How frequent is osteogenesis imperfecta in patients with idiopathic osteoporosis?

Case reports

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Abstract

Rationale: The term idiopathic osteoporosis itself is quite a non-specific disease label, which fails to address the etiological understanding. Bone mineral density alone is not a reliable parameter to detect patients at high risk of fracture. The diversity of the clinical phenotypes of discolored teeth, blueness of the sclera, back and joint pain, cardiovascular disease, Diabetes type II, hearing problems and a long list of orthopedic problems are have to be considered.

Patients concerns: Our study has been designed in accordance with the clinical and radiological phenotype of eleven index cases with the provisional diagnosis of OI, which was followed by genotypic confirmation. This was followed by the invitation of siblings, parents, grandparents and other relatives to participate in the interviews, and to discuss the impact of the diagnosis. Proper collaboration with these families facilitated the process to identify other subjects with a history of fractures and other deformities/disabilities which were seemingly correlated to heritable connective tissue disorder. In total, 63 patients (27 children and 36 parents/grandparents and relatives) were enrolled in the study. Two groups of children were not included in our study. We excluded children with incomplete documentation and children who manifested de novo mutation. The term idiopathic osteoporosis (IOP) has been given to these families in other Institutes and was considered as a definite diagnosis. IOP was solely based on T scores, BMD and certain laboratory tests. Surprisingly, no single adult patient underwent clinical and or radiological phenotypic characterization.

Diagnoses: A constellation of significant disease associations with osteoporotic fracture risk have been encountered. The index cases showed mutations in COL1A1 (17q21.31.q22) and COL1A2 (7q22.1), the genes encoding collagen type I. The phenotype/genotype confirmation in 11 children was the key factor to boost our research and to re-consult each family. Comprehensive clinical and radiological phenotypic documentation has been applied to most of other family subjects who principally received the diagnosis of IOP.

Interventions: All adult patients had normal serum calcium and only three patients showed an average of low serum phosphate of 0.7–0.61 mmol/l. Serum crosslaps in six parents was in the average of (2.9–3.8nM) and PTH levels were normal in all patients (the average showed 8.73 pg/ml).

Outcomes: Our efforts to minimize and constrain the usage of the term idiopathic osteoporosis and to understand the sequence of pathological events that occurred in these families were emphasized. These efforts evolved into a remarkable and unique constellation of clinical findings. Strikingly, fracture represented a portion in a series of skeletal and extra-skeletal deformities and abnormalities which are all correlated to connective tissue disorder. This was achieved mainly through comprehensive phenotype/genotype confirmation, followed by scrutinizing the records of each family, clinical examination of the adults and revising the archives of our Hospitals and other Institutes.

Lessons: The sequence of diverse pathological events recorded within each family would be almost incomprehensible without a proper etiological understanding of the natural history of each child/family deformity that led to their occurrences. We wish to stress

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that, our current study is just an attempt to cover only a tiny fraction of the tip of the iceberg and to profoundly explore one of the most under-estimated causes of idiopathic osteoporosis.

Abbreviations: BMD = bone mineral density, COL1A1/A2 = collagen 1alpha 1 and 2, DEXA = dual-energy x-ray absorptiometry, FRAX tool = fracture risk assessment tool, IOP = idiopathic osteoporosis, OI = osteogenesis imperfecta, PTH = parathyroid hormone.

Keywords: case reports, COL1A1/A2 mutation, fractures, hearing loss, idiopathic osteoporosis, osteogenesis imperfecta

1. Introduction

Osteoporosis has been defined as a skeletal disorder characterized by compromised bone strength, predisposing a person to an increased risk of fracture.[1] Osteoporosis that affects young and otherwise healthy individuals is operationally defined as “idiopathic” osteoporosis (IOP). IOP commences in middle-to-late childhood, and usually affects the axial skeleton more severely than the extremities, and it is not associated with Wormian bones, ocular, or dental defects.[2,3]

The vast majority of physicians considers IOP as a diagnosis, accounting solely on bone mineral density (BMD) and T scores.[3] Genetic factors account for as much as 80% of the variance in peak bone mass, whereas other potential determinants of bone mass at maturity include exercise, dietary calcium intake, smoking, alcohol consumption, and age at puberty.[4,5]

In addition, in osteoporosis, BMD heritability has been estimated from 50% to 85% and, more variably, fracture heritability has ranged from 25% to 68%.[6,7]

In the milder forms of osteogenesis imperfecta (OI) the radiographic features are that of osteoporosis, though the cortices are thin; and in the medullary canal, the bone trabeculae are somehow thin. In this group of patients, fractures vary in frequency and age occurrence, and the presentation is almost misleading. In OI with collagen 1alpha (COL1A1) mutation there is low BMD and increased fracture risk, but the severity varies from perinatal lethality to asymptomatic patients, in other words, the clinical presentation is highly heterogeneous and confusing.[8–11]

The etiological understanding of osteoporosis must emerge from the fact that osteoporosis has to be regarded as a symptom complex rather than a diagnosis. The detailed clinical and radiographic phenotypic characterization in addition to the natural history of the disease of every patient (child or adult) is the cornerstone of proper management. Therefore, we feel reluctant to accept the guidelines derived from the patients’ electronic records in primary health care.

2. Materials and methods

Through our collaboration and research partnership with other colleagues in Tunisia and Russia we were able to collect a number of children who were diagnosed with OI. The family pedigree search was the baseline tool to correlate the diagnosis of OI with other skeletal and/or extraskeletal abnormalities recorded in parents, siblings, and grandparents. The latter procedures guided us to collect the data and to correlate the existing pathologies in the index cases with those of the other family subjects. The study protocol was approved by the Medical University of Saint Petersburg, Russia (Ethics Committee, EK Nr. 16–2106) and Axial Skeleton and Neurosurgery Department, Restorative Traumatology and Orthopaedics, Ilizarov Center, Kurgan, Russia (EK Nr. 41501/2016). Informed consent was obtained from the patients’ guardians. This study was conducted based on clinical and radiographic evaluation of a group of children and their parents/grandparents and relatives, and was carried out between April 1, 2007 and December 2013.

2.1. Study design

The index cases and their families were designed and grouped into 4 sections, each tied together via scientific evidence. The first section concerned clinical and radiological phenotypic characterization. The second section was the genotypic confirmation. The third section was inviting parents, siblings, grandparents, and other family subjects for further examinations. The fourth section was to analyze and to scrutinize the files of the parents, grandparents, and other family subjects.

The mainstay of the study was based on the clinical phenotype (height, craniofacial features and contour, teething, ophthalmological, auditory, neurological, cardiological, skin, genitalia, and musculoskeletal) and the radiologic phenotype (these were primarily interpreted by the author with the help of expert radiologist). Echocardiography was used in children with asymptomatic abnormal heart sounds.

Each patient underwent anthropometric measurements (occipitofrontal circumference, weight, standing and sitting heights, arm span, ratio of upper and lower segments, and ratio of arm span to height). Eleven index cases (ages 9–17 years) of different ethnic origins presented with variable forms of orthopedic abnormalities and were the key figures of our study. They were enrolled through the osteogenetic department (Orthopaedic Hospital of Speising, Vienna, Austria; the Paediatric Orthopaedic Surgery Department, Children’s Hospital, Tunis; and Pediatric Orthopedic Institute n.a. H. Turner, Saint Petersburg and Ilizarov Center, Kurgan, Russia).

The clinical and the radiographic phenotype were the baseline tool. Clinically, variable degrees of frontal bossing, opalescent teeth, and varying degrees of blueness of the sclera have been observed. History of congenital hip dislocation (DDH), frequent elbow dislocations, easy bruisability, scoliosis and asymptomatic mitral valve prolapse, and so forth were part of their natural history of the disease. Skeletal survey of this group of patients showed.

Compressive vertebral fractures of T5-10 overwhelmed by osteoporosis could be seen through a lateral spine radiograph of a 13-year-old boy (Fig. 1). Wormian bones were evident via a lateral skull radiograph of a 10-year-old girl (Fig. 2A). 3D reformatted CT scan of the cranium of the same girl at the age of 13 years showed massive ossification of the cranium and the facial bones with residues of Wormian bones after the administration of intravenous pamidronate therapy for 2 years; in cycles of 1 mg/kg daily over 3 consecutive days at a mean cycle interval of 3.8 months administered for 2 successive years along with supplemental calcium and vitamin D (Fig. 2B). Genotypic confirmation has been performed in all children groups. The natural history of the disease of the index cases and siblings are summarized in Table 1.
3. Results

We revised the dual-energy x-ray absorptiometry (DEXA) scan records of parents/grandparents (age range: 35–65 years). The average readings of their BMD was 0.661 g/cm² in L1-L4, and the femoral neck corresponding to a T-score of different readings of −4.3 to −2.8 and an average of BMD of −0.5 to −3.5, and in the femoral neck was corresponding to an average of T-score of −2.5 to −1.4. All had normal serum calcium and 3 patients showed an average of 0.7 to 0.61 mmol/L of low serum phosphate (normal: 0.83–1.48 mmol/L). Serum CrossLaps in 6 parents was in the average of 2.9 to 3.8 nM (normal: 0.00–7.78 nM) and parathyroid hormone (PTH) levels were normal in all patients (the average showed 8.73 pg/mL (normal: 8.3–68.0). In the light of the aforementioned results of low BMD, all patients were given the diagnosis of IOP.

We observed a constellation of abnormalities and significant disease associations with osteoporotic fracture risk in these families. We documented each adult patient through clinical and radiological phenotypic characterizations.

Spondylolisthesis (fractures of the pars interarticularis), subclinical basilar impression, calcification of the aortic valve and so forth were common disease association in the parents/grandparents group. Radiographic documentation of the adult group showed; Compressive vertebral fractures and aortic aneurysm were common disease associations (as seen via sagittal 3D CT scan of the thoracic region) in a 35-year-old female patient associated with sclerosis of the superior and inferior surfaces of the vertebral bodies with features of discovertebral degeneration after receiving treatment with 20 μg teriparatide (subcutaneous injections) for 18 months (Fig. 3A).

She had also a history of rupture of the symphysis pubis and symphyseal diastasis of 6 cm during vaginal delivery. 3D reconstruction CT of the cranium of the same patient showed the increased distances of the edges of the sutures which signifies progressive softness of the skull bones (Fig. 3B). 3D reconstruction CT scan of a 41-year-old woman with a history of post-adulthood kyphoscoliosis showed a compression vertebral fracture associated with downward force causing effectively shattering of the vertebral body of the osteoporotic vertebrae. Note the intravertebral vacuum clefts which are actually common in symptomatic, fracturing, osteoporotic vertebrae.

Figure 1. Lateral spine radiograph in a 13-year-old boy showed compressive vertebral fractures of T5-10.

Figure 2. (A) Lateral skull radiograph of a 10-year-old girl showed Wormian bones. (B) 3D reformatted CT scan of the cranium of the same girl at the age of 13 years showed massive ossification of the cranium and the facial bones with residues of Wormian bones after the administration of intravenous pamidronate therapy for 2 years (in cycles of 1 mg/kg daily over 3 consecutive days at a mean cycle interval of 3.8 months administered for 2 successive years along with supplemental calcium and vitamin D).
| Index case | Age     | Clinical presentation                  | Clinical phenotype                                                   | Radiologic phenotype                                                                 | Siblings-clinical phenotype                                                                 | Family-history -affected subjects                                                                 | Genotype of the index case                                                                 |
|------------|---------|----------------------------------------|----------------------------------------------------------------------|---------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1          | 10-y-old boy | Frequent elbow dislocation             | Short stature (~1 SD), frontal bossing, opalescent teeth, ligamentous hyperlaxity, and easy bruising | Wormian bones and skeletal survey revealed osteoporosis                               | Two sisters with normal phenotype and with no history of fractures, apart from ligamentous hyperlaxity as the dominating features | Four affected subjects: mother, 2 sisters, and grandfather                          | Mutation in COL1A2 (7q22.1)- OI type I                                              |
| 2          | 13-y-old boy | Persistent back pain                   | Normal height, blue sciera, moderate ligamentous hyperlaxity, and myopia (−1 diopter) | Compressive vertebral fractures of T5-10 and skeletal survey showed osteoporosis (Fig. 1) | One younger brother with opalescent teeth                                                    | Three affected subjects: mother and grandmother                                    | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
| 3          | 10-y-old girl | Irritable hip pain                    | Blue sciera and opalescent teeth                                     | Wormian bones of the skull (Fig. 2A), 3D reformatted CT scan of the cranium showed massive sclerosis with trace of Wormian bones after administration of pamidronate therapy for 2 y (Fig. 2B) | Two sisters with ligamentous hyperlaxity and blue sciera were the dominating clinical feature— no history of fractures | Three affected family subjects: grandmother, mother, and a male cousin                | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
| 4          | 13-y-old girl | Genu varum (bowing of the legs)       | Short stature, frontal and temporal bossing, and blue sciera         | Progressive deformity and bowing of the demineralized long bones with no fractures     | One elder brother with a history of asymptomatic mitral valve prolapse                      | Grandfather, mother, and a maternal sister                                          | Mutation in COL1A2 (7q22.1)- OI type III                                          |
| 5          | 9-y-old boy   | At birth he manifested unilateral hip dislocation and was treated with Pavlik harness—recently he developed scoliosis | Normal height, opalescent teeth, and myopia (−1 diopter) | Wormian bones of the skull and generalized osteoporosis                               | One elder brother with a history of ligamentous hyperlaxity and asymptomatic mitral valve prolapse | Three affected subjects: a female cousin, grandmother, and grandmother’s sister     | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
| 6          | 17-y-old girl | Frequent elbow dislocation             | Obesity and ligamentous hyperlaxity                                 | Bilateral mild bowing of the radius and ulna associated with osteoporosis               | Two younger male siblings—14 y old with a history of 2 fractures of radius, 9 y old with ligamentous hyperlaxity and blue sciera | Four affected subjects: mother, 2 sisters, and a grandfather                          | Mutation in COL1A2 (7q22.1)- OI type I                                              |
| 7          | 14-y-old boy | Irritable hip pain started at age of 9 y | Frontal bossing, opalescent teeth, and blue sciera                  | Bilateral fragmentation of the capital femoral epiphyses, coxa vara, and osteoporosis | One younger sister with boxing of the long bones (no history of fracture)—echocardio-Doppler showed asymptomatic mitral valve prolapse | Four affected subjects: grandmother, mother’s sister, 2 index case uncles             | Mutation in COL1A2 (7q22.1)- OI type I                                              |
| 8          | 13-y-old boy | Frequent elbow dislocations and 2 times fractured fingers | Opalescent teeth, generalized ligamentous hyperlaxity, and easy bruising | Thin and demineralized long bones                                                     | Two male cousins with a history of fractures                                                | Three affected family subjects: father, brother, and grandfather                      | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
| 9          | 15-y-old girl | Preadolescent scoliosis               | Short stature, opalescent teeth, and easy brusility                  | Defective ossification of the skull associated with spinal osteoporosis                | One elder sister recently developed headache and sleep apnea                                | Four affected family subjects: father, 2 paternal siblings, and grandmother           | Mutation in COL1A2 (7q22.1)- OI type I                                              |
| 10         | 16-y-old boy | Scoliosis                             | Short stature and opalescent teeth                                  | Defective ossification of the skull and demineralized spine                            | Two younger sisters with ligamentous hyperlaxity                                           | Three affected family subjects: father, uncle, and grandfather                        | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
| 11         | 14-y-old girl | History of frequent elbow fractures  | Opalescent teeth, generalized ligamentous, and hyperlaxity          | Mild platyspondyly and osteoporosis                                                   | One younger brother was born with bilateral hip dislocation                                  | Two affected family subjects: father and grandmother                               | Mutation in COL1A1 (17q21.31-q22) OI type I                                       |
the vertebral height is done by measuring between the anterior part of the fractured vertebra and the anterior part of the adjacent level (Mutation in COL1A2 (7q22.1)-OI type I).

3D reconstruction CT scan of a 60-year-old man with a history of post-adulthood scoliosis showed severe fragmentations and fractures of the thoracic cage along several ribs (arrowheads). Note excessive thinning and stretching of fragile ribs causing effectively progressive collapse of the thoracic cage. In total, 63 patients (27 children and 36 parents/grandparents and relatives) were enrolled into the study (Tables 1 and 2).

4. Discussion

Bone is a composite material of approximately one-third organic (mostly collagen) and two-thirds inorganic components. The
Table 2

Describes the phenotype of parents/grandparents, abnormalities, and the disease associations.

| Families | Parents/Grandparents | DEXA 1/4 | DEXA Hip | Fractures/disease associations | Phenotype of the parents | Diagnosis and treatment | Other family subjects/disease associations |
|----------|----------------------|----------|----------|-----------------------------|--------------------------|------------------------|---------------------------------------------|
| Family of index case 1 | Mother: 35-y-old | −43 | −2.5 | Compressive vertebral fractures (as seen via sagittal 3D CT scan of the thoracic region) associated with idiopathic osteoporosis | Normal height, history of multiple spontaneous abortions, and easy bruising | Received parathyroid hormone | Aunts of age 61 and 66 y underwent arthroplasty |
| Family of index case 2 | Mother: 38-y-old | −23 | −2.0 | Frequent wrist fractures in connection with minute trauma (Colle fracture) | Short stature, obese, easy bruising, and mild blueness of the sclera | Treated with bisphosphonate | One obese sister with hearing loss (diabetes mellitus type II) |
| Family of index case 3 | Mother: 41-y-old | −40 | −2.1 | Compressive vertebral fractures (Fig. 4) | Normal phenotype | Received bisphosphonate | Elder brother is with hearing loss and had a history of frequent shoulder and elbow dislocations. Grandmother with a history of hearing loss (diabetes mellitus type II). A cousin died because of infective endocarditis secondary to undiagnosed asymptomatic mitral valve prolapse |
| Family of index case 4 | Mother: 40-y-old | −26 | −3.0 | Compressive vertebral fractures | Normal phenotype with mild blueness of the sclera | Orthopedic intervention | Other sister with low-legs, hearing loss and diabetes mellitus type II. Father has kyphosis |
| Family of index case 5 | Grandmother: 59-y-old | −34 | −2.1 | Thoracolumbar (T12-L1) compressive fractures | Normal phenotype | Orthopedic intervention | Grandmother’s sister with hearing, diabetes mellitus type II. Female cousin, 16-y-old, with frequent elbow fractures |
| Family of index case 6 | Mother: 48-y-old | −39 | −2.1 | Vertebral fractures | Normal height, obesity, and diabetes mellitus type 2 | Treated with bisphosphonate | A sister (65-y-old) with congenital glaucoma. A cousin, 38-y-old with hearing loss, kyphosis, and cervical spine arthrosis. Two maternal uncles—41-y-old uncle with a history of kyphosis, and 38-y-old uncle with kyphosis |
| Family of index case 7 | Grandmother: 65-y-old | −42 | −2.6 | Vertebral fractures | Short stature and kyphosis | Treated with bisphosphonate, vitamin D, and calcium supplementation, and vitamin D | Grandmother’s sister (61-y-old) with hearing loss and kyphosis. Maternal sister with hearing loss and cervical spine ankylosis. Two maternal uncles—41-y-old uncle with a history of kyphosis, and 38-y-old uncle with hearing loss |
| Family of index case 8 | Father: 55-y-old | −23 | −2.6 | Frequent wrist fractures started at the age of 48 | Normal phenotype, moderate blueness of the sildena, and osteoporosis | Treated with bisphosphonate | Mother had a history of spino-osteo lymphoma. Father brother had a history of hearing loss. Grandfather with history of hip fracture (not operated) died 4 mo later |
| Family of index case 9 | Father: 53-y-old | −30 | −2.8 | Kyphosis on top of T10-L1 fracture | Short stature | Treated with parathyroid hormone, Grandfather underwent vertebroplasty | Grandfather developed headache, nystagmus, and hyposthenia because of basilar impression |
| Family of index case 10 | Father: 60-y-old | −40 | −2.8 | History of wrist fractures; recently: Progressive rib fractures (Fig. 5) | Short stature and frontal bossing | Orthopedic intervention | Paternal brother with hearing loss, and kyphosis |
| Family of index case 11 | Father: 62-y-old | −34 | −2.6 | Compressive vertebral fractures at the age of 51 | Normal phenotype apart from kyphosis | Treated with parathyroid hormone, Grandfather underwent vertebroplasty | Grandmother with hearing loss. Grandfather with hearing loss and kyphosis |

DEXA = dual-energy x-ray absorptiometry, IOP = idiopathic osteoporosis, PTH = parathyroid hormone.
inorganic component consists of crystals of basic carbonate that contains a form of calcium phosphate called hydroxyapatite.\textsuperscript{1,2} Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue and a decrease in bone mass, resulting in fragile, weakened bones that fracture easily, even in the absence of trauma.\textsuperscript{3} According to the Oxford Medical Database, there are more than 132 syndromic entities in which osteoporosis and fractures are symptom complexes.\textsuperscript{4}

Osteoporosis, a condition in which there is parallel loss of bone mineral and matrix, is the most common cause, whereas rickets, a pathological loss of mineralized bone caused by a reduction in calcium-phosphate levels with resultant accumulation of non-mineralized matrix (osteoid), is less common. Defects in bone formation associated with congenital or developmental diseases such as OI, homocystinuria, galactosemia, or various forms of skeletal dysplastic disorders, may lower BMC and can lead to bone fragility. In particular, Bruck syndrome and Cole-Carpenter syndrome have marked fragility, and their heterogeneous genetic bases overlap with OI.\textsuperscript{5,6}

Osteopenia, as referred to by the World Health Organization, is a loss of bone > 1 but < 2.5 SD below the mean reference for the young adult population. Senile osteoporosis, is the result of bone mass decreasing with age, and is the most common skeletal disorder in the world, second only to arthritis as a leading cause of musculoskeletal morbidity in the elderly.\textsuperscript{7} BMD measurements have been used as the anchor for the prediction of fracture risk in the postmenopausal female and elderly male populations. In addition, it has been used to monitor diseases that may negatively affect bone and the response to therapies which are designed mainly to increase skeletal strength without proper clinical and radiographic assessment of the after effects of different therapies.\textsuperscript{8} Several previous studies attempted to discuss the etiological understanding of osteoporosis via variable genotypic and molecular approaches.

Hippisley-Cox and Coupland,\textsuperscript{9,10} Kush et al,\textsuperscript{11} Kanis et al,\textsuperscript{12} Weiner and Traub,\textsuperscript{13} Siris et al,\textsuperscript{14} Liu et al,\textsuperscript{15} Kiel et al,\textsuperscript{16} Rivadeneira et al,\textsuperscript{17} Efstathiadou et al,\textsuperscript{18} and Ralston et al\textsuperscript{19} admitted that their study design was not totally immune to biases, and the measurement error with misclassification in phenotype or genotype tends to diminish the observed ORs. Noncomprehensive clinical documentation can seriously affect the genetic results.

None of the aforementioned studies took into consideration the necessity of performing a comprehensive phenotypic/genotypic characterization of every single patient/family. The natural history of osteoporosis should be based on the assumption of being a symptom complex until proven otherwise. The correlation between osteoporosis and concomitant illnesses in the adult group of patients such as hearing loss, hip replacement, progressive collapse of the thoracic cage, vertebroplasty, cardiovascular diseases, diabetes mellitus type 2, and others (see Tables 1 and 2) are to be considered and are mostly related to connective tissue disorders as seen in OI type 1.\textsuperscript{19} OI is a genetically programmed disorder which is notoriously unpredictable with a diverse age of onset of manifestations. The detailed phenotypic characterization of every osteoporotic patient should be based on individualistic findings. Throwing all osteoporotic patients in one basket caused enormous harm to the patients’ management and may lead to ill-defined prognostication.

The inexperienced clinicians may (partly through fear of litigation) engage mechanically and defensively with decision support technologies, stifling the development of a more nuanced clinical expertise that embraces accumulated practical experience, tolerance of uncertainty, and the ability to apply practical and ethical judgment in a unique case.\textsuperscript{20} Thence, the National Osteoporosis Society should be involved in presenting a clearer definition and better understanding of osteoporosis.

OI type I is the most common form of OI and inherited as an autosomal dominant condition. OI classically occurs due to a reduction in the quantity of collagen type I protein following a stop frame shift or splice site mutation in either COL1A1 or COL1A2. As this leads to a quantitative defect, the phenotype of this group is mild with patients attaining normal height and having minimal functional limitations. These patients can rarely have fractures of the long bones, although in some, fracture may occur when the child starts walking but they are particularly at more risk of vertebral compression fractures, later in life. A number of skeletal disorders can have similar features as OI. Osteoporosis pseudoglioma syndrome, Cole-Carpenter and Bruck syndromes have severe bone fragility with low bone-mineral content.\textsuperscript{21–23}

4.1. In summary

BMD results and the other risk factors of the fracture risk assessment (FRAX) algorithm are just cofactors and in genuine practice are not diagnostic. The false and common conception among the vast majority of physicians is that intrinsic bone disorders are rare entities. This resulted in underestimating the real occurrence and the significance of diagnosing intrinsic bone disorders and the related disorders. The wide spectrum of confusing clinical and radiographic phenotypes made the task even harder.

We wish to stress that from the patient selection process to follow-up care, this study pulled together the results of many years of clinical observations, radiographic interpretations, and exhaustive patient/family evaluation. Nevertheless, the primary limitation in our study is the limited number of adult patients with the diagnosis of IOP. This poses as an incentive for further encroachment in the field of orthopedic traumatology and underscores our commitment to conduct quality investigations. OI was diagnosed in patients with various ethnic backgrounds (Austria, Russia, and Tunisia), which concludes that OI secondary to COL1A1–2 has to certain extent the same natural history despite its being considered as a heterogeneous and unpredictable connective tissue disorder.

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