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Occlusion of patients with Osteogenesis Imperfecta: A comparison with the severity of the syndrome

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Occlusion of patients with Osteogenesis Imperfecta
A comparison with the severity of the syndrome

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Résumé

Introduction

L'ostéogenèse imparfaite (OI) est un désordre de collagène héréditaire caractérisé par du tissu conjonctif défectueux et dont l'incidence est de 1 sur 20 000 naissances. Il y a une surreprésentation marquée de malocclusion de Classe III et d'occlusion croisée antérieure et postérieure dans la population d'OI. L'objectif principal de cette recherche est d'évaluer si la sévérité des malocclusions présentes chez les patients atteints d'OI est proportionnelle à la gravité du syndrome. L'objectif secondaire de cette recherche est d'évaluer si la sévérité de la malocclusion augmente avec l'âge.

Matériels et méthodes

Cette étude rétrospective observationelle fut effectuée par calcul du *Discrepancy Index* (DI) de 56 modèles dentaires de patients atteints d'OI. Les résultats du DI ont été comparés à trois variables qui caractérisent la gravité du syndrome: le type de OI, le type génétique et le z-score de la grandeur de chaque patient. En outre, l'analyse longitudinale d'un sous-ensemble de 20 modèles a été faite pour déterminer si la sévérité de la malocclusion augmente avec le temps.

Résultats

La médiane du DI était de 33,5 [1, 109]. Le DI est plus augmenté chez les patients atteints d'un type de OI plus sévère ($p = 0,001$) ainsi que chez les patients avec un z-score de grandeur plus petit ($p < 0,0001$). L'analyse longitudinale a démontré une augmentation statistiquement significative du DI au fil du temps ($p=0.05$).

Conclusion

La malocclusion des patients atteints d'OI semble liée à la gravité de ce syndrome. En outre, la sévérité de la malocclusion semble augmenter avec l'âge.

Mots-clés: ostéogenèse imparfaite, malocclusion, *Discrepancy Index*

Abstract

Introduction: Osteogenesis imperfecta (OI) is an inherited collagen disorder characterized by defective connective tissue with an incidence of 1 in 20,000 births. There is a marked over-representation of Class III malocclusion, negative overjet and lateral openbite in the OI population.

Objectives: Primary objective is to evaluate whether the severity of the malocclusions present in OI patients is proportional to the severity of the syndrome. Secondary objective is to evaluate whether the malocclusion severity increases with age.

Methods: Retrospective observational study performed by calculating the *Discrepancy Index* (DI) of 56 dental casts of patients with mild to severe OI. DI scores were compared to three variables that characterize the severity of the syndrome: OI type, genetic type and height z-score of each patient. In addition, longitudinal analysis of a subset of 20 OI casts was done to determine whether the malocclusion increases in severity with time.

Results: The median DI score was 33.5 [1, 109]. The DI score increased with increasing severity of OI type ($p=0.001$) and decreasing height z-score ($p<0.0001$). In addition, longitudinal analysis of 20 OI patients demonstrated a statistically significant increase in DI over time ($p=0.05$).

Conclusion: The malocclusion characteristic of OI patients seems linked to the severity of the syndrome. In addition, the malocclusion severity seems to increase with age.

Keywords: Osteogenesis imperfecta, malocclusion, *Discrepancy Index*

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Introduction

Osteogenesis Imperfecta

Overview

Osteogenesis Imperfecta (OI) is a complex genetically inherited disorder characterized by defective connective tissue with an incidence of 1 for every 20 000 births. [1] This heterogeneous disorder has been categorized into types from I to VII, based on clinical, radiographic and genetic criteria. [2, 3] Within these seven types, the pattern of heredity can be autosomal dominant or recessive; however, the genes that cause this syndrome always affect the primary structure of Type I collagen or alter the pathway of its production. [4] Consequently, individuals born with OI have increased bone fragility and low bone mass. These patients are susceptible to spontaneous bone fractures and may show a number of other defects, such as joint laxity, hearing impairments, malformed long bones, growth deficiency, muscle weakness, blue sclera, dentinogenesis imperfecta and/or dental malocclusion. The severity of these clinical manifestations is widely variable, ranging from mild forms with no apparent features and perinatal death. [2]

Pathogenesis

OI is a connective tissue disorder characterized by a hereditary defect in the production of Type I collagen. [2, 5] Collagen is the most abundant protein in the body and serves as the major extracellular component of bone. [6] It is also found in the skin, connective tissue, blood vessel walls, sclera, cornea of the eye, etc. [7] Although this protein is found throughout the body, there are different types of collagen and their structural differences are based on their role in each organ. [7, 8]

Type I collagen has a particular structure that is extremely important for proper functioning. This fibrous protein is initiated as procollagen, a triple helical molecule of three intertwined polypeptide chains, two pro-α1 chains and one pro-α2 chain. [6, 9] (Figure 1) These chains are composed of a repeating amino acid sequence, with the most important feature being a glycine molecule in every third position. Glycine, the smallest amino acid, is

essential since its small shape allows for the three pro-α polypeptide to join together as a well bound pro-collagen triple helix. [2, 5, 7, 10-12]

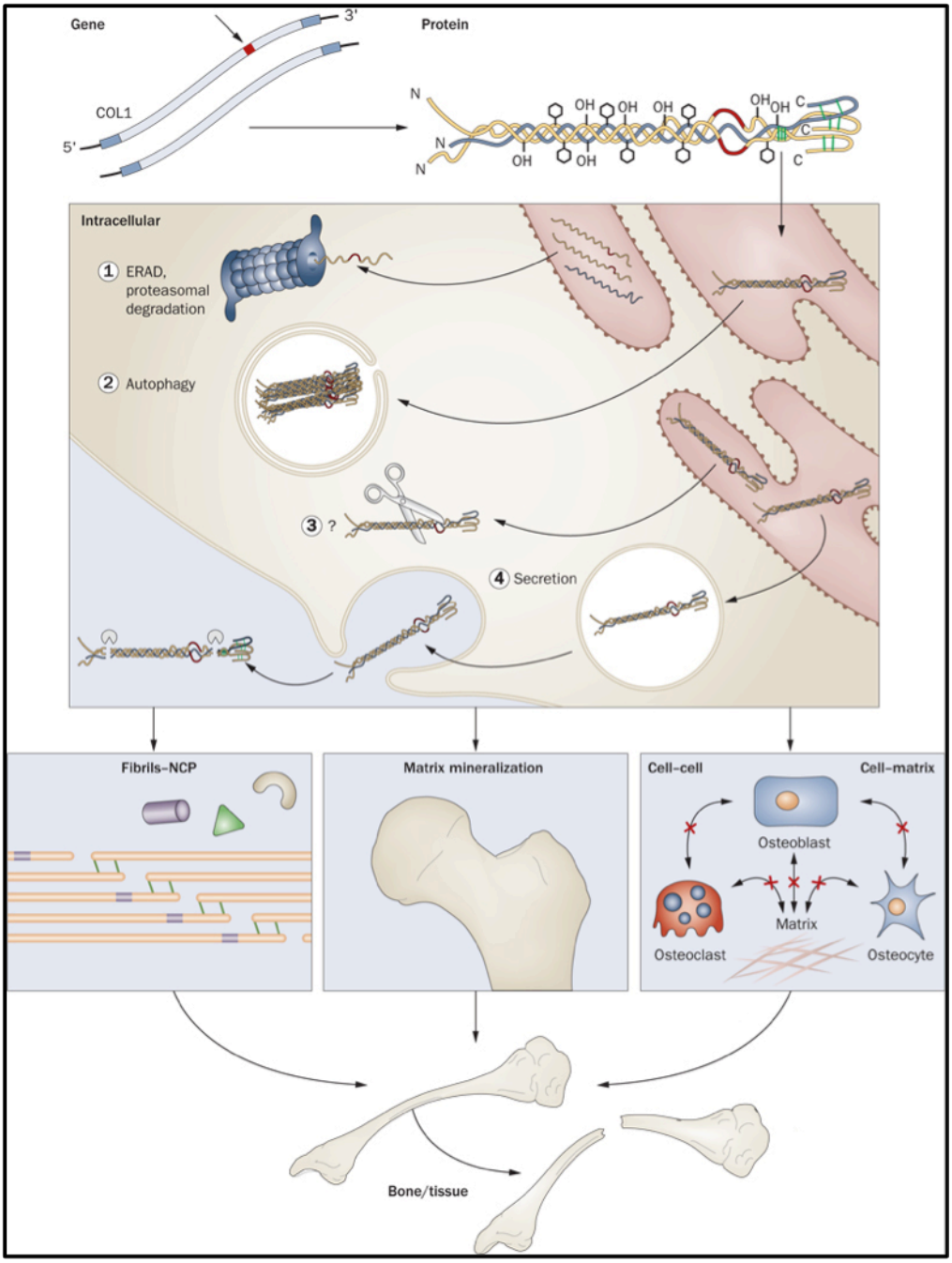

Figure 1: Mechanisms contributing to autosomal dominant osteogenesis imperfecta bone dysplasia: from mutant type I collagen gene to bone defect. [4]

This triple helix is then exported to the endoplasmic reticulum where it is modified extensively by hydroxylation and glycosylation. [6] For example, cartilage-associated protein (CRTAP), cyclophilin B (CyPB) and prolyl 3-hydroxylase (P3H1) come together as collagen 3-hydroxylation complex in order to hydroxylate the proline amino acid in each polypeptide chain and adequately fold the pro-collagen helix. [4, 9] The N- and C- propetides are then cleaved in the extracellular space, which then allows the mature tropocollagen molecules to assemble together and form collagen fibrils. [6]

Since type I collagen is the main protein in bone extracellular matrix, any aberrations in its synthesis can create an OI phenotype. [2, 6] Once a deficient collagen molecule is produced, it will either be degraded or incorporated into the body's structures. The former will create a quantitative defect, while the latter will create a qualitative one. Defective tropocollagen protein secreted into the cell matrix not only affects fibrillogenesis and bone mineralization, but also cell-to-cell communication. [4, 11] In fact, the OI phenotype created by the various genetic mutations will depend on which protein structures are affected and which organs harbor these proteins. [13]

Inheritance

Over 800 mutations in the Type I collagen genes have been linked to the OI syndrome. [5, 11] The majority of patients (90%) with OI have an autosomal dominant mutation in the COL1A1 gene on chromosome 17 or COL1A2 gene on chromosome 7. [6, 9, 14] These genes encode the amino acid sequence in the pro-α1 chains and pro-α2 chains respectively. [2, 4, 6, 9, 10, 15] DNA mutations at these sites alter the structure and/or quantity of Type I collagen in the affected individual and the severity will range from clinically undetectable to lethal. [4] In addition to autosomal dominant forms of OI, there are autosomal recessive inheritance patterns that have also been discovered. [4, 6]

Type I OI, the mildest and most common form of the disease, is produced via a premature stop codon in the COL1A1 gene. The mRNA produced by the mutated allele will be degraded by nonsense-mediated decay, which leads to a haploinsuffuciency and diminishes the total amount of Type I collagen in the body. [2, 5, 11, 12] The result is a mild phenotype of the syndrome characterized by minimal bone fragility, blue sclera and hearing loss. [5, 9, 10]

Types II, III and IV, are caused by mutations leading to a distorted three-dimensional structure of type I procollagen. [5] The most common type of DNA mutation changes the amino acid sequence by substituting the obligatory glycine molecule for a bulkier amino acid. [2, 12] This substitution will impair the triple helical folding mechanism, as well as post-translational hydroxylation and glycosylation. In addition, improper splicing, deletions and insertions have also been discovered as other types of possible mutations. [6] Consequently, the amino acid sequence of the procollagen protein is altered which produces a less functional Type I collagen molecule. Mutations in the COL1A1 genes are more commonly lethal, whereas mutations in COL1A2 genes are 80% non-lethal. [5, 11]

In recent years, more types of OI have been discovered and added to the classification system. OI Types V, VI and VII are typically recessive in autosomal inheritance and usually produce severe phenotypes of the disease. [4, 6]

Clinical manifestations

The OI syndrome has a very broad phenotypic range. Patients with the same type of OI will present with different clinical manifestations and varying degrees of severity.

Bone Fragility

Bone fragility is the principal clinical characteristic in the OI syndrome, with its severity increasing in the following order: Type I < Type IV, V, VI, VII < Type III < Type II. [2, 16] Due to the abnormal collagen production, there are several disturbances in the organic and mineral compounds of the body, and these changes have a deleterious effect on bone mass, strength and stiffness. [2, 4, 16] The bone that is formed has an abnormal and irregular morphology, as well as an increased mineral density. [2, 4] Consequently, OI bone breaks much more easily when deformed even though the increased mineralization makes it harder in consistency. [2, 17] Furthermore, histomorphometric analysis of bone from OI patients revealed an increased number of osteoclasts and osteoblasts, an overall increase in the rate of bone formation, but a decreased volume of trabecular and cancellous bone volume. [2, 12, 16] (Figure 2) There is a reduction in bone volume because although there is an increase in the

number of osteoblasts, each OI osteoblast secretes less bone than normal and bone resorption is amplified by the simultaneous increase in osteoclast numbers. [2, 4, 12, 16]

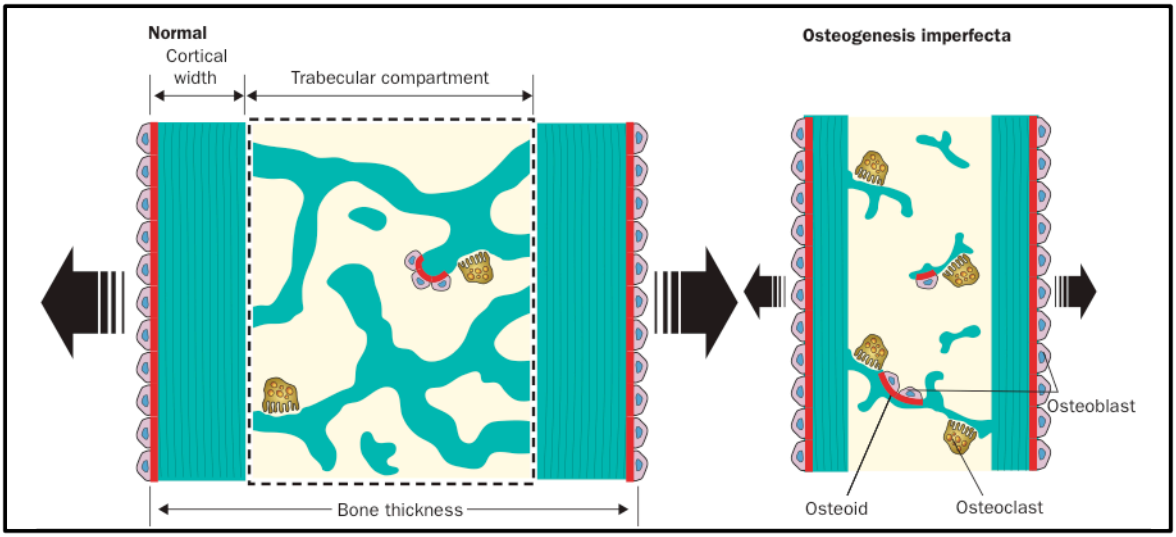

Figure 2: "Summary of histological bone abnormalities in OI : Osteogenesis imperfecta bone has a smaller than normal external size (bone thickness) because of sluggish periosteal bone formation. Trabeculae are reduced in number and are abnormally thin. Although individual osteoblasts produce less bone than normal, the overall bone formation rate in the trabecular compartment is amplified, because the number of osteoblasts is raised. However this increase does not lead to a net gain in trabecular bone mass, because the activity of bone resorption is also enhanced." [2]

Consequently, the skeleton is more fragile and it fractures much more easily. There is an increase in number of lower limb fractures, deformity and bowing of long bones and scoliosis caused by vertebral crush fractures. [2, 9] (Figure 3)

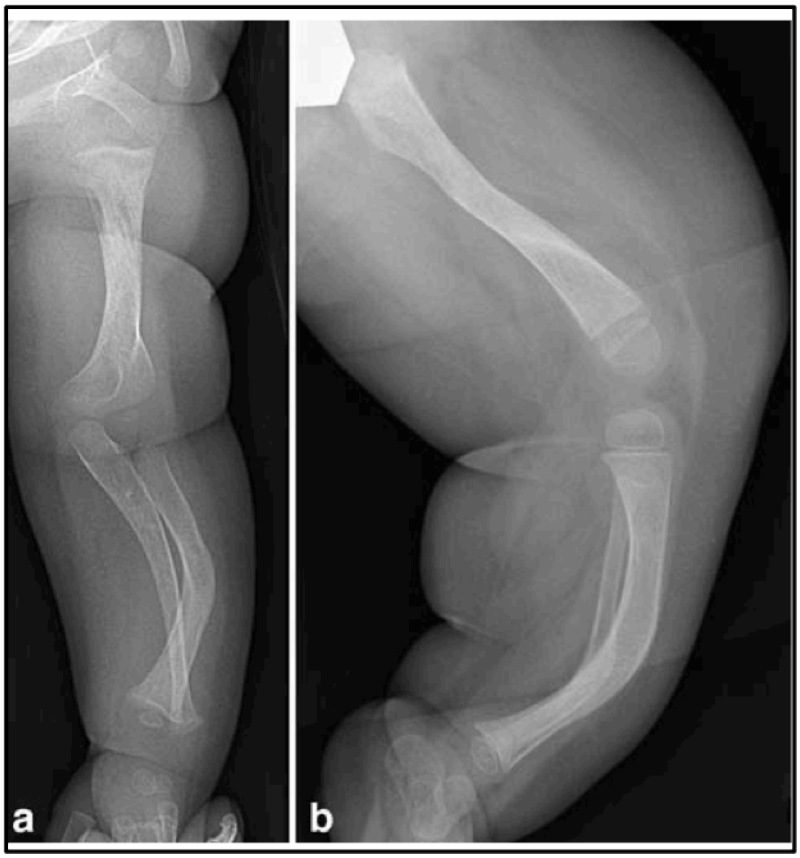

Figure 3: “Bowing of the radius (a) and tibia (b) in a baby with OI type III” [10]

Growth

A decrease in height is one of the chief clinical characteristics in patients with OI. [4, 6, 18] Even children with OI Type I, who seem to be in the normal range, are often below the 50th percentile range. [6, 9] Patients with the more severe Type III OI have a very short stature, typically within 90 to 120 cm. [10] (Figure 4) In fact, *Jensen & Lund* have demonstrated that height is significantly reduced in patients with the more severe phenotypes of the disease, which suggests that height is a predictor of disease severity in the OI syndrome. [18]

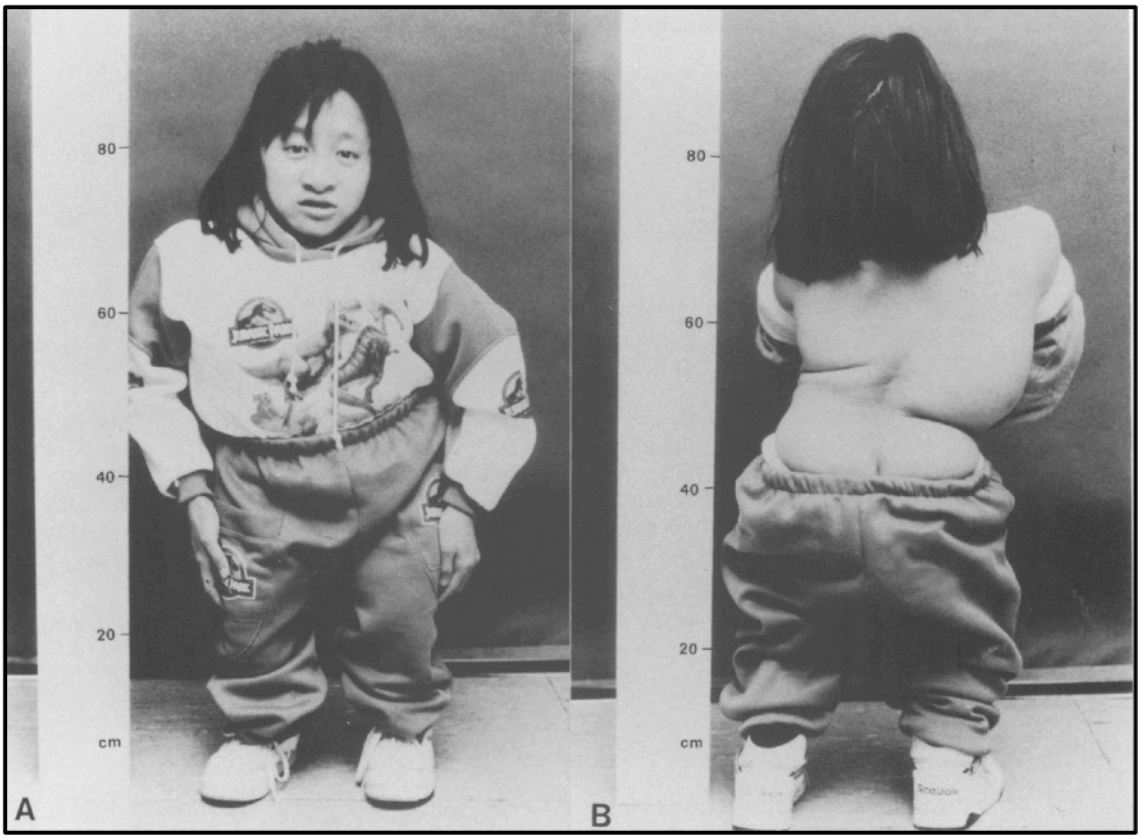

Figure 4: Female with short stature and scoliosis; height = 93cm. [19]

Hearing Loss

Hearing loss is a common secondary feature in individuals with an autosomal dominant form of OI, which affects about 50% of adult patients. [20] This condition is caused by a combination of conductive and sensorineural defects and usually manifests itself between the second and fourth decade of life. [4, 6, 20] However, about 5% of children with OI have been found to show signs of early-onset hearing loss. *Kuurila et al*. recommend an audiometrical analysis be performed in children with osteogenesis imperfecta even without symptoms of hearing loss starting at the age of 10 years, with a repetition every 3 years. [20] No cases of hearing defects have been reported in patients with a recessive form of OI. [6]

Blue Sclera

Blue sclera is caused by abnormal collagen fibers in the sclera, which create the characteristic blue hue of the cornea. [21] Not all patients with OI present with blue sclerae. In cases of those who do, the scleral hue is variable. In Type I and Type III OI, blue sclerae are present at birth and persist throughout life, whereas in Type IV, the scleral hue becomes progressively normal with age. (Figure 5) In the perinatal-lethal form of OI, the sceral hue is often the darkest, sometimes even reaching a shade of black. [9]

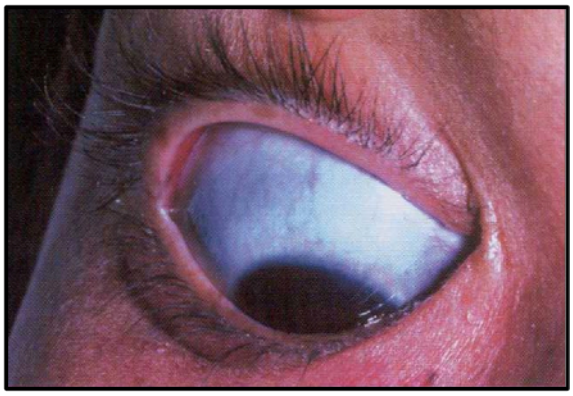

Figure 5: Blue Sclera [14]

Oral Manifestations

There are several oral manifestations within the OI syndrome, the most widely reported feature being dentinogenesis imperfecta. Dentinogenesis imperfecta is a dental pathology characterized clinically by an amber-brown to blue grey opalescent hue of the teeth, thin/cracking enamel and severe attrition. (Figure 6) The radiographic findings include short roots, bulbous crown structure, obliteration of the pulp chamber and frequent peri-radicular radiolucencies. [22-24] The primary dentition is often affected more severely than the permanent dentition. [23, 25] Approximately 80% of patients with autosomal dominant OI have dentinogenesis imperfecta, but it is extremely rare in autosomal recessive types of OI. [6, 23, 26]

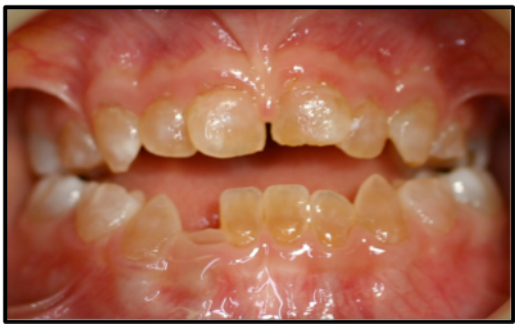

Figure 6: Dentinogenesis imperfecta of primary dentition (courtesy of the Montreal Children's Hospital)

Many authors have described dentinogenesis imperfecta in detail, but very few have documented another important facet of the OI syndrome: the dental malocclusion. A study by *Rizkallah et al.* in 2012 revealed that the malocclusions present in the OI population are more severe than those present in the general population. They confirmed that there is a distinct over-representation of Class III malocclusion, negative overjet and lateral openbite in patients with OI. [27] (Figure 7)

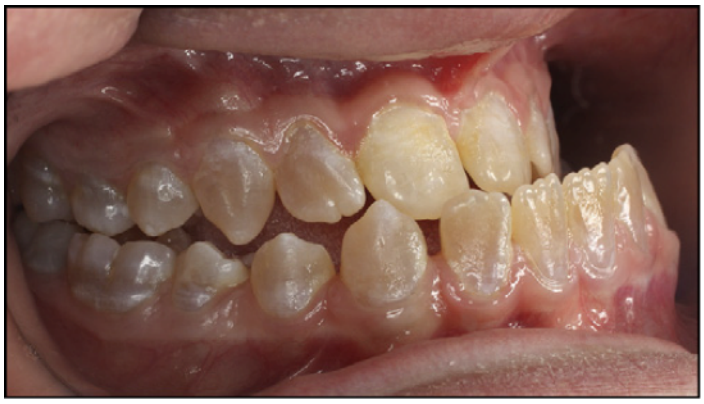

Figure 7: OI patient exhibiting Class III malocclusion, anterior openbite, lateral posterior crossbite and opalescent teeth [27]

Diagnosis

The diagnosis of OI is usually done on a clinical basis. It is often clear in individuals with a positive family history in whom several cardinal manifestations are present. However, it can be quite difficult when other family members are unaffected and bone fragility is the only

indication of the syndrome. In addition, there is no agreed minimum number of criteria that can establish a clinical diagnosis of the syndrome. [2] Thus, practitioners typical rely on a complete clinical examination as well as genetic work-up to establish a diagnosis of the disease. DNA analysis of the genes involved in the biosynthesis of Type I collagen can be performed and are highly sensitive. [2, 9] However, results that do not detect a genetic mutation in COL1A1, COL1A2, CRTAP and SERPINF1 do not rule out a diagnosis of OI. [2]

If a diagnosis of OI seems possible but is inconclusive with a mere clinical exam and genetic analysis, other analyses can be done. Radiographs can detect bowing of the long bones, presence of crush vertebral factures and scoliosis. [9] Bone histomorphometry can help distinguish OI from other osteoporotic conditions. In addition, when polarized light microscopy is used, OI types V and VI can be diagnosed. [2, 9] (Figure 8) However, this invasive method is usually avoided whenever possible since it depends upon a bone biopsy retrieved under general anesthesia. [9]

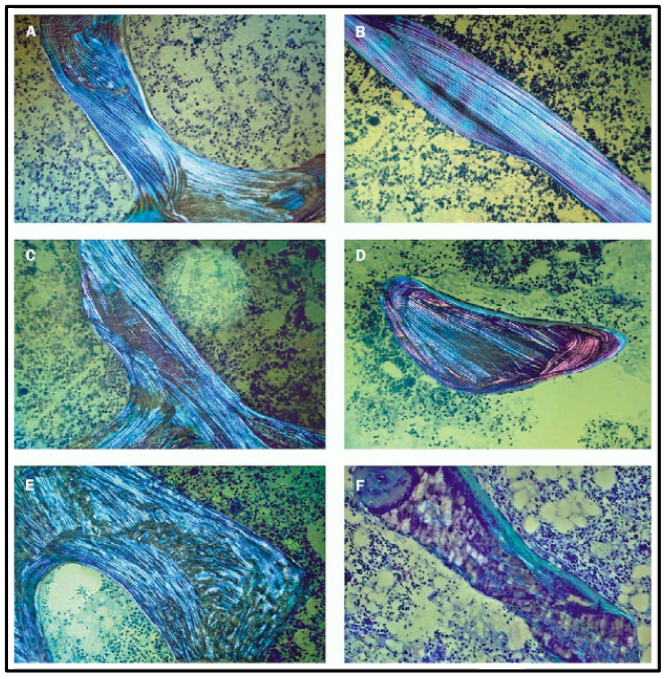

Figure 8: "Bone lamellation pattern as seen under polarized light (A) Healthy control. (B) OI type I; lamellae are thinner than normal, but lamellation is smooth. (C) OI Type III; lamellation is slightly irregular. (D) OI type IV; lamellation is similar to type III disorder. (E) OI type V; mesh-like pattern. (F) OI Type VI; fish-scale pattern." [2]

There are a variety of differential diagnoses available for OI, which depend on the age of presentation, clinical manifestations and the severity of the signs and symptoms. [9] (summarized in Table 1)

Table 1: Differential diagnosis of osteogenesis imperfecta [2, 9]

Condition	Childhood phenotype	Inheritance	Pathophysiology
Non-accidental injury	Multiple unexplained childhood fractures	--	Pathologic fractures
Bruck syndrome	Moderate to sever. Congenital joint contractures; scoliosis; white sclerae	AR	Deficiency of telopeptide lysyl hydroxylase
Cole-Carpenter syndrome	Severe. Normal at birth; short stature; osteoporosis; diaphyseal fractures; hydrocephalus; ocular proptosis; distinctive facial features	Uncertain	No abnormality of type I collagen
Hypophosphatasia	Mild to severe. Low alkaline phosphatase activity; very variable clinical expression; early loss of teeth	AD/AR	Mutation in ALPL
Idiopathic hyperphosphatasia or juvenile Paget disease	Severe. Raised alkaline phosphatase activity; very variable phenotype; thickened skull; widened diaphysis; progressive deformity; scoliosis; deafness	AR	Osteoprotegerin deficiency due to mutation in TNFRSF11B in the majority of cases
Panostotic fibrous dysplasia	Sever. Characteristic lesions in all bones.	Somatic	Somatic mutation in GNAS
Osteoporosis pseudoglioma syndrome	Moderately severe. Congenital blindness; torus palatinus	AR	Mutation in LRP5
Idiopathic juvenile osteoporosis	Mild to moderately sever. Transient osteoporosis; prepubertal presentation; metaphyseal fractures; neo-osseous osteoporosis; no extraskeletal manifestations	Uncertain	Unknown etiology in the majority of cases; sometimes associated with heterozygous mutation in LRP5

Classification

The classification of OI has proven to be quite difficult, given that the syndrome is highly heterogeneous. In 1979, *Sillence et al.* categorized OI patients into four types based on clinical presentation. [28] In recent years, there has been further subdivision of these four types according to genetic factors and bone histology techniques. (Table 2) [2, 3] Presently, eleven types of OI have been described. [4, 9] These subdivisions are mainly based on differences in the genetic factors leading to the disease, even though the clinical phenotype may be very similar to the pre-existing OI types. In other words, OI Type V, VI and VII are very often clinically undistinguishable from OI Type IV. [29] Some authors have stated that this intermingling of genetic and clinical classification is very confusing and problematic. [6, 29] For the purpose of simplicity, the classification system used in this paper will be from *The Lancet*'s 2004 seminar on osteogenesis imperfecta. [2]

Table 2: Expanded Sillence classification of osteogenesis imperfecta [2-4, 6, 9]

Type	Clinical severity	Mode of inheritance	Typical features	Typically associated mutations*
I	Mild non-deforming osteogenesis imperfecta	AD	Normal height or mild short stature; blue sclera; no dentinogenesis imperfect	Premature stop codon in COL1A1
II	Perinatal lethal	AD	Multiple rib and long-bone fractures at birth; pronounced deformities; broad long bones; low density of skull bones on radiographs; dark sclera	Glycine substitutions in COL1A1 or COL1A2
III	Severely deforming	AD	Very short; triangular face; severe scoliosis; greyish sclera; dentinogenesis imperfect	Glycine substitutions in COL1A1 or COL1A2
IV	Moderately deforming	AD	Moderately short; mild to moderate scoliosis; grayish or white sclera; dentinogenesis imperfecta	Glycine substitutions in COL1A1 or COL1A2

V	Moderately deforming	AR?	Mild to moderate short stature; dislocation of radial head; distinctive histology; mineralised interosseous membrane; hyperplastic callus; white sclera; no dentinogenesis imperfecta	Unknown
VI	Moderately to severely deforming	AR	Moderately short; scoliosis; accumulation of osteoid in bone tissue, fish-scale pattern of bone lamellation; white sclera; no dentinogenesis imperfecta	Homozygous SERPINF1 mutations
VII	Moderately deforming	AR	Mild short stature; short humeri and femora; white sclera; no dentinogenesis imperfecta	Homozygous CRTAP mutations

*May or may not be detectable in a given patient

Treatment

The medical management of patients diagnosed with OI is a multidisciplinary approach that combines physical therapy, orthopedic surgery and pharmacotherapy. Treatments are usually focused on improving functional ability by decreasing bone fragility and increasing mobility in patients with more severe OI phenotypes. [30, 31] The key to successfully treat these patients is to combine a multidisciplinary approach with early diagnosis. [5, 31]

Physical Therapy

The primary goal of physical therapy is to improve motor function and reduce immobility-induced bone-loss. [30] Many children with severe phenotypes of OI have very limited mobility and are often wheelchair-bound. These patients benefit greatly from physical therapy, especially in the lower extremities.

Orthopedic surgery

Orthopedic surgery is very common in the treatment of severe OI phenotypes. Surgical intervention often consists of the placement of intramedullary rods in the long bones to correct

deformities and stabilize the bone. [4, 30] This kind of corrective surgery enables walking and improves overall mobility in OI patients. [4]

Pharmacotherapy

Pharmocotherapy is currently the most widely used medical intervention for children with moderate to severe OI. [10] The ultimate goal is to reduce fracture numbers, prevent long bone deformities and increase functional mobility. [2] The most popular medication used today are bisphosphonates, but new advances in the use of recombinant human growth factor have also been made in recent years. [13]

Bisphosphonates have an inhibitory effect on osteoclasts and therefore, decrease bone resorption. [2, 10, 13, 31] When treated with this medication, the quality of the new bone formed does not improve, but the skeleton does benefit from an increase in bone volume and an overall increase in mechanical strength. [10, 31] The most popular bisphosphonate used today is cyclic intravenous pamidronate, given in cycles of three days every two to four months. [2, 10] In a study by *Glorieux et al.* in 1998, more than 50% of the OI patients treated with cyclic pamidronate had an improvement in mobility, as well as a decrease in overall fracture rate. [31] In the moderate to severe OI phenotypes, bisphosphonate therapy should be started as early as possible in order to benefit from the growth process. On the other hand, mild forms of OI should not receive bisphosphonate therapy as the negative side effects (abnormal bone metabolism, risk of osteonecrosis, etc.) may outweigh the benefits of this treatment modality. [2, 10, 13]

Growth hormone has also been studied in the past as a treatment for the OI syndrome, given that short stature is one of its more common features. [32] In a study in 2003, *Marini et al.* revealed that the baseline growth rate of about 50% of the OI patients treated with recombinant human growth hormone doubled during the first year of treatment. [4, 33] This study also showed that bone turnover rates were increased, a secondary effect that is potentially harmful to OI patients. [33] For this reason, it is probably beneficial to combine recombinant human growth hormone with bisphosphonate therapy, but this treatment still needs to be adequately investigated in the future. [2, 10, 13, 33]

Conclusion

Osteogenesis imperfecta (OI) is a complex genetically inherited disorder characterized by defects in biosynthesis of Type I collagen. Consequently, individuals affected by OI are susceptible to spontaneous bone fractures, long bone deformities, short stature, hearing impairments, muscle weakness, blue sclera, dentinogenesis imperfecta and/or dental malocclusion. [2] It is well known that the OI syndrome is caused by alterations in the collagen type I biosynthesis pathway, but the exact mechanism by which the genetic defects cause abnormal bone formation have not been described. [16] A better understanding of the disease pathway and the resulting phenotypic expression can aid in the diagnosis, classification and the efficient treatment of this debilitating disease. Great advances have been made in the understanding of the OI syndrome and the help that is now available to these patients is extensive; however, the morbidity of the more severe phenotypes is still astounding. No cure for the disease has been found, so more must be done in order to optimize their mobility, autonomy and quality of life. [10, 13]

Malocclusion

Overview

The study of orthodontics and the treatment of malocclusion have become increasingly popular in the last century. However, malocclusion has been a part of human history since antiquity and attempts at correcting misaligned, protruding, and irregular teeth have been documented since 1000 B.C. Dentistry has come a long way since the 18th and 19th centuries, and the same is true for orthodontics, the branch of dentistry focused on correcting malocclusion. In the 1890's, Edward H. Angle, the so-called "father of orthodontics", subdivided the major types of malocclusion and proposed a classification system that is still widely used today. [34]

Classification

A classification system proposed by Angle was based on the position of the upper first molar. Angle believed that in order to have a normal occlusion, two cardinal features must be present. First, the mesiobuccal cusp of the upper first molar must occlude with the buccal groove of the lower molar (Figure 9) and second, all the teeth must be arranged on a standard smoothly-curving line of occlusion. [34] (Figure 10)

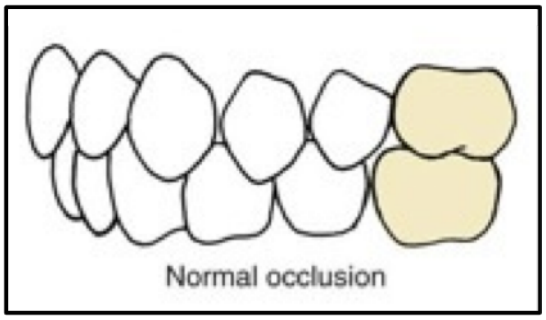

Figure 9: Mesiobuccal cusp of upper first molar occludes with buccal groove of lower first molar [34]

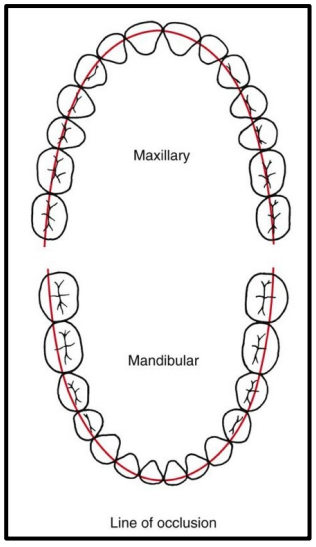

Figure 10: Upper and lower lines of occlusion [34]

Angle then described three distinct classes of malocclusion based on aberrations in the two previous features.

Class I Malocclusion

Mesiobuccal cusp of upper first molar occludes with buccal groove of the lower first molar, but the teeth are not well aligned on the line of occlusion. (Figure 11)

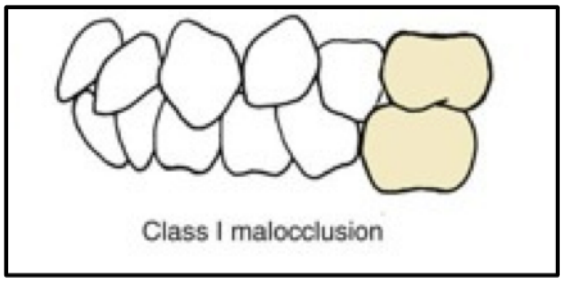

Figure 11: Class I malocclusion [34]

Class II Malocclusion

Mesiobuccal cusp of upper first molar positioned mesial relative to the lower first molar; teeth may or may not be well aligned on the line of occlusion. (Figure 12)

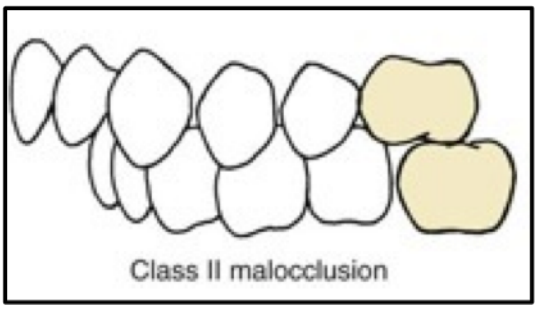

Figure 12:Class II malocclusion [34]

Class III Malocclusion

Mesiobuccal cusp of upper first molar positioned distal relative to the lower first molar; teeth may or may not be well aligned on the line of occlusion. (Figure 13)

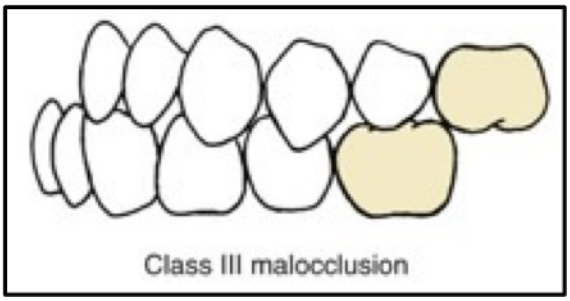

Figure 13: Class III malocclusion [34]

Class I malocclusions (69.7%) are the most common, followed by Class II malocclusions (23.8%) and finally, a small number of the population possess a Class III malocclusion (6.5%). [34-36] Many studies have been done on the incidence of malocclusion in different populations. The previous percentages are limited to the American Caucasian population. [36]

Terminology

Other important features of a malocclusion that are not part of Angle's classification system are as follows: anterior and posterior crossbites, anterior and posterior openbites, increased overbite and increased overjet.

Overjet

Overjet is the horizontal measurement between the maxillary and mandibular incisors. (Figure 14) A normal overjet is typically 2mm when measuring from the labial surface of the mandibular incisor to the labial surface of the maxillary incisor. A negative overjet or anterior crossbite will result if the mandibular incisors are anterior to the maxillary incisors. [34]

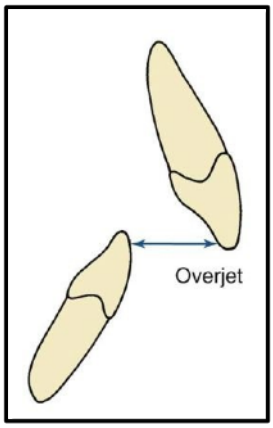

Figure 14: Overjet between the maxillary and mandibular incisors [34]

A posterior crossbite would result if the posterior overjet is reversed. More specifically, to have a posterior crossbite, the maxillary posterior teeth would be positioned more lingual than the mandibular posterior teeth. A posterior crossbite can be unilateral or bilateral.

Overbite

Overbite is the vertical measurement between the upper and lower incisors. (Figure 15) Normally, the maxillary incisors overlap the mandibular teeth by 2mm. [34]

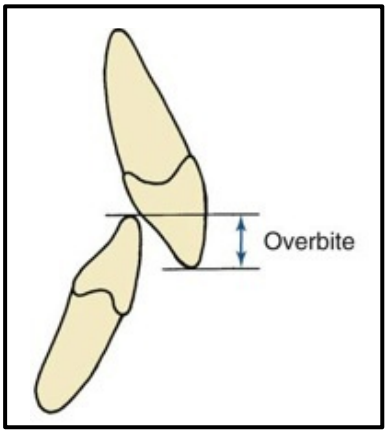

Figure 15: Overbite between the maxillary and mandibular incisors [34]

When a space exists between the maxillary and mandibular teeth, this is referred to as an openbite. (Figure 16) An openbite can be anterior, posterior, unilateral or bilateral.

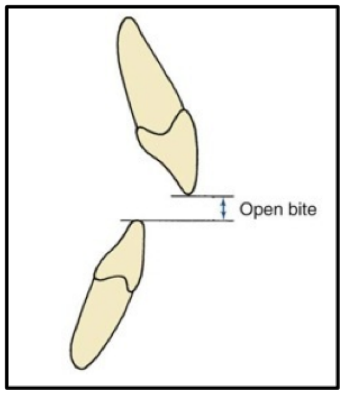

Figure 16: The presence of an anterior openbite [34]

In order to make Angle's classification more complete, *Mills* suggested the addition of more information as an aid in describing the various malocclusions that exist. (Summarized in Table 3) [35]

Table 3: Expanded Angle Classification [35]

Class	**Type**	**Clinical Characteristics**
I	I	Crowded incisors; the canines are frequently labial
	II	Protrusion or labioversion of the maxillary incisors
	III	Presence of anterior crossbite
	IV	Presence of posterior crossbite
	V	Mesial drifting of molars resulting from premature loss of teeth
II	Division 1	Proclined maxillary incisors (labioversion)
	Division 2	Retroclined maxillary central incisors
III	I	Maxillary and mandibular teeth in good alignment, but incisors in edge-to-edge occlusion
	II	Maxillary teeth in good alignment, mandibular teeth crowded; mandibular incisors lingual to maxillary teeth
	III	Maxillary teeth crowded, mandibular teeth in good alignment; mandibular incisors labial to maxillary incisors

Etiology

As previously stated, Angle's classification of the 3 types of malocclusion is highly simplified. He fails to take into account several important components critical in assessing the etiology of the malocclusion, which are: "(a) the size of the maxilla, (b) the size of the mandible, body and ramus, (c) the factors that determine the relationship between the maxilla and mandible, which are genetic and environmental, (d) the arch form, (e) the size and morphology of the teeth, (f) the number of teeth present, and (g) the soft tissue morphology." [37]

A malocclusion can have a skeletal etiology, a dentoalveolar etiology, or a combination of the two. A skeletal malocclusion is one in which there is an aberrant relationship between the maxilla, mandible and/or cranial base. A dentoalveolar malocclusion can be due to an abnormal arch form, abnormal tooth size and/or missing teeth. All malocclusions result from a combination of genetic and environmental factors which affect craniofacial growth, arch size, tooth size, tooth loss, etc. [34, 37] Diagnosing the etiology of the malocclusion is essential in providing the best treatment.

Severity

Angle's "normal occlusion" is actually quite rare in the human population and should be considered as the ideal. [34] Furthermore, great variability exists when measuring the incidence of malocclusion in our society. There are several reasons for the lack of consensus; there is a wide divergence in the definition of a normal and abnormal occlusion, the presence of diagnostic error and a lack of a universal index. [35] In recent years, several indices have been developed to assess the presence and severity of the malocclusions in the general population. The American Board of Orthodontics uses the discrepancy index. [38]

The discrepancy index (DI) is used as a means of quantifying the severity of malocclusions. Normally, assessing a malocclusion can be very subjective. With the use of the discrepancy index, various easily measured clinical components are tabulated to give an overall severity score. Cephalometric radiographs, panoramic radiographs and dental casts with a proper bite registration are needed in order to take measurements of the following: overjet, overbite, open bite, crowding, occlusal relationship, crossbite, presence of missing

teeth, and several cephalometric values. The more the measurements differ from ideal in each component category, the greater the complexity and severity of the overall malocclusion. [38]

Treatment

The presence of a malocclusion does not necessarily mean that the individual requires treatment. When assessing malocclusion, the discrepancy index can be very useful in quantifying the severity and difficulty expected for the orthodontist. An orthodontic treatment is usually reserved for the more severe malocclusions or when patients are not content with their oral functions and/or dental esthetics. There are several treatment modalities available when correcting a malocclusion based on its severity and etiology. The three main options are: traditional orthodontics, orthognathic surgery and a combination of the two. Osteodistraction can also be used in severe craniofacial anomalies when surgical movements will be extreme.

Malocclusion in patients with osteogenesis imperfecta

Overview

Osteogenesis imperfecta is a syndrome that has been characterised with a high prevalence of malocclusion. [26, 39] Several authors have reported an increased development of Class III molar relationships, posterior and anterior openbites, crossbites and impacted teeth. [25-27] The precise etiology of the malocclusion is not yet known; however, it seems that the abnormal craniofacial growth present in OI patients results in aberrations in the relationship of the upper and lower jaws, dental arches and teeth. [40-43] Several authors have reported that the more severe phenotypes of OI seem to produce the more severe craniofacial abnormalities, but this hypothesis does not always seem to be true and merits an investigation. [18, 25, 40] Mild forms of OI are often very hard to diagnose and an investigation of the dental malocclusion may prove to be a cardinal diagnostic aid. [23, 44]

Clinical characteristics

Considerable variation exists in the expression of the dental phenotype within the different types of OI. [25] A different combination of dental characteristics and severity will be present in each individual and the reasons for these differences are still unknown. Although, there is considerable variation, there are several craniofacial and dentoalveolar features that have a high prevalence in patients with OI.

Craniofacial features

Patients with OI usually have a triangular-shaped face, a broad forehead, macrocephaly and basilar invagination. [19, 26, 45] (Figure 17)

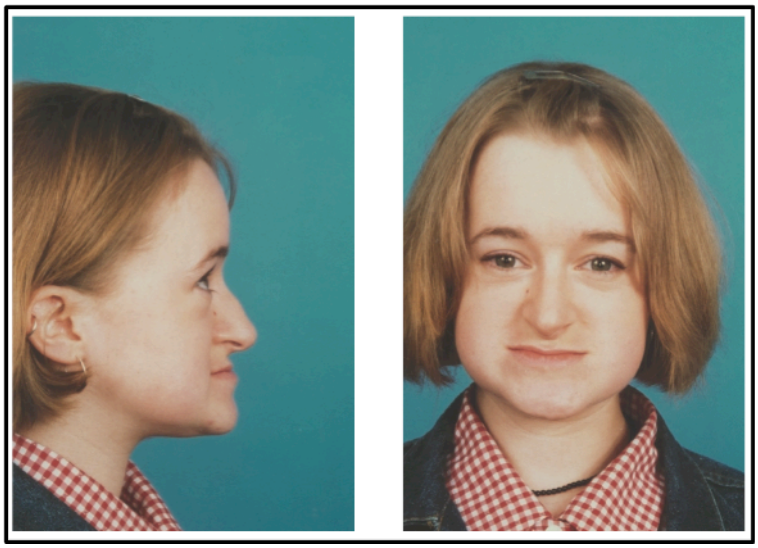

Figure 17: Patient with OI exhibiting a triangular shaped face, broad forehead and midface hypoplasia [45]

Due to these changes in growth and associated abnormal posture, panoramic and cephalometric radiographs may be very difficult to obtain. [46] There seems to be a higher incidence of craniofacial disproportion in Types III and IV than in Type I. [18, 43, 45] Nevertheless, facial bones were found to be smaller than normal in all types of the syndrome. [43] More specifically, vertical facial dimensions, maxillary and mandibular lengths and the anterior/posterior cranial base lengths are all significantly shorter in OI patients. [41] The high proportion of Class III skeletal malocclusion is characterized primarily by midface hypoplasia. [25, 41-43] According to *Waltimo-Siren et al*, "the growth deficiency was more pronounced in the severely affected patients than in those with type I OI". [43]

Dentoalveolar characteristics

Dental malocclusion is very common in patients with OI and has proven to be significantly more severe than that found in the general population. [27] There is an increased presence of Class III malocclusions, further compounded by a negative overjet, posterior crossbites and lateral openbites. [25-27]

The incidence of Class III molar occlusions in the OI population is elevated and has been found to range from 9.6-80%. [25, 26, 41, 47] The large range in these studies can be explained by the variability in phenotypic severity seen between the OI types. Most studies

have found the incidence of Class III malocclusion to be closer to 62.5%-80%, which is significantly greater than the 6.5% previously found in the general population. [25, 26, 35, 36, 41] The only study with a 9.6% incidence of Class III malocclusion was composed of a sample with 79% of the milder type I form of OI. [47] Other studies that found a higher incidence of malocclusion, also had a higher percentage of the more severe OI phenotypes in their sample. [25, 26, 41] These results support the theory that the more severe phenotypes of OI seem to produce more severe craniofacial abnormalities.

In addition to the high proportions of Class III malocclusion in the OI population, there is also a high degree of lateral openbite and posterior crossbite. [27] Interestingly enough, lateral openbites are extremely rare in the general population. [26, 27] However, *O'Connell and Marini* found a 27% incidence of lateral openbite in Type III OI patients and 33% in patients with type IV. He also observed that the severity of the lateral openbite seems to increase with age. Within the 40 patient sample, none of the children younger than 9 years of age experienced posterior openbites whereas 46% had a either unilateral or bilateral posterior openbite after that age. [26]

Other features are also commonly found in the OI population. Posterior crossbites were present in 65% of a heterogeneous OI sample by *Schwartz & Tsipouras*, whereas *O'Connell and Marini* found 38% of Type III OI patients and 47% of Type IV OI patients possessed this debilitating feature. [25, 26] OI patients also have an increased number of impacted teeth, permanent tooth agenesis and a high prevalence of ectopic eruption of first and second molars. [23, 25-27, 39, 41, 47]

Etiology

The same bony defects that cause malformed long bones in OI patients seem to also affect the craniofacial complex. There is an aberrant growth pattern of the upper and lower jaws that results in abnormal facial characteristics and severe malocclusion. [42] The typical craniofacial features observed are: triangular face, maxillary hypoplasia, mandibular prognathism, basilar invagination and broad forehead. [18, 26, 43] The etiology of these facial characteristics seems to be the increased bone fragility, which changes bone morphology, function and subsequently the growth pattern in these patients. [43]

The inability of the poor-quality bone to withstand the weight of the brain and/or head causes changes in bone morphology and its growth pattern. [18] According to Moss' functional matrix theory, growth is highly dependent on function and any change in the latter will have considerable consequences on the former. [48] In OI patients, the weight of the head on the osteoporotic bone of the cervical area creates a basilar invagination, which will change the patient's posture and functional capacities. Subsequently, growth in the craniofacial complex will be altered. [18, 26, 43] The result will depend on the phenotypic severity of the OI syndrome. [17, 39, 40, 49, 50]

OI patients develop more severe malocclusions than the general population. [27] Researchers claim that the typical malocclusion associated with the syndrome is primarily caused by maxillary hypoplasia, mandibular protrusion or a combination of the two. [19, 25, 26, 39, 41, 42, 51] When examining dental casts and cephalometric radiographs of OI patients, the maxilla is usually short in length and the mandibule is either normal in length or slightly shorter. These findings lead to the assumption that the Class III skeletal pattern is primarily due to a midface hypoplasia. [42, 43] Other features of the craniofacial growth include: a strong closing growth rotation of the mandible, a short condyle, underdeveloped alveolar bones in both jaws, and a decrease in vertical lower face height. The decrease in vertical growth seems to be the most pronounced growth abnormality in the craniofacial aspect of the syndrome. [43] Therefore, the Class III dentoskeletal malocclusion present in OI patients seems to be caused by a smaller than normal upper and lower jaw, an increased closing growth rotation of the mandible and a decreased vertical facial development. [41, 43]

In addition to a Class III malocclusion, there is a high incidence of lateral openbites, anterior/posterior crossbites and impacted teeth. Lateral openbites are extremely rare in the general population, and can be particularly debilitating in OI patients. The high incidence of this feature in the OI population could be explained by an abnormal vertical dentoalveolar development and a lack of dental compensation. [26] The high incidence of anterior and posterior crossbites seems to be created by the disharmony resulting from a hypoplastic maxilla opposed by a normal mandible. [42]

At present, the reason for the increased incidence of malocclusion present in the OI population is unknown. However, a multifactorial process is surely the key to understanding

the variable craniofacial phenotypes of this syndrome. Longitudinal prospective studies in this area of the OI syndrome are needed. [26]

Treatment

Despite the frequent functional and esthetic dental aberrations in OI patients, major treatments such as bone augmentation, orthodontics and orthognathic surgery are extremely rare in this population. [51] Very little has been published about orthodontic treatment in these patients and the only type of data available is in case report format. There are no controlled trials researching the outcomes of orthodontic treatments with or without orthognathic surgery in this patient population, nor is there any focusing on the variability in orthodontic outcomes in OI patients treated with bisphosphonates. [46] Nevertheless, the severe malocclusions seen in patients with this syndrome usually requires a combined orthodontic/surgical approach. [45] Furthermore, some authors have recently succeeded in doing osteodistraction and bone augmentation in these patients despite the morbidity of osseous surgery associated with the OI syndrome. [51]

Traditional orthodontics

Orthodontic therapy seems to be possible in the OI population, but there are only a few documented cases in the literature. More knowledge on this subject could be very useful because there are many facets of the OI syndrome that can become problematic during an orthodontic treatment. More specifically, the poor quality of the bone, the presence of dentinogenesis imperfecta and treatment with bisphosphonates may make traditional orthodontics very difficult.

Successful orthodontic therapy is dependent on the bone remodeling process. In order for tooth movement to be effective, osteoblasts and osteoclasts need to perform their role adequately around the periodontal ligament. Osteoblasts are the bone-forming cells, while osteoclasts are the bone-resorbing cells. The cycle of bone formation and resorbtion provides the very important balance usually seen in bone remodeling. [34] As previously stated, osteoblasts in OI patients do not function normally and the quality of the bone formed is poor. [2] In addition, in patients treated with bisphosphonates, osteoclast activity is inhibited. [31,

34] Thus, the bone remodelling process is disrupted on many levels in the OI patient treated with bisphosphonates. Since bone remodeling is essential for orthodontic therapy, the changes in bone metabolism can decrease the amount and rate of tooth movement achieved in these patients. [52] The magnitude and duration of the orthodontic forces may have to be adjusted in order to counterbalance the deficiency in collagen production created by the syndrome and the decreased bone resorption caused by bisphosphonate therapy. [39]

Patients with OI combined with dentinogenesis imperfecta may also present another challenge for the orthodontist. Due to a qualitative abnormality in the dentin, the enamel in patients with a dentinogenesis imperfecta phenotype usually fractures very easily. [23, 26] These fractures can cause significant amounts of attrition and can lead to early tooth loss. [26] The adhesive forces of orthodontic bracketing may not be strong enough to withstand normal intra-oral forces and regular debonding can cause significant damage to these teeth. Bands with welded brackets can be used when the enamel is not strong enough for regular bracketing procedures. [46] Dentinogenesis imperfecta may complicate orthodontic therapy, but it is definitely still possible in these patients.

In the future, researchers should document more cases of orthodontic therapy in this patient population. Recent functional therapy with a Frankel Type III appliance has shown promising results. [43] If appliance therapy is successful and started at the right time, the need for orthognathic surgery may decrease in patients with OI.

Orthognathic surgery

Orthognathic surgery, such as maxillary advancement and mandibular set-back, has been successful in many patients with OI and is often combined with traditional orthodontics. A diagnosis with this syndrome does not seem to be a contraindication for a surgical intervention; however, great care must be taken when treatment planning, explaining the procedure to the patient and obtaining informed consent. [46, 53] Several authors have written case reports detailing maxillofacial surgery on OI patients, and claim to have achieved acceptable results, improving both function and esthetics. [40, 46, 49, 50, 53, 54] (Figure 18 and 19)

Orthognathic surgery in OI patients has proven to be extremely variable. Some are uneventful, while others can lead to unfavourable osteotomy fractures, massive hemorrhage

and respiratory distress. [44, 46, 49] Remarkably, the most severe sequelae do not seem to correspond to the most severe clinical phenotypes of the syndrome. [46, 49, 50] Complications seem to arise more when performing a Le Fort I maxillary osteotomy when compared to mandibular procedures. To help prevent a negative surgical experience, it is very important to properly diagnose a patient with OI, especially with a mild phenotype, and incorporate this

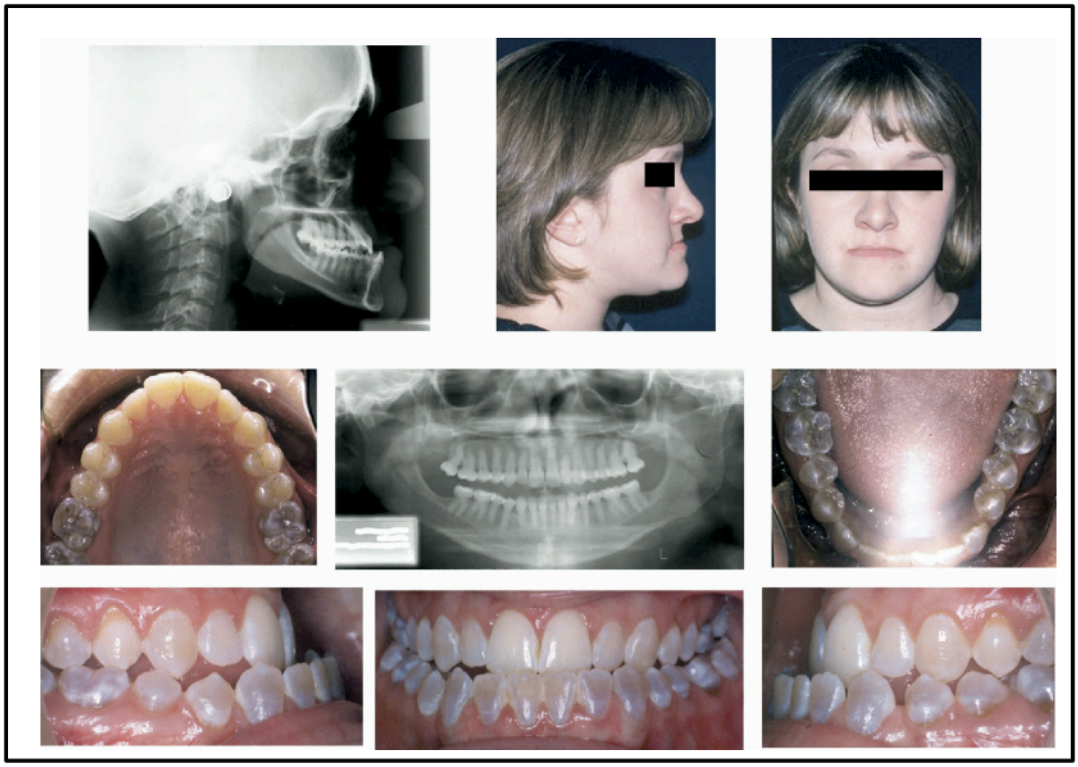

Figure 18: Pre-orthognathic surgery photos in a woman with OI and a Class III malocclusion [46]

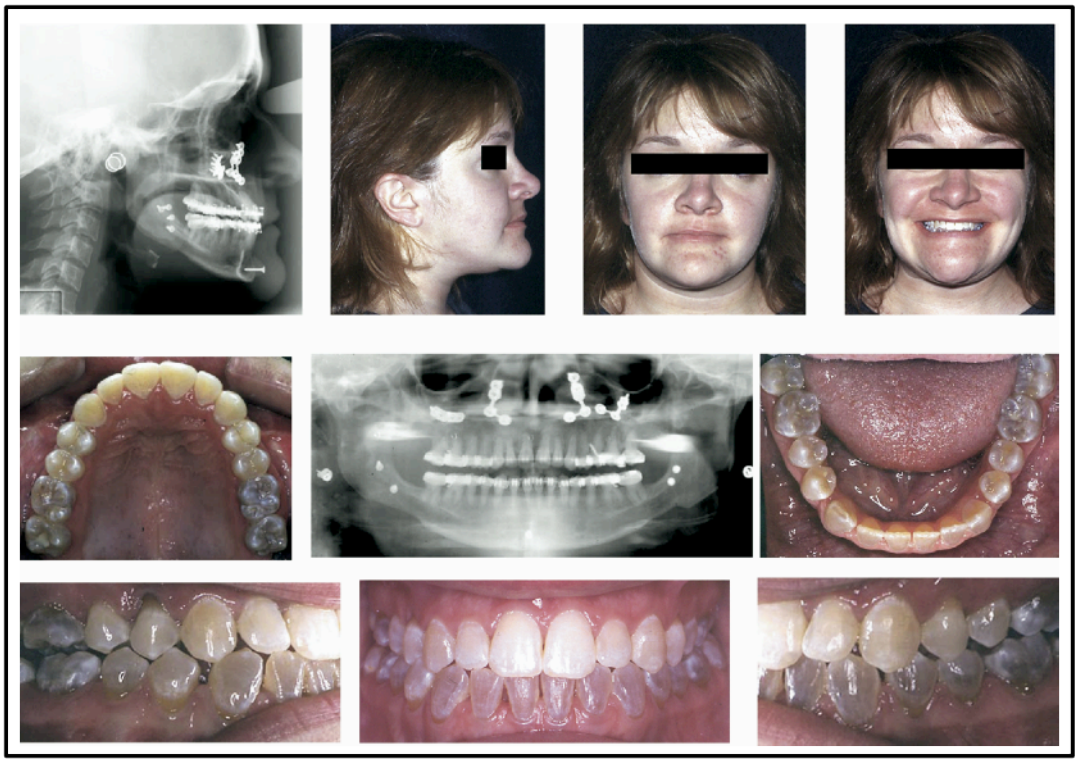

Figure 19: Post-orthognathic surgery photos in a woman with OI and a Class III malocclusion [46]

diagnosis in the treatment planning process. [53] Great care must be taken to minimize the tendency for unfavourable fractures due to poor bone quality and thin maxillary and mandibular walls. [53, 55]

Despite the increased bone fragility in OI patients, previous studies have shown that there is adequate bone healing after orthognathic surgery. [19, 40, 51] However, *Rauch et al.* have demonstrated that abnormal bone remodelling exists in all OI patients. [16] Consequently, *Tashima et al.* recommend intermaxillary fixation for up to 5 to 6 weeks to prevent fracture during the healing period. [53] Successful surgery in OI patients is definitely possible, but the surgeon must keep in mind that the chances of encountering complications are more common in this subset of patients. [17, 53, 54]

Osteodistraction

Osteodistraction of the maxilla is a viable treatment alternative that can decrease the number of unfavourable fractures that occur during conventional orthognathic surgery in OI patients.

[51] Since most complications occur during the down-fracture of a Le Fort I osteotomy, osteodistraction has been proposed to replace this part of the surgery. [51, 53] Bone biopsy 6 months after osteodistraction and 4 months after augmentation showed adequate callus formation and good bone healing. These results are very promising when trying to diminish complications observed during orthognathic surgery. [51]

Conclusion

Patients with OI have been identified as a "high-risk group for the development of malocclusion". [26, 39] There is a higher prevalence of Class III molar occlusion, posterior and anterior openbite, crossbite and impacted teeth in these patients. [25-27] In addition, considerable variation exists in the expression of the dental and craniofacial phenotype within the different types of OI as well as in patients with the same collagen type I abnormality. [18, 25] Due to the extreme variability in the phenotype of the syndrome, every time an OI patient is treated, he/she should be viewed as a unique case with a wide range of possible treatment options. [46] Whatever treatment is chosen, a multidisciplinary approach should be adopted in order to optimize function and esthetics, as well as minimize any adverse consequences. [45] More importantly, diagnosis of the milder OI type I patients must be done prior to any decision with regards to treatment, in order to prevent any avoidable adverse consequences. In the future, the characteristic malocclusion present in OI patients may be used as an additional diagnostic feature.

Hypotheses and study aims

Purpose

Osteogenesis imperfecta is a connective tissue disorder characterized by a hereditary defect in the production of Type I collagen. [2, 5] Patients affected by OI are susceptible to spontaneous bone fractures and may show a number of other defects, such as joint laxity, hearing impairments, malformed long bones, growth deficiency, muscle weakness, blue sclera, dentinogenesis imperfecta and/or malocclusion. The syndrome is extremely heterogeneous, producing a variety of phenotypes ranging from clinically undetectable to perinatal lethal. [2] In fact, the milder forms of the syndrome are sometimes extremely difficult to diagnose; thus, more must be done to aid the diagnosis and classification of this debilitating disease.

It seems that the same disease pathway that creates the severe skeletal deformity in these patients, also creates growth disturbances in the craniofacial complexe. [18, 39] Consequently, there is an increased incidence of Class III molar occlusion, posterior and anterior openbite, and posterior and anterior crossbite. [25-27] The aim of this study is to evaluate whether the severity of the malocclusion present in the OI population is proportional to the severity of the systemic bone disease. If so, the malocclusion present may serve an important diagnostic role when trying to identify and classify the multiple forms of this syndrome.

Study aims

The primary aim of this study is to compare the severity of the malocclusion present in OI patients with the severity of their systemic bone disorder. The study aim will be achieved by fulfilling the two following objectives:

1. The malocclusion observed in a retrospective examination of OI patients will be quantified using the Discrepancy Index at one point in time.

2. The severity of the malocclusion quantified with the DI will be compared to other variables that characterize the severity of the OI syndrome (OI type, height z-score, type of genetic mutation)

The secondary aim of this study is to evaluate whether the severity of the malocclusion present in OI patients changes with time. The secondary study aim will be achieved by fulfilling the following objective:

1. The discrepancy index for a subgroup of OI patients will be tabulated at several points in time in order to determine the longitudinal progression of the malocclusion.

Hypothesis

The hypothesis for the primary study aim is as follows:

Research Hypothesis: The severity of the malocclusion observed in OI is related to the severity of the systemic bone involvement. As the severity of the malocclusion increases, there will be :

- A decrease in height
- An increase in the presence of the more severe types of OI (Type I < Type IV, V, VI, VII < Type III < Type II)
- An increase in the more severe genetic mutations

Null Hypothesis: The severity of malocclusion in OI is unrelated to the severity of the systemic bone involvement.

The hypothesis for the secondary study aim is as follows:

Research Hypothesis: The severity of malocclusion in OI increases as the child ages.

Null Hypothesis: The severity of malocclusion in OI does not increase with time.

Materials and methods

Study design and setting

A retrospective observational study was conducted involving 3 administrative facilities: the Montreal Shriners Hospital, the Montreal Children's Hospital, and the University of Montreal. The physicians at the Shriners Hospital follow the largest cohort of patients with OI in North America. Consenting patients seen at the Shriners are referred to the Montreal Children's Hospital dental clinic, where complete dental examination is done and required treatment is provided. Consequently, over the past decade, the dental clinic has documented oral records for over 70 OI patients. Whenever possible and/or appropriate, intra-oral and extra-oral findings, panoramic and cephalometric radiographs, intra- and extra-oral photos, and dental casts with bite registration were obtained.

The ethics review board of the Montreal Children's Hospital approved the study (study 13-486-PED). Scientific merit and approval was given by the review board at the University of Montreal. Informed consent was obtained from the legal guardians and/or patients when age-appropriate.

Subjects

The study population consists of 73 patients with varying types of OI who were referred to the Montreal Children's Hospital by the Shriners Hospital between the period of July 2006 and July 2013.

Inclusion criteria for the study sample were defined as:

- definite diagnosis of OI
- regular follow-up at the Montreal Shriners Hospital
- adequate casts and radiographs available
- informed consent with regards to participation in the study

Exclusion criteria were set as:

- a history of orthodontic treatment
- a history of orthognathic surgery
- presence of an inadequate bite registration
- several missing teeth (>8 missing teeth)

All OI patients had received or were still receiving intravenous bisphosphonate therapy.

Variables

Information regarding the following variables was collected:

- Age
- Gender
- Presence of dentinogenesis imperfecta
- Height z-score
- OI type
- Mutated gene
- Type of genetic mutation
- Position of amino acid substitution
- Molar relation
- Discrepancy Index (DI)

All information, except for the molar relationship and DI score, was collected through chart review at the Shriners Hospital in Montreal. Height measurements had been converted to age- and sex-specific Z-scores on the basis of reference data published by the Centers for Disease Control and Prevention. [12, 56] For the genetic mutation type, genomic DNA had been isolated in the laboratory of Dr. Frank Rauch at the Montreal Shriners Hospital from either blood or saliva using standard extraction methods. [12] The types of genetic mutations identified in this sample were: triple helical defect, protein complex defect, splice mutation,

stop codon, or was unidentified. Sequencing had been done with a polymerase chain reaction using primers. Helical mutations were numbered according to the position of the mutated amino acid within the triple helix of each alpha chain. [12] The mutated genes identified in this sample were: COL1A1, COL1A2, CRTAP, SERPINF1 or was unidentified. The OI classification by type had been done by the Montreal Shriners Hospital based on clinical, radiographic and genetic information. The types of OI present in this sample were: type I, III, IV, VI.

Molar relationship was determined while calculating the DI of the malocclusion using each patient's dental cast at the Montreal Children's Hospital. The severity of the malocclusion was assessed using the DI scoring system by evaluating the overjet, overbite, open bite, crowding, occlusal relationship, crossbite and presence of missing teeth. [38] The cephalometric component of the DI was not included in the analysis as lateral cephalograms were not possible for patients with severe craniofacial deformations. The DI scores for each component were measured by one investigator, and then tabulated to give a final DI score of the malocclusion. (Figure 20) Measurements were taken using a Carrera Precision CP7908 8-inch fractional digital LCD caliper from Whitworth.

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DISCREPANCY INDEX

CASE CATEGORY _____
TOTAL D.I. SCORE _____
CAST EVAL. SCORE _____

OVERJET

0 mm. (edge to edge)	=	1 pt.
1 – 3 mm.	=	0 pts.
3.1 – 5 mm.	=	2 pts.
5.1 – 7 mm.	=	3 pts.
7.1 – 9 mm.	=	4 pts.
> 9 mm.	=	5 pts.

Negative OJ (x-bite) 1 pt. per mm. per tooth =

Total = _____

OVERBITE

0 – 3 mm.	=	0 pts.
3.1 – 5 mm.	=	2 pts.
5.1 – 7 mm.	=	3 pts.
Impinging (100%)	=	5 pts.

Total = _____

ANTERIOR OPENBITE

0 mm. (edge to edge) = 1 pt.
then 2 pts. per mm. per tooth

Total = _____

LATERAL OPENBITE

2 pts. per mm. per tooth
Total = _____

CROWDING

0 – 3 mm.	=	1 pt.
3.1 – 5 mm.	=	2 pts.
5.1 – 7 mm.	=	4 pts.
> 7 mm.	=	7 pts.

Total = _____

OCCLUSION

Class I to end on	=	0 pts.
End on Class II or III	=	2 pts. per side
Full Class II or III	=	4 pts. per side
Beyond Class II or III	=	1 pt. per mm. Additional

Total = _____

LINGUAL POSTERIOR X-BITE

1 pt. per tooth Total = _____

BUCCAL POSTERIOR X-BITE

2 pts. per tooth Total = _____

CEPHALOMETRICS

ANB > 5.5 or < -1.5	=	4 pts.
Each Additional Degree	=	1 pt.
SN-GO-GN 27 deg. – 37 deg.	=	0 pts.
SN-GO-GN > 37 deg.	=	2 pts. per degree
SN-GO-GN < 27 deg.	=	1 pt. per degree
IMPA > 98 deg.	=	1 pt. per degree

Total = _____

OTHER 2 Points = _____
(See instructions)

INDICATE PROBLEM _____

_____

_____

Figure 20: DI scoring sheet [38]

Statistical analysis

Descriptive statistics are presented for demographic and clinical characteristics. DI measurements in 56 OI patients at one point in time are presented as medians for continuous variables and proportions for categorical variables. Statistical significance was established as $p < 0.05$.

For the primary aim, DI measurements were compared with height z-score, genetic mutation and classification type for univariate analysis with one-way ANOVA if the data followed a gaussian distribution and via Spearman correlation, Mann Whitney U test and Kruskal-Wallis test for non-normally distributed data. Bonferoni adjusted p-values were calculated when indicated.

For the secondary aim, Spearman correlations for repeated measures were used to characterize the change over time in a sample of 20 OI patients measured at two points.

The intra and inter reliability of the quantified malocclusion (Discrepancy Index) were assessed by calculating the Kappa score. Fifteen subjects were measured twice by the same rater (intra-rater reliability) and twenty-nine subjects were measured once by another rater (inter-rater reliability).

All calculations were performed using Statistical package for social sciences (SPSS, version 20.0, Chicago, IL, USA)

Results

Of the 73 OI patients referred to the Montreal Children's Dental Clinic between July 2006 and July 2013, 56 fulfilled the eligibility criteria. (Figure 21)

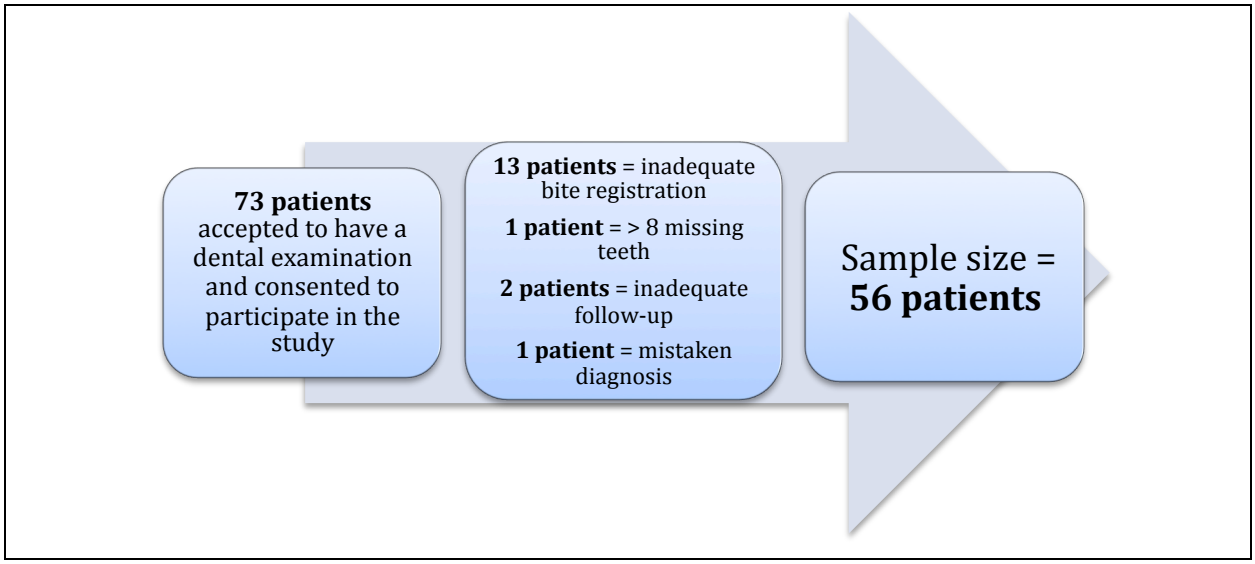

Figure 21:Inclusion and exclusion criteria for sample size

Table 4: Descriptive characteristics of OI study sample (n = 56)

Gender		**Gene Mutated**, n (%)	
Males, n (%)	28 (50%)	COL1A1	28 (50.0%)
Age		COL1A2	23 (41.1 %)
Years, (mean±SD)	10.82 ± 3.87	CRTAP	1 (1.8%)
Years, n (%)		LEPRE1	1 (1.8%)
0-7	12 (21.4%)	SERPINF1	2 (3.6%)
8-13	32 (57.1%)	Unidentified	1 (1.8%)
14-21	12 (21.4%)	**Type of genetic mutation**, n(%)	
Molar relationship, n (%)		Triple helical defect	41 (73.2%)
Class I	13 (23.2%)	Protein complex defect	4 (7.1%)
Class II	6 (10.8%)	Splice mutation	9 (16.1%)
Class III	36 (64.2%)	Stop codon	1 (1.8%)
No class	1 (0.2%)	Unidentified	1 (1.8%)
Dentinogenesis Imperfecta		**Position of amino acid substitution**	
Affected, n (%)	45 (80.4%)	1-499	14 (37.71%)
OI Type, n (%)		500-999	18 (43.61%)
I	9 (16.1%)	1000-1500	9 (40.56%)
III	13 (23.2%)	**Height Z-score**	
IV	32 (57.1%)	Z-score, (mean±SD)	-3.37 ± 2.33
VI	2 (3.6%)	Z-score, percentiles	
		25	-5.46
		50	-3.67
		75	-1.77

n= number of patients
SD= standard deviation

Table 4 shows selected demographic statistics of the study population. The sample was composed of 50% males. The mean age was 10.82 (± 3.87) years, with a range (minimum-maximum) of 4-21 years. The great majority (64.2%) of OI patients presented with a class III malocclusion. One patient could not be classified with Angle's molar

occlusion because the lower first molars were absent. In addition, the bulk of the OI patients (45 of 56 patients) were diagnosed with OI Type III (23.2%) or Type IV (57.1%), which produce the more severe phenotypes of the syndrome compatible with survival. There are no patients with OI Type II in the sample because this type of OI is perinatally lethal. Most subjects (51 of 56 patients) had genetic mutations in either COL1A1 (50%) or COL1A2 (41%), which is consistent with the literature to date. [6, 9] One patient had an unidentified genetic mutation and the other patients (4 of 56 patients) had recessive mutations in CRTAP, LEPRE1 and SERPINF1. The majority of the patients (41 of 56 patients) had an amino acid substitution, which created a triple helical defect in the procollagen molecules.

Malocclusion Severity

The total DI scores broken down into individual components are presented in Table 5. The values represent the frequency that a particular facet of the malocclusion was seen in the OI sample, as well as the median [minimum, maximum] total DI score (33.5 [1,109]). The three major contributing factors to the DI score for OI patients were discrepancies in overjet, lingual posterior crossbite and occlusion. Specifically, we observed that 51/56 OI patients (91.1%) had a disparity in overjet. Lingual posterior crossbite was present in 50/56 OI patients (89.3%) and occlusal relationships were divergent from normal in 43/56 OI patients (78.2%). No OI subjects presented with a buccal posterior crossbite.

Table 5: DI scores of OI study sample (n = 56)

Measured parameters	DI Scores (Median [min, max])
Total	33.5 [1,109]
Overjet	6 [0, 49]
Overbite	0 [0, 5]
Anterior openbite	1 [0, 22]
Lateral openbite	1 [0, 40]
Crowding	1.5 [1, 7]
Occlusion	8 [0, 10]
Lingual posterior crossbite	3 [0, 7]
Buccal posterior crossbite	None
Other	2 [0, 16]

n= number of patients
min = minimum
max = maximum

Spearman correlations were done to determine the greatest statistically significant correlations between the total DI score and each individual component. (Table 6) The highest correlations ($p<0.0001$) in this population were seen between total DI and overjet, lateral openbite, lingual posterior crossbite, occlusion and the others category. Also, patients with dentinogenesis imperfecta had statistically significant higher DI scores according to the Spearman correlation ($p = 0.017$).

Table 6: Spearman correlation between DI score and individual components

DI Components	Spearman's Rho	p-value
Overjet	0.734	0.0001
Overbite	-0.015	0.91
Anterior openbite	0.387	0.003
Lateral openbite	0.769	0.0001
Crowding	0.089	0.515
Occlusion	0.834	0.0001
Lingual posterior crossbite	0.646	0.0001
Buccal posterior crossbite	–	–
Other	0.625	0.0001

The kappa scores for inter-rater and intra-rater reliability for DI measurements were 0.943 and 0.992 respectively.

DI score vs OI Type

The DI score increased with increasing severity of OI type (p=0.001). More specifically, OI type I had a median [minimum, maximum] DI score of 12 [3, 24], followed by OI type IV / VI with 38.5 [1, 89] and OI Type III with 53 [6, 109]. (Figure 22) Bonferroni adjusted P-values for the 3 groups showed that the major differences existed between OI Type I and Type III (p=0.001), followed by OI type I and type IV/VI (p=0.008). No statistical difference was found in the DI score between OI type III and and OI type IV/VI.

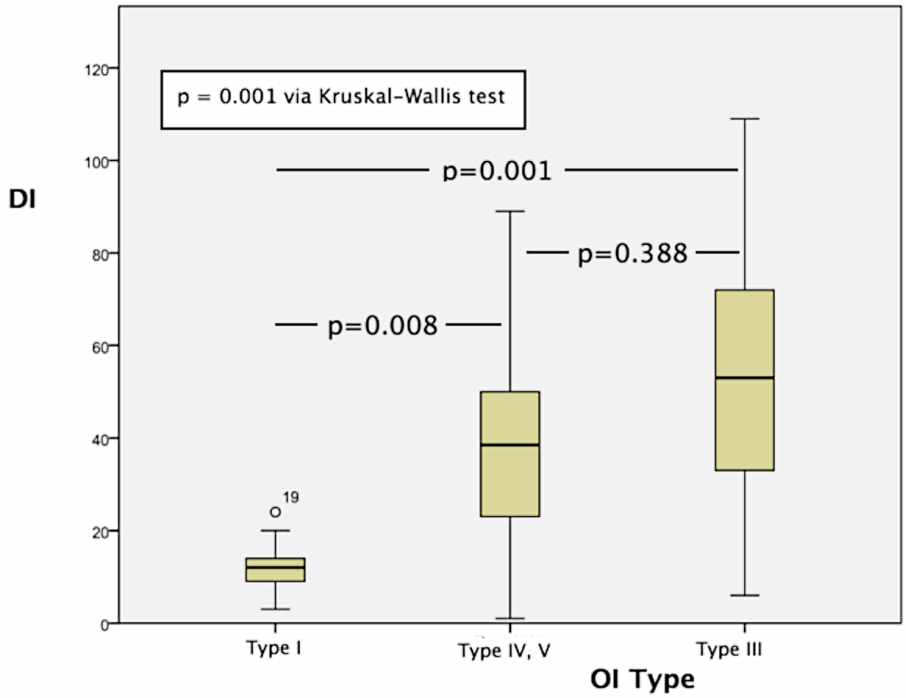

Figure 22: Discrepancy Index vs. OI Type

In addition, there is a statistically significant correlation between the increase in DI and an increase in OI severity. (Gamma = 0.0530, p<0.001)

When age is added as a covariable using the Brunner-Langer test, the DI score was also found to increase with increasing severity of OI type (p<0.0001). The p-value for the co-variable of age was found to be 0.035. Bonferroni adjusted P-values for the 3 groups also demonstrated that the major differences existed between OI Type I and Type III (p=0.0001),

followed by OI type I and type IV/VI (p=0.0001); however, there was no statistical difference found in the DI score between OI type III and and OI type IV/VI (p=0.6229).

DI score vs. Height z-score

The average height z-score (mean ± standard deviation) of our study was sample was -3.37 ± 2.33. All the patients included in our study sample had a height z-score below 0, demonstrating that their heights are below those expected in age- and sex-matched healthy controls. The DI score increased with decreasing height z-score (Spearman rho = -0.521, p<0.0001). (Figure 23)

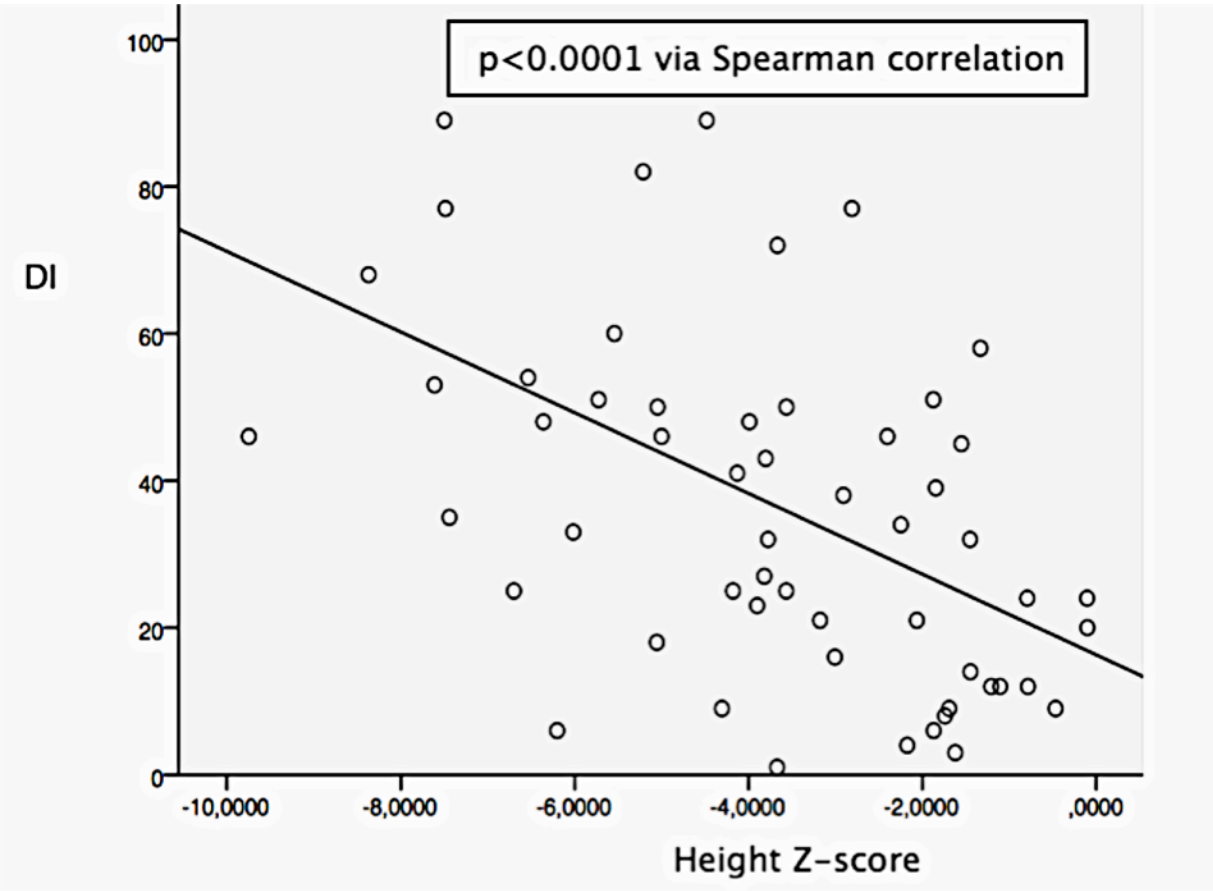

Figure 23: Discrepancy index (DI) vs. height z-score

DI scores vs. Genetic mutation

Of the 56 OI patients analyzed, 28 had a mutation in COL1A1 and 23 had a mutation in COL1A2. The DI score was significantly lower in patients with genetic mutations in the COL1A1 gene than in patients with mutations in COL1A2 (p=0.021). Median [minimum, maximum] DI scores for patients with COL1A1 mutations was 25 [1, 109], while COL1A2 mutation was 43 [12, 89]. (Figure 24)

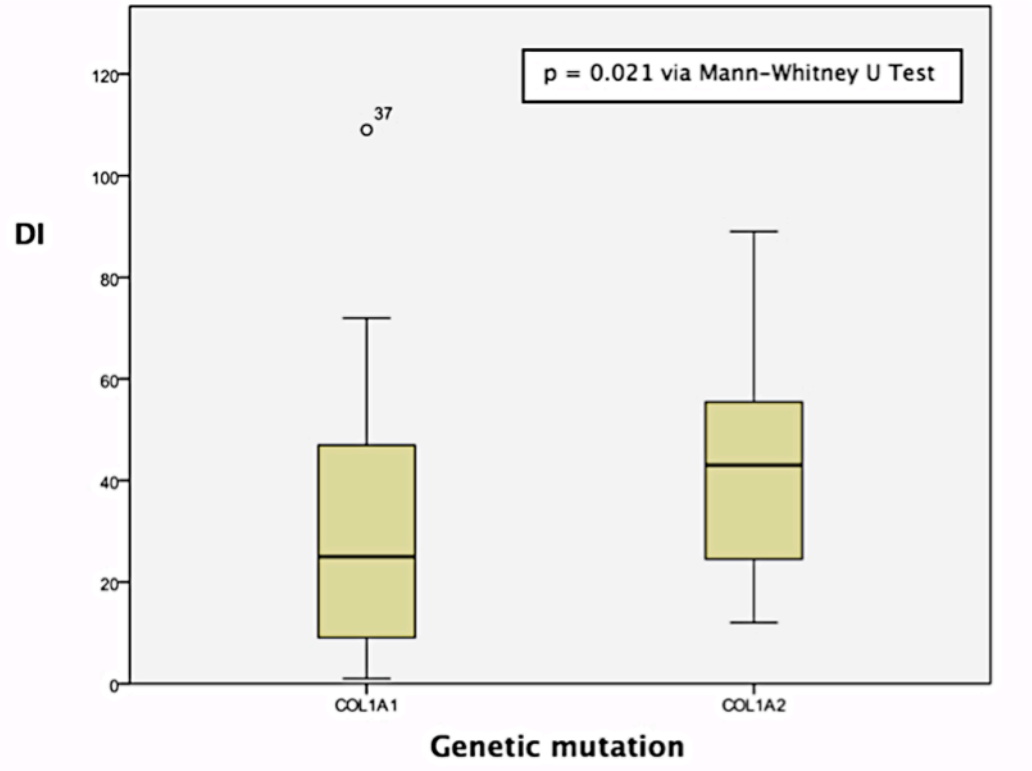

Figure 24: Discrepancy index vs. genetic mutation

When looking at the type of mutation present in the OI patients analyzed, 41 had a triple helical defect as opposed to 9 patients who had a splice defect. Patients with an amino acid substitution had significantly higher DI scores than patients with splice mutations (p= 0.020). Median [minimum, maximum] DI scores for patients with triple helical defects was 38 [1, 109] as opposed to splice mutations, which had a median [minimum, maximum] DI score of 14 [3, 58]. (Figure 25)

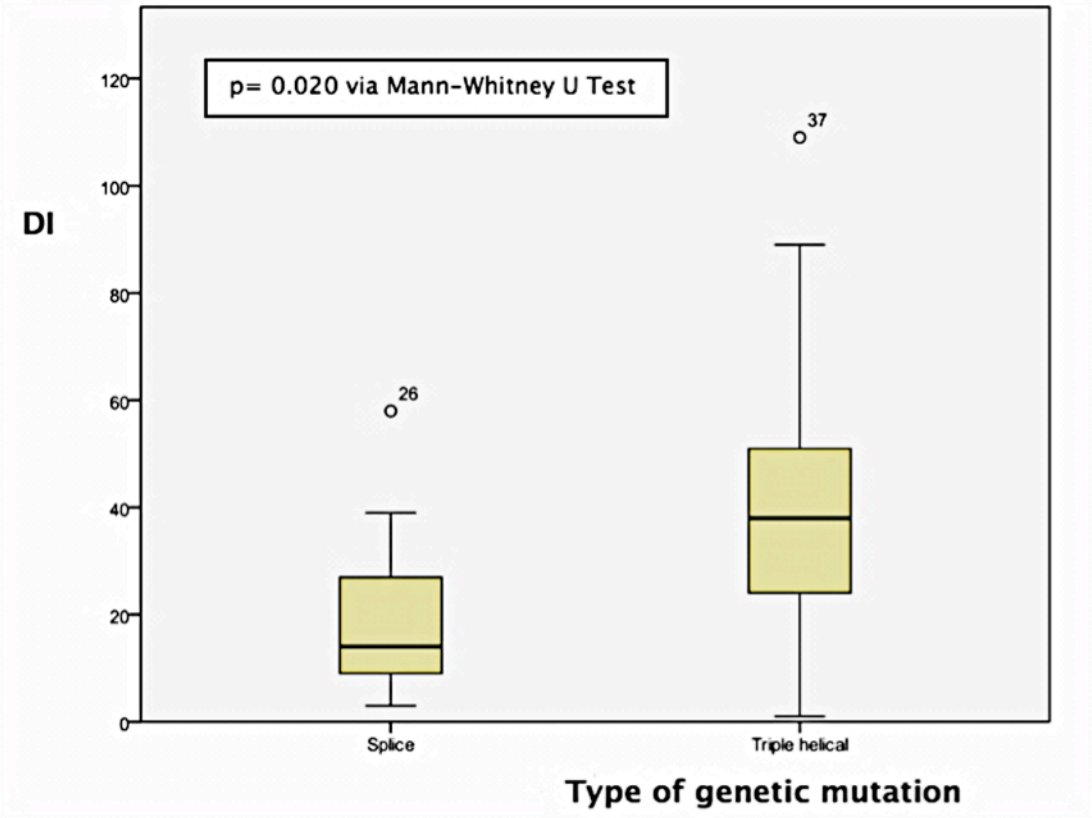

Figure 25: Discrepancy index vs. type of genetic mutation

When helical defect mutations were analyzed more closely, it was discovered that there were 14 OI patients with a mutation in the first 499 amino acids in the pro-α poplypeptide, 18 patients with a mutation between amino acid 500-999, and 9 patients with a mutation between amino acid 1000-1500. When investigating the effect of the position of the amino acid substition in the procollagen chain on the DI score, no statistically significant difference was found. (Figure 26 and 27)

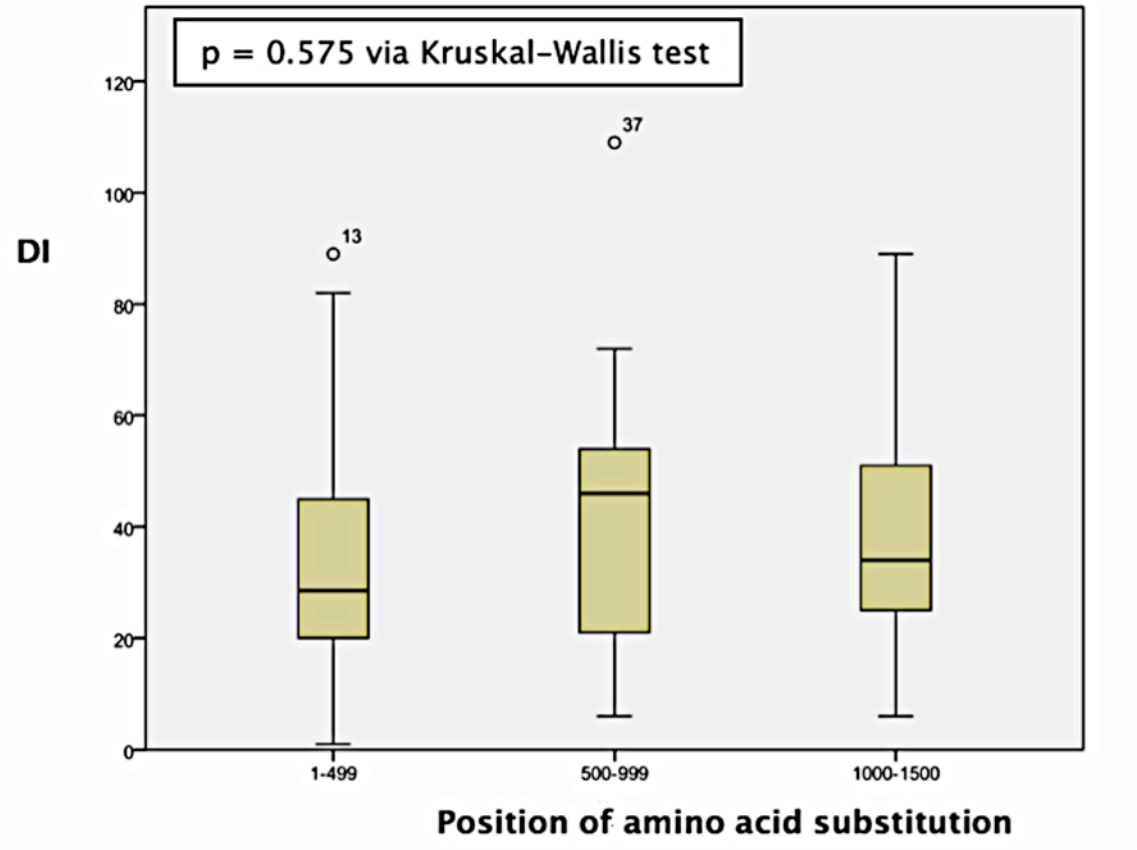

Figure 26: Discrepancy index vs. position of genetic mutation

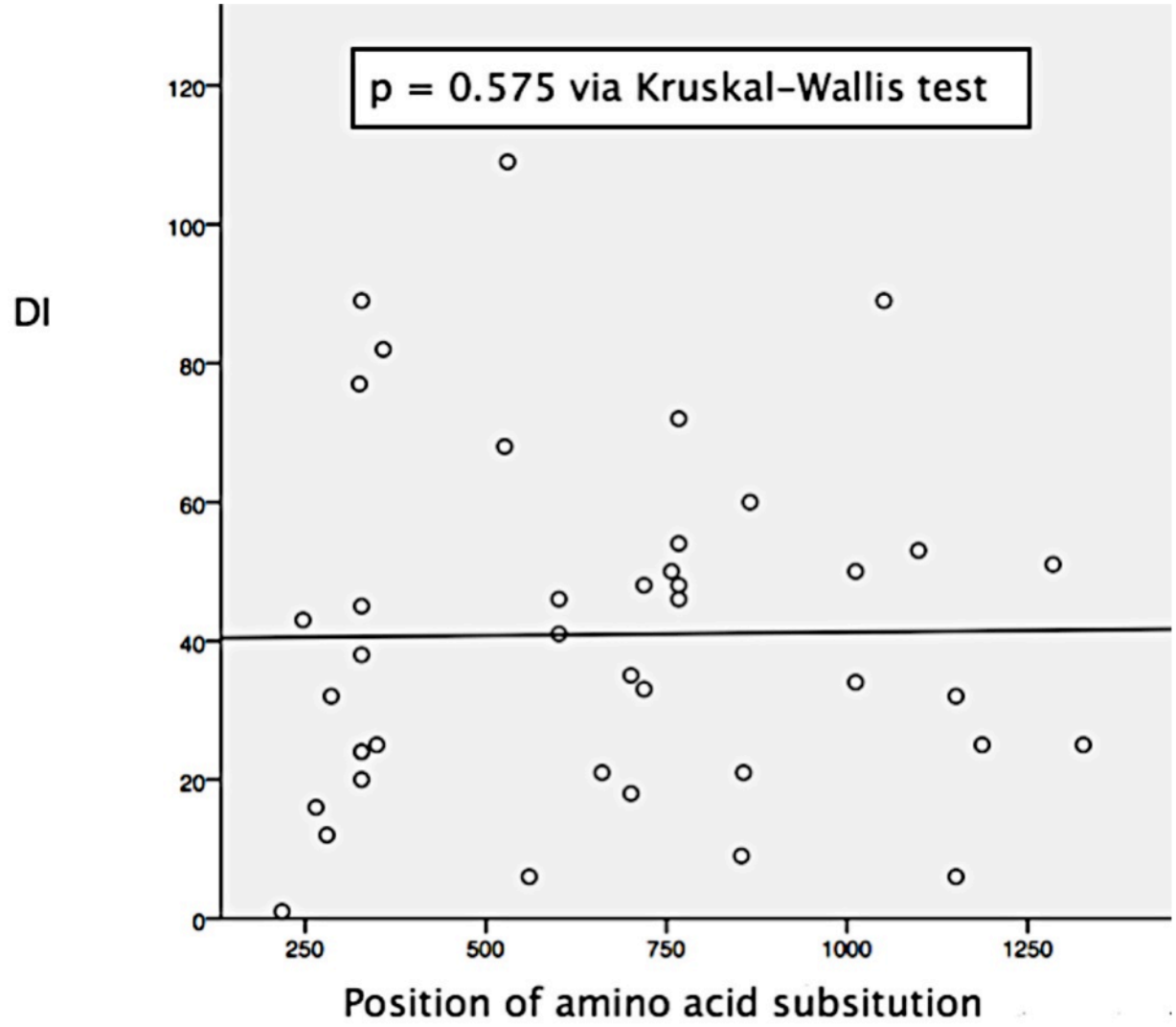

Figure 27：Discrepancy index vs. position of amino acid substitution

Longitudinal Analysis

Of the 73 OI patients referred to the Montreal Children's Dental Clinic, 34 patients had several dental casts that were available for longitudinal analysis. However only 20 patients fulfilled the eligibility criteria. (Figure 28) The time interval (mean ± SD) between the two dental cast impressions was 1.46 (± 0.75) years.

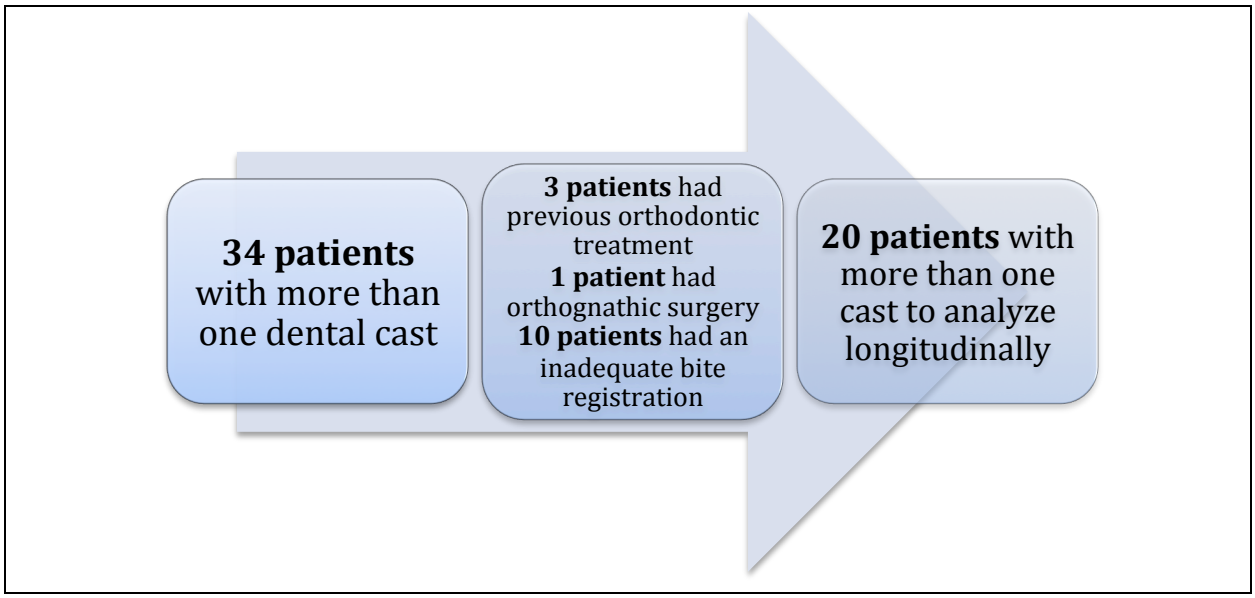

Figure 28: Inclusion and exclusion criteria for longitudinal analysis

Table 7: Descriptive characteristics of OI longitudinal study sample (n = 20)

Gender		**Gene Mutated**, n (%)	
Males, n (%)	8 (40%)	COL1A1	11 (55%)
Molar relationship, n (%)		COL1A2	9 (45%)
Class I	6 (30%)	**Type of genetic mutation**,n(%)	
Class II	2 (10%)	Triple helical defect	17 (85%)
Class III	12 (60%)	Splice mutation	3 (15%)
Dentinogenesis Imperfecta		**Position of amino acid substitution**, n (%)	
Affected, n (%)	16 (80%)	1-499	7 (35%)
OI Type, n (%)		500-999	4 (20%)
I	4 (20%)	1000-1500	6 (30%)
III	3 (15%)	Missing (splice mutations)	3 (15%)
IV	13 (65%)		

n= number of patients

SD= standard deviation

Table 7 shows selected demographic statistics of the 20 patients included in the longitudinal analysis. The sample was composed of 40% males. Again, the majority (60%) of OI patients presented with a class III malocclusion. In addition, the bulk of the OI patients (16 of 20 patients) were diagnosed with OI Type III or Type IV, which produce the more severe phenotypes of the syndrome. All subjects had genetic mutations in either the COL1A1 or COL1A2. The majority of the patients (17 of 20 patients) had an amino acid substitution, which created a triple helical defect in the procollagen molecules.

Table 8: Age, DI and height at T1 and T2 (n=20)

	T1	T2	p-value
Age Years, (mean ± SD)	9.62 ± 3.17	11.08 ± 3.40	
Discrepancy Index Score, (median [min-max])	25.5 [1-77]	35 [1,66]	0.05
Height Z-score Z-score, (mean ± SD)	minus2.91 ± 1.95	minus2.8 ± 1.99	0.557

n= number of patients
SD= standard deviation
min = minimum
max = maximum

The age, DI and height z-score were recorded at two time points (T1 and T2). At T1, the age distribution (mean ± SD) was 9.62 (±3.17) years, with a range (minimum-maximum) of 4-17 years. The median [minimum, maximum] total DI score at T1 was 25.5 [1,77]. At T2, the age distribution (mean ± SD) was 11.28 (± 3.47) years, with a range (minimum-maximum) of 5-19 years. The median [minimum, maximum] total DI score increased significantly to 37 [1,66]. (Table 8) Fifteen patients had an increase in DI, three subjects had a decrease in DI, and two subjects exhibited no change.

The change in DI over time was found to be statistically significant (p=0.05). The change in overjet, as well as the change in lingual posterior crossbite was also found to be statistically significant (p=0.05 and p=0.009). The change over time in the other DI components was not statistically significant.

Figure 29: Change in DI correlated vs Age at T1

Spearman correlations were done to determine the significant associations between the time between the two appointments and the change in total DI score, as well as each individual component. (Figure 29) The only statistically significant correlations existed between the change in total DI score (Spearman rho=0.563, p=0.01) and the change in anterior openbite (Spearman rho=0.466, p=0.038). Thus, as more time passes, there is more of an increase in total DI score as well as anterior open bite score.

Discussion

Overview

Within the limits of the study, the results suggest that the malocclusion characteristic of OI patients is linked to the severity of the syndrome. The severity of the malocclusion present in 56 OI patients was quantified using the Discrepancy Index (DI) and the median [minimum, maximum] total DI score was found to be 33.5 [1,109]. The three factors that contributed most to the malocclusions in this OI sample were discrepancies in overjet, lingual posterior crossbite, and the molar relationship. Lateral openbite also demonstrated a high correlation with a higher DI severity. Moreover, when the DI score was compared to three factors that characterize the severity of the OI syndrome (height z-score, classification type and genetic type), the higher DI scores were associated with a decrease in height z-score and an increase in the more severe OI Types. In addition, this is the first study to analyze the malocclusions of OI patients in a longitudinal manner. The longitudinal analysis of 20 OI patients demonstrated a statistically significant increase in DI over time.

As *Rizkallah et al.* discovered in 2013, OI patients are a high-risk population for severe malocclusion. This conclusion was re-confirmed with our study sample, taken from the same OI population as the *Rizkallah* group. [27] In our study, not only was the malocclusion severity found to be increased (33.5 [1,109]), there was a distinct over-representation of Class III malocclusion, negative overjet and lingual posterior crossbite. Forty-five OI patients (64.2%) had a Class III molar relationship as compared to the 3 to 8% observed in the general population of previous studies. [26, 36] Our results are similar to other authors who have also observed the high number of Class III molar relationships present in the OI population. (Figure 30) *Schwartz* and *Tsipouras* found a 67% Class III relationship in their 28 OI patient sample, *O'Connell & Marini* found a 70% Class III relationship in 40 OI patients and *Chang et al.* found a 62.5% Class III relationship in 16 OI patients. [25, 26, 41] The maxillary and mandibular arch discrepancy present in the OI phenotype not only creates a Class III molar relationship, but also a high incidence of severe anterior and posterior crossbites. Our study

not only looked at the type of malocclusion characteristic of the OI population, it also demonstrated that this malocclusion correlates with the syndrome's phenotypic severity.

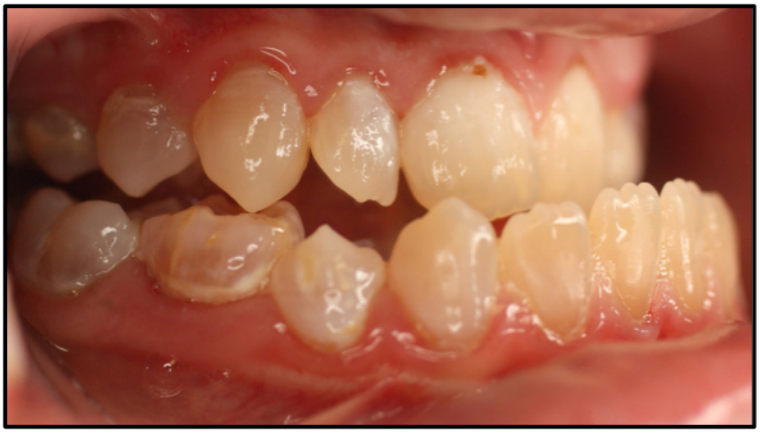

Figure 30: Anterior crossbite and class III malocclusion in an OI patient (courtesy of the Montreal Children's Hospital)

Much controversy exists concerning the maxillary and mandibular arch discrepancy present in the OI population. In fact, the etiology of the malocclusion remains unclear. Some researches have proposed the problem originates from a prognathic mandible and others, a hypoplastic maxilla. [41, 43] Regardless of the etiology, often the maxilla of an OI patient is much smaller in relation to the mandible, creating severe anterior and posterior crossbites. Our sample presented with a median [minimum, maximum] DI score for overjet of 6 [0,49]. When using the DI, negative overjet is tabulated as 1 point per millimeter per tooth in anterior crossbite. Thus, a median of 6 points with a range of 0-49 shows the high incidence of negative overjet in the OI population as well as the great variability within patients. Lingual posterior crossbites ranked as the third highest facet of the OI malocclusion, with a median [minimum, maximum] DI score of 3 [0,7]. Both anterior and posterior crossbites can greatly impede proper oral function and are difficult to treat without surgical intervention when severe.

One of the DI measures with a highly statistically significant correlation with large total DI scores was the lateral openbite. (Figure 31) Probably the most debilitating facet of the malocclusion, the lateral openbite had a median score of 1 [0,40]. The high range shows the great variability in the presence of lateral open bite; however, the high correlation with the DI

shows that when the DI score was elevated, so was the presence of lateral openbite. The common combination of mandibular pseudo-prognathism and deficient contact between upper and lower posterior teeth produces a debilitating malocclusion, which may hinder oral function for OI patients.

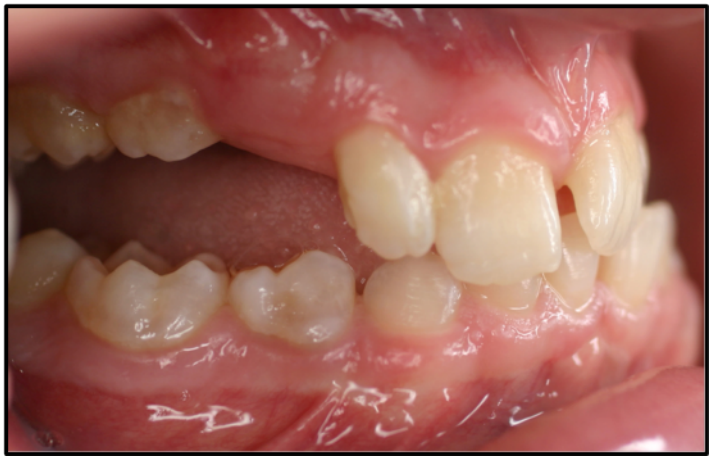

Figure 31: Severe lateral openbite in an OI patient (courtesy of the Montreal Children's Hospital

The severity of the malocclusion in the OI population correlated positively with the height z-score and classification type of the OI syndrome. The factor that correlated the most with the DI score was the patients' height. Analysis with spearman correlation demonstrated that as the DI score increased, the height z-score decreased. Thus, the severe phenotypes that impede normal skeletal growth and development also create the more debilitating malocclusions. In addition, the patients with a type of OI associated with the more severe phenotypes also possessed the higher DI scores. The DI score increased with increasing severity of OI type. More specifically, the null hypothesis was rejected when comparing the DI score of OI Types I and III, as well as of OI types I and IV/VI. No statistical difference was found in the DI score between OI type III and OI type IV/VI because usually these types produce phenotypes of similar severity.

The relationship between the genetic type and the DI score is harder to extrapolate. In our study, the DI score was significantly lower in patients with genetic mutations in the COL1A1 gene than in patients with mutations in COL1A2. However, to date, there is no consensus regarding the link between the genotype and phenotype expressed in the OI

syndrome. Many researchers have tried to decipher the connection between the two with no success, but all agree that the OI phenotype is dependent on a multitude of factors. According to *Rauch et al*, the clinical severity caused by an autosomal dominant mutation is governed by a multifactorial process which may be related to: "the type of α chain affected, the type of amino acid substituted for glycine and the position of the mutation within the α chain." [11, 12] Therefore, when analyzing the genetics of OI it does not suffice to merely look at the gene affected; the amino acid substitution and the position of the mutation on the α chain must be specified. We attempted to incorporate mutation position into our results to better understand the relationship between genotype and the malocclusion phenotype. However, no statistically significant difference was found between the mutation position and the total DI score. Perhaps with a larger sample size, this relationship can be re-explored.

In addition, *O'Connell & Marini* have suggested the severity of the malocclusions present in OI patients actually increases with age. In their sample, none of the children younger than 9 years had a posterior openbite, whereas 46% of the older children showed signs of this type of malocclusion. [26] In our study, we investigated a subset of 20 patients in a longitudinal manner at two points in time. Although our sample size was quite small, we found that the DI score increases significantly over time in the majority of OI patients. Only three subjects demonstrated a decrease in DI score. Two of these subjects had a decrease of two points or less, whereas the third subject exhibited a decrease of 23 points. However, the only two DI categories that decreased in this patient were the anterior open bite (4 points) and lateral openbite (20 points). A logical explanation for this decrease would be the natural eruption of teeth that occurs during the mixed dentition, which may create a temporary open bite and contribute to an increased DI score. This patient's malocclusion was most likely over-estimated at the first time point.

Overjet and lingual posterior crossbite were the only two DI components that increased significantly with time. This can be explained by the fact that the mandible continues to grow in the sagittal plane after the maxilla has ceased to grow in both the sagittal and transverse planes. Thus, the findings in this study are consistent with patients who have a Class III skeletal malocclusion. In addition, Spearman correlations demonstrated that as more time passes, there is more of an increase in DI scores and anterior open bite scores in OI patients. Thus, since we know that the maloclusion of OI patients tends to increase with time,

preventive strategies to modify growth in the hopes of reducing the malocclusion severity and morbidity is highly indicated.

Study limitations

Although this study had many strengths, there were also some limitations. The number of patients treated at the Montreal Shriners Hospital is one of the largest in North America. Consequently, our sample size is larger than other comparable studies. However, the study sample was not large enough to detect a correlation during some of the statistical analyses performed. For example, a correlation between the position of the helical mutation and the severity of the malocclusion could not be adequately assessed due to insufficent power. Conversely, in our longitudinal analysis, a statistically significant increase in DI score was found even though our sample consistent only of 20 subjects.

Another limitation of this study is that the sample is not representative of the actual OI population. Patients that are followed by the Montreal Shriners Hospital are usually those with more severe phenotypes requiring bisphosphonate therapy. Type I OI is "the most common and mildest form" of the syndrome, whereas 80.3% of the patients in our study possessed OI Type III and Type IV. [14] *Jensen & Lund* found less severe malocclusions in their study, but their sample contained more OI Type I patients. [18] Thus, the high prevalence of increased total DI scores in our study group could be explained by the higher degree of skeletal involvement in these OI types as compared to OI type I (19.7% of our sample).

In addition, the treatment with intra-venous bisphosphonates could not be controlled for and produces a bias in this study. Bisphosphonates impair osteoclastic activity and consequently affect bone remodeling and growth. [2] As dental eruption and dentoalveolar development requires constant bone remodeling, it is possible that the reduced osteoclastic activity has a significant impact on posterior occlusal development. However, none of the subjects studied by *Schwartz & Tsipouras*, *O'Connell & Marini*, or *Waltino-Siren et al*, had received any treatment with bisphosphonates and similar malocclusions were present in their OI sample. [25, 26, 43] Their findings confirm our assumption that the facial growth impairment is part of the phenotype of OI and not bisphosphonate therapy.

Difficulties encountered

Several obstacles arose during this research study. The major obstacle was the lack of adequate bite registrations for many OI dental casts. Without a proper bite registration, it is impossible to adequately evaluate the occlusion of most OI patients. Usually placing models in maximal intercuspation could suffice; however, the occlusions seen in these patients are so irregular that a proper bite registration taken in centric relation is absolutely necessary. The Montreal Children's Hospital dental residents took bite registrations for the OI sample, and their possible inexperience as well as the young age and difficult cooperation of some patients may have lead to inaccurate registrations. Consequently, 13 patients were removed from our sample, greatly reducing its size and leading to a decrease in power.

Also, it was very difficult to accurately evaluate the presence of lateral openbite because most of our sample was in mixed dentition. The average age (mean + standard deviation) was 10.82 ± 3.87 years and only 21.4% of our sample was above 14 years of age. Since canines, premolars and second molars are often still in eruption before 14 years of age, it was sometimes difficult to determine if a lateral openbite was present or if eruption was incomplete.

Lastly, the radiographic component of the DI could not be incorporated into the analysis due to a lack of cephalometric radiographs for the majority of our study sample. In OI patients, the weight of the head on the osteoporotic bone of the cervical area creates a basilar invagination, which will alter the patient's posture and neck anatomy. [18, 26, 43] The resulting deformity in the cervical area makes it quite difficult to take a cephalometric radiograph in patients that are severely affected. Consequently, the total DI score that was calculated was underestimated since it lacks a major component of the malocclusion assessment.

Future studies

Future studies are definitely needed to broaden our knowledge of the extremely complex OI syndrome. First and foremost, the classification of OI must be revisited. [18] The Sillence classification was made before the molecular basis of the syndrome was discovered. [3, 12]

The subdivision of the four original types may have been necessary, but the intermingling of genetic and clinical classification is extremely confusing and inefficient. [2, 3, 6, 29]

In addition, a greater understanding of the genotype and phenotype relationship is necessary in the hopes of better understanding the disease pathway of the OI syndrome. Future studies should investigate the different types of genetic mutations and their respective effects on the craniofacial complex. According to *Jensen & Lund*, patients with a qualitative defect of collagen Type I were significantly more affected in their craniofacial region than patients with a quantitative defect, irrespective of the OI type. However, the disease progression is most definitely multifactorial since patients with identical collagen abnormalities did not present with the same craniofacial phenotype. *Jensen & Lund* suggest to link cephalometric evaluation with biochemical analysis (fibroblast activity) in order to better characterize the phenotype and better understand the etiology of the malocclusion. [18] With the identification of the genetic and biochemical abnormalities in each patient, an improvement in diagnosis, classification and treatment of the various OI types may follow.

Radiographic evaluation must be included in future studies in order to analyze the craniofacial abnormalities that develop in OI patients. Previous research studies have attempted to look at cephalometric radiographs of OI patients. In 2007, *Chang et al.* evaluated cephalometric radiographs of 16 OI patients and found several craniofacial abberrations present in his sample. However, this study had a small sample size and an exclusively Asian population; therefore the results may not be extrapolated to the general OI population. [41] In 2005, *Waltino-Siren et al.* examined the lateral cephalograms of 59 OI patients. They found a normal SNB angle and normal measures for the Harvold jaw-size difference. These 'normal' results seem surprising when one looks at the severe clinical Class III jaw relationships present in our study. They concluded that the landmarks used in cephalometric measurements were not positioned normally in OI patients; thus, the cephalometric analysis of OI patients is consistently inaccurate. [43] In the future, another type of cephalometric analysis may be used, such as the one created by *Delaire*. In the latter, the analysis is based on the relationship of the maxillary facial bones to the cranium of the individual, which would have eliminated the previous inaccuracies. [57] In addition, radiographic examination with CBCT to replace panoramic and cephalometric radiographs may be indicated. CBCT provides much more information concerning craniofacial development then a regular panoramic and cephalometric

series. Although there is a higher dose of radiation, *Proffit* states that CBCTs are indicated in syndromic patients, especially when the disease is progressive. [34]

In conclusion, there are little studies that combine the genetic mutation, collagen type I defects and the result on skeletal development. Also, those who have tried have limited sample sizes. [12] Since the disease pathway in OI is multifactorial and extremely heterogeneous, in order to discover the etiology of the OI phenotype, a study must be designed to take all the previously mentionned factors into account. All aspects of the somatic development must be assessed, including the craniofacial region. Essentially, a prospective longitudinal study is required on this topic. The malocclusions characteristic of the OI population are debilitating and extremely taxing on quality of life. More must be done to determine the etiology of the disease pathway and redefine classification in order to improve treatment options.

Conclusion

Several authors have proposed that the severity of the malocclusion and facial characteristics seen in OI patients reflect the severity of the syndrome. [18, 19] Based on our study results, the malocclusion characteristic of OI patients seems linked to the severity of the syndrome. The higher DI scores were associated with a decrease in height z-score and an increase in the more severe OI Types. In addition, our longitudinal analysis demonstrated that malocclusion severity increases with age in OI patients. More specifically, the change in overjet, as well as the change in lingual posterior crossbite was found to be statistically significant. In the future, longitudinal prospective studies will be needed to study the craniofacial features characteristic of the OI population in order to determine their etiology and possible treatment options in extreme cases.

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