Medicine®

OPEN

How frequent is osteogenesis imperfecta in patients with idiopathic osteoporosis?
Case reports

Ali Al Kaissi, MD, MSc[a,*], Christian Windpassinger, MD[b], Farid Ben Chehida, MD[c], Maher Ben Ghachem, MD[d], Nabil M. Nassib, MD[d], Vladimir Kenis, MD[e], Eugene Melchenko, MD[e], Ekatrina Morenko, MD[e], Sergey Ryabykh, MD[f], Jochen G. Hofstaetter, MD[a], Franz Grill, MD[a], Rudolf Ganger, MD, PhD[a], Susanne Gerit Kircher, MD, MSc[g]

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. Serumcrosslaps in six parents was in the average of (2.9–3.8 nM) 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

---

Al Kaissi et al. Medicine (2017) 96:35

Medicine

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 corner stone 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). Echocardio-Doppler 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.
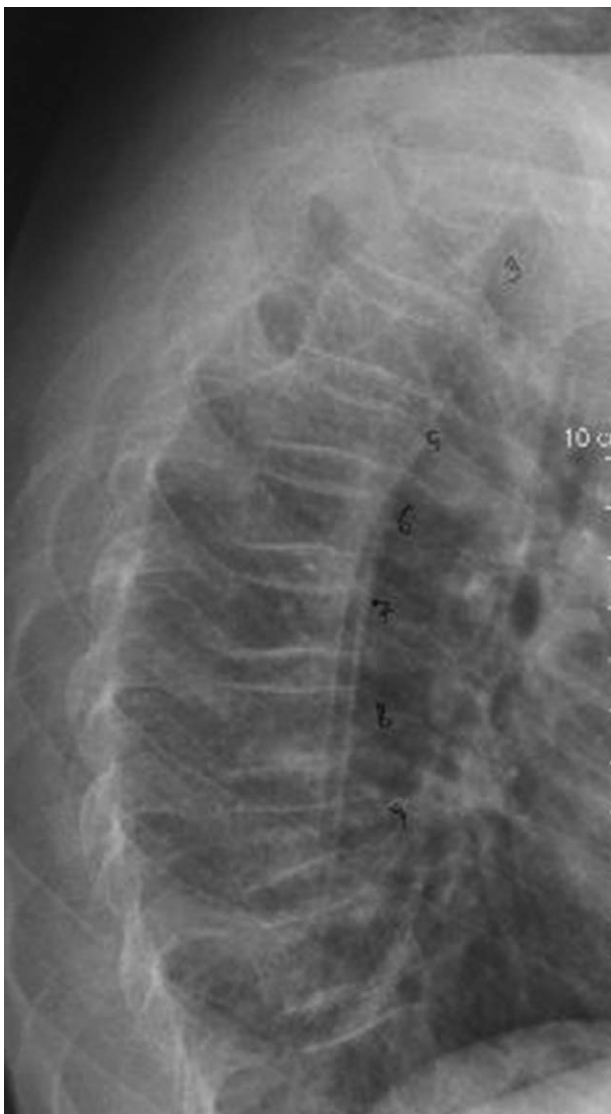
Al Kaissi et al. Medicine (2017) 96:35

www.md-journal.com

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

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/cm^2 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 shatterning of the vertebral body of the osteoporotic vertebrae. Note the intravertebral vacuum clefts which are actually common in symptomatic, fracturing, osteoporotic vertebrae. Evaluation of
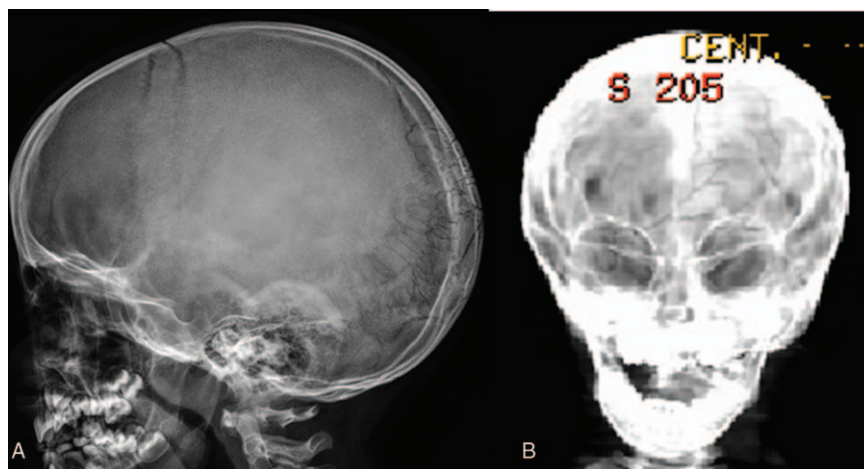
Figure 2. (A) Lateral skull radiograph of a 10-year-old girl showed Wormian bones. (B) 3D reformatted CT scan of the cranium of the same girl at the age of 13 years showed massive ossification of the cranium and the facial bones with residues of Wormian bones after the administration of intravenous pamidronate 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).

Al Kaissi et al. Medicine (2017) 96:35

Medicine

Table 1

The clinical and radiographic phenotype and the genotype of the index cases and siblings.

| 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 bruisability	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 sclera, moderate ligamentous hyperlaxity, and myopia	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 sclera 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 sclerae 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 sclera	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 sclera	Four affected subjects: mother, 2 sisters, and a grandfather	Mutation in COL1A1 (17q21.31-q22) OI type I
7	14-y-old boy	Irritable hip pain started at age of 9 y	Frontal bossing, opalescent teeth, and blue sclera	Bilateral fragmentation of the capital femoral epiphyses, coxa vara, and osteoporosis	One younger sister with bowing of the long bones (no history of fracture)—echocardio-Doppler showed asymptomatic mitral prolapse	Four affected subjects: grandmother, grandmother'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 bruisability	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 bruisability	Defective ossification of the skull associated with spinal osteoporosis	One older 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 tooth	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

Al Kaissi et al. Medicine (2017) 96:35

www.md-journal.com
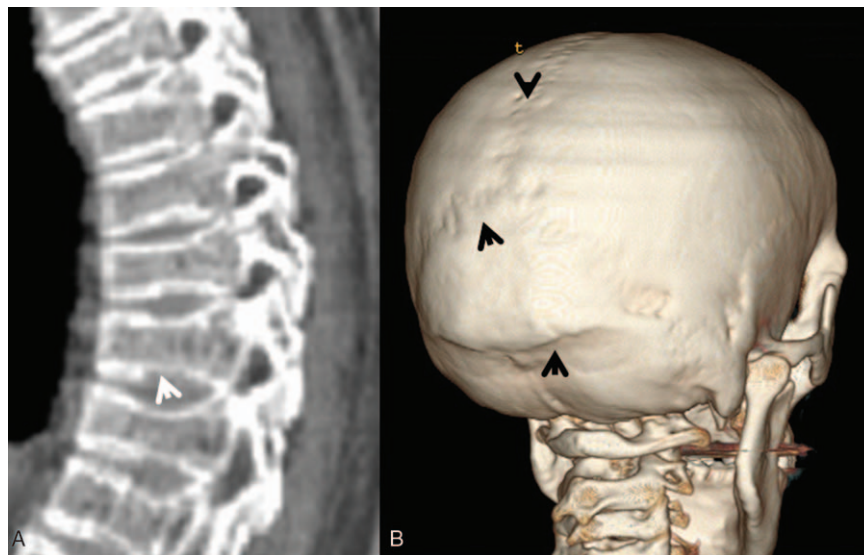
Figure 3. (A) Compressive vertebral fractures (seen via sagittal 3D CT scan of the thoracic region) associated with sclerosis of the superior and inferior surfaces of the vertebral bodies after receiving treatment with 20 μg teriparatide (subcutaneous injections) for 18 months. Note features of discovertebral degeneration (arrowhead). (B) 3D reconstruction CT of the cranium of the same woman showed the increased distances of the edges of the sagittal suture and the lambdoid sutures which signifies progressive softness of the skull bones (arrowheads).

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 (Fig. 4).

Figure 4. 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. Evaluation of the vertebral height, 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 (Fig. 5). 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
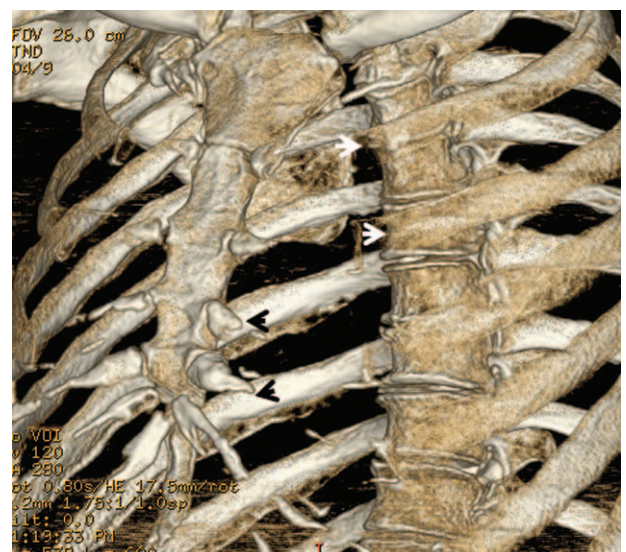

Figure 5. 3D reconstruction CT scan of a 60-year-old man with a history of post-adulthood scoliosis showed severe fragmentations and fractures of the thoracic cage along several ribs (arrowheads). Note excessive thinning and stretching of fragile ribs causing effectively progressive collapse of the thoracic cage.

Table 2

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

Families	Parents/Grandparents	DEXA L1/4	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	−4.3	−2.5	Compressive vertebral fractures (as seen via sagittal 3D CT scan of the thoracic region) 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 mo. (Fig. 3A). She also had a history of rupture of the symphysis pubis and symphyseal diastasis of 6 cm during vaginal delivery. 3D reconstruction CT scan of the cranium of the same woman showed the increased distances of the edges of the sutures which signifies cranial softness (Fig. 3B)	Normal height, history of multiple spontaneous abortions, and easy bruisability	IOP: She underwent surgery 2 wk following the event and plate fixation was performed	Aunts of age 61 and 66 y underwent arthroplasty because of hip fracture. Grandfather was operated for hip replacement and died at age of 72 y—8 mo postoperatively (history of diabetes mellitus type II)
Family of index case 2	Mother: 38-y-old	−2.3	−2.0	Frequent wrist fractures in connection with minute trauma (Colle fracture)	Short stature, obese, easy bruisability, and mild blueness of the sclerea	IOP: She was treated with 20 μg PTH 1–34 s.c. and 0.5 μg calcitriol daily for 18 mo	One obese sister with hearing loss (diabetes mellitus type II). Grandmother had a history of multiple fractures and mild aortic root dilatation
Family of index case 3	Mother: 41-y-old	−4.0	−2.1	Compressive vertebral fractures (Fig. 4)	Normal phenotype	IOP: She received calcium supplements and vitamin D and she refused 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	−2.6	−3.0	Compressive vertebral fractures	Normal phenotype with mild blueness of the sclerea	IOP: At the age of 35 the mother was treated with 20 μg PTH 1–34 s.c. and 0.5 μg calcitriol daily for 24 mo	Older sister with bow legs, hearing loss and diabetes mellitus type II. Grandfather has kyphosis
Family of index case 5	Grandmother: 59-y-old	−3.4	−2.1	Thoracolumbar (T12-L1) compressive fractures	Normal phenotype	IOP: vertebroplasty	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	−3.9	−2.1	Vertebral fractures	Normal height, obesity, and diabetes mellitus type 2	IOP: bisphosphonate	A sister (55-y-old) with congenital glaucoma. A sister with a history of vertebral fractures and hearing loss. Grandfather developed hip fracture at the age of 57
Family of index case 7	Grandmother: 65-y-old	−4.2	−2.6	Vertebral fractures	Short stature and kyphosis	IOP: bisphosphonate, calcium supplementation, and vitamin D	Grandmother's sister (61-y-old) with hearing loss and kyphosis. Maternal sister with hearing loss and cervical spine arthrosis. Two maternal uncles—41-y-old-uncle with a history of frequent fractures and received bisphosphonate, 38-y-old uncle with hearing loss
Family of index case 8	Father: 55-y-old	−2.3	−2.6	Frequent wrist fractures started at the age of 48	Normal phenotype, moderate blueness of the sclera, and osteoporosis	IOP: bisphosphonate	Mother had a history of spondylolisthesis. Paternal 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	−3.0	−2.8	Kyphosis on top of T10-L1 fracture	Short stature	IOP: vertebroplasty, Grandfather underwent ventral decompression	Grandmother developed headache, nystagmus, and hyperreflexia because of basilar impression
Family of index case 10	Father: 60-y-old	−4.0	−2.8	History of wrist fractures; recently: Progressive rib fractures (Fig. 5)	Short stature and frontal bossing	IOP: spinal fusion	Paternal brother with hearing loss. Grandfather with hearing loss and kyphosis
Family of index case 11	Father: 62-y-old	−3.4	−2.6	Compressive vertebral fractures at the age of 51	Normal phenotype apart from kyphosis	IOP: vertebroplasty	Grandmother with history of late onset fractures (first fracture at the age of 47 y)

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.[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.[2] According to the Oxford Medical Database, there are more than 132 syndromic entities in which osteoporosis and fractures are symptom complexes.[11]

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.[8,11,12]

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.[13] 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.[3–5] Several previous studies attempted to discuss the etiological understanding of osteoporosis via variable genotypic and molecular approaches.

Hippisley-Cox and Coupland,[14,15] Kush et al,[16] Kanis et al,[17] Weiner and Traub,[18] Siris et al,[19] Liu et al,[20] Kiel et al,[21] Rivadeneira et al,[22] Efstathiadou et al,[23] and Ralston et al[24] 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.[25] 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.[26] 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, frameshift 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 occurs 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.[27–29]

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.

References

[1] NIH Conference Development PanelOsteoporosis prevention, diagnosis and therapy. JAMA 2001;285:785–95.

[2] Finkelstein JS. Goldman L, Ausiello D. Osteoporosis. Cecil Textbook of Medicine 22nd ed.Saunders, Philadelphia, PA:2004;1547–55.

[3] Kandoi MR. Juvenile osteoporosis. Clinical Aspects in Osteoporosis. 2005;Jaypee Brothers Medical Publishers, 245–58.

[4] WHO Study Group ReportAssessment of fracture risk and its application to screening for postmenopausal osteoporosis. World Health Organ Tech Rep Ser 1994;843:1–29.

[5] Siris ES, Miller PD, Barrett-Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results from the National Osteoporosis Risk Assessment. JAMA 2001;286:2815–22.

[6] Deng HW, Chen WM, Recker S, et al. Genetic determination of Colle's fracture and differential bone mass in women with and without Colle's fracture. J Bone Miner Res 2000;15:1243–52.

[7] Richards JB, Zheng HF, Spector TD. Genetics of osteoporosis from genome-wide association studies: advances and challenges. Nat Rev Genet 2012;13:576–88.

[8] Sillence DO, Senn A, Danks DM. Genetic heterogeneity in osteogenesis imperfecta. J Med Genet 1979;16:101–16.

[9] Smith R. Osteogenesis imperfecta: from phenotype to genotype and back again. Int J Exp Pathol 1994;75:233–41.

[10] Constantinou CD, Pack M, Young SB, et al. Phenotypic heterogeneity in osteogenesis imperfecta: the mildly affected mother of a proband with a lethal variant has the same mutation substituting cysteine for alphaI-glycine 904 in a type I procollagen gene (COL1A1). Am J Hum Genet 1990;47:670–9.

[11] Baraitser M, Winter R. Oxford Dysmorphology database, London, version 2009.

[12] Lachman E. Osteoporosis: the potentialities and limitations of its roentgenologic diagnosis. Am J Roentgenol 1955;74:712–7.

[13] National Institute for Health and Clinical Excellence. Systematic reviews of clinical effectiveness prepared for the guideline: osteoporosis assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk. 2008:1–205.

[14] Hippisley-Cox J, Coupland C. Predicting risk of osteoporotic fracture in men and women in England and Wales: prospective derivation and validation of QFractureScores. BMJ 2009;339:b4229.

[15] Hippisley-Cox J, Coupland C. Derivation and validation of updated Qfracture algorithm to predict risk of osteoporotic fracture in primary care in the United Kingdom: prospective open cohort study. BMJ 2012;344:e3427.

[16] Kush RD, Helton E, Rockhold FW, et al. Electronic health records, medical research, and the Tower of Babel. N Engl J Med 2008;358:1738–40.

[17] Kanis JA, McCloskey EV, Johansson H, et al. Development and use of FRAX in osteoporosis. Osteoporos Int 2010;21(suppl 2):S407–13.

[18] Weiner S, Traub W. Bone structure. From angstroms to microns. FASEB J 1992;6:879–85.

[19] Siris ES, Miller PD, Barrett- Connor E, et al. Identification and fracture outcomes of undiagnosed low bone mineral density in postmenopausal women. Results from the National Osteoporosis Risk Assessment (NORA). JAMA 2001;286:2815–22.

[20] Liu YZ, Liu YJ, Recker RR, et al. Molecular studies of identification of genes for osteoporosis: the 2002 update. J Endocrinol 2003;177:147–96.

[21] Kiel DP, Demissie S, Dupuis J, et al. Genome-wide association with bone mass and geometry in the Framingham Heart Study. BMC Med Genet 2007;8(suppl 1):S14.

[22] Rivadeneira F, Styrkársdottir U, Estrada K, et al. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. Nat Genet 2009;41:1199–206.

[23] Efstathiadou Z, Tsatsoulis A, Ioannidis JP. Association of collagen Ialpha 1 Sp1 polymorphism with the risk of prevalent fractures: a meta-analysis. J Bone Miner Res 2001;16:1586–92.

[24] Ralston SH, Uitterlinden AG, Brandl ML, et al. Large-scale evidence for the effect of the COLIA1 Sp1 polymorphism on osteoporosis outcomes: the GENOMOS study. PLoS Med 2006;3:e90.

[25] Al Kaissi A, Ben Chehida F, Grill F, Ganger R. Progressive collapse of the the thoracic cage. Am J Med 2016;129:

[26] Glasziou P, Moynihan R, Richards T, et al. Too much medicine; too little care. BMJ 2013;347:f4247.

[27] Roughley PJ, Rauch F, Glorieux FH. Osteogenesis imperfecta-clinical and molecular diversity. Eur Cell Mater 2003;5:41–7.

[28] Spranger JW, Brill PW, Poznanski AK. Bone Dysplasias: An Atlas of Genetic Disorders of Skeletal Development. Oxford University Press, New York, NY:2000.

[29] Cheung MS, Glorieux FH. Osteogenesis imperfecta: update on presentation and management. Rev Endocr Metab Disord 2008;9:153–60.