Spine* 68, no. 2 (2001): 125-9.

Osteogenesis imperfecta is a group of inherited diseases responsible for varying degrees of skeletal fragility. Minimal trauma is sufficient to cause fractures and bone deformities. The classification of osteogenesis imperfecta has recently been improved by the inclusion of additional clinical and histomorphometric data. The diagnosis is often readily made in infancy; some cases, however, go unrecognized until adulthood. Lifelong multidisciplinary management is imperative. Pamidronate therapy in childhood is the most extensively studied treatment and has been proved beneficial. Other bisphosphonates are being evaluated, particularly in adults. Prevention of vitamin D and calcium deficiency is essential throughout life. Pain is common and should be given adequate attention.

5. Engelbert, R. H., H. E. Pruijs, F. A. Beemer, and P. J. Helden. "**Osteogenesis Imperfecta in Childhood: Treatment Strategies.**" *Arch Phys Med Rehabil* 79, no. 12 (1998): 1590-4.

Osteogenesis imperfecta (OI) is a skeletal disorder of remarkable clinical variability characterized by bone fragility, osteopenia, variable degrees of short stature, and progressive skeletal deformities. Additional clinical manifestations such as blue sclerae, dentinogenesis imperfecta, joint laxity, and maturity onset deafness are described in the literature. OI occurs in about 1 in 20,000 births and is caused by quantitative and qualitative defects in the synthesis of collagen I. Depending on the severity of the disease, a large impact on motor development, range of joint motion, muscle strength, and functional ability may occur. Treatment strategies should primarily focus on the improvement of functional ability and the adoption of compensatory strategies, rather than merely improving range of joint motion and muscle strength. Surgical treatment of the extremities may be indicated to stabilize the long bones to optimize functional ability and walking capacity. Surgical treatment of the spine may be indicated in

patients with progressive spinal deformity and in those with symptomatic basilar impression.

6. Forlino, A., and J. C. Marini. "**Osteogenesis Imperfecta: Prospects for Molecular Therapeutics.**" *Mol Genet Metab* 71, no. 1-2 (2000): 225-32.

Osteogenesis Imperfecta (OI) is a dominant negative disorder of connective tissue. OI patients present with bone fragility and skeletal deformity within a broad phenotypic range. Defects in the COL1A1 or COL1A2 genes, coding, respectively, for the alpha1 and alpha2 chains of type I collagen, are the causative mutations. Over 150 mutations have been characterized. Both quantitative defects, such as null COL1A1 alleles, and qualitative defects, such as glycine substitutions, exon skipping, deletions, and insertions, have been described in type I collagen. Quantitative and structural mutations are associated with the milder and more severe forms of OI, respectively. A more detailed relationship between genotype and phenotype is still incompletely understood; several models have been proposed and are being tested. Transgenic and knock-out murine models for OI have previously been created. We have recently generated a knock-in murine model (the Brittle mouse) carrying a typical glycine substitution in type I collagen. This mouse will permit a better understanding of OI pathophysiology and phenotypic variability. It will also be used for gene therapeutic approaches to OI, especially mutation suppression by hammerhead ribozymes. The present review will provide an update of OI clinical and molecular data and outline gene therapeutic approaches being tested on OI murine models for this disorder.

7. Glorieux, F. H. "**Bisphosphonate Therapy for Severe Osteogenesis Imperfecta.**" *J Pediatr Endocrinol Metab* 13, no. Suppl 2 (2000): 989-92.

Osteogenesis imperfecta (OI) is a heterogeneous group of disorders principally affecting type I collagen. Children with the severe forms of the condition suffer recurrent fractures resulting in limb and spine deformities, and restricted ambulation. Recently, cyclical intravenous administration of pamidronate has proven of benefit to children with the severe forms of OI. Bone mineral density increased, and the incidence of fractures decreased. The treatment does not alter fracture healing, growth rate, or growth plate appearances. Dependence on mobility aids is reduced and there is substantial relief of chronic pain and fatigue. No significant adverse side effects have been noted. New bisphosphonates are under investigation to compare their effects to those of pamidronate. Although the use of bisphosphonates does not address the basic abnormalities that underlie the OI syndromes, it represents the first therapy to significantly alter the natural course of the disease and improve patients' clinical status and quality of life.

8. Glorieux, F. H., N. J. Bishop, H. Plotkin, G. Chabot, G. Lanoue, and R. Travers. "**Cyclic Administration of Pamidronate in Children With Severe Osteogenesis Imperfecta.**" *N Engl J Med* 339, no. 14 (1998): 947-52.

BACKGROUND: Severe osteogenesis imperfecta is a disorder characterized by osteopenia, frequent fractures, progressive deformity, loss of mobility, and chronic bone pain. There is no effective therapy for the disorder. We assessed the effects of treatment with a bisphosphonate on bone resorption. **METHODS:** In an uncontrolled observational study involving 30 children who were 3 to 16 years old and had severe osteogenesis imperfecta, we administered pamidronate intravenously (mean [+/-SD]

dose, 6.8 \pm 1.1 mg per kilogram of body weight per year) at 4-to-6-month intervals for 1.3 to 5.0 years. Clinical status, biochemical characteristics reflecting bone turnover, the bone mineral density of the lumbar spine, and radiologic changes were assessed regularly during treatment. RESULTS: Administration of pamidronate resulted in sustained reductions in serum alkaline phosphatase concentrations and in the urinary excretion of calcium and type I collagen N-telopeptide. There was a mean annualized increase of 41.9 \pm 29.0 percent in bone mineral density, and the deviation of bone mineral density from normal, as indicated by the z score, improved from -5.3 \pm 1.2 to -3.4 \pm 1.5. The cortical width of the metacarpals increased by 27 \pm 20.2 percent per year. The increases in the size of the vertebral bodies suggested that new bone had formed. The mean incidence of radiologically confirmed fractures decreased by 1.7 per year (P<0.001). Treatment with pamidronate did not alter the rate of fracture healing, the growth rate, or the appearance of the growth plates. Mobility and ambulation improved in 16 children and remained unchanged in the other 14. All the children reported substantial relief of chronic pain and fatigue. CONCLUSIONS: In children with severe osteogenesis imperfecta, cyclic administration of intravenous pamidronate improved clinical outcomes, reduced bone resorption, and increased bone density.

9. Horwitz, E. M., D. J. Prockop, L. A. Fitzpatrick, W. W. Koo, P. L. Gordon, M. Neel, M. Sussman, P. Orchard, J. C. Marx, R. E. Pyeritz, and M. K. Brenner. "**Transplantability and Therapeutic Effects of Bone Marrow-Derived Mesenchymal Cells in Children With Osteogenesis Imperfecta.**" *Nat Med* 5, no. 3 (1999): 309-13.

In principle, transplantation of mesenchymal progenitor cells would attenuate or possibly correct genetic disorders of bone, cartilage and muscle, but clinical support for this concept is lacking. Here we describe the initial results of allogeneic bone marrow transplantation in three children with osteogenesis imperfecta, a genetic disorder in which osteoblasts produce defective type I collagen, leading to osteopenia, multiple fractures, severe bony deformities and considerably shortened stature. Three months after osteoblast engraftment (1.5-2.0% donor cells), representative specimens of trabecular bone showed histologic changes indicative of new dense bone formation. All patients had increases in total body bone mineral content ranging from 21 to 29 grams (median, 28), compared with predicted values of 0 to 4 grams (median, 0) for healthy children with similar changes in weight. These improvements were associated with increases in growth velocity and reduced frequencies of bone fracture. Thus, allogeneic bone marrow transplantation can lead to engraftment of functional mesenchymal progenitor cells, indicating the feasibility of this strategy in the treatment of osteogenesis imperfecta and perhaps other mesenchymal stem cell disorders as well.

[See related comments: Bishop, N. J. "Osteogenesis Imperfecta Calls for Caution." *Nat Med* 5, no. 5 (May 1999): 466-7. Gerson, S. L. "Mesenchymal Stem Cells: No Longer Second Class Marrow Citizens." *Nat Med* 5, no. 3 (March 1999): 262-4. Marini, J. C. "Osteogenesis Imperfecta Calls for Caution." *Nat Med* 5, no. 5 (May 1999): 466-7.]

10. Horwitz, E. M., D. J. Prockop, P. L. Gordon, W. W. Koo, L. A. Fitzpatrick, M. D. Neel, M. E. McCarville, P. J. Orchard, R. E. Pyeritz, and M. K. Brenner. "**Clinical Responses to Bone Marrow Transplantation in Children With Severe Osteogenesis Imperfecta.**" *Blood* 97, no. 5 (2001): 1227-31.

Preclinical models have shown that transplantation of marrow mesenchymal cells has the potential to correct inherited disorders of bone, cartilage, and muscle. The report

describes clinical responses of the first children to undergo allogeneic bone marrow transplantation (BMT) for severe osteogenesis imperfecta (OI), a genetic disorder characterized by defective type I collagen, osteopenia, bone fragility, severe bony deformities, and growth retardation. Five children with severe OI were enrolled in a study of BMT from human leukocyte antigen (HLA)-compatible sibling donors. Linear growth, bone mineralization, and fracture rate were taken as measures of treatment response. The 3 children with documented donor osteoblast engraftment had a median 7.5-cm increase in body length (range, 6.5-8.0 cm) 6 months after transplantation compared with 1.25 cm (range, 1.0-1.5 cm) for age-matched control patients. These patients gained 21.0 to 65.3 g total body bone mineral content by 3 months after treatment or 45% to 77% of their baseline values. With extended follow-up, the patients' growth rates either slowed or reached a plateau phase. Bone mineral content continued to increase at a rate similar to that for weight-matched healthy children, even as growth rates declined. These results suggest that BMT from HLA-compatible donors may benefit children with severe OI. Further studies are needed to determine the full potential of this strategy.

11. Marini, J. C., S. Bordenick, G. Heavner, S. Rose, and G. P. Chrousos. **"Evaluation of Growth Hormone Axis and Responsiveness to Growth Stimulation of Short Children With Osteogenesis Imperfecta."** *Am J Med Genet* 45, no. 2 (1993): 261-4. Growth deficiency is a cardinal manifestation of severe Osteogenesis Imperfecta (OI) and occurs frequently in moderate to mild OI. We have investigated the status of the hormones related to growth in 28 children with OI. Our goals were to determine whether there were any abnormalities of these hormones, whether the abnormalities correlated with types of OI, and whether OI bone could be safely stimulated to grow. The study group included 14 females and 14 males. Using the criteria developed by Sillence et al. [1979], 13 children had OI type III, 12 had OI type IV, and 3 had OI type I. Evaluation included 3 standard hGH provocative tests (AITT, L-Dopa), GRF stimulation, 24 hr q20 minute sampling of unstimulated growth hormone, and a somatomedin generation test. All patients except one had normal responses to standard provocative stimuli. Responses to GRF fell into 2 groups: one with a mean response similar to that of normal children, and one with a mean response resembling that of GH deficient children. The group with low response to GRF had a significantly lower area under the curve in the 24-hr test of unstimulated GH than did the normal response group. The OI children as a group showed a blunted IGF-1 response during the Somatomedin Generation Test, with 18/28 children having less than a two-fold stimulation. No test results correlated with OI type. Ten OI children were enrolled in a pilot growth stimulation study. Two children received protropin and 8 received clonidine for at least 6 months. Both children treated with protropin and 4/8 treated with clonidine experienced at least a doubling of their pre-treatment growth rates. Lack of growth hormone response did not correlate with type of OI or parameters from the hormonal evaluation. We speculate that there is a group of OI children who have a hypoactive growth hormone axis. Some OI bone appears to respond to GH and a treatment trial with protropin is planned for a larger number of children.

12. Marini, J. C., S. Bordenick, G. Heavner, S. Rose, R. Hintz, R. Rosenfeld, and G. P. Chrousos. "**The Growth Hormone and Somatomedin Axis in Short Children With Osteogenesis Imperfecta.**" *J Clin Endocrinol Metab* 76, no. 1 (1993): 251-6.
Growth deficiency is a cardinal feature of severe osteogenesis imperfecta (OI) and a frequent feature of mild to moderate forms of this disease. We have investigated the status of hormones related to growth in 22 short prepubertal children, 13 males and 9 females, with various types of OI. Ten children had Sillence type III OI, 10 had type IV, and 2 had type I. Evaluation included GRH stimulation, three standard GH provocative tests (arginine-insulin tolerance test, L-dopa), 24-h sampling for measurement of unstimulated GH secretion and a somatomedin-C generation test. None of these children had GH deficiency by standard criteria. We found that 9 OI children had decreased responsiveness to GRH, similar to the GRH response of GH-deficient children. Overall, however, mean 24-h GH values and mean peak GH response to provocative agents of OI children were within the normal range. In the somatomedin generation test, the OI children as a group showed a blunted response, with 13 of 22 having less than a 2-fold stimulation of somatomedin-C by GH. This suggested resistance of the liver and other somatomedin-C secreting tissues to GH. The group with blunted insulin-like growth factor-I response did not correlate significantly with the group with decreased GRH response. To investigate the responsiveness of OI bone to growth stimulation, six OI children with less than average integrated GH secretion were enrolled in a pilot study in which one child received exogenous GH and six received clonidine for at least 6 months. The child treated with exogenous GH and three of six treated with clonidine experienced at least a 4.7 cm/yr increase over their pretreatment growth rates. Growth response could not be predicted from baseline studies. We conclude that abnormalities of the GH-somatomedin axis exist in some children with OI. Administration of GH or clonidine may augment growth rates in OI children; however, the effect of these agents on final stature is unknown.
13. Marini, J. C., and N. L. Gerber. "**Osteogenesis Imperfecta. Rehabilitation and Prospects for Gene Therapy [Clinical Conference].**" *JAMA* 277, no. 9 (1997): 746-50.
A selected case study introduces this article which includes a discussion of the genetics and biochemistry of Osteogenesis Imperfecta (OI). Treatments including rehabilitation and growth hormone are described. Gene therapy is presented as it relates to a dominant negative disorder, such as OI. The prospects for the two approaches to gene therapy - cell replacement therapy and antisense therapy - are explained. (ORBD~NRC abstract)
14. Millington-Ward, S., B. O'Neill, A. S. Kiang, P. Humphries, P. F. Kenna, and G. J. Farrar. "**A Mutation-Independent Therapeutic Strategem for Osteogenesis Imperfecta.**" *Antisense Nucleic Acid Drug Dev* 9, no. 6 (1999): 537-42.
Given the genetically heterogeneous nature of many dominantly inherited disorders, it will be imperative to design mutation-independent therapeutic strategies to circumvent such heterogeneity. Intragenic polymorphism represents a genomic resource that may be harnessed in the development of allele-specific mutation-independent therapeutics. A hammerhead ribozyme, Rzp11a1, selectively cleaves a common single-nucleotide polymorphism (SNP) of the human COL1A1 transcript (heterozygosity frequency of 2 pq = 0.4032, from Hardy-Weinberg equilibrium). One SNP variant contains a hammerhead ribozyme cleavage site, and the other does not. Kinetic evaluation shows

Rzpolla1 to be both specific and extremely efficient in vitro. Thus, a single efficient ribozyme has been characterized that should be valuable in the development of a gene therapy suitable for up to 1 in 5 dominant-negative osteogenesis imperfecta (OI) patients, where over 150 different mutations have been identified to date. Given the increasing characterization of intragenic SNP, it is predicted that such a mutation-independent strategy, based on selective silencing of mutant alleles at SNP, may become increasingly important in future genomics-driven drug development for many heterogeneous dominant disorders and complex traits.

15. Niyibizi, C. , P. Smith, Z. Mi, P. Robbins, and C. Evans. **"Potential of Gene Therapy for Treating Osteogenesis Imperfecta."** *Clin Orthop*, no. 379 Suppl (2000): S126-33.
Osteogenesis imperfecta is a heterogeneous group of genetic disorders that affect connective tissue integrity, with bone fragility being the major clinical feature. Most forms of osteogenesis imperfecta are the result of mutations in the genes that encode the pro alpha1 and pro alpha2 polypeptide chains of Type I collagen. Because osteogenesis imperfecta is an incurable genetic disease, cell therapy and gene therapy are being investigated as potential treatments. Gene therapy for osteogenesis imperfecta however is a major challenge; because most of the mutations in osteogenesis imperfecta are dominant negative, supplying the normal gene without silencing the abnormal gene may not be beneficial. Null mutations in which an allele is not expressed or absent may be amenable to gene therapy or alternatively after silencing a mutant allele, a normal gene could be supplied. In addition, overexpression of the normal collagen gene in cells expressing mutant collagen polypeptide chains potentially could lead to synthesis of a sufficient percentage of normal molecules to normalize clinical status. The authors currently are examining the possibility of developing gene therapy for treating a mouse model of human osteogenesis imperfecta (oim) using bone marrow stromal cells as vehicles for delivering normal collagen genes to bone. In the current study, the potential of gene therapy for treating osteogenesis imperfecta is discussed in the context of the complexity of the mutations in Type I collagen genes that lead to different osteogenesis imperfecta phenotypes.
16. Oyama, M., A. Tatlock, S. Fukuta, K. Kavalkovich, K. Nishimura, B. Johnstone, P. D. Robbins, C. H. Evans, and C. Niyibizi. **"Retrovirally Transduced Bone Marrow Stromal Cells Isolated From a Mouse Model of Human Osteogenesis Imperfecta (Oim) Persist in Bone and Retain the Ability to Form Cartilage and Bone After Extended Passaging."** *Gene Ther* 6, no. 3 (1999): 321-9.
Bone marrow stromal cells isolated from a model of osteogenesis imperfecta (oim) mice, were transduced with a retrovirus (BAG) carrying the LacZ and neor genes after passage 21. The transduced cells retained the ability to express alkaline phosphatase activity in vitro when treated with recombinant human bone morphogenetic protein two (rhBMP-2), formed cartilage in vitro in aggregate cultures and formed bone in ceramic cubes after 6 weeks of implantation in nude mice. X-gal staining of ceramic cubes seeded with the transduced cells demonstrated the presence of LacZ-positive cells on the edges of bone and also in the lacunae of the newly formed bone 6 weeks after implantation. After infusion into femurs of oim mice, the transduced cells were detected in the marrow cavity and on the edges of the trabecular bone of the injected and contralateral femurs by X-gal staining and PCR analysis at 4, 10, 20, 30 and 40 days after injection. The LacZ gene was also detected in the lung and liver of the recipient

mice at 4 and 10 days after injection but not at later time-periods. The present findings suggest that long-term cultured bone marrow stromal cells from osteogenesis imperfecta (OI) animals have the potential to traffic through the circulatory system, home to bone, form bone and continue to express exogenous genes. These findings open the possibility of using these cells as vehicles to deliver normal genes to bone as an alternative approach for the treatment of some forms of OI and certain other bone acquired and genetic diseases.

17. Plotkin, H., F. Rauch, N. J. Bishop, K. Montpetit, J. Ruck-Gibis, R. Travers, and F. H. Glorieux. "**Pamidronate Treatment of Severe Osteogenesis Imperfecta in Children Under 3 Years of Age.**" *J Clin Endocrinol Metab* 85, no. 5 (2000): 1846-50.
Severe osteogenesis imperfecta (OI) is a hereditary disorder characterized by increased bone fragility and progressive bone deformity. Cyclical pamidronate infusions improve clinical outcome in children older than 3 yr of age with severe OI. Because earlier treatment may have potential to prevent deformities and improve functional prognosis in young children, we studied nine severely affected OI patients under 2 yr of age (2.3-20.7 months at entry) for a period of 12 months. Pamidronate was administered i.v. in cycles of 3 consecutive days. Patients received four to eight cycles during the treatment period, with cumulative doses averaging 12.4 mg/kg. Clinical changes were evaluated regularly during treatment, and radiological changes were assessed after 6-12 months of treatment. The control group consisted of six age-matched, severely affected OI patients, who had not received pamidronate treatment. During treatment bone mineral density (BMD) increased between 86-227%. The deviation from normal, as indicated by the z-score, diminished from -6.5 +/- 2.1 to -3.0 +/- 2.1 ($P < 0.001$). In the control group the BMD z-score worsened significantly. Vertebral coronal area increased in all treated patients (11.4 +/- 3.4 to 14.9 +/- 1.8 cm²; $P < 0.001$), but decreased in the untreated group ($P < 0.05$). In the treated patients, fracture rate was lower than in control patients (2.6 +/- 2.5 vs. 6.3 +/- 1.6 fractures/year; $P < 0.01$). No adverse side-effects were noted, apart from the well known acute phase reaction during the first infusion cycle. Pamidronate treatment in severely affected OI patients under 3 yr of age is safe, increases BMD, and decreases fracture rate.
18. Rauch, F., R. Travers, H. Plotkin, and F. H. Glorieux. "**The Effects of Intravenous Pamidronate on the Bone Tissue of Children and Adolescents With Osteogenesis Imperfecta.**" *J Clin Invest* 110, no. 9 (2002): 1293-9.
Cyclical pamidronate infusions increase bone mass in children suffering from osteogenesis imperfecta. The histological basis for these effects remains unknown. Therefore, we compared parameters of iliac bone histomorphometry from 45 patients before and after 2.4 +/- 0.6 years of pamidronate treatment (age at the time of the first biopsy, 1.4-17.5 years; 23 girls). Although biopsy size did not change significantly ($P = 0.30$), cortical width increased by 88%. Cancellous bone volume increased by 46%. This was due to a higher trabecular number, whereas trabecular thickness remained stable. Bone surface-based indicators of cancellous bone remodeling decreased by 26-75%. There was no evidence for a mineralization defect in any of the patients. These results suggest that, in the growing skeleton, pamidronate has a twofold effect. In remodeling, bone resorption and formation are coupled and consequently both processes are inhibited. However, osteoclasts and osteoblasts are active on different surfaces (and are thus uncoupled) during modeling of cortical bone. Therefore

resorption is selectively targeted, and continuing bone formation can increase cortical width.

19. Shapiro, J. R., E. F. McCarthy, K. Rossiter, K. Ernest, R. Gelman, N. Fedarko, H. T. Santiago, and M. Bober. **"The Effect of Intravenous Pamidronate on Bone Mineral Density, Bone Histomorphometry, and Parameters of Bone Turnover in Adults With Type IA Osteogenesis Imperfecta."** *Calcif Tissue Int* 72, no. 2 (2003): 103-12. The type IA osteogenesis imperfecta (OI) phenotype is characterized by multiple fractures, blue sclerae, and minimal skeletal deformity without dentinogenesis imperfecta. The object of this study was to determine the effect of treatment with intravenous pamidronate (30 mg) every 3 months on bone density and bone histomorphometry in adults with type IA OI. After an initial iliac crest bone biopsy eight subjects, 5 women and 3 men, entered a treatment program lasting 21-30 months. Five subjects, all women, completed the study which included a posttreatment iliac crest bone biopsy. Pamidronate treatment led to significant increases in bone mineral density (BMD), measured by DXA, in the lumbar spine at 12 months ($P = 0.05$) and in the femur neck ($P = 0.02$) at 24 months. Significant increases in BMD were also seen in femoral trochanter at 12 months ($P = 0.05$) and at 24 months ($P = 0.02$), and in Ward's triangle at 12 months ($P = 0.02$) and 24 months ($P = 0.05$). Mean osteocalcin levels decreased 32%, C-terminal procollagen peptide and bone alkaline phosphatase declined 12% and 47% at 15 and 21 months, respectively. Deoxypyridinoline crosslink excretion decreased 31%. Posttreatment bone biopsy revealed a significant 6.3% increase in mean bone trabecular volume ($P = 0.01$). Mean cortical thickness increased from 848 μm to 1384 μm ($P = 0.01$) and cortical porosity decreased 13.2% ($P = 0.01$). Bone formation rate increased significantly in all 5 patients from 6.6 to 15.3 mm^2/yr ($P = 0.01$). Mineral apposition rate was unchanged. These results indicate that intravenous pamidronate, 30 mg every 3 months, may have significant effects on bone density and histomorphometry in adults with type IA OI. Responses at higher doses remain to be evaluated.
20. Smith, R. **"Severe Osteogenesis Imperfecta: New Therapeutic Options?"** *BMJ* 322, no. 7278 (2001): 63-64.

5.2 Rehabilitation

1. Binder, H., A. Conway, S. Hason, L. H. Gerber, J. Marini, R. Berry, and J. Weintrob. **"Comprehensive Rehabilitation of the Child With Osteogenesis Imperfecta."** *Am J Med Genet* 45, no. 2 (1993): 265-9. Children with osteogenesis imperfecta (OI) that results in considerable deformity are often viewed as poor candidates for aggressive physical therapy and rehabilitation. To determine if this view is realistic, we have entered almost 50 children with OI type III and OI type IV into a comprehensive graduated rehabilitation program, based at the National Institutes of Health, but designed to be implemented by continuing involvement of community resources. Children are begun in the program early with emphasis on gain of head and trunk control and progression to sitting and walking, if possible, with the aid of a variety of physical supports, including internal and external bracing. Although not conducted in a randomized fashion, the program's success in

bringing children into graded exercise regimes and fostering their increased involvement in school and social situations suggest that aggressive physical therapy and rehabilitation have a major place in the overall care of the infants and children with OI.

2. Daly, K., A. Wisbeach, I. Sanpera Jr, and J. A. Fixsen. "**The Prognosis for Walking in Osteogenesis Imperfecta.**" *J Bone Joint Surg Br* 78, no. 3 (1996): 477-80.

We report a postal survey of 59 families of children with osteogenesis imperfecta. From the 51 replies we collected data on developmental milestones and walking ability and related them to the Sillence and the Shapiro classifications of osteogenesis imperfecta. Twenty-four of the patients had been treated by intramedullary rodding. Both classifications helped to predict eventual walking ability. We found that independent sitting by the age of ten months was a predictor for the use of walking as the main means of mobility with 76% attaining this. Of the patients who did not achieve sitting by ten months, walking became the main means of mobility in only 18%. The developmental pattern of mobility was similar in the rodded and non-rodded patients. [See related comment: Wilkinson, J. M., B. W. Scott, and M. J. Bell. "The Prognosis for Walking in Osteogenesis Imperfecta." *J Bone Joint Surg* 79, no. 2 (March 1997): 339.]

3. Engelbert, R. H., F. A. Beemer, Y. van der Graaf, and P. J. Helders. "**Osteogenesis Imperfecta in Childhood: Impairment and Disability--a Follow-Up Study.**" *Arch Phys Med Rehabil* 80, no. 8 (1999): 896-903.

OBJECTIVES: To evaluate differences over time (mean follow-up, 14 months) on impairment parameters (range of joint motion and muscle strength), functional limitation parameters (functional ability), and disability parameters (caregiver assistance in achieving functional skills) in osteogenesis imperfecta (OI), related to the different types of the disease. DESIGN: A prospective, descriptive study. MATERIALS AND METHODS: Fifty-four children with OI and their parents participated at the start of the study. At the end, 44 children participated in the assessment of functional skills and 42 of them participated in clinical assessment (OI type I, n = 19; OI type III, n = 13; OI type IV, n = 10). Range of joint motion was measured by means of goniometry. Generalized hypermobility was scored according to Bulbena. Manual muscle strength was scored by means of the MRC grading system. The level of ambulation was scored according to Bleck, and functional skills and caregiver assistance were scored with the Pediatric Evaluation of Disability Inventory. RESULTS: The different types of OI have impact on impairment, functional limitation, and disability. Almost all impairment parameters did not change significantly over time, whereas some disability parameters seemed to improve significantly. CONCLUSIONS: Impairment parameters in OI are presumably not always preconditions for functional limitation and disability. A 1-year follow-up revealed no significant changes in impairment parameters, whereas some disability parameters improved. Treatment strategies in OI should, therefore, focus primarily on improving functional ability, with respect to the natural course of the disease, and not only on impairment parameters.

4. Engelbert, R. H., V. A. Gulmans, C. S. Uiterwaal, and P. J. Helders. "**Osteogenesis Imperfecta in Childhood: Perceived Competence in Relation to Impairment and Disability.**" *Arch Phys Med Rehabil* 82, no. 7 (2001): 943-8.
OBJECTIVES: To examine the perceived competence of children with different types of osteogenesis imperfecta (OI) and to investigate the possible relationships between their perceived competence and impairment parameters. DESIGN: Cross-sectional study. SETTING: National referral center (hospital) for the treatment of children with OI. PATIENTS: Forty children with OI (type I = 17; type III = 11; type IV = 12) with a mean age +/- standard deviation of 12.6 +/- 3.2 years. INTERVENTIONS: Measured joint range of motion (ROM) in the upper extremities (UEs), and lower extremities (LEs), muscle strength, functional skills, ambulation, and perceived competence. MAIN OUTCOME MEASURES: Joint ROM in UE and LE; muscle strength (using the manual muscle testing criteria of the Medical Research Council); functional skills using the Pediatric Evaluation of Disability Inventory in 3 domains (self-care, mobility, social function). Ambulation (according to Bleck and classified as nonwalking, therapy walking, household walking, neighborhood walking, community walking with or without the use of crutches), and perceived competence (using the Harter Self-Perception Profile for Children, which was cross-culturally validated for Dutch children). RESULTS: In children with type I, joint ROM and muscle strength were almost comparable to the healthy population. In children with type III, a severe decrease in joint ROM was measured, especially in the LEs, and muscle strength was severely decreased in the UEs and LEs. In children with type IV, joint ROM and muscle strength decreased, especially in the LEs. In all types, fairly to strongly positive perceived competence was measured except for fairly negative perceived competence in the athletic performance subscale in type I and a fairly negative perceived competence in the romance subscale in type III. No correlations were found between (1) joint ROM and athletic performance and physical appearance, (2) muscle strength and athletic performance or physical appearance, or (3) the functional skills, concerning self-care and mobility, with the subscales of the perceived competence. CONCLUSIONS: Although joint ROM, muscle strength, and functional and walking ability were related to the severity of the disease and differed significantly between the different types of OI, overall perceived competence in children with OI was fairly to strongly positive, without significant differences between the different types of OI. Copyright 2001 by the American Congress of Rehabilitation Medicine and the American Academy of Physical Medicine and Rehabilitation

5. Engelbert, R. H., C. S. Uiterwaal, V. A. Gulmans, H. Pruijs, and P. J. Helders. "**Osteogenesis Imperfecta in Childhood: Prognosis for Walking.**" *J Pediatr* 137, no. 3 (2000): 397-402.
OBJECTIVES: We studied the predicted value of disease-related characteristics for the ability of children with osteogenesis imperfecta (OI) to walk. STUDY DESIGN: The severity of OI was classified according to Sillence. The parents were asked to report the age at which the child achieved motor milestones, the fracture incidence, and the age and localization of the first surgical intervention. The present main means of mobility was classified according to Bleck. RESULTS: There were 76 replies to the 98 questionnaires, of which 70 were included (type I, 41; type III, 11; type IV, 18). The type of OI was strongly associated with current walking ability, as was the presence of dentinogenesis imperfecta. Patients with type III and IV had a lower chance of

ultimately walking compared with those with type I. Children with more than 2 intramedullary rods in the lower extremities had a reduced chance of walking than patients without rods. Rolling over before 8 months, unsupported sitting before 9 months, the ability to get in sitting position without support before 12 months, and the ability to get in a standing position without support before 12 months showed positive odds ratios. In Bleck $> \text{ or } = 4$, multivariate analysis revealed that only the presence of rodding (yes/no) in the lower extremities had additional predictive value to the type of OI. The presence of dentinogenesis imperfecta and rodding (yes/no) had additional value in Bleck $> \text{ or } = 5$. **CONCLUSION:** The type of OI is the single most important clinical indicator of the ultimate ability to walk. Information about motor development adds little. The early achievement of motor milestones contributes to the ability of independent walking when the type of OI is uncertain. Intramedullary rodding of the lower extremities is primarily related to the severity of the disease and in this way provides consequences for the ability to walk.

6. Engelbert, R. H., C. S. Uiterwaal, V. A. Gulmans, H. E. Pruijs, and P. J. Helders. **"Osteogenesis Imperfecta: Profiles of Motor Development As Assessed by a Postal Questionnaire."** *Eur J Pediatr* 159, no. 8 (2000): 615-20.

This study was performed to achieve more detailed information regarding the age and sequence in the development of motor milestones in the different types of osteogenesis imperfecta (OI). The parents of 98 patients with a diagnosis of OI were sent a questionnaire regarding the age at which patients achieved motor milestones. All patients were attending the outpatient clinic for children with OI at the Wilhelmina Children's Hospital. The motor milestones were classified into static motor milestones and dynamic motor milestones and all data were checked with health care records. The age of development of motor milestones was compared to reference values of the healthy population. The severity of the disease was classified according to Sillence based on clinical, genetic and radiological data. The age of intramedullary rodding of the first nail in the lower and upper extremity and the localisation was noted. A total of 76 parents responded to the 98 questionnaires (78%). In OI type I, a delay exists in achieving motor milestones, comparable to the 95th percentile of the normal population. In type III, the development of all motor milestones was significantly delayed compared to types I and IV with a discrepancy between static and dynamic milestones. In OI type IV, a retardation in motor development developed after the milestone 'sitting without support' was achieved. Motor development in types I and IV was not influenced by intramedullary rodding of the lower extremities, since rodding was rarely performed before the milestone 'unsupported standing' was achieved. In type III, the influence of intramedullary rodding on the age of achieving motor milestones remains questionable. **Conclusion:** The severity of osteogenesis imperfecta has a large influence on the age and sequence in the development of motor milestones. No influence of intramedullary rodding of the lower extremities on motor development was found in osteogenesis imperfecta types I and IV, whereas the influence in type III remains questionable.

7. Gerber, L. H. , H. Binder, R. Berry, K. L. Siegel, H. Kim, J. Weintrob, Y. J. Lee, S. Mizell, and J. Marini. "**Effects of Withdrawal of Bracing in Matched Pairs of Children With Osteogenesis Imperfecta.**" *Arch Phys Med Rehabil* 79, no. 1 (1998): 46-51.
OBJECTIVES: To evaluate the effects of withdrawal of long-leg braces (hip-knee-ankle-foot orthoses [HKAFO]) on activity and ambulation in children with osteogenesis imperfecta. DESIGN: A prospective, randomized cross-over trial, that describes the effects of withdrawing HKAFO. PATIENTS: Ten children who were ambulatory with the assistance of braces. All had type III or IV osteogenesis imperfecta. Children were paired for age and clinical severity. Strength testing, fractures, and independence in daily activity were monitored at 4-month intervals for 32 months (16 months each of braced and unbraced periods). Gait was analyzed during braced and unbraced conditions. RESULTS: Muscle strength declined .35 grade during unbraced and .1 grade during braced intervals. Children spent more time in upright activity during braced intervals than during unbraced intervals ($p = .17$). Children were more independent in daily activities during braced than during unbraced periods ($p = .14$). Seventeen fractures of lower extremities occurred during all the unbraced periods, and 8 occurred during the braced intervals ($p = .08$); the fracture rate was higher during unbraced intervals. ($p = .06$) Bracing was associated with increased hip flexion and stride length and decreased transverse plane pelvic rotation. CONCLUSION: Withdrawal of HKAFO in children with osteogenesis imperfecta who had achieved upright activity was not associated with significant decrease in muscle strength or independence, but there was an associated increase in fracture rate that nearly reached significance.

8. Gerber, L. H. , H. Binder, J. Weintrob, D. K. Grange, J. Shapiro, W. Fromherz, R. Berry, A. Conway, S. Nason, and J. Marini. "**Rehabilitation of Children and Infants With Osteogenesis Imperfecta. A Program for Ambulation.**" *Clin Orthop* , no. 251 (1990): 254-62.
Management of children and infants with osteogenesis imperfecta (OI) poses difficult decisions for pediatricians, orthopedists, and physiatrists. These children are frequently frail with disabling bone and joint deformities and fractures. In an eight-year cumulative management of 12 children with OI, a comprehensive program included strengthening exercises to the pelvic girdle and lower extremity muscles, in addition to pool exercises and molded seating to support upright posture. Long leg braces were fitted when the children were able to sit unsupported. All 12 were fitted with braces; nine were functional ambulators, and three were home ambulators. Six children required femoral plating or rodding, two of whom subsequently had the metal removed. Lower extremity fractures averaged one and one-half per year prior to bracing for nine children who had fractures. There was 0.83 fracture per year for the ten children who had fractures after bracing. The degree of femoral bowing increased in four, decreased in four, and remained unchanged in four, while the degree of tibial bowing increased in two, decreased in nine, and remained unchanged in one during the observation period. A comprehensive rehabilitation program and long leg bracing with surgical operations on the femur result in a high level of functional activity for children with OI with an acceptable level of risk for fracture.

9. Mirzayan, R., V. Cepkinian, J. Yu, M. D. Wellisch, and L. E. Zionts. **"Skewfoot in Patients With Osteogenesis Imperfecta."** *Foot Ankle Int* 21, no. 9 (2000): 768-71.
We report skewfoot deformities in two patients who have osteogenesis imperfecta. A discussion will follow proposing etiologies of skewfoot, speculating that the ligamentous laxity often present in children who have osteogenesis imperfecta may predispose the development of skewfoot.
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5.3 Surgical Management

1. Chotigavanichaya, C., A. Jadhav, R. M. Bernstein, and H. G. Watts. **"Rod Diameter Prediction in Patients With Osteogenesis Imperfecta Undergoing Primary Osteotomy."** *J Pediatr Orthop* 21, no. 4 (2001): 515-8.
SUMMARY: Because the cross-sectional shape of the long bones of patients with osteogenesis imperfecta is often elliptical, the use of preoperative radiographs to determine intramedullary rod diameter in these patients undergoing osteotomy may be misleading. To investigate this, the authors correlated the narrowest inner bone diameter (NID) on preoperative radiographs to the rod diameter (RD) on postoperative radiographs. The authors evaluated 79 bones in 27 patients undergoing primary osteotomy with intramedullary fixation. Only 5% of the bones had an equal NID and RD, with 81% of bones having a smaller RD than the measured NID. Although a positive correlation was found between RD and NID (correlation coefficient 0.76), measurement of the NID on preoperative radiographs did not provide a good prediction of the actual RD used in this series of children with osteogenesis imperfecta.
2. Engelbert, R. H., P. J. Helders, W. Keessen, H. E. Pruijs, and R. H. Gooskens. **"Intramedullary Rodding in Type III Osteogenesis Imperfecta. Effects on Neuromotor Development in 10 Children."** *Acta Orthop Scand* 66, no. 4 (1995):361-4.
We studied retrospectively gross motor development and the impact of intramedullary rodding in 10 children with type III osteogenesis imperfecta (OI). There was a pronounced delay in motor development and the order in achieving gross motor milestones differed from the normal developmental sequence. Static milestones developed at an earlier stage than dynamic milestones. Intramedullary rodding of the lower extremities prior to the age of 3.5 years enhanced neuromotor development, especially regarding the milestones supported standing, rolling from prone to supine and crawling with abdomen on the floor. The different sequence in achieving gross motor milestones should have implications for future rehabilitation programs and for orthopedic surgery.
3. Feifel, H. **"The Surgical Treatment of Mandibular Fractures in a Child With Osteogenesis Imperfecta."** *Int J Oral Maxillofac Surg* 25, no. 5 (1996): 360-2.
The treatment of multiple mandibular fractures in an 8-year-old child suffering from osteogenesis imperfecta is described. The use of microplates is presented while some specific problems in relation to the disease are discussed.

4. Gargan, M. F. , A. Wisbeach, and J. A. Fixsen. "**Humeral Rodding in Osteogenesis Imperfecta.**" *J Pediatr Orthop* 16, no. 6 (1996): 719-22.

Seven patients with osteogenesis imperfecta who have undergone humeral rodding were reviewed. Satisfactory functional results were obtained in six of seven patients. We discuss the indications for surgery in our unit, the complications, and the results in comparison with those of other centres.

5. Harrison, W. J., and K. C. Rankin. "**Osteogenesis Imperfecta in Zimbabwe: a Comparison Between Treatment With Intramedullary Rods of Fixed-Length and Self-Expanding Rods.**" *J R Coll Surg Edinb* 43, no. 5 (1998): 328-32.

The results of surgical treatment of 15 children with osteogenesis imperfecta in Bulawayo, Zimbabwe are reviewed. A total of 23 self-expanding and 27 fixed-length rods were used. Outcome was measured in terms of mobility status, growth, incidence of refracture, need for reoperation, and complications. Eight of the children improved their mobility status over the course of treatment. Self-expanding rods appeared to confer more benefit to growth than fixed-length rods. Refracture was more common in bones splinted with fixed-length rods and more often necessitated revision surgery in these bones. The complication rate was high in all cases, but the complications associated with outgrown fixed-length rods were a particular problem. The 15 children benefited from surgical treatment. The self-expanding rods performed better than fixed-length rods in reducing the number of surgical interventions. They also appear to facilitate growth. The self-expanding rods may be used to good effect in appropriate centres in the developing world.

6. Janus, G. J., L. A. Vanpaemel, R. H. Engelbert, and H. E. Pruijs. "**Complications of the Bailey-Dubow Elongating Nail in Osteogenesis Imperfecta: 34 Children With 110 Nails.**" *J Pediatr Orthop B* 8, no. 3 (1999): 203-7.

The Bailey-Dubow nail, inserted in the femur or tibia of 34 children with osteogenesis imperfecta (OI), was studied retrospectively. Comparing the various groups of OI, no significant difference was found. Location of the nail (tibia or femur) did not influence the complication rate significantly. The reoperation rate was 29%, a rate comparable to that reported in earlier studies. The part of the nail located around the knee had a significantly higher migration rate ($P = 0.005$ at obturator ends and $P = 0.007$ at sleeve ends). Migration of the nail was the reason to reoperate in 50% of the patients. Better anchoring of the T-piece will substantially decrease the complication rate. In consideration of the different functional capacities of the OI population, the complications are likely related more to the hardware than to the patient.

7. Jerosch, J., I. Mazzotti, and M. Tomasevic. "**Complications After Treatment of Patients With Osteogenesis Imperfecta With a Bailey-Dubow Rod.**" *Arch Orthop Trauma Surg* 117, no. 4-5 (1998): 240-5.

The purpose of this study was to analyse the complications using the Bailey-Dubow expanding intramedullary rods in patients with osteogenesis imperfecta. Between 1985 and 1996 intramedullary rodding of 107 long bones with expanding Bailey-Dubow rods was performed in 29 patients suffering from osteogenesis imperfecta. Indications for using rods included osseous deformities and bone deformities in combination with fractures. The average follow-up was 3.5 years (range 2 months to 9 years). The total complication rate in these patients was 63.5% (68 rods). The main complication was

rod migration often combined with perforation of joint, bone and soft tissue. Additionally, there was a high incidence of new fractures as well as refractures. Other complications like infections, pseudarthrosis, lack of elongation or over-elongation of the rods, and loosening of the T-piece were only rarely seen. Based on our experience and the information available in the literature, the Bailey-Dubow rod is currently the most successful way to stabilize the growing long bones of patients suffering from osteogenesis imperfecta. However, when using this device, the surgeon as well as the parents of the patient must be aware of the high incidence of complications.

8. Khoshhal, K. I., and R. D. Ellis. "**Effect of Lower Limb Sofield Procedure on Ambulation in Osteogenesis Imperfecta.**" *J Pediatr Orthop* 21, no. 2 (2001): 233-5. Ambulation status was evaluated in 34 patients pre- and post-Sofield procedure in patients with osteogenesis imperfecta. Three percent had improved ambulation, 42.4% remained the same and 54.6% were worse. Only 41.2% were ambulating postoperatively compared to 73.5% preoperatively. The Sofield procedure did not improve ambulation status.
9. Li, Y. H., W. Chow, and J. C. Leong. "**The Sofield-Millar Operation in Osteogenesis Imperfecta. A Modified Technique.**" *J Bone Joint Surg Br* 82, no. 1 (2000): 11-6. We have reviewed the results of the Sofield-Millar operation on 58 long bones in ten patients. If more than three osteotomies were undertaken the time to union of the bone was significantly prolonged ($p < 0.001$) with significant thinning of the bone ($p < 0.02$). We have used a modified technique in order to minimise surgical trauma and devascularisation of the bone. The rod is introduced under the control of an image-intensifier. Small surgical exposures are made only at the sites of corrective wedge osteotomies. The number of osteotomies is kept to the minimum.
10. Luhmann, S. J., J. J. Sheridan, A. M. Capelli, and P. L. Schoenecker. "**Management of Lower-Extremity Deformities in Osteogenesis Imperfecta With Extensible Intramedullary Rod Technique: a 20-Year Experience.**" *J Pediatr Orthop* 18, no. 1 (1998): 88-94. Twelve patients (seven boys, five girls) who had osteogenesis imperfecta were treated with an extensible-rod system in 21 femurs and 15 tibias. Indications for use of extensible rods were multiple fractures, long-bone deformity prohibiting bracing and ambulation, and significant remaining linear growth. The average patient age at the time of placement of the extensible rods was 6 + 8 years (range, 2 + 4-10 + 10). Six femurs were treated with overlapping Rush rods; Bailey-Dubow rods were used in the remaining femurs and in all tibias. The average length of follow-up was 5 + 9 years (range, 2 + 0-3 + 2). Preoperatively, four of the 12 patients had never walked; postoperatively, all were ambulators with varying levels of assistance. Fourteen complications occurred, 12 of which required operative revision of the extensible rods. The average time between primary extensible rodding and revision was 5 + 1 years. No complications have occurred to date related to the use of overlapping Rush rods. No growth disturbance resulted from the use of the extensible-rod systems.
11. Mulpuri, K., and B. Joseph. "**Intramedullary Rodding in Osteogenesis Imperfecta.**" *J Pediatr Orthop* 20, no. 2 (2000): 267-73. The results of intramedullary rodding of long bones of 16 children with osteogenesis imperfecta, over a 10-year period, were analyzed. Sheffield elongating rods or non-

elongating rods were used. The frequency of fractures was dramatically reduced after implantation of either type of rod, and the ambulatory status improved in all instances. The results were significantly better after Sheffield rodding with regard to the frequency of complications requiring reoperations and the longevity of the rods. Migration of the rods, encountered frequently, appears to be related to improper placement of the rods in the bone. It seems likely that if care is taken to ensure precise placement of a rod of appropriate size, several of these complications may be avoided.

12. Porat, S., E. Heller, D. S. Seidman, and S. Meyer. "**Functional Results of Operation in Osteogenesis Imperfecta: Elongating and Nonelongating Rods.**" *J Pediatr Orthop* 11, no. 2 (1991): 200-3.

Gait capacity, operative intervention, and complications of operation were evaluated in 20 patients with osteogenesis imperfecta (OI). Thirty-two Bailey-Dubow (B-D) rods and 24 nonelongating rods were used. Postoperatively, gait capacity improved in eight patients, regressed in three, and remained unchanged in nine. No preoperative ambulator regressed to a nonambulatory status. The Silience disease type was not a prognostic indicator of gait capacity. The complication rate was 72% for the B-D rod and 50% for the nonelongating rod, although the percentage requiring reoperation was similar for both types of nails. There was no difference in longevity between the two nails.

13. Ring, D., J. B. Jupiter, P. K. Labropoulos, J. J. Guggenheim, D. F. Stanitsky, and D. M. Spencer. "**Treatment of Deformity of the Lower Limb in Adults Who Have Osteogenesis Imperfecta.**" *J Bone Joint Surg Am* 78, no. 2 (1996): 220-5.

The Ilizarov method of lengthening was used to correct deformities of the lower extremity in six patients who had type-1 osteogenesis imperfecta, as categorized by Silence et al. The average age was thirty-one years (range, fourteen to fifty-one years). The deformities included shortening of four tibiae and three femora as well as an angular malalignment (average, 28 degrees; range, 20 to 40 degrees) of all four tibiae and one femur. One patient also had a non-union of the right femur. The average angular correction was 23 degrees (range, 20 to 30 degrees). The seven limb segments gained an average of 6.6 centimeters (range, two to eleven centimeters) in length. All limb-length discrepancies were corrected to within two centimeters of the length of the contralateral limb. At an average of three years and four months (range, one year and seven months to six years), the roentgenographic appearance of the fully matured bone was comparable with that of the original bone. There was no fractures or increases in the angulation of the segment of new bone. Two patients had pain when walking; it was related to a chronic pin-track infection in one and to osteoarthritis of the ankle in the other. The functional status of four patients was improved and that of the other two patients was unchanged. All six patients were pleased with the outcome of the procedure. There was eighteen complications: stiffness of the knee in two patients; a peroneal nerve palsy in two; a superficial pin-track infection in three; and a deep pin-track infection, greater-than-normal loss of blood intraoperatively, loosening of two pins, worsening of the instability of the knee, and an infection in the knee in one patient each. In another patient, a Rush rod that had been placed before correction of the deformity migrated proximally and had to be removed after completion of the correction. There were five fractures.

14. Wilkinson, J. M., B. W. Scott, A. M. Clarke, and M. J. Bell. "**Surgical Stabilisation of the Lower Limb in Osteogenesis Imperfecta Using the Sheffield Telescopic Intramedullary Rod System.**" *J Bone Joint Surg Br* 80, no. 6 (1998): 999-1004.
The Sheffield Expanding Intramedullary Rod System was developed after experiencing problems with existing rod systems in the management of osteogenesis imperfecta. Between 1986 and 1996 we treated 74 bones in the lower limb in 28 children at a median follow-up of 5.25 years. We have reviewed 24 children with a total of 60 rods. Before surgery, all children had had multiple fractures of the lower limb. At review eight patients had experienced no further fractures, but three had suffered five or more subsequently. Before initial stabilisation, 15 children had never walked, and only three (13%) used walking as their main means of mobility. After surgery, half of those who showed motor arrest were able to walk ($p = 0.016$). The number of patients able to walk, with or without aids, increased to 17 ($p = 0.0001$). We have experienced no evidence of epiphyseal damage after the procedure, and complication rates requiring rod exchange have been low (7%).

15. Yip, K. M., and S. C. Huang. "**Surgical Management of Patients With Osteogenesis Imperfecta: 10 Years' Experience.**" *J Formos Med Assoc* 95, no. 2 (1996): 132-7.
The orthopedic problems of osteogenesis imperfecta (OI) are multiple and formidable, if not untreatable. Controversy surrounds the timing and method of its management and to date, no reports have been published on the orthopedic treatment of these patients in Taiwan. This paper reports the surgical treatment of eight OI patients (average age, 3 yr 5 mo) who were unable to walk before surgery. Preoperatively, the incidence of long bone fracture ranged from once per month to twice per year. The average degree of femoral and tibial bowing as measured from leg radiographs at the first visit were 42 degrees and 32 degrees, respectively. Four patients underwent intramedullary nailing of both the femur and tibia while another four patients underwent intramedullary nailing of the femur only in the primary operation. The implants used were mostly Steinmann pins or Rush nails, and a femoral Kuntscher nail was used in one case. At the mean postoperative follow-up period of 5 years 4 months, five patients could walk independently without support. Two walked with wheel-carts and one could rise and stand with minimal support. We conclude that patients with OI can benefit from early surgical correction and stabilization and experience improvement in their ambulatory status despite the multiple procedures required.

16. Zions, L. E., E. Ebramzadeh, and N. S. Stott. "**Complications in the Use of the Bailey-Dubow Extensible Nail.**" *Clin Orthop*, no. 348 (1998): 186-95.
The results of 40 extensible intramedullary nailing procedures in 15 children who had osteogenesis imperfecta were reviewed to identify risk factors leading to complications of this method of treatment. There were 40 complications, 17 major and 23 minor. The 17 major complications led to 15 additional procedures, 10 of which were to remove or replace the implant. The prevalence of major complications was highest in patients who were younger than 5 years when the nail was inserted. Nails placed in the tibia tended to produce a higher incidence of major complications than did those placed in the femur, but this difference was not statistically significant. By survivorship analysis, patients had a greater risk of requiring a revision procedure when a technical error occurred at the time the nail was inserted. Patients who had nails placed in the femur tended to have a lower risk of needing revision surgery than did those who had nails placed in the tibia,

but this difference was not statistically significant. The results suggested that the extensible nail is most advantageous in the femur and in patients older than 5 years. Avoiding technical errors when inserting the nail may improve the longevity of the device.

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