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BISPHOSPHONATE TREATMENT
OF
CHILDREN AND ADOLESCENTS
WITH
OSTEOGENESIS IMPERFECTA
(OI)
EFFECTS ON CLINICAL SYMPTOMS
AND BONE TURNOVER

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Stockholm 2007
Cover: photo of mother and APD-treated son with OI. All photos and radiographs are printed with the kind permission of parents and patients and figures in the introduction with permission from the publishers/authors. Helena Lundstedt created the OI-team logotype.
“No one is perfect”
Finishing words in the last scene of the movie
“SOME LIKE IT HOT” from 1959
featuring Jack Lemmon, Tony Curtis and Marilyn Monroe

To all the children and adolescents with OI
and their parents
and to the OI-team
ABSTRACT

**Background:** Osteogenesis imperfecta (OI) is a group of genetic diseases with a wide spectrum of severity, ranging from very mild bone fragility to lethal forms. Without treatment the more severe forms have multiple fractures leading to progressive bone deformities with extreme shortness, frequent skeletal pain and immobilisation. Before Study I there was no effective symptomatic treatment of these patients.

**Aims:** The overall aim of these studies were initially to find and later to optimise a symptomatic treatment of children and adolescents with osteogenesis imperfecta including assessments of untreated children of different ages and types of OI to find criteria for and to monitor treatment.

**Patients and Methods:** Studies I-V involve 130 children and adolescents with different types OI of which 69 were treated with bisphosphonates. Treatment was given as monthly infusions of disodium pamidronate (APD). Assessments were done according to a prospective observational study protocol every six month for 1-2 years then annually. In Study I three adolescents with severe OI were treated during 2-5 years. In Study II we treated 28 children aged 0.6-18 years during 2-9 years. They had severe or milder forms of OI with vertebral compression fractures. In Study III eleven infants aged 3-13 months were treated during 3-6 years and were at the latest recording at the median age of 4.8 years compared to our own historic control group of untreated age and type-matched children with OI. In the retrospective Study IV all 64 patients treated with APD over 0.5 years were assessed due to alarm reports of osteonecrosis of the jaw (ONJ) after dental surgery in patients treated with second- and third-generation bisphosphonates. APD infusions were administered for 0.5-12.5 years. Ten patients continued treatment with oral alendronate and two with infusions of zoledronate. In Study V we assessed bone turnover markers in 130 untreated children and in 69 of those also during treatment for 1.0-12.5 years.

**Results:** Patient diaries showed less pain and improved well-being during treatment. Bone mineral density (BMD) measured by DXA increased gradually. Mobility and vertebral height improved more in younger children. Treated infants achieved the motor milestones earlier and more complete than controls. Mobility, vertebral height and BMD improved greatly during treatment and differed much compared to controls where some even had deteriorated. Bone turnover markers in serum and urine decreased gradually. Significant differences in bone markers, however, not sufficient for clinical sub typing, were found in the larger untreated group. Comparison with 14 untreated immobilised controls indicated that the immobilisation per se was not the cause of these differences. No ONJ was seen after 38 dental surgical procedures in 22 of the APD treated patients or in any other of the treated patients.

**Conclusions:** APD is an effective symptomatic treatment of children and adolescents with severe OI and milder forms with vertebral compression fractures. Bone turnover markers cannot predict vertebral compressions or therapy response on BMD, mobility or pain. Serum ALP and urine deoxypyridinoline are sensitive in monitoring treatment. The risk of ONJ after dental surgery in this patient group must be considered so low that the patients with indications for treatment should be treated and get the chance to experience the well-documented beneficial effects.
LIST OF PUBLICATIONS


LIST OF ABBREVIATIONS

ALP  Alkaline phosphatase (total and isoforms B/I bone/intestinal, B1 bone1, B2 bone2)
APD  Disodium pamidronate
ATP  Adenosine triphosphate
BI   Basilar impression/invagination
BMD  Bone mineral density
CTX-I C-telopeptide of collagen I
DI   Dentinogenesis imperfecta
DPD  Deoxypyridinoline
HPLC High-performance liquid chromatography
ICTP Carboxy-terminal telopeptide of type I collagen
IL1  Interleukin 1
IL6  Interleukin 6
IRMA Immunoradiometric assay
NTX-I N-telopeptide of collagen I
OI   Osteogenesis imperfecta
PTH  Parathyroid hormone
PICP Procollagen type I C-terminal propeptide
PINP Procollagen type I N-terminal propeptide
PYD  Pyridinoline
RANKL Receptor activator of nuclear factor κB ligand
RIA  Radioimmunoassay
Z-score Standard deviations (SD) >or< the mean for age and gender
T-score Number of standard deviations (SD) >or< the average BMD of young healthy white woman
1 INTRODUCTION

1.1 OSTEOGENESIS IMPERFECTA (OI)

1.1.1 History

The name osteogenesis imperfecta dates back to an anatomist from Amsterdam 1849 (1). However the condition has been found in an ancient Egyptian mummy from approximately 1000 BC (2). Ivar Ragnarsson “the Boneless”, a Viking leader and son of the Norwegian king Ragnar Lodbrok, was described conquering parts of England carried on a shield in the 900th century. Familiar mild OI with blue sclerae was first described in 1788 by O J Ekman in Uppsala, Sweden when he in his doctoral thesis described cases dating back to 1678 (3).

1.1.2 Genetics

Osteogenesis imperfecta is in most cases a congenital disease of collagen with a prevalence at birth of 6-20/100 000 (4-6). More than 800 mutations have been reported in the COLIA1 and COLIA2 genes, localised to chromosomes 17 and 7, respectively (7). These genes encode the \( \alpha_1(\text{I}) \) and \( \alpha_2(\text{I}) \) chains of collagen and the mutations leads to reduced amounts of type I collagen with or without structural defects (8-10). The genotype is, in general, an unreliable predictor of the phenotype and severity, and a classification based on the different mutations has not yet been devised.

1.1.3 Classification

There is a large variation in phenotype. In milder forms the fracture rate is only slightly increased and the stature is normal or slightly decreased. In severe forms of the disease, the softness of the bone and multiple fractures leads to progressive bone deformities with extreme shortness, frequent skeletal pain and confinement to an electric wheelchair and there are lethal forms. For many years OI was subdivided into “congenita” and “tarda”. The current classification into four major subgroups (types I-IV), based on clinical findings, was proposed by Sillence in 1979 and has since been dominating (11, 12). In most cases these show autosomal dominant inheritance. Type I and IV were further subdivided into A and B on the basis of absence or presence of dentinogenesis imperfecta, DI (13). Although OI type III is not always associated with DI this type is not subclassified according to the absence or presence of dentinogenesis imperfecta (14).

**OI Type I**: the mildest form with blue sclerae (Fig.1, 2).

**OI Type II**: the most severe lethal pre- or perinatal form.

**OI Type III**: a severe form with multiple fractures, extreme growth retardation and immobilisation (Fig 1).

**OI Type IV**: an intermediate form, ranging between type I and III, with white sclerae after the first years of life (Fig 1).

Recent modifications encompass additional, even less common, types of the disease. The *International Nosology and Classification of Constitutional Disorders of Bone* 2001/revised 2003 proposed six main OI-types with a delineation of OI type V and VI from OI type IV, and later an addition of OI Type VII was proposed (15-19).
**OI Type V**: moderate-severe form with hyperplastic callus formation and dislocated head of radius. DI is common. No gene or chromosomal region has been linked to the disease.

**OI Type VI**: moderate-severe form with defect mineralisation (bone biopsy diagnosis). No gene or chromosomal region has been linked to the disease.

**OI Type VII**: moderate-severe form with rhizomelia but bone biopsy findings resembles mild OI. This type shows autosomal recessive inheritance and has been mapped to chromosome 3 (3p22-24.1).

*OI associated syndromes* were also listed:

**Cole-Carpenter syndrome**: normal appearance at birth but at some months of age clinical occurrence of bone fragility, craniosynostosis, progressive facial dysmorphism including ocular proptosis and extremely short stature. No mutation has so far been described and due to the few cases published no Mendelian trait of inheritance has been possible to identify.

**Bruck syndrome**: bone fragility and arthrogryphosis, long bone bowing and scoliosis due to vertebral deformities. The disease has been linked to chromosome 17 (17p12) and is an autosomal recessive disorder associated with normal collagen type I (20).

**Osteoporosis pseudoglioma syndrome**: mild/moderate bone fragility and congenital eye pathology leading to blindness. It has an autosomal recessive inheritance. Human genetic studies have provided compelling evidence that the low-density lipoprotein receptor-related protein 5 (*LRP5*) (11q12-q13) is involved (21).

### 1.1.4 Symptoms

Symptoms are common from tissues where collagen type I is the main structural protein as bone, tendons, skin, dentin and sclerae. Hearing can be affected sometimes leading to deafness. There are also an increased disposition for bruises and haematoma and insufficiency of the valves of the heart.

**Bone fragility** due to the softness of the bone can lead to a variety of fractures, curvatures, vertebral compressions, kyphoscoliosis and basilar invagination/impression (BI). In severe forms prenatal fractures and bowings occur. In mild forms curvatures are uncommon.

**Basilar impression (BI)** is a pathological anatomic condition where the uppermost part of the cervical vertebrae intrudes into the foramen magnum. In severe cases this can lead to many neurological problems, but mild and moderate forms are often free of symptoms.

**Basilar invagination (BI)** is a radiological designation for a status where the head is positioned abnormally inferiorly in relation to the uppermost cervical vertebrae, and most patients with basilar impression also fill the criteria of basilar invagination. BI in OI (*Fig. 3*) is often a combination of both (22).

**Dental problems** are usual. As a consequence of defect collagen type I the dentin is affected in many cases. This aberration is called dentinogenesis imperfecta (DI), and is in different degrees of severity, present in 43-73% (14). The teeth are characterised by a greyish-blue to brown hue (*Fig. 4*) and radiographically the teeth show short roots, bulbous crowns and a pulpal calcification. The enamel is often dislodged, exposing the soft dysplastic dentin, which may lead to a rapid and extensive attrition. The prevalence is higher in OI type III. The primary dentition is generally more affected than the permanent teeth. The diagnosis can usually be made by clinical and radiographic
examination. In mild cases a histological examination of a sectioned tooth preferably with the root can confirm the diagnosis. Agenesis (Fig. 5) and impaction of second permanent molars are other frequent abnormalities. Anterior and/or posterior cross bite are also common. These anomalies have been described as a consequence of the high thorax found in OI patients, but can be seen even in patients with a mild form of OI type I and a normal thorax configuration (14).

**Ears; hearing impairment** appears in over 50% of patients with OI and in 90% it is bilateral. Subtle audiometric changes are common and impairment is described in children but most often beginning in adulthood. There is with increasing age often a progression from conductive form to combined form including sensorineuronal damage. The degree can vary between different family members with OI (23-26).

**Vertigo** is common in adults with OI, often a short floating or rotational sensation at head movements. Is more common in patients with hearing loss but is not correlated to the type of hearing loss, BI or type of OI (27).

**Eyes** can have blue sclerae (Fig. 2) but this is also seen in healthy infants and young children. Less common is keratoconus, a degenerative non-inflammatory thinning disorder leading to more conical shape of the cornea that causes distortion and reduced vision.

**Growth retardation** depends on the type of OI and treatment. Untreated patients with OI type III did usually stop growing at 8 years of age with a final height of 90-110 cm while mild OI can reach their target height. The short stature in severe forms is usually a combination of curved extremities, vertebral compression fractures and severe kyphoscoliosis (28, 29).

**Ligament laxity** is present in most patients with OI and can in milder forms give more problems than the bone fragility. Especially valgus positioning of the feet and hyper extension in the knees are common. The risk of hyper mobility of the neck must be taken into consideration before general anaesthesia.

**Blood vessels, heart valves and coagulation** can be affected. Two thirds of the patients report a tendency for haematoma. Coagulation defects that can be shown by clinical laboratory tests are also common; one third have increased capillary fragility, one third deficient platelet aggregation, more than one fifth reduced factor VIII and less common are reduced von Willebrand factor and prolonged bleeding time (30). It is important with careful monitoring since those with normal tests also can have profuse bleeding at operations. Fragility of the blood vessels can be problematic in administering intravenous lines. Heart valve insufficiency is uncommon in childhood.

**Excessive sweating** is often reported by the parents of children with OI, the significance of this is unclear.

### 1.1.5 Diagnostics

Clinical examination and family history can often confirm the diagnosis. Skeletal X-ray can confirm the diagnosis in cases of moderate/severe OI, for instance demonstrating bowing of the bones in legs and arms, wormian bones in the sutures of the skull (Fig. 6) and fractures often including vertebral compressions and osteopenia. Type II, the most severe form, has multiple characteristic skeletal malformations seen on X-ray. In milder forms the colour of sclerae, hypermobility of joints, fractures and presence of dentinogenesis imperfecta (DI) also can lead to diagnosis.
Fig. 1 Appearance of OI type I, III and IV (from left to right).

Fig. 2 Blue sclerae.

Fig. 3 Schematic drawings from standardized lateral skull radiographs:
A. Normal skull base anatomy, with dens (d) situated below the level of the foramen magnum (line 1; McRaes line) and not exceeding the reference line 2 (mod. Chamberleins line) by 10 mm or more.
B. Simultaneous presence of basilar impression (tip of dens above line 1; dashed area) and basilar invagination (tip of dens > 10 mm above line 2).
From Waltimo-Sirén 2005

Fig. 4: A 10 year old girl with OI type III and DI. Note posterior cross bite.

Fig. 5: Panoramic radiograph of a 9 year old boy with OI type I without DI. Arrows indicate missing permanent tooth germs.
**Fig. 6** Wormian bones in the sutures of the skull. To the right is an enlargement of the marked area on the left image.

**Fig. 7** Whole body DXA of APD-treated children with OI type I (left) and III (middle), note intramedullary rods. DXA lumbar spine and age-matched reference intervals, Z-scores (right).

**Fig. 8** Curved right femur in a child with OI type III before and after operation with intramedullary rods due to fracture.

**Fig. 9** Intramedullary rods after osteotomies in femur and tibia.
Bone mineral density (BMD) assessment is a commonly used clinical tool in OI diagnostics (Fig. 7).

Analysis of collagen from fibroblasts from a skin biopsy confirms abnormal collagen production in almost 90% of patients with clinical presentation of OI (31). DNA analysis detects abnormal alleles in up to 96% of cases of severe OI and up to 60% in suspected mild cases (31). Prenatal diagnosis can be made from the 9th week in case of a known mutation in the family by identification of this in foetal cells. In severe forms of OI prenatal diagnosis can also be made with intrauterine ultrasound at the 14-18th gestational week.

1.1.6 Differential diagnosis

The intrauterine early diagnosis of severe OI with ultrasound can be difficult due to similarities to other diagnoses with short extremities or fractures such as thanatophoric dysplasia and hypophosphatasia (32). In the neonatal period whole body X-ray is often diagnostic.

Physical child abuse is much more common than OI and can cause any type of fracture but most frequent are metaphyseal fractures and posterior rib fractures (31, 33). Bone fragility due to metabolic disease is rare. Osteoporosis due to malnutrition, medical treatment, or immobilisation must be considered in older children.

1.1.7 Bone density (BMD)

BMD in children is clinically usually assessed by dual-energy X-ray absorptiometry (DXA) of the whole body and/or lumbar spine (Fig. 7). It determines the amount of mineral in a given region providing a measure of bone mineral content (BMC) and bone area (BA) which are used to calculate areal BMD as BMC/BA. Paediatric reference values are available although more inaccurate in infancy due to smaller reference materials. According to the 1994 WHO criteria osteopenia was defined as a T-score less than -1.0 and osteoporosis as lower than -2.5 (34). In 2001 the definition shifted from a condition of low bone mass to one of compromised bone strength that predisposes an individual to an increased risk of fracture (35). In 2004 the International Society of Clinical Densitometry published recommendations that BMD Z-scores using the best available paediatric reference data should be used for children and adolescents with Z-score of < -2.0 representing low BMD for chronological age (36). Although a number of different approaches to correcting DXA results for size have been suggested, there is currently no consensus on which best predicts clinical bone fragility. DXA does not provide a direct measure of bone geometry or distinguish between cortical and trabecular bone (37). In the presence of intramedullary rods and other metal devices the whole body DXA will show falsely high BMD (Fig. 7, 8, 9).

1.1.8 Bone

Bone is a dynamic viscoelastic tissue with the ability of continuous adaptation to changes in its physiological and mechanical environment and thus subjected to constant remodelling. It is composed of cells, mineralised matrix, organic matrix and small amounts of lipids and glucosaminoglycans. There are two types of bone. Cortical bone consists of concentric layers of mineralised hardened collagen providing strength by
being highly resistant to bending and torsion and is mainly present in long bone shafts. Cancellous bone is rigid but spongy with a vast surface area created by an interconnecting trabecular meshwork and is found primarily in the axial skeleton and at the ends of long bone (38).

Bone cells are osteoblasts, osteocytes and osteoclasts. Osteoblasts are derived from bone marrow mesenchymal cells transformed to preosteoblasts which become functional osteoblasts. Their functions are synthesis of most proteins of the extracellular bone matrix, expression of genes necessary for calcification, induction and down regulation of osteoclasts. Osteocytes are inactive osteoblasts that have been incorporated in bone tissue. Osteoclasts are derived from the monocyte/macrophage lineage. They are resorbing the bone surface by dissolving the hydroxyapatite crystals and transporting the degraded organic and inorganic products to the free surface of the osteoclast and released. Hydroxyapatite is the crystalline salt of calcium making up most of bone mineral. Pyrophosphate is an endogenous regulator inhibiting mineralization in connective tissue.

Collagen is the most prevalent protein in the human body. There are 28 types of collagen, of which type I is most abundant and providing both strength and elasticity to the tendons, ligaments and bone. Of the organic matrix in bone 80% is type I collagen (39, 40).

Bone turnover is regulated by multiple factors including RANKL, 1,25dihydroxy-vitamin D, PTH, IL1, IL6, corticosteroids, estrogens, calcitonin and calcium. Bone deposition and bone resorption are ongoing dynamic processes. About 10% of bone is replaced each year. If osteoblast production is increased or osteoclast production decreased bone mass is increased. Osteopetrosis potentially impairs bone marrow function. If osteoclast production is increased or osteoblast production is decreased bone mass is decreased. Osteoporosis results in potential susceptibility to fractures (38, 41).

Bone quality encompasses a number of bone turnover dependant bone tissue properties that govern mechanical resistance; such as bone geometry, cortical properties, trabecular micro-architecture, mineralisation, quality of collagen and apatite.

### 1.1.9 Markers of bone turnover

**Markers of bone formation:**

The enzyme alkaline phosphatase (ALP) is the most frequently used marker for osteoblastic bone formation. At least four gene loci are encoding for the ALP isoenzymes; tissue-nonspecific, placental, germ cell and small intestine locus (42). ALP from the tissue-nonspecific locus is expressed in tissues such as bone, liver and kidney. In serum from healthy adults, at least 6 different ALP isoforms can be separated and quantified: 3 bone ALP isoforms (B/I, B1, and B2) and 3 liver ALP isoforms (L1, L2, and L3) (43). ALP has a relatively long half-life of 1-2 days in serum and is stable when sampled, and also resistant to repeated freeze-thaw cycles. The activity is correlated to growth velocity.

Osteocalcin (bone GLA protein) is a bone matrix protein synthesised and secreted by osteoblasts and specific to bone except for a small amount synthesised by odontoblasts in dentine. Osteocalcin is relatively unstable and is cleared by the kidneys, thus affected by reduced kidney function, and has a reported half-life in serum of about 5 minutes. It
has a significant circadian variation with the highest serum concentrations in the morning. Samples must be frozen immediately and freeze-thaw cycles reduce the serum concentration.

About 95% of the total amount of collagen in bone is type I collagen, which is secreted by osteoblasts and fibroblasts as type I procollagen (Fig. 10). The C-terminal and N-terminal regions of the procollagen molecule are removed by extracellular proteases and released to the circulation. We have analysed PICP (type I procollagen C-terminal propeptide) but methods for analysis of PINP (type I procollagen N-terminal propeptide) has also become available. The PICP concentration is correlated to growth velocity and has a circadian variation with the highest values in the early morning and lowest in the afternoon. Serum samples are stable for several months during and after freeze-thaw cycles (44, 45).

**Markers of bone resorption:** After the collagen molecules have been formed by removal of the propeptide regions they spontaneously assemble into fibrils. These fibrils are cross-linked by bounds of pyridinolines (PYD), deoxypyridinoline (DPD), and pyrroles, in order to strengthen these collagen fibrils.

All bone resorption markers are products of collagen degradation. Each molecule of type I collagen is composed of two $\alpha 1$(I) chains and one $\alpha 2$(I) chain that forms a triple helix strand. Many collagen strands are joined together by cross-links located between the nonhelical ends of one collagen molecule and the helical region of another molecule.

The two cross-links PYD and DPD are formed by oxidation of lysine and hydroxylysine residues. DPD is only found in bone and dentin in contrast to the non bone-specific PYD. During bone resorption, osteoclasts release enzymes that cleave cross-linked type I collagen, releasing PYD and DPD into the circulation for further excretion in urine in free form or bound to the N- or C-terminal telopeptide of type I collagen. The free fraction is 40% in urine and the bound fraction is 60%, and both can be measured. They are not influenced by the diet but have a diurnal variation with the highest values early in the morning and lowest in the evening. Spot tests are well correlated to 24h collections. They are stable if frozen and kept in the dark.

Cross-linked telopeptides are short fragments of N- and C-terminal domains still cross-linked through PYD and DPD entering the circulation. They are specific and sensitive markers of bone resorption. We measured serum carboxy-terminal telopeptide of type I collagen (ICTP). Other now available methods are N-telopeptide (NTX-I) in urine and C-telopeptide (CTX-I) in urine and serum. Highest values are found in neonates and early puberty.

Hydroxyproline (Hyp) and hydroxylysine (Hyl) are hydrolyzed amino acids unique to collagen, formed intracellular during the posttranslational phase of collagen synthesis.
They are products of mature collagen from many different types of tissues, are influenced by diet and have circadian variations (44, 45).

**The use of markers of bone turnover:**
Bone ALP and PINP are the most promising markers of bone formation where bone ALP is stable and has no circadian variations. Of the bone resorption markers urinary DPD, NTX-I and CTX-I appear to be the most sensitive and specific markers. It has been recommended to establish reference values in four subpopulations for pediatrics: infant, prepubertal, pubertal and postpubertal period (45). Results for most markers of bone turnover cannot be compared between laboratories without previous cross-calibration (46).

1.1.10 Bone turnover in OI

Previous studies of patients with OI have reported increased (47-52) or a normal to low turnover (53-55). More recent research on OI has shown that the defective collagen biosynthesis results in less bone formation by osteoblasts with thinner primary trabeculae. Aberrant post-transcriptional modifications and incorporation of the mutant chain into a collagen triple helix affect the intrinsic stability of the trimer. Mutations leading to collagen helices lacking the normal mix of COL1A1 and COL1A2 chains can alter cellular functions. Such bone is more likely to suffer micro-damage which also attracts targeting remodelling. This leads to a shift favouring resorption, in the balance between bone formation and resorption, which normally favours formation and allows thickening and strengthening of trabeculae during childhood (56). Iliac bone histomorphometry has shown increased remodelling of cancellous bone formation (49).

1.1.11 Earlier treatments in OI

Before our study treatment of children with OI were based on physiotherapy and selective orthopaedic surgery, mostly intramedullary rodding. Attempts with different pharmaceutical approaches had been made. Some of these showed limited effects but none of them significantly improved the daily life. Sodium fluoride tablets in therapeutic doses given to children resulted in severely mottled enamel and had no significant beneficial effects. Calcitonin infusion had some effect but also severe adverse effects with flushing, nausea and vomiting. Trials with growth hormone could not show improvement of bone fragility (57).

In the late eighties two case reports of positive effects of oral APD treatment, each to one adolescent with OI were published (58, 59).

1.2 Bisphosphonates

The first bisphosphonate was synthesised 1897 but the first medical clinical use was in a case of myositis ossificans 1969 (60). Bisphosphonates are a group of synthetic stable analogues of pyrophosphate, which have been used extensively for treatment of hypercalcemia and diseases involving excessive bone resorption such as osteoporosis and osteolytic bone metastases (61-66). The presence of a carbon rather than oxygen atom at the centre of the molecule prevents its breakdown leading to a long half-life in bone. Two phosphate groups are attached directly to the carbon atom from which also the R1 and R2 side chains are attached (Fig. 11). The R1 chain is usually a hydroxyl group and increases the affinity of the bisphosphonate for bone mineral, in particular at
sites of active bone resorption leading to a concentration in osteoclasts. The R2 chain confers the differential potency of the different bisphosphonates (relative in vitro potency presented in Fig. 12).

The older non-nitrogen-containing bisphosphonates, etidronate and clodronate, are incorporated into adenosine triphosphate and form nonhydrolysable cytotoxic ATP analogues which accumulate in osteoclasts, inhibit ATP-dependant intracellular enzymes and leads to apoptosis (67). The newer amino-bisphosphonates interfere with osteoclast-mediated bone resorption and inhibit farnesyl-pyrophosphate synthase, resulting in failure of lipid attachment which blocks protein tethering to the cell membrane and inhibits biological function, ultimately leading to osteoclast apoptosis (41, 66, 68-70). They accumulate in bone to be slowly released over time with a half-life of up to 10 years (71).

![Pyrophosphate and Bisphosphonate](image1)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Potency</th>
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<tbody>
<tr>
<td>Etidronate</td>
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</tr>
<tr>
<td>Clodronate</td>
<td>10</td>
</tr>
<tr>
<td>Pamidronate</td>
<td>100</td>
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<tr>
<td>Olpadronate</td>
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<td>Ibandronate</td>
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<td>Alendronate</td>
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<td>Risedronate</td>
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<td>Zoledronate</td>
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\[Fig. 11 \text{Structure of pyrophosphate and bisphosphonate (From Shaw 2005).}\]

\[Fig. 12 \text{Relative potency of bisphosphonates (in vitro).}\]

![Radiograph](image2)

\[Fig. 13 \text{Each APD-treatment leads to the accumulation of a thin band of mineralised tissue at the interface between growth plate and metaphysis. As growth plate activity continues the bands become apparent on X-ray as metaphyseal lines.}\]

\[Fig. 14 \text{Appearance of “bone in bone” on radiograph taken three years after discontinuation of APD treatment.}\]
2 AIMS OF THE THESIS

The overall aim of these studies were initially to find and later to optimise a symptomatic treatment of children and adolescents with osteogenesis imperfecta including assessments of untreated children of different ages and types of OI to find criteria for and to monitor treatment.

1. To investigate if disodium pamidronate (APD) would be efficient as symptomatic treatment of adolescents with severe OI.

2. To assess and describe treatment effect in a larger group of children including effects in younger still growing children and effects on vertebral compression fractures in milder forms of the disease.

3. To evaluate effects of start of APD treatment in infancy on achievement of motor milestones, mobility, bone density and vertebral compression fractures.

4. To estimate the risk of osteonecrosis of the jaw (ONJ) after dental surgery in patients treated with nitrogen containing bisphosphonates.

5. To investigate if biochemical markers of bone turnover were related to type of OI or reflected the degree of immobilisation. Furthermore, if they could have a role in monitoring treatment response and predict vertebral compression fractures in children with milder forms of OI.
3 MATERIAL AND METHODS

3.1 SUBJECTS

During 1991-2006 a total of 193 patients were referred to the Centre for Children and Adolescents with OI at the Karolinska Hospital in Stockholm, Sweden for assessment. All children were assessed by the multidisciplinary team. Of those 43 had other diagnosis or were healthy. Of the 150 patients with OI six were adults. In nine no bone turnover markers were analysed. During the later part of this period four had already started treatment with bisphosphonate or calcitonin elsewhere with osteoporosis as treatment indication and one with growth hormone due to GH-deficiency. Bone turnover markers were analysed in a total of 130 children and adolescents with different types of OI, of which 69 had multiple or progressing vertebral compression fractures and offered APD treatment and all accepted. Of the 130 patients classified according to Sillence 84 had type I, 21 had type III and 25 had type IV. Of the treated 69 patients 29 were diagnosed as OI type I, 19 as type III and 21 as type IV.

Of the three adolescents in Study I the two younger also were included in Study II. Of the 28 children in study II the three youngest were included in Study III and the pre-treatment assessments of patient 4-14 were used as a historic untreated control group. All patients in Studies I-III were also included in study VI and V.

3.2 STUDY DESIGN

3.2.1 Paper I, II, III and V

For the prospective studies a protocol was designed. Instructions were made for parents and local treating teams since most treatments according to the plan were given at the patient’s local hospital or by home healthcare teams. We almost always administered the first treatment and further monitored treatment effects every six month during 1-2 years then every year, except radiographs which were taken annually to every second year depending on the subject’s age, with a higher frequency in younger children. ALP isoforms were analysed in Linköping by author 2 in paper V. During 2-5 years we monitored beneficial and conceivable adverse effects. Due to the positive effects of treatment and absence of any serious negative effects, the study was in two steps expanded to younger children and milder forms of the disease.

3.2.2 Paper IV

The study was a retrospective assessment of all children treated with APD for more than 0.5 years where all data concerning the bisphosphonate administration was evaluated with respect to doses, duration and accumulated dose. All patients had been examined every six month by a dentist and/or a physician. Oral radiographs, which had been taken in all but two children younger than three years of age, were examined.

3.3 TREATMENT

The intravenous route was chosen to prevent differences in bioavailability from interfering with the interpretation of results and avoid gastrointestinal adverse effects. After hydration, APD was given as monthly infusions of 10 mg/m² for three months, 20
mg/m² for the following three months, and subsequently with 30 mg/m² upon further treatment. After one to several years of treatment less than half of the patients received an increased monthly APD dose of 40 mg/m². To compensate for a noticed pronounced decrease in serum calcium levels half of the 69 patients, mostly older children, were also given oral treatment with 1,25-dihydroxycholecalciferol.

After several years of monthly APD infusions ten adolescents continued with oral alendronate and two with zolendronate infusions. This change was initiated because the effects of intravenous therapy were well evaluated in these children with improvement of BMD and vertebral height and they were tired of monthly intravenous treatment. Furthermore they had reached an age when they could take oral medication. Some of the adolescents had reached an age when no further vertebral growth could be seen. The risk of irreversible loss of beneficial effects was thus considered low.

3.4 ASSESSMENTS

3.4.1 Clinical assessments

Well-being, based on parents’ and patients’ subjective assessment was registered in special diaries using an arbitrary 10-grade scale, where 10 represents maximal well-being. Any number between 1 and 10 could be chosen. Pain was reported as the number of days with pain per month (72-74). Analgesic medication was also reported in Study I and II.

Ambulation was in study V assessed with a simple three-degree scale where 1) represents full mobility, 2) ability to walk short distances but use of wheelchair for longer distances and 3) a constant need of wheelchair (75). In study II, III and V the more discriminating Wilson scale of nine levels was also used to monitor the effects of treatment: 1) Functional walking without aid in all surroundings. 2) Functional walking without aid in secluded surroundings. 3) Functional walking with crutches in all surroundings. 4) Walking with crutches in secluded surroundings. 5) Functional walking with key-walker in all surroundings. 6) Walking with key-walker in secluded surroundings. 7) Reciprocal crawling with arms and legs. 8) Any other form of locomotion. 9) Sitting with support and no mobility. This scale shows better the changes in mobility in non-walkers includes two grades of non-walking locomotion, including crawling and bottom shuffling (any other form), which are important for functional needs and independent living in the severe forms of OI. We also used the five-degree scale according to the criteria of Bleck in Study II and III, to facilitate comparison with other studies. Bleck divided ambulation into: 1) Non-walker. 2) Not functional, physiotherapy walker. 2) Household walker. 3) Outside but only neighbourhood walker. 4) Community Walker (76).

In Paper III parents reported the age of achieving motor milestones.

Stature was measured in the supine position.

Dental assessments were made at each clinical follow-up.

3.4.2 Radiographic and ultrasound measurements

Areal BMD, whole body and lumbar spine (L1-L4), was assessed by dual-energy X-ray absorptiometry (DXA) using the Lunar DPX system. The new and more rapid Hologic QDR 4500 system was acquired after several years of the study. Duplicate
measurements with both equipments showed only minor differences within the variation of the respective equipment. The number and extent of vertebral compression fractures and vertebral height were regularly assessed by conventional X-ray in frontal and lateral projections. To screen for basilar impression a lateral projection of the skull base was done every second year. In paper III each lumbar vertebra was measured by a single observer (author 2) in lateral projection; the central superior-caudal height divided with the anterior-posterior width gave a quotient, from which the mean of all lumbar quotients was calculated.

Bone age was determined according to the method of Greulich & Pyle before and after two and four years of treatment (77).

An ultrasound examination for possible micro calcifications of the kidneys was initially carried out after one, three and six years of treatment. After the first case found with micro calcifications also pre-treatment assessments were made and cases were followed-up every six month.

### 3.4.3 Biochemical determinations

All samples were, with a few exceptions, taken between 9 and 11 a.m. due to known diurnal variations and not within two months after sustained fractures or orthopaedic surgical procedures. Serum calcium, phosphate, sodium, potassium, magnesium, alanine aminotransferase, aspartate aminotransferase, albumin, creatinine and parathyroid hormone (PTH) as well as haemoglobin, leukocyte and platelet counts, and urinary calcium/creatinine were determined by standardised and certified procedures. **Markers of bone formation:** The serum total alkaline phosphatase (total ALP) activity was determined by an autoanalyzer. In Paper V the bone ALP isoforms, B/I, B1, and B2, were determined by weak anion-exchange high performance liquid chromatography (HPLC)(42, 43). Serum osteocalcin was determined by an immunoradiometric assay, and serum type I procollagen carboxy-terminal propeptide (PICP) was determined by radioimmunoassay (RIA). **Markers of bone resorption:** Serum carboxy-terminal telopeptide of type I collagen (ICTP) was determined by RIA, and urinary free deoxypyrindinoline (DPD) was measured by enzyme immunoassay.

### 3.4.4 STATISTICAL ANALYSIS

In Studies II and III Wilcoxon matched-pairs signed ranks test was used to evaluate the difference between pre-treatment levels and levels after two years of treatment and at the latest recording. The tests were two-tailed and P<0.05 was chosen to indicate significant deviation from the null hypothesis. Since the results were not normally distributed medians were generally used. However in the tables we showed both medians and means to facilitate comparison with other studies. In study V we used Wilcoxon matched-pairs signed ranks test (One-way analysis of variance; ANOVA) with Tukey-Kramer multiple comparisons test, Kruskal-Wallis test (Nonparametric ANOVA) with Dunn’s post test; Spearman rank correlation test, Friedman test (Nonparametric repeated measures ANOVA). Friedman test was used for repeated measurements on the same individual but in cases of missing data Kruskal-Wallis test was used.
3.4.5 ETHICAL CONSIDERATIONS

All studies were approved by the ethics committees and all parents/patients gave their informed consent. After the beneficial effects shown in Study I and in the absence of other symptomatic treatments and after nine years of experience of bisphosphonate treatment without noticed significant side effects we found it unethical not to treat all patients with multiple or progressing vertebral compression fractures.
4 RESULTS

4.1 STUDIES OF BISPHOSPHONATE TREATMENT

PROSPECTIVE OBSERVATIONAL STUDIES I, II, III and V

The first noted result was decreased pain within weeks after start of treatment. Patient diaries showed less pain and improved well-being during treatment. Mobility and vertebral height improved more in younger children. In the adolescents however, we observed slower or no further progress of the vertebral compressions but no bone regeneration. Study 2 showed that 13/22 non-walkers achieved walking ability, at the median age at start of treatment of 6.4 years ranging from 1.1 to 17.3 years. In Study V 75% improved their mobility and 25 of 38 non-walkers (66%) achieved walking ability, of those 14/25 (56%) was over 2.5 years at start of treatment. Bone mineral density (BMD) measured by DXA increased gradually. At the latest recording in Study V the BMD increase was up to 700% (median 126%); however, the oldest patient experienced almost no improvement.

Bone age measured before and after 2 years of treatment followed the chronological changes in bone maturity, with median values of ±0 SD, and was not affected by the treatment.

Paper II and III showed a slight positive effect on growth. Treated infants achieved the motor milestones earlier and more complete than untreated children with OI used as historical controls. Mobility, vertebral height and BMD improved greatly during treatment and differed significantly compared to controls where some even had deteriorated. One infant had before treatment a mild scoliosis that remained unchanged and no one developed scoliosis, kyphosis or basilar impression. All treated infants achieved walking ability and at the latest recording at median 4.8 years of age five had normal mobility for their age. In the control group at median 4.6 years of age only two had walking ability and six had lost previous motor milestone abilities.

Bone turnover markers in serum and urine decreased gradually. All markers of bone turnover decreased over the treatment period, 1.0-12.5 years (median 4.3 years) in Study V, but with different relative amounts. These changes were not correlated to the gradual increase in BMD (lumbar spine), improvement of mobility, or decrease in pain. The change in serum calcium before and after the utmost first APD treatment was not correlated to changes in pain or BMD after one year of treatment, but to the change in mobility after one year. Those with less or no decrease in serum calcium during the utmost first treatment period improved less in mobility (p<0.05). Of those 42% received 1,25-dihydroxy-cholecalciferol during the first year due to calcium decrease during further treatments.

4.2 ASSESSMENT OF UNTREATED CHILDREN WITH OI

STUDY V

In 130 untreated children and adolescents, aged 0.25-20.9 years (median 6.7 years) with OI type I, III or IV we found significant differences in bone markers, however, not sufficient for clinical sub typing. Comparison with 14 untreated immobilised controls indicated that the immobilisation per se was not the cause of these differences. No
differences in these markers were observed between age-, type-, and mobility-matched subgroups with and without vertebral compression fractures.

4.3 STUDY OF ONJ IN YOUNG PATIENTS TREATED WITH BISPHOSPHONATE

RETROSPECTIVE STUDY IV
The 64 patients had been treated with APD during 0.5-12.5 years (median 4.0 years) after which ten continued with oral alendronate during 1.0-6.8 years (median 3.5 years) and two with zoledronate infusions during 1 year. Totally 38 dental surgical procedures were done in 22 of the 64 patients at the age of 3.5-31.9 years (median 12.3) after 0.03-7.9 years of APD treatment (median 3.4 years). Two of these patients had also been treated with alendronate for 1.5 and 4 years respectively before the surgery. Tooth extractions and/or surgical removal of teeth had been made in 19 patients of which surgery had been performed at more than one occasion in nine, endodontic treatment in one, insertion of implants in one, and orthognatic surgery comprising both maxilla and mandible in one individual. Clinical and radiographic dental examinations were made one year after surgery or later. No signs of osteonecrosis were found in any of the patients exposed to oral surgery or in the children during the period of tooth shedding or in any of the other bisphosphonate treated patients with OI.
5 GENERAL DISCUSSION

The low incidence and heterogeneity of the disease makes it difficult to run randomised studies. The only to me known randomised study of intravenous bisphosphonate treatment in prepubertal children has confirmed the effects on bone density and fracture rate (78). However larger studies are needed to minimise the risk of randomising to non comparable subgroups in this heterogenic disease. With the established beneficial effect of bisphosphonates such studies will also raise ethical problems. In fact it is surprising that so many individuals with so different mutations although in a limited amounts of genes are so helped by an unspecific therapy like bisphosphonates. If you treat in infancy you can never know how the outcome would have been without treatment, except when you have some family members with OI. Furthermore parents with OI did probably not have access to the present knowledge of intramedullary rodding procedures and intensive physiotherapy and might not be entirely comparable to the outcome of their children. The prognosis of severe forms of OI without treatment is poor with repeated fractures and fissures leading to progressive skeletal deformation with severe kyphoscoliosis, pain and immobilisation. Thus we found it unethical not to treat infants with early and progressive vertebral fractures. Whether early treatment can prevent development of kyphosis, scoliosis and basilar impression is not clear, but our results in Paper III seem promising. Treatment may improve final height, prevent respiratory impairment and may even improve life expectancy in this group of patients. In children with milder forms of OI with vertebral compression fractures treatment might also prevent scoliosis. However treatment given after development of major skeletal deformities may have lesser effect in preventing further scoliosis since this condition itself leads to an unfavourable load on the compressed vertebrae. Intravenous administration of amino-bisphosphonates have proven effective in treating children and adolescents with severe forms of OI and milder forms with vertebral compression fractures and it seems to be a safe treatment of this group of patients. The intravenous route was chosen mainly to prevent differences in bioavailability from interfering with the interpretation of results. Oral intake of tablets is also most difficult for infants and toddlers. Oral treatment can free the patients from monthly intravenous infusions and hospital contacts after achievement of a good intravenous treatment response and an age-related ability to swallow tablets. If gastrointestinal adverse effects occur there is always the possibility to resume intravenous administration. Serum calcium and parathyroid levels should be followed during the treatment and supplementation of vitamin D administered if needed, to prevent secondary hyperparathyreoidism. The untreated infants often have serum calcium levels above the reference intervals and can have micro calcifications in the kidneys. Infants with severe OI who become walkers have an increased risk of spondylolysis and spondylolisthesis of the 5th lumbar vertebra. This must thus be investigated with a lateral X-ray of the lumbo-sacral region in these children since pronounced or rapid progression of the spondylolisthesis can give neurological damage if untreated. Bone is accumulated, the remodelling rate is reduced and increased amounts of calcified cartilage have also been reported (79, 80). It is unclear if the increase of calcified cartilage has a detrimental effect. Residual levels are measurable after many years and they might continue to exert effects as they gradually are released from bone even after treatment is discontinued (56, 66). Other adverse effects of treatment have been reported as
affecting metaphyseal modelling (Fig. 13) causing widening of metaphyses, but also causing osteopetrosis and bone in bone formation (Fig. 14) (74, 81, 82). ONJ was first described 2003 (83). The first report of an effect of bisphosphonate on bone resorption in a human dates back to 1971 when etidronate was used in Paget’s disease (64). During time there have been a shift against intravenous treatment and newer generations of bisphosphonates (65, 84). The greatest risk of developing ONJ appears to be with monthly or three weekly zoledronate treatment (85, 86)). The aminobisphosphonates inhibit in vitro growth of human myeloma, melanoma, breast and prostate carcinoma cell lines (87). The treatment of endothelial cells with clodronate, risedronate, ibandronate or zoledronate reduces proliferation, induces apoptosis and decreases capillary-like tube formation of endothelial cells and zoledronate is a potent inhibitor of angiogenesis (88). Those effects must be considered when initiating treatment of infants and young children. As the long-term consequences of treatment are still unknown it may be desirable to limit the exposure of growing children.

On the other hand it has been discussed if treatment discontinuation is justified until end of growth as it might result in suboptimal effect that can not be corrected later (89, 90). Oral bisphosphonate treatment to children with OI also improves BMD and reduces fracture rate but has not been shown to have the beneficial effects on mobility. Two placebo-controlled studies showed no difference in functional outcome compared between the treated and untreated children (91, 92). Bone acquisition early in life is considered an important predictor of osteoporosis risk later in life (93). Prophylactic treatment of all children with OI with BMD below Z -1.0 has also been debated (66). My opinion is that there is a risk of unnecessary treatment since OI bone cannot be compared with osteoporotic bone in general. During the years as we have followed children with OI we have found that some children improve the BMD without treatment and only have few fractures. Others will have decreasing BMD and vertebral compression fractures. Markers of bone turnover can not prospectively discriminate between those groups. Until long-term safety data are available, treatment should be reserved for those where the benefits clearly outweigh the potential side effects of treatment. Further investigations to optimise monitoring and treatment of children and adolescents with OI is mandatory. Long-term prospective studies, during and after treatment, including different treatment strategies, are as important as the monitoring of untreated children in order to optimise the care of each patient. Bisphosphonate treatment has changed the physiotherapeutic and orthopaedic treatment of children with OI. The combination of these therapeutic entities could be used more efficiently during and after bisphosphonate therapy. Renewal of intramedullary rods due to growth is more seldom needed. With the more mineralised skeleton treatment with braces are possible and scoliosis operations are more effective. Children with more severe forms of OI are gaining walking ability (Fig. 15, 16, cover) with more need of orthopaedic concern for feet, knees and hips including problems with laxity of ligaments. The APD treatment has become the golden standard. Other newer bisphosphonates and other treatments should therefore to be compared with APD in trials before they are more widely introduced on this indication. Waiting for a curative therapy most patients could with APD therapy be kept in shape as never earlier has been possible. Multidisciplinary team assessments and early treatment optimises the prospects for improvement.
6 CONCLUSIONS

APD is an efficient symptomatic treatment for infants, children and adolescents with OI, but additional orthopaedic surgery is often needed. Early treatment may prevent scoliosis and basilar impression. Long term follow up is important.

Markers of bone turnover cannot predict vertebral compression fractures, response in BMD, mobility or pain after treatment. Despite the significant differences observed between the different types of OI, bone markers are not clinically useful for classification; however, serum ALP and urinary deoxypyridinoline appears to be the most sensitive markers in monitoring bisphosphonate treatment in the individual child.

Based on our study of children and adolescents treated with APD during long time, the risk of ONJ in these patients must be considered so low that the patients with indications for treatment should be treated and get the chance to experience the well documented beneficial effect for children with severe OI. Although the number of patients is not large in this study this is a specific group of patients with high exposition for bisphosphonates. Furthermore there has so far not been any report of ONJ in this group of patients. However, until more information has been collected it is recommended that before start and during bisphosphonate therapy to refer the patients to a dentist for examination and follow up.

Fig. 15 Mother and her newborn son with OI (left) and when the boy is 3½ years of age after three years of APD treatment.  Fig. 16 Boy with OI type III after 7 years of APD treatment.
THE DIRECTION OF FUTURE RESEARCH

A considerable amount of research is dedicated to improve the understanding of the mechanisms of bone turnover and treatment effects in vitro and in mouse models with different OI mutations. Over 800 different mutations have been reported in OI (7). RANKL is a final effector molecule of osteoclastic bone resorption. Preclinical trials with anti-RANKL therapy have succeeded and resulted in phase 3 clinical trials of postmenopausal women osteoporosis or lytic bone metastases (94, 95).

Clinical trials of mostly different bisphosphonates and different administration strategies are ongoing but still no international consensus exists. Other medications are tried and used primarily in adults with osteoporosis. Such are parathyroid hormone and nasally administered calcitonin. A substantial proportion of young rats treated with parathyroid hormone (PTH) developed osteosarcoma limiting the future options of pediatric trials, further preclinical studies are needed (96, 97). Studies of combinations of available medical therapies as bisphosphonates, growth hormone and calcitonin could also be considered.

Also more curative attempts as intrauterine mesenchymal stem cell transplantations have been made in OI (98, 99). However, although early gene therapy would be the optimal approach it still seems distant in the future and complex. Both the fact that the mutant allele first must be inactivated for not to interact with the normal protein chains and that the normal allele has to be introduced and turned on in a controlled fashion for the synthesis of normal procollagen are problems that have to be controlled.
8 SUMMARY IN SWEDISH

SVENSK SAMMANFATTNING.

Bakgrund: Osteogenesis (OI) är en grupp av genetiska sjukdomar med stor variation i svårighetsgrad från mild till mycket svår benskörhet. Utan behandling har de svårare formerna multipla frakturer ledande till progressiva skelettfelställningar med extrem kortvuxenhet, skelettsmärtor och immobilisering. Före studie I fanns ingen effektiv symptomlindrande behandling till dessa patienter.

Målsättning: Den övergripande målsättningen för dessa studier var initialt att finna och senare att optimera en symptomatisk behandling till barn och ungdomar med OI, inkluderande bedömning av obehandlade barn i olika åldrar och med olika typer av OI för att finna kriterier för och utvärdera behandlingen.

Patienter och metoder. Studier I-V involverar 130 barn och ungdomar med olika typer av OI. Av dessa behandlades 69 med intravenös infusion av pamidronat (APD) en gång per månad och utvärdering skedde halvårsvis i 1-2 år, sedan årligen. I studie I behandlades tre tonåringar med svår OI under 2-5 år. I studie II behandlades 28 barn i åldrarna 0.6-18 år under 2-9 år. De hade svår OI eller mildare form med kotkompressioner. I studie III behandlades 11 yngre barn i åldrarna 3-13 månader under 3-6 år och vid den senaste bedömningen vid 4.8 års ålder jämfördes de med vår egen historiska kontrollgrupp av obehandlade barn matchade för ålder och typ av OI. Den retrospektiva studie IV utfördes p.g.a. larmrapporter om osteonekros i käken (ONJ, osteonecrosis of the jaw) efter tandkirurgiska ingrepp hos patienter behandlade med kväveinnehållande bisfosfonater. Alla de 64 patienter som vi behandlat längre än 6 månader undersöktes. De hade fått APD-infusioner under 0.5-12.5 år. Ti hade sedan fortsatt med alendronat tabletter och två med zolendronat infusioner. I studie V utvärderades benomsättningsprover i blod och urin hos 130 obehandlade barn och hos 69 av dessa också under APD-behandling under 1.0-12,5 år.


Ingen ONJ fanns hos de 64 APD-behandlade patienterna där 38 tandkirurgiska ingrepp hade utförts på 22 av dem.

9 THE OI-TEAM FOR CHILDREN AND ADOLESCENTS

The Swedish specialist team for children and adolescents with OI was established in 1991 as collaboration between paediatricians, orthopaedic surgeons and dentists in Stockholm and Uppsala. It developed to become a paediatric multidisciplinary team of dentist, neurologist, nurse, nurse’s aid, orthopaedic surgeon, orthopaedic engineer, physiotherapist, occupational therapist and radiologist. The team has also a list of paediatric consultants: anaesthesiologist, endocrinologist, dietician, geneticist, psychologist, ophthalmologist and otologist, almoner, neurosurgeon and also a gynecologist.

After each individualised assessment by the team at Astrid Lindgren Children’s hospital the results and advice are rapidly reported to the child’s local habilitation team.
10 GUIDELINES FOR MANAGEMENT OF CHILDREN WITH OI

Here follow some guidelines for management of children with OI based on clinical experiences from the OI-team. Since each person/family with OI has their own unique mutation the management of these children must be individualised. These children benefits from the competence of a multidisciplinary team.

10.1 THE NEWBORN WITH SEVERE FORM OF OI

The child must be handled with gentle care. Fractures should be fixated with very light-weight materials. The newborn should be lying on a foam-rubber mattress or a cushion placed on a tray. This makes it possible to lift the child, with the mattress and tray, without causing further fractures. Analgesics should be given in case of new unhealed fractures. Pain relief is important and should be timed to have good effect at breastfeeding.

During the first 24 hours an X-ray of the whole body should be taken to localise all fractures and subtype the OI in order to be able to inform the parents about the prognosis.

Blood tests of serum calcium, phosphate, parathyroid hormone, alkaline phosphatase and D-vitamins are important to rule out other, possibly treatable, diseases.

Contact with a physiotherapist should be established as soon as possible. When the fractures begin to heal, usually after 1-2 weeks, treatment in comfortably warm water should start.

Information to the parents about the disease, mode of handling and treatment possibilities is important.

10.2 THE INFANT WITH SEVERE FORM OF OI

At 2-3 months of age a contact with a specialist team is recommended for assessment and decision about intravenous pamidronate treatment. There are two different schedules one with infusions one day each month and the other with infusions on three consecutive days each third month. Treatment is generally recommended to infants with severe but not lethal forms of OI (type III and severe forms of type IV).

Prolonged supine position until the child has achieved the motor stability to sit without support is recommended, in order to spare the spine and skull base from pressure. On the other hand it is important not to restrain the infant’s spontaneous motor development.

A temper-foam cushion, to lie or sit on, is recommended in case of jolting activities.

Continuous follow-up by physiotherapist is most important. Training in a warm temperate pool is recommended.

10.3 THE TODDLER WITH SEVERE OI

Most children with OI have hyper-mobile ankle joints and are prone to the valgus position. It is important with indoor and outdoor shoes that combine light weight with good fixation of the ankle. Medial padding of the soles are often needed.
Operations with osteotomy and intramedullary rodding procedures are often needed and have generally been done at the first fracture of a much curved femur, but some recommend preventive operations at the time when the child begins to stand up. In many cases these operations are also needed in case of tibial fractures or curvatures. In case of fractures light-weight plaster or casts should be used. Weight-bearing on the skeleton is of utmost importance both to bone strength and growth. All toddlers with OI should have some standing and if possible walking. It is better to walk and risk fractures than sit and avoid them since the latter leads to increased bone fragility. Jolting activities in the sitting position should be avoided and a temper-foam cushion is recommended if these can not be avoided.

10.4 GENERAL RECOMMENDATIONS CONCERNING CHILDREN WITH OI

10.4.1 General anaesthesia concerns
There is an increased risk of hyper mobility of the neck.
There is a risk of basilar impression.
Bleeding and coagulation should be checked-up before operation, since these disorders are common and prophylactic treatments are available.
Malignant hyperthermia can occur during anaesthesia.
In severe form of OI with a high fracture risk, a parent may be the optimal person to lift the child to the operating table.

10.4.2 Basilar impression (BI)
Many with BI will never have any symptoms and thus do not need any treatment. An extensive neurosurgical operation is used in case of progressive neurological symptoms. In case of severe BI without symptoms it is important to plan where a potential future operation shall be done.

10.4.3 Hearing
Tests are recommended each third year from seven years of age, and more often in case of hearing impairment.

10.4.4 Teeth
The spectrum of disturbances in tooth development ranges from no detectable abnormalities in 22 % to severe abnormalities in 47 %. This stresses the importance of a detailed and thorough dental investigation by a dentist familiar with OI. Since malocclusions are common collaboration with specialists in different fields in dentistry should collaborate (14).

10.4.5 Physiotherapy
Most children with OI will at some point need physiotherapy and for those with hypermobility or fractures continuous follow-up by a physiotherapist is most important. Training in a warm temperate pool is recommended and after infancy also loading in the standing position.
10.4.6 Orthopaedic treatment

Hyper-mobility of the joints are common, and the especially the valgus position of the ankles often need to be treated with special shoes or orthoses.

Intramedullary rodding is the state of art treatment of femur fractures in children with OI and conservative treatment with traction should be avoided, except shortly while waiting for an operation. Tibial rods are also frequently used if internal fixation is needed. Long-term immobilisation should be avoided since this increases the bone fragility.

Bisphosphonate treatment has changed the orthopaedic treatment of children with OI. Renewal of intramedullary rods due to growth is more seldom needed. With the more mineralised skeleton treatment with braces are possible and scoliosis operations are more effective. Children with more severe forms of OI are gaining walking ability with more need of orthopaedic concern for feet, knees and hips.

10.4.7 Bisphosphonate treatment

Amino-bisphosphonates have proven effective in treating children and adolescents with OI of severe form and milder forms with vertebral compressions. So far studies of intravenous treatment have reported more beneficial effect then studies of oral treatment. They accumulate in bone and reduces remodelling rate and residual levels are measurable after many years and they might continue to exert effects as they gradually are released from bone even after treatment is discontinued. Until long term safety data are available treatment should be reserved for those for whom the benefits clearly outweigh the risks. Children with milder forms of OI should be followed.

Skeletal pain and frequent fractures, including vertebral compression fractures are indications for bisphosphonate treatment. In adolescents when no further vertebral regeneration can be expected, oral bisphosphonates are often used. No severe negative effects have so far been seen but there are no long- term safety data in children and it is important to follow the patients into late adulthood.
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