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Research Article

The Profile of Osteogenesis Imperfecta in Dr. Moewardi General Hospital Year 2020-2021: A Retrospective Study

Profil Osteogenesis Imperfecta di RSUD Dr. Moewardi Tahun 2020-2021: Sebuah Penelitian Retrospektif

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ABSTRACT

Osteogenesis imperfecta (OI) is a heritable bone dysplasia characterized by bone fragility and long bone deformities. This study aims to report the profile of osteogenesis imperfecta in Dr. Moewardi General Hospital. The patients were searched from the medical record, registered from January 1, 2020, to December 31, 2021, in Dr. Moewardi General Hospital, a tertiary hospital in Surakarta, Indonesia. The data were recorded and described in tables as age, sex, type of OI according to Sillence, clinic, ward admission, signs and symptoms, bisphosphonate therapy and its discipline, as well as the surgical/non-surgical treatment. The quantity of male patients is higher than that of females, OI type IV is the most common, the most common sign/symptoms are fracture and blue sclera, and the most common bone to be fractured is the femur. More than half of patients received bisphosphonate therapy, but only a quarter received it routinely. More than half of patients have performed surgery as the treatment of fractures. Osteogenesis imperfecta patients require an interdisciplinary and tailored treatment that involves both medical and surgical components.

Keywords: *Bisphosphonate, epidemiology, osteogenesis imperfecta, signs, surgery, symptoms*

ABSTRAK

Osteogenesis imperfecta (OI) adalah displasia tulang herediter yang ditandai dengan kerapuhan tulang dan deformitas tulang panjang. Penelitian ini bertujuan untuk memberi gambaran profil osteogenesis imperfecta di RSUD Dr. Moewardi. Data pasien dicari dari rekam medis, yang terdaftar pada 1 Januari 2020–31 Desember 2021 di Rumah Sakit Umum Daerah Dr. Moewardi, Rumah Sakit Tersier di Surakarta, Indonesia. Data tersebut akan dicatat, dan dideskripsikan dalam tabel seperti umur, jenis kelamin, tipe OI menurut Sillence, klinis, rawat inap, tanda dan gejala, terapi bifosfonat dan kedisiplinannya, serta penanganan bedah/nonbedah. Jumlah pasien laki-laki lebih banyak daripada perempuan, OI tipe IV paling sering ditemukan, tanda/gejala yang paling umum adalah fraktur dan sklera biru, dan tulang yang paling sering mengalami fraktur adalah femur. Lebih dari setengah pasien OI mendapatkan terapi bifosfonat, tetapi hanya seperempat pasien OI yang mendapatkannya secara rutin. Lebih dari separuh pasien OI menjalani operasi sebagai penanganan fraktur. Pasien osteogenesis imperfekta memerlukan penanganan interdisipliner dan penyesuaian yang melibatkan komponen medis dan bedah.

Kata Kunci: bifosfonat, epidemiologi, gejala, operasi, osteogenesis imperfecta, tanda

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INTRODUCTION

Osteogenesis imperfecta (OI) is defined as bone dysplasia, heritable and characterized by long bone deformities and bone fragility. About 85% of OI are caused by dominant autosomal mutations of type I collagen coding genes (*COL1A1* and *COL1A2*), which affect the structure or quantity of collagen (1). The prevalence of OI is approximately 1 in 10,000–20,000 births (2). A hallmark of this disease is frequent fractures caused by low trauma (3).

Classification from D.O. Sillence is based on clinical and radiological data. Sillence identified 4 types written in Roman numerals (4). Type II is the most severe, followed by types III, IV, and I (1).

Type I is characterized by blue sclerae, frequent fractures at an early age, hearing impairment, often normal stature, rare limb deformities, and rare imperfect dentinogenesis. Type II is characterized by a fatal form in perinatal, the most severe signs, blue or grey sclerae, short limbs with arcuate deformations, death caused by respiratory failure, and pneumonia due to lung tissue abnormality. Type III patients have progressive limb deformities and can experience hundreds of fractures in their lifetime, often triangular with frontal tubers face shape, blue or grey sclera, with very short stature. Sometimes, scoliosis, dentinogenesis imperfecta, compression fracture of the vertebral body, and platibasia also happen. Type IV (moderate severity) patients can experience tens of fractures in their lifetime; most of them can walk. They often have dentinogenesis imperfecta, hearing impairment, basilar depression, and growth variability. Additional classification type V was added, which is characterized by frequent fractures. The peculiarity consists of hypertrophic callus formation and interosseous membrane ossification on the forearm (1).

Through the development of genetic knowledge, scientists can identify responsible genes for OI. There are 18 types of osteogenesis imperfecta based on genetic classification. However, applying this gene classification in routine clinical practice is difficult because of the unclear differences between the classical four types of Sillence and the new types (1,5).

Differential diagnostics are similar to connective tissue dysplasia, such as Brooke–Spiegler syndrome of types I and II, perinatal and pediatric hypophosphatasia, Carpenter syndrome of types I and II, Ehlers–Danlos syndrome, idiopathic juvenile osteoporosis, and osteoporosis–pseudo glioma syndrome (6).

Data on the publication of osteogenesis imperfecta in Indonesia is still very small. Meanwhile, cases in every hospital are always there. The lack of research data can affect the push for hospitals to buy new, more sophisticated equipment to make the diagnosis easier to make. Furthermore, it can influence the policyholders of each hospital to facilitate the treatment of osteogenesis imperfecta. This study aims to report the profile of osteogenesis imperfecta in Dr. Moewardi General Hospital.

METHOD

This is a retrospective descriptive study with a cross-sectional design. The research was performed in March 2022. Patients were searched from the medical record, registered from January 1, 2020, – December 31, 2021, in Dr. Moewardi General Hospital, a referral hospital in Surakarta, Indonesia. The inclusion criteria included all Osteogenesis Imperfecta patients registered in orthopedic and non-orthopedic clinics and admitted to the ward. The exclusion criteria included all patients/their families who refuse to participate in this study and have incomplete data.

The data were recorded and described in tables as age, sex, type of OI according to Sillence classification, clinic admission, ward admission, signs and symptoms, bisphosphonate therapy and the discipline, and the surgical/non-surgical therapy.

RESULTS

The results from the database show that the illness of 13 patients is diagnosed as osteogenesis imperfecta in 2 years.

Table 1. Patients data registered in the hospital year 2020–2021

Patient Number	Name	Age (on Jan 1, 2022)	Sex	OI Type (Sillence)	Examined at Clinic		Ward Admission
					Orthopedic	Non-Orthopedic	
1.	ANK	9 y	F	4	Yes	Pediatric	Yes
2.	AHZ	7 y	M	3	Yes	Pediatric, ENT-HN	Yes
3.	ARU	5 y	M	1	Yes	No	No
4.	MHN	3 y	M	4	Yes	No	Yes
5.	MDFA	10 y	M	1	Yes	Pediatric	No
6.	ANP	9 m	M	NM	Yes	Pediatric	No
7.	AAM	3 y	M	4	Yes	Pediatric	Yes
8.	RR	10 y	M	NM	Yes	No	Yes
9.	SAN	12 y	M	NM	Yes	No	Yes
10.	NP	30 y	F	NM	No	Internal Medicine	No
11.	RWA	3 y	M	4	No	Pediatric, ENT-HN	Yes
12.	SKA	3 y	F	1	No	Pediatric	No
13.	NFM	5 m	F	NM	No	Pediatric	Yes

Note: M: Male; F: Female; NM: Not Mentioned; ENT-HN: Ear Nose Throat-Head Neck

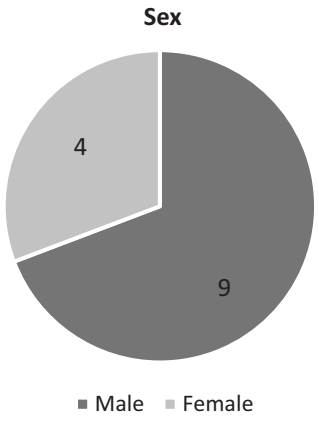

Figure 1. Pie chart of sex from registered OI patient

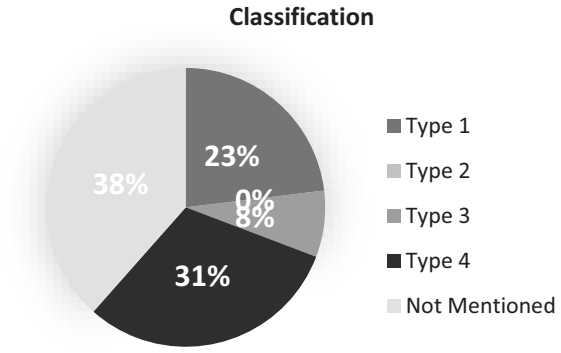

Figure 2. Pie chart of classification from registered OI patient

The age from Table 1 ranged from 5 months to 30 years (on January 1, 2022). Nine patients are male (69.2%) while four patients are female (30.8%) (Figure 1). There are 3 patients diagnosed as having OI type I (23.08%), 1 patient diagnosed as having OI type III (7.69%), 4 patients diagnosed as having OI type IV (30,8%), and 5 patients diagnosed as having OI but the type is unknown (38.46%) (Figure 2).

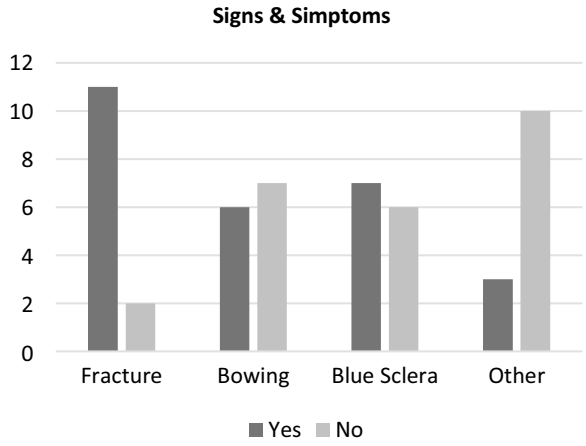

Figure 3. Bar chart of signs and symptoms from registered OI patient

From 13 patients, the most common signs and symptoms are fractures, bowing, and blue sclera (Table 2 and Figure 3). A total of 11 patients have fractures (84.62%), and 6 of them are multiple fractures (54.55%). There are 6 patients with bowing extremities (46.15%) and 7 patients without bowing (53.85%). There are 7 patients with blue sclera (53,85%) and 6 patients without blue sclera (46.15%). Other symptoms are dentinogenesis in 1 patient (7.69%), low nutrition in 2 patients (15.38%), bad nutrition in 1 patient (7.69%), and dwarf in 1 patient (7.69%). The most common bone to be fractured is the femur in 5 patients (45.45%), followed by the tibia in 3 patients (27.27%), fibula in 3 patients (27.27%), humerus in 3 patients (27.27%), and vertebrae in 1 patient (9.09%).

Table 3. Patient's treatment of osteogenesis imperfecta

Patient Number	Bisphosphonate		Treatment	
	Given	Time Acceptance	Surgery (ORIF/TENS)	Non-Surgery
1.	Yes	Irregular	Yes	-
2.	Yes	Irregular	No	U-slab
3.	Yes	Irregular	Yes	-

Table 2. Patient's signs & symptoms of osteogenesis imperfecta

Patient Number	Signs/Symptoms				
	Fracture	Bowing	Blue Sclera	Other	Bone Fracture
1.	4x	Yes	Yes	Dentinogenesis, low nutrition, dwarf	Femur R/L
2.	1x	Yes	Yes	Bad nutrition	Humerus L
3.	4x	Yes	Yes	Low nutrition	Tibia R, Fibula R
4.	1x	Yes	No	-	Humerus L
5.	11x	No	Yes	-	Humerus L, Tibia R
6.	2x	Yes	No	-	Femur R, Fibula R
7.	-	Yes	No	-	-
8.	1x	No	Yes	-	Neck Femur R
9.	1x	No	No	-	Subtrochanter Femur L
10.	1x	No	Yes	-	Vert Th11-L1
11.	6x	No	No	-	Femur R
12.	2x	No	Yes	-	Femur R, Tibia L, Fibula L
13.	-	No	No	-	-

Note: R: Right; L: Left

Table 3. Patient's treatment of osteogenesis imperfecta (Cont.)

Patient Number	Bisphosphonate		Treatment	
	Given	Time Acceptance	Surgery (ORIF/TENS)	Non-Surgery
4.	Yes	Regular	No	-
5.	Yes	Irregular	Yes	LAS, LAC, LLC
6.	Yes	Regular	No	-
7.	No	-	No	Conservative
8.	Yes	Irregular	Yes	-
9.	No	-	Yes	-
10.	No	-	No	Physiotherapy
11.	Yes	Irregular	Yes	-
12.	No	-	Yes	Hemispica Cast, LLC
13.	No	-	No	Conservative

Note: LAC: Long Arm Cast; LAS: Long Arm Slab; LLC: Long Leg Cast

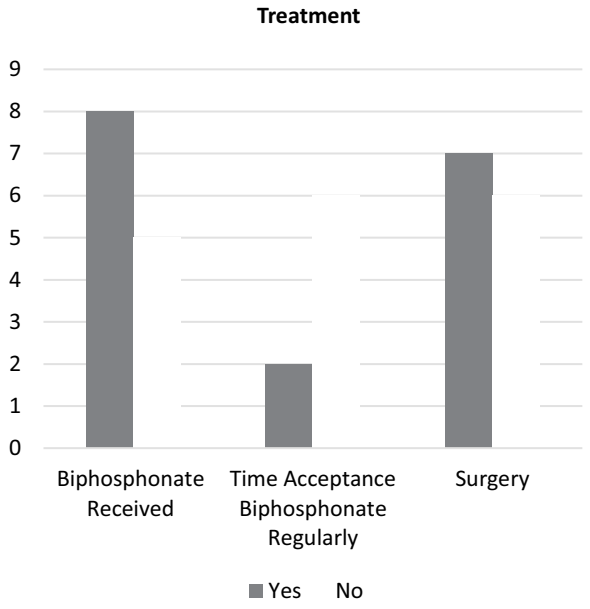

Figure 4. Bar chart of treatment from registered OI patient

Of 13 patients in Table 3 and Figure 4, 8 patients received bisphosphonate therapy (61.54%). Of those 8 patients, only 2 patients (25%) received routine bisphosphonate as their schedule while 6 patients (75%) did not get therapy regularly. A total of 7 patients performed surgery as ORIF/TENS (53,85%), and 6 patients (46,15%) performed non-surgery treatment in their fractures as cast, slab, splint (bone other than the surgery bone if they are multiple fractures with surgery treatment), conservative, or physical therapy.

We can see illustrations of patients in this study with OI from the X-ray radiograph. Figure 5 shows a radiograph patient with both thigh and leg bowing. Figure 6 shows a radiograph patient with bowing in his both thigh and a fracture in his left femur that was treated conservatively with a hemispica cast. Figure 7 shows a radiograph patient with bowing in his both upper arm and a fracture in his right humerus treated with an intramedullary nail and a fracture in his left humerus treated with closed reduction and U-slab. Figure 8 shows a radiograph patient with bowing in both thighs and fracture in both femurs treated operatively, in which the right femur was treated by ORIF with plate and screw, and the left femur was treated by ORIF with a rush nail. Figure 9 shows a radiograph patient with bowing in his right leg and a fracture in his tibia-fibula treated operatively. He was treated by ORIF with TENS for the fibula. The right picture shows the radiograph vertebra from one patient. It shows scoliosis with the abnormal shape of the vertebra (Appendix).

DISCUSSION

From the results above, we will discuss the sex, classification, signs and symptoms, bisphosphonate therapy, and treatment for the fracture.

Sex

In this study, the number of male patients is higher (69,2%) than that of females (30.8%).

It is different from what Lindahl *et al.* mentioned that gender distribution was not skewed significantly (7). Martin *et al.* Shapiro also supported that OI occurs worldwide without gender preference (8).

The number of male patients is higher than that of females in this study due to the X-linked chromosomal inheritance. Male patients (hemizygous) are usually more severe because of osteoporosis, but female patients (heterozygous) may be asymptomatic. However, most male patients have mild OI in the OI spectrum (9).

Classification

According to Sillence's classification in this study, OI type IV is the most common (30.8%), followed by OI type I (23.08%) and OI type III (7.69%). Other OI did not mention the type (38.46%).

It is different from Lindahl *et al.* who mentioned that the distribution of OI from the Swedish pediatric population was 70% in type I, 12% in type III, and 18% in type IV. Sequencing is more expensive and can make a bias, causing more frequent referrals for genetic testing (7).

Type V in the literature was not found in this study. Zhytnik explained that patients with OI type V are described to mimic symptoms of OI type IV with moderate severity of long-bone deformities, vertebral compression fractures, scoliosis, and the same number of fractures. However, unlike type IV, patients with OI type V were claimed not to develop dentinogenesis imperfecta or blue sclera. Recent studies have introduced variability in the OI type V phenotypes, which has been expanded with phenotypes mimicking OI type I and III (10).

Signs/Symptoms

The most common signs/symptoms are fracture (84.62%) and blue sclera (53.85%). The most common bone to be fractured is the femur (45.45%).

Osteogenesis imperfecta (OI) is characterized by susceptibility to fractures and increased bone fragility. Bone fragility and risk of fracture increase in the order of Type 2> Type 3> Type 4.5> Type 1 (11). Lindahl *et al.* mentioned that BMD does not account for bone quality in OI (7). This study supported Storoni et al that mentioned bone fragility as the most common patient issue. In addition, the disease also affects extraskeletal tissues in the form of dentinogenesis imperfecta, hearing loss, and cardiopulmonary disease. These can severely affect OI patients' quality of life and life expectancy due to a decline in function capabilities, well-being, and subsequent

morbidity (12).

Blue sclera was reported at about 80%. There was no association between gender and blue sclera. Patients with a COL1A1 null allele had blue sclera. The blue sclera is more common in individuals with collagen I mutations than those without in OI types III and IV. In 2010, Rauch et al. reported that N-terminal helical mutations in COL1A1 (not COL1A2) were associated with blue sclerae and C-terminal helical mutations were associated with Dentinogenesis Imperfecta in both genes (13). Mild phenotypes will not necessarily be detected until later in life (7). OI adults tend to develop femur fractures and non-unions. Especially in type 4 OI adults treated for shaft fractures conservatively, they have a high risk of non-unions (11).

Bisphosphonate Therapy

A total of 61.54% of patients received bisphosphonate therapy, but only 25% received routine bisphosphonate as their schedule while 75% did not get routine therapy.

Bisphosphonate treatment aims to increase bone strength and decrease the number of fractures (8). Bisphosphonates are the most promising pharmacologic therapy routinely used for OI. The research consistently shows bone mineral density (BMD) improvements in OI patients. Bisphosphonates act by inactivating osteoclasts. The cells break down bone tissue and inhibit bone resorption (14).

Oral alendronate compared to intravenous pamidronate in a large multicenter trial concludes that bone density improves following oral alendronate. However, some children with OI types III and IV are described as unresponsive to intravenous pamidronate. The reasons for this difference are not clear (8).

In this study, 75% of patients who received bisphosphonate did not get therapy routinely because there is a long wait for the treatment of bisphosphonate that is given at the same time. Martin et Shapiro explain some factors of why bisphosphonate treatment is difficult; they are (1) uncontrolled studies; (2) different bisphosphonates, doses, and schedules; (3) varied calcium and vitamin D supplements that are recommended (8).

In this study, the authors used Bisphosphonate as a therapy. It's supported by Ruggiero that explained the mechanism of action is based on the increase in the level of bone mineralization through the inhibition of osteoclastic activity and the induction of osteoblastic activity. Recent studies also attribute bisphosphonates an antineoplastic activity, due to the ability of these drugs to inhibit neo angiogenesis, inhibiting the proliferation of endothelial cells. Bisphosphonates have several common properties, including poorly absorbed orally, high affinity for bone minerals, inhibitory effects on osteoclastic bone resorption, prolonged bone retention, and elimination in the urine. However, Bisphosphonates have serious side effects such as hypocalcemia, renal impairment, and aseptic osteonecrosis of the jaw (15).

Treatment of Fracture

There were 7 patients performing surgery as ORIF/TENS (53.85%), and 6 patients (46.15%) performed non-surgery treatment in their fractures as cast, slab, splint (bone other than the surgery bone if they are multiple fractures with surgery treatment), conservative, or physical therapy.

Like a case reported by Hastopraja Nasution, they reported a young woman that may have OI type 1, treated by surgery following rehabilitation. They mentioned one of the treatments for the fracture is internal fixation. The rods are inserted in the bone marrow canal in the center of the long bones and are used to align and stabilize fractures (16).

Surgery at a young age is often important to improve growth and quality of life. Osteogenesis imperfecta patients require an interdisciplinary treatment from both medical and surgical components. Hidalgo and Green recommend osteogenesis imperfecta treatment with bisphosphonates before surgical intervention and using Fassier-Duval rods in a surgical setting to correct lower extremity deformities and fractures (17).

Intramedullary nailing is the standard treatment in case of a femoral shaft fracture in non-OI adults, which provides the advantages of optimal mechanical stability, efficient load transfer, minimization of stress concentration, preservation of soft tissues, fracture hematoma, and periosteal blood supply, and early mobilization of hip and knee (11). Limiting excessive immobilization to reduce secondary disuse osteopenia as well as excessive muscle weakness is very important in OI. Plate fixation should also be avoided because of the risk of secondary fracture events (18). A multidisciplinary approach is essential for the management of OI including counseling and genetic analysis, medical treatment, orthosis application, rehabilitation, and surgical intervention (19).

Osteogenesis imperfecta (OI) is a bone dysplasia, heritable, and characterized by long bone deformities and bone fragility. In this study, the quantity of male patients is higher than that of females, the OI type IV is the most often to be found, the most common signs/symptoms are fractures and blue sclera, and the most common bone to be fractured is the femur. More than half of patients received bisphosphonate therapy, but only a quarter received it routinely. More than half of patients performed surgery as the treatment of fractures. Osteogenesis imperfecta patients require an interdisciplinary and tailored treatment that involves both medical and surgical components.

ACKNOWLEDGMENT

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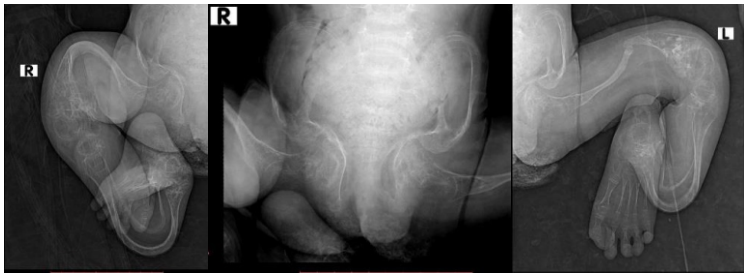

Figure 5. A radiograph patient with bowing in his both thigh and leg

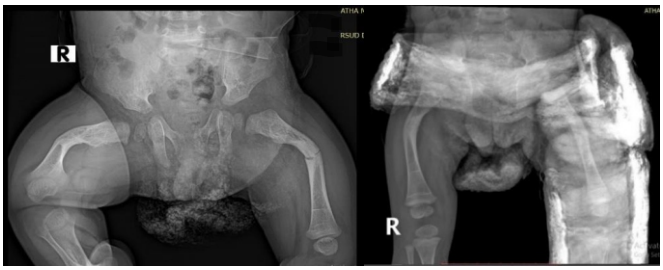

Figure 6. A radiograph patient with bowing in both thighs and a fracture in his left femur was treated conservatively with hemispica cast.

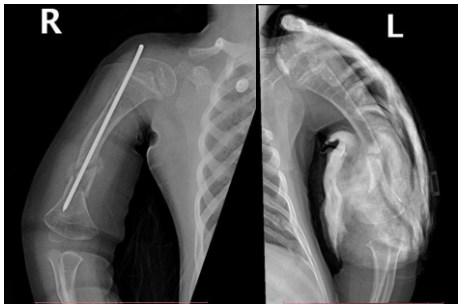

Figure 7. A radiograph patient with bowing in his both upper arm and a fracture in his right humerus was treated with an intramedullary nail and a fracture in his left humerus was treated with closed reduction and U-slab

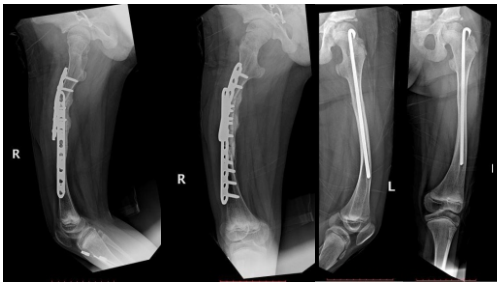

Figure 8. A radiograph patient with bowing in both thighs and a fracture in both femur were treated operatively. The right femur was treated by o with a plate and screw, and the left femur was treated by orif with a rush nail.

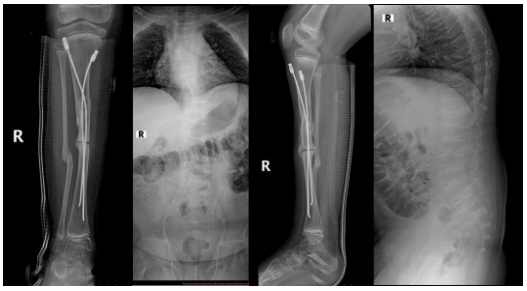

Figure 9. A radiograph patient with bowing in his right leg and a fracture in his tibia-fibula was treated operatively. He was treated by ORIF with TENS for the fibula. The right picture shows the radiograph vertebra from one patient. It shows scoliosis with the abnormal shape of the vertebra.