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CURRENT CONCEPTS REVIEW

Osteogenesis imperfecta: an overview

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Abstract

Osteogenesis imperfecta (OI) is a metabolic bone disorder commonly encountered in orthopaedic practice within the context of a multidisciplinary team. Although relatively rare, it is among the most researched of the skeletal dysplasias, making it challenging for the general orthopaedic surgeon to keep abreast with current evidence. The aim of this review article is to provide a comprehensive overview of OI for the general orthopaedic surgeon. It touches on the relevant epidemiology, pathology and clinical aspects of the condition. A discussion of the background and current topical issues surrounding the classification systems, and the medical and orthopaedic management aspects follows. The main focus of this review is on the peri-operative orthopaedic care of the appendicular musculoskeletal system. We trust it will equip the general orthopaedic surgeon with concise, up-to-date and relevant information to efficiently manage affected patients and caregivers in South Africa.

Level of evidence: Level 5

Keywords: osteogenesis imperfecta, type 1 collagen, multidisciplinary management, bisphosphonates, Fassier-Duval rods

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Introduction

Osteogenesis imperfecta (OI) is an inherited collagen type 1 disorder with varying clinical manifestations.[1,2] Hallmarks include bone fragility, blue sclera, impaired hearing, defective dentition and hyperlaxity.[1,3] The diversity of age at presentation and bone fragility best demonstrate the broad clinical spectrum of this condition. The clinical presentation ranges from mild forms to severe and lethal forms. [1,2] Milder forms generally present in later stages of life, often with long bone fractures after minor trauma while the more severe forms can present with marked skeletal dysplasias, delayed milestones and even perinatal or early childhood death.[1,2]

Type 1 collagen, a major extracellular protein constituent of bone, dentin, sclera, skin, vessels and heart valves, plays a central role in the pathogenesis of OI. Nearly 90% of patients have an identifiable mutation in genes encoding for either the type 1 collagen or those involved in its post-translational modification, resulting in qualitative and/or quantitative defects.[1,4] The modes of inheritance range from autosomal dominant to autosomal recessive but may also frequently arise as a spontaneous de novo mutation.[1] The autosomal dominant forms arise from defective genes directly involved in type 1 collagen synthesis, whereas the recessive forms arise from defects in genes encoding the proteins which play a role in the post-translational modification of type 1 collagen.[1] The International Nomenclature group for Constitutional Disorders of the Skeleton (INCDS) has modified the Sillence classification into five types, OI types I–V. This article aims to provide a broad overview of OI, including the medical and orthopaedic aspects of management.

Epidemiology

The subtypes of OI diverge in both their incidence and prevalence rates, with OI types I and IV comprising more than half of all total cases worldwide.[5] The global incidence of OI is approximately one per 20 000 live births and the prevalence is about six to seven per 100 000.[5]

There is a relative paucity of literature on the incidence and prevalence of OI in South Africa. Beighton *et al*. found an estimated minimum population frequency of 0.6/100 000 for OI type III in the black African population residing in the Johannesburg region and 0.1/100 000 for OI type I in the same group.[6] However, in the Southern African indigenous population, OI type III tends to occur with greater frequency compared to other geographical regions.[7]

Pathogenesis

Genetic mutations involving the two genes (*COL1A1* and *COL1A2*) encoding for the synthesis and/or post-translational modification of collagen type 1 have been implicated in about 90% of OI patients.[1,5] *COL1A1*, which encodes for the pro-α1 procollagen chain, is located on the long arm of chromosome 17, while *COL1A2*, which encodes for the pro-α2 procollagen chain, is located on the long arm of chromosome 7.[1] These two chains form the triple helix molecule that is type 1 collagen.[1,5] A working knowledge of the normal collagen biosynthesis and the errors in the metabolic process seen in OI is essential for understanding both the pathophysiology and the wide variability of this disorder.[1,5]

Pathology

The principal defect in most OI cases is either a critical reduction in the amount of normal type 1 collagen or the production of a wholly ineffectual and inferior variant.[8,9] Histologically, these may manifest in more than one way depending on the type of OI.[8,9] Woven bone may be more prominent, particularly in the more severe phenotypes.[8,9] In 2000, Rauch *et al*. reported the finding of normal bone mineralisation but with significant reductions in cortical width, cancellous bone volume and trabecular number and width in 70 children with OI. They also noted an increased bone turnover in nearly all types of OI, approximately a 70% increase compared with age-matched controls.[8,9]

Osteopaenia, hypoplasia and gross deformities characterise the involved bone in OI.[1] These are particularly poignant as the severity tends to worsen.[1] Secondary skeletal deformities (e.g. asymmetric physeal growth disturbance and angular or torsional deformities) frequently develop, compounding an already untenable situation.[1] Compression fractures and wedging of the vertebral bodies may be accompanied by kypho-scoliosis.[1] In the skull, multiple centres of ossification occur, particularly in the occipital region. Wormian bones (accessory skull bones completely surrounded by a suture line) are a well-recognised radiological feature of OI.[1]

Classification

In 1979, Sillence *et al*. described four distinct types of OI based on clinical features and patterns of inheritance.[1,3] They described them as follows: type I (autosomal dominantly inherited OI with blue sclerae); type II (lethal perinatal OI with radiographic features of crumpled femora and beaded ribs); type III (progressively deforming OI); and type IV (dominantly inherited OI with normal sclerae).[1,3] Of note, the mode of inheritance for types II and III was not yet conclusively confirmed as being exclusively autosomally recessive in nature as only some, but not all, of their patients displayed this pattern.[1,3]

Following the discovery of a genetic cause of OI type II in 1983 by Chu *et al*., *COL1A1/COL1A2* genes were subsequently implicated in all OI types, but there still remained some without a genetic explanation.[1,3,10] In 1984, Sillence *et al*. subdivided OI type II into OI type II-A, B and C based on radiographic features.[1] In 2004, Rauch *et al*. further modified the Sillence classification to add OI types V–VII where they presupposed an autosomal dominant for type V and an autosomal recessive mode of inheritance for types VI–VII.[1,8,10-12]

At present, there are over 19 OI types based on genetic and clinical features but with much overlap.[5,10] Orthopaedic surgeons may prefer a more pragmatic system such as the modified Sillence according to the INCDS, as given in *Table I*.

Clinical and radiographic features

Clinical manifestations vary widely depending on the severity. These are typified by bone fragility (brittle bones), short stature, scoliosis, basilar skull deformities, blue sclerae, presenile deafness, opalescent teeth, joint hyperlaxity, Wormian bones and easy bruisability. Bone fragility is the defining feature.[10] Significantly decreased mineral bone density has been identified in genetically confirmed cases of OI.[10] Increased bone turnover with net

Table I: INCDS modified Sillence classification of OI

Type (Sillence)	OI syndrome name (INCDS)	Mode of inheritance	Clinical features	Severity	Prognosis
I	Non-deforming OI with blue sclerae	Autosomal dominant	Blue-grey sclerae, variable bone fragility, presenile deafness, straight long bones Subdivided into A (normal teeth) and B (dentinogenesis imperfecta)	Mild form	Survives to adulthood, ambulant
II	Perinatal lethal	Autosomal recessive	Blue sclerae, very severe bone fragility often with crumpled bones (accordion femora) and beaded ribs	Perinatal death	Poor
III	Progressively deforming	Autosomal recessive	Normal sclerae, dentinogenesis imperfecta, severe bone fragility, bowing of long bones, rib fractures, marked short stature	Severely deforming	Die at end of second decade without bisphosphonates
IV	Common variable OI with normal sclerae	Autosomal dominant	Moderate bone fragility, bowing of long bones, vertebral crush fractures, short stature Subdivided into A (normal teeth) and B (dentinogenesis imperfecta)	Moderately deforming	Fair
V	OI with calcification in interosseous membranes	Autosomal dominant	Moderate to severe bone fragility, hyperplastic callus formation, juxtaphyseal radiodense band	Moderately deforming	Fair

Adapted from Van Dijk and Sillence[10]

Table II: Key clinical features of OI

	Prenatal findings (20 weeks gestation)	Postnatal findings	DEXA scan/ radiographic
Mild OI (usually type I or IV)	No in-utero abnormalities	Rarely congenital fractures Fully ambulant Normal/near normal growth velocity and height Minimal vertebral crush fractures Minimal chronic pain Pre-pubertal fracture rate >1 p/a Pre-senile deafness	L-spine Z-score > –1.5 but < +1.5
Moderate OI	Rarely long bone bowing/ fractures	Occasional congenital fractures Decreased growth velocity and height Bowing of long bones Pre-pubertal fracture rate >1 p/a Pre-senile deafness	L-spine Z-score > –2.5 but < –1.5
Severe OI	Long bone shortening/bowing/ fractures Under-remodelling Some rib cage abnormalities	Congenital fractures Non-ambulatory Significantly decreased growth velocity and height Bowing of long bones Chronic bone pain Pre-pubertal fracture rate >3 p/a	L-spine Z-score < –3.0
Extremely severe OI (usually OI type II)	Marked long bone shortening/ bowing/ fractures with severe under-remodelling and crumpling Marked rib cage abnormalities Decreased mineralisation	Thighs held in fixed abduction and external rotation Restricted range of motion of most joints Decreased mineralisation of most bones (flat and long) Small thorax with hypoplastic femora and vertebrae Severe chronic pain Lethal perinatal course	

Adapted from Van Dijk and Sillence[10]

osteoclastogenic resorption combined with immobilisation also plays a role.[8,10,11] In 2018, Peddada *et al*. suggested that transverse humerus, olecranon and diaphyseal humerus fractures are most commonly associated with OI, whereas physeal and supracondylar humerus fractures were least likely to indicate OI.[13]

Associated features include dentinogenesis imperfecta, which presents as a yellow or greyish hue of teeth with apparent translucency and are prone to early wear.[14-16] Some skeletal deformities, such as scoliosis and basilar impression, are considered as secondary deformities.[15,16] Other non-skeletal features include cardiovascular deformations such as valvular dysfunction and aortic root dilatation.[15,16] For ease of use, the features have been grouped into categories of severity as defined by the INCDS in *Table II*.

Diagnosis

The diagnosis of OI is based on the clinical features and is often straightforward in patients presenting with bone fragility and a positive family history or several extra-skeletal manifestations.[1,15,16] However, in the absence of these features, diagnosis may be challenging. The diagnosis of OI relies heavily on clinical and radiographic features. Under exceptional circumstances where the diagnosis is equivocal, the following investigations may be handy in assessing bone metabolism and in excluding other conditions.[8,15-19]

Biochemical markers of increased bone turnover may be elevated, especially in the more severe phenotypes of OI.[8,15-18] As such, elevated levels of C-telopeptide of type 1 collagen, serum alkaline phosphatase and hypercalciuria have been reported, while levels of C-terminal propeptide of type 1 procollagen may be lower.[8,15-19] Although there are no definitive laboratory tests, progress in molecular genetic testing holds promise of readily accessible tests in future.[15,16] Type 1 collagen can be assayed by performing gel electrophoresis of samples from cultured dermal fibroblasts.[1,15,16] These can reveal a qualitative or quantitative defect.[15,16] Sequence analysis of the dermal fibroblasts or genomic DNA testing of leukocytes for mutations in *COL1A1* and *COL1A2* is also available, but these carry a false negative rate of about 10%.[1,15,16] In South Africa, genetic testing for the *FKBP10* gene is available.

Table III: Common differential diagnoses of OI

Condition	Clinical features
Non-accidental injury	May be distinguished by metaphyseal, rib and skull fractures[1,15,16]
Rickets	Distinguished by typical radiographic features[1,15,16]
Congenital hypophosphatasia	Lethal, presents with diminished phosphatase levels and excessive excretion of phosphorylethanolamine in urine[1,15,16]
Camptomelic dwarfism	Congenital bowing and angulation of long bones may be mistaken for OI but fractures not common[1]
Achondroplasia	Rhizomelia with enlarged head; radiographs sufficient to differentiate[1,15,16]
Idiopathic juvenile osteoporosis	Self-limiting disorder characterised by its pre-pubertal onset[1]

Differential diagnosis

Common differentials include non-accidental injury and rickets. Abused children can have multiple fractures in many stages of healing.[15,16] They may also have metaphyseal, rib and skull fractures; however, OI is rarely the cause of such fractures.[1] Allegations of abuse in children with OI and, conversely, presumptions of OI in abused children, are known to occur.[1,15,16] Every child with suspicious fractures must be prudently evaluated to confirm or exclude OI. When typical features are present, the diagnosis is straightforward. However, in the absence of such, it is more cumbersome. It behoves the attending clinician to exclude OI, especially in the setting of

suspected non-accidental injury. Because a specific diagnosis is clinically important, genetic testing may be required.[1,15,16] Rickets can mimic OI clinically, but radiographic features usually suffice to exclude OI.[1,15,16] *Table III* outlines the key features of the common differential diagnoses.

Management

The management should consist of a multidisciplinary team.[1,20-22] Moreover, bisphosphonate therapy should preferably be overseen by a paediatrician well versed in genetic bone diseases.[20] It is recommended that a diagnosis of osteoporosis in children requires a dual energy X-ray absorptiometry (DEXA) scan bone mineral density (BMD) Z-score of less than -2.0 accompanied by recurrent (minimum two) low trauma long bone fractures.[20] Moreover, a diagnosis can be made in the presence of pathological vertebral compression fractures alone.[20]

Bisphosphonates

Bisphosphonates, a class of pyrophosphate-derived drugs which inhibit osteoclastic bone resorption, form the keystone of medical management.[20,22] While their use is associated with reduced bone resorption, bone growth and modelling continues unimpeded.[20-22] This results in significant increases in bone mass and strength in the growing child.[20,21] Intravenous bisphosphonates should be considered for use in severe OI types.[20] Oral bisphosphonates should be considered for mild to moderate cases while severe OI cases should continue therapy on a long-term basis.[20]

The best agent, dose or bisphosphonate frequency is as yet undetermined. In current practice, pamidronate is used in children under two years while zoledronate is used for children older than two years.[20,21] The dosage will be guided by the age-, sex- and height-adjusted BMD Z-scores. Once a child with OI stops growing, it is recommended that therapy be suspended and the child monitored.[20] The treatment recommendations from the Consensus Guidelines on the use of bisphosphonate therapy in children and adolescents have gained widespread use. Routine biochemical testing, dental review and BMD are recommended for children on bisphosphonate treatment.

Short-term complications include transient fever, bone pain and hypocalcaemia and/or hypophosphataemia during IV bisphosphonate administration.[20,21] Administration of paracetamol, slowing the infusion, giving a first-ever reduced bisphosphonate dose, ensuring adequate calcium, phosphate and vitamin D levels prior to treatment initiation and provision of post-treatment calcium and vitamin D supplementation, can avert these complications.[20,21] Metaphyseal bands of increased density have been reported after long-term bisphosphonate therapy.[21] Long-term complications may include delayed healing following osteotomy (but not traumatic fracture), osteopetrosis, persistence of primary spongiosa and rarely osteonecrosis of the jaw.[21] Clearly, a more detailed understanding of the long-term biological activity of bisphosphonates treatment is warranted.

Orthopaedic intervention

The aim of any orthopaedic intervention is to optimise function, avoid or remedy any deformity and to monitor for any potential complications of OI.[23-25] Care must be tailored to the individual patient. In milder forms, orthopaedic management rarely goes beyond conservative measures.[23] Furthermore, the orthopaedic surgeon is rarely, if ever, called to assist in OI type II (perinatal death).[1,23-26] It is the more moderate-to-severe phenotypes (OI types III to V) that often require specialised orthopaedic care.[23-25]

Most fractures heal spontaneously. Recurrent fractures are common, and prolonged immobilisation worsens incipient osteopaenia.[1,26] Perinatal fractures may require external bracing only when the fracture is unstable or interferes with care.[1] Minimising immobilisation helps to avoid muscle deconditioning and disuse atrophy.[1,26] Caregiver counselling regarding handling is essential.[26] Fracture rates decline after puberty, but may recur in post-menopausal women and in men above the age of 60 years.[26]

Prophylactic bracing is the mainstay of conservative orthopaedic management in OI.[1] In infancy and childhood, physiotherapy and external orthoses may facilitate normal development of milestones.[1,23-26]

Closed treatment techniques are the mainstay of fracture management.[1,26] Fractures heal with abundant callus but with incremental deformities predisposing to further fracturing.[24,26] Avoiding prolonged immobilisation and heavy splints is essential.[1,26] Early mobilisation is actively encouraged.[1,23-26]

Surgical realignment and intramedullary rodding is reserved for recurrent fractures and severe long bone deformities in children who are attempting to stand.[1,23-26] The lower limbs are typically more involved than the upper extremities.[1,26] Medical treatment alone will not decrease lower extremity fracture rates.[24] The best timing for surgery is controversial and some authors discourage operative intervention prior to ambulation. Recent studies have shown no advantage in delaying surgery; however, early operative intervention must balance the beneficial effects of improved milestone attainment against the possibility of early revision surgery.[24,26]

Pre-operative work-up should include evaluation for craniocervical and coagulation abnormalities.[24] The cervical spine must be carefully stabilised during intubation.[24] Intra-operatively, the anaesthetist should carefully observe for any hyperthermia, blood loss or metabolic derangements and avoid atropine use.[24,26] Sullivan *et al.* demonstrated the safety of non-invasive blood pressure (BP) cuffs and invasive BP monitoring devices as well as tourniquet use in their retrospective review.[27] The entire operative team must be educated in the care and handling of these children, especially during patient positioning, to avoid iatrogenic fractures.[24,27] Post-operative pain management may also be challenging, as many of the children may have been exposed to analgesics throughout their lives.[26] Spasms are often a major component of post-operative discomfort and therefore short-term, low-dose diazepam may be beneficial.[26]

The goals of surgery are the attainment and maintenance of optimal alignment with total correction of the deformity using an intramedullary rod which will act as an internal splint.[1,23-26] As intramedullary rods are load-sharing, their misuse can result in stress-shielding.[24]

General principles in the surgical management of OI include avoiding plate-and-screw fixation in favour of intramedullary fixation and the use of gentle techniques for muscle preservation and minimisation of soft-tissue bleeding.[1,23-26] Hancock *et al*. reported in their retrospective review, decreased blood loss with intra-operative tranexamic acid administration in a cohort of patients undergoing deformity alignment.[28] Fluoroscopic use is essential as the deformities are often three-dimensionally complex.[26]

With the Sofield-Millar technique, the individual fragments should be as long and as straight as possible.[23] Placement of osteotomies in diaphyseal regions enhances stability with intramedullary rods.[24,26] Some bone shortening may be necessary when there are severe deformities, as the taut soft-tissue structures on the concave side can be stretched excessively when a deformity is corrected.[24] Reaming may be necessary for rod placement.[24] Violation of the growth plate should be avoided. Immobilisation until union is almost always necessary.[1,23-26]

Various techniques have been described for deformity correction, including closed reduction with traction followed by pneumatic splints (Morel technique), closed reduction with percutaneous intramedullary nailing, multiple corrective osteotomies with both non-telescopic (Sofield-Millar technique) and telescopic intramedullary rods (Bailey-Dubow, Sheffield, Fassier-Duval, etc.).[24,26] With each of these having their own advantages and pitfalls, surgeon preference will guide decision-making.[24,26]

In 1959, Sofield and Millar described their technique of sub-periosteal exposure and multiple osteotomies (fragmentation) of a long bone deformity within the diaphysis and affixing these fragments onto an intramedullary rod (shish-kebab).[1,23-26] They used static intramedullary rods (Rush rods, K-wires, etc.) which proved to be very successful. This revolutionised the operative management of these severely deformed long bones, improving the mechanical characteristics of the bone and helping prevent further deformity and decreasing the risk of refractures.[1,23-26] However, the children outgrew their rods, and complications such as rod migration were common.[1]

A decade later, as a solution, new telescopic rods were designed.[24,29] These rods had both proximal and distal fixation in the epiphyses of the long bones, and elongated as the child grew.[24,29] One such design was the Bailey and Dubow rod. These telescopic rods decreased the number of reoperations required; however, they were plagued with high complication rates of proximal rod migration and disengagement of the epiphyseal T-piece.[23-26] In the 1980s, the Sheffield group improved this telescopic rod design with a fixed T-piece on either end that was rotated intra-operatively for better fixation within the epiphysis.[24] They reported fewer implant-related complications and a 20% reoperation rate, but the insertion technique of the two telescoping components still required a knee arthrotomy for femoral rod insertions and ankle arthrotomies for tibial rod insertions.[1,23-26]

In 2003, the Fassier-Duval telescopic rod was introduced as having the advantage of a single proximal entry point and improved 'screw-in' fixation in the epiphyses plus a revision rate of 14%.[24] It is inserted through small incisions under fluoroscopic control in conjunction with percutaneous osteotomies, whenever possible.[1,23-26] Rigid post-operative immobilisation is unnecessary.[24,26] The procedure requires meticulous technique and experience.[24,26] Moreover, multiple bones may be treated simultaneously, reducing the operative burden on patients.[1,23-26]

Later in 2007, the interlocking intramedullary (IM) rod was introduced, initially for use in tibial deformities but then later expanded for use in the femur.[30] It has a single proximal entry and a distal interlocking telescopic rod.[24,30] The reported revision rates are 9% at two years and 28% at three years.[24,30] This device appears to have the same rates of revision surgery as the Fassier-Duval rod.[30] Revision surgery may be required for persistent pain, progression of deformity, progressive signs of stress reaction or if the child sustains a fracture.[24,30] Fractures commonly occur distal to the proximally migrating nail, or near the male/female nail interface.[1,23-26] There is a paucity of strong evidence as to which method of fixation is best.[1]

Spinal deformities in OI can be challenging to manage.[1,26] Truncal shortening of thoracolumbar spinal segments can occur secondary to collapse of osteopaenic vertebrae.[1,26] If the patient is symptomatic, a soft spinal orthosis is helpful.[26] Scoliotic and kyphoscoliotic curves often progress rapidly.[26] Bracing is ineffectual in the setting of a severely deformed rib cage and truncal shortening.[26] In milder forms of OI, bracing can be utilised for curves of between 20 to 40 degrees or kyphosis greater than 40 degrees.[26] Spinal fusion has been recommended for scoliotic curves greater than 45 degrees to halt progression.[1,26] For patients with more severe involvement, fusion is recommended for curves over 35 degrees, as these curves are most often progressive and potentially severe.[1,26] There is a high incidence of complications from spinal fusion in OI, because internal fixation is limited by poor bone quality, autogenous iliac-crest bone graft is limited, and patients have a propensity to bleed.[1,26] However, further discussion of spine-related issues falls outside the scope of this paper.

Conclusion

Osteogenesis imperfecta is a broad condition, with varying clinical presentations. Even though a rare disorder, it is one of the most common congenital bone disorders encountered by the orthopaedic surgeon. Although precise epidemiological data is lacking for sub-Saharan Africa, there are major differences in terms of the patterns of the prevalence of certain sub-types. Although the classification has significantly evolved since Sillence's original description, there is no universal consensus yet. Sillence has lent his support for the revised classification system published by the International Nomenclature group for Constitutional Disorders and its adoption is growing, especially in research communication.

An understanding of the more subtle clinical and radiographic features of OI aids in differentiating it from other metabolic bone diseases and in its diagnosis, particularly in a resource-constrained setting such as ours. The orthopaedic surgeon well versed in the basic sciences underpinning this condition is better equipped to manage and avoid the devastating outcomes common to this condition. Although newer medical, surgical and rehabilitative therapies hold much promise for the future, a multidisciplinary approach remains the bedrock of comprehensive and sustainable positive outcomes and is gaining traction within our setting.

Ethics statement

The authors declare that this submission is in accordance with the principles laid down by the Responsible Research Publication Position Statements as developed at the 2nd World Conference on Research Integrity in Singapore, 2010.

Declaration

The authors declare authorship of this article and that they have followed sound scientific research practice. This research is original and does not transgress plagiarism policies.

Author contributions

SP and RG performed the literature review, contributed to the conceptualisation, preparation and revision of the manuscript. MK contributed to the conceptualisation of the article and performed manuscript review.

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