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ASSESSMENT ON MICROSTRUCTURE OF BONE WITH OSTEOGENESIS IMPERFECTA USING MEDICAL IMAGING TECHNIQUES: A REVIEW

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ABSTRACT

Osteogenesis imperfecta (OI) is a genetic disease which affecting the bones. In a severe case, this disease can cause the death to the patients. The microstructure of OI bone tissue can be oberseve by variation of imaging technique such as Computer Tomography (CT) scan, Scanning Electron Microscopy (SEM), Fourier Transform Infrared spectroscopy (FTIR) and Magnetic Resonance Imaging (MRI). The observation on microstructural behaviour of OI bone tissue allows more finding on the orientation and behaviour of the damaged tissue in OI. OI bone tissue appears to have less bone mineral density (BMD) than in control group. This information helps in providing the suitable treatment needed by OI patients such as bisphosphate therapy (BP).

Keywords: osteogenesis imperfect, imaging technique, microstructure.

1. INTRODUCTION

Osteogenesis imperfecta (OI) is a genetic disorder which mainly affects the bone. It is also known as Lobstein's disease, brittle-bone disease, blue-sclera syndrome, and fragile bone disease is a generalized disease of connective tissue where it involved any or none blue sclerae, triangular facies, macrocephaly, hearing loss, defective dentition, barrel chest, vertebral compression and scoliosis, limb deformity and fracture, joint laxity and varying degree of growth retardation [1] [2]. The disease was first discovered by Lobstein in 1835 who identified and understand both the aetiology and pathophysiology of the disease [1], [3]. To date, it was reported that osteogenesis imperfecta could affecting approximately 6 or 7 per 100,000 people and occurring in approximately 1 in 20,000 births with no gender dependence or race dependence [1].

Gene mutation which leads to damaged collagen formation or degradation in collagen formation will cause the low bone mass and high bone fragility which can be observed in all cases related with osteogenesis imperfecta diseases [1]. Bone mainly made up of collagen where type I collagen is the most abundant which cover up almost 95% of the entire bone formation [4]. Type I collagen is the result of cross link between two main gene named collagen type 1 alpha 1 (COL1A1) and collagen type 1 alpha 2 (COL1A2) where the alteration in one of these two genes will lead to abnormal structure collagen produced in bone where it causes low bone mass and bone fragility [5]. It was reported that average bone mineralization density likely to be greater in OI bone compared to normal bone [6].

Generally, OI can be classified into four main type consist of type I, type II, type III & type IV. Type I is the mildest type among other types where it is considered as non-deforming with little or no deformity. The main feature which can be observed in type I are little bone fragility, blue sclera, onset of fracture during childhood but dramatically decrease after puberty. Type II is the most severe where the death normally take place during in uterus due to bones crushed between the thumb and forefinger or within 24 hours of birth as result from the respiratory failure. Other features that can be classified into type II are concertina femur, beaded ribs and dark blue sclera. Type III can be distinguish through its feature such as progressive deformity of long bones and spine from the childhood into adult life, short stature, bluish sclera and hearing problem [3]. Type IV showed feature as sclerae, bone fragility and normal hearing [7].

Studying the microstrucutre behavior of OI bone tissue is one of the appoach used for better understanding and help to provide more information on the characteristics and mechananical properties of the bones. Most of the time, this microstructure imaging studies perform through medical equipment such as Computer Tomography (CT) scan, Scanning Electron Microscopy (SEM), Fourier Transform Infrared spectroscopy (FTIR) and Magnetic Resonance Imaging (MRI). These imaging tool used to assess the micro size level deep into the body system to provide more detail image resolution on the actual condition of the osteogenesis imperfeta bone. In fact, those techniques discuss above are able to provide the mechanical structure behaviour such as bone mineral density and tissue mineral density to better understanding on the mechanical properties of OI bone. Generally, different types of OI can be distinguish physically based on the outer appearance possess by OI patients, however these imaging microstructural studies contribute on the how the structure and organization of the tissue structure in the highly complex hierarchical of the composite bone material in OI behave. In addition, it helps the doctors to provide the suitable care based on the severity of the disease.

Computer Tomography (CT) scan produce the high quality image which enable a 360° view of the internal organ prodvide more detail image orientation of organs, bones, soft tissue, and blood vessel. Thus, it can be guidance to diagnose diseases such as cancer,

muscleskelaton disorder nor infectious disease. For OI diseases, the image produced illustrated the severity bowing angle of bending bones. On the other hand, FTIR allow the observation on tiny molecule of body tissue to indentify the presence of abnormalities in the tissue. SEM is a technique used where a sample is scan under focus electron beam and deliver the detail of the image. On the contrary, MRI uses a powerful magnet and radio waves to create high resolution cross sectional image of soft structure inside the body. This technique enables to analyse bone and joint problems.

This paper presents on the review of various imaging technique used to observe the microstructural and microarchitectural on OI. It will highlight on how these different technique provide the detail on micrsostrucutral parameters of the OI bone struture.

2. COMPUTED TOMOGRAPHY (CT) SCAN

Computed tomography (CT) scan is one of the highly-favoured methods used in medical specially to observe the microstructure behavior of OI bone due to its adjunctive problem-solving.

To study the bone mineral density (BMD) and bone microstructure on OI bone, Jameson *et al* used micro-computed tomography (μCT) for the 3D analysis of lower extremity long bones [8]. Eight bone fragments obtained from five OI patients Type III and Type IV. Three out five patients had been given bisphosphonate drug therapy prior to the experiment to improve the bone mass. The result from μCT showed that the OI trabecular bone have less organized architecture. BMD result with a median of 339.3 mg/cm^3, however, unable to relate the correlation between severity and bone mineral metrics. Somehow it appears to be those patients who been received drug therapy prior to the experiment showing some increment in BMD, bone mineral content (BMC), bone volume fraction (BV/TV), trabecular number (Tb.N) and connectivity density (Eu.Conn.D). On the other hand, it was observed that connectivity density and trabecular number were highly correlated (R^2 =0.81) which indicates its relationship with level of severity in OI. In a follow-up study, through μCT to investigate the OI bone structure, mineralization, and strength and to distinguish the porosity in lower extremity long bone, Jameson *et al* found that OI bone rise dramatically in cortical porosity, canal diameter, and connectivity [9]. The bone specimens were collected from 13 OI patients of Type I, Type III and Type IV and 5 healthy subjects act as control group. Microstructural parameter including volumetric tissue mineral density (TMD), canal connectivity density (Ca.ConnD), canal separation (Ca.Sp), canal diameter (Ca.Dm), canal surface to tissue volume (Ca,S/TV) and cortical porosity (Ca,V/TV) were observed through μCT with a synchrotron light source. Both control group and OI bone were seen to be statistically significantly ($p<0.05$) in all the microstructural parameter which implied that there is a wide range of heterogeneity in the pore network. In addition, OI bone saw an increase in cortical porosity, canal diameter, and connectivity. Nonetheless, among all the OI types group, there were no clear trends observed as the radiography image showed almost the similar pattern orientation of the microstructural arrangement. In comparison with others three OI groups, Type I OI exhibits the highest cortical porosity where indicated the low elastic modulus. However, a recent nanoindentation study conducted by Albert *et al* claimed that the elastic modulus was found to be 7% higher in OI Type I rather than other OI types [6]. This finding seems contrasted with the current result which lead to suggestion that there might be some material level adaptation in Type I as proposed by the James.

In a study which set out to investigate the structural and mechanical properties of OI bone treated with bisphosphonates (BP) comparing to control group, Imbert *et al* used high-resolution computed tomography (HR-pQCT) on long bone for both OI patients and healthy subjects [10]. It was discovered that BMD in OI patients was somewhat lower with a mean of 0.819 gHA/cm^3 than in control group of mean 0.952 gHA/cm^3. Reinus *et al* mentioned that an increase in porosity eventually cause a decrease in BMD is proven in this study [11]. In contrast, tissue mineral density (TMD) was found to be higher in OI bone with a mean value of 1.103 gHA/cm^3 than the control group (0.988 gHA/cm^3). This might be related to the BP treatment which is believed to increase the mineral density [12]–[15]. This result comes to the same agreement with Roschger *et al* and Boyle *et al* where OI bone is more mineralized than normal bone [16] [17]. Vascular intracortical porosity also showed a significantly higher in OI bone with a mean of 25.4% compared to 3.6% in control group. It comes to conclude that the OI bone fragility mainly affected by both tissue quality and porosity.

Similarly, to analyze the relationship between mechanical properties and structural parameter, Albert *et al* conducted an experiment involving 12 cortical bone specimens from nine OI patients of diaphysis long bone, both femur and tibia of OI Type I, III and IV using μCT oriented either longitudinally or transversely [18]. Mean volumetric tissue mineral density was found to be 1.63 g/cm3 (standard deviation 0.14 g/cm3). There was unusually high intervascular porosity detected within the range of 3% - 42% among all the bone specimens. This comes to no surprise as previous study also obtained similar observation [10]. As mentioned in the current study, the location for measurement was a slightly far from the microstructure bone where usually contain smaller pore of flaws such as microda mage and osteocyte lacunae which unlikely to effect on the high porosity count. In fact, it was pointed out by several previous studies that the dimension of 1 μm in thickness and 100 μm in length/width in cortical bone, will cause less than 0.5% of the total bone volume [19]-[22]. A negative correlation was found between the vascular porosity and longitudinal plane, while in the transverse plane, however, those relationships were not statically correlated. This finding is similar to the previous study by Dong and Guo where the cortical porosity was not significantly correlated with transverse tensile and shear moduli [23]. These results reflect that those properties are more anisotropic

along the longitudinal plane compared to the transverse plane.

To assess the bone microarchitecture and volumetric BMD, Kocijan et carried out HR-pQCT technique on 30 OI patients ranging from mild to severe (Type I, Type III and Type IV) and 30 healthy persons at the ultra-distal radius and distal tibia [24]. It was observed that in the tibia, cortical volumetric BMD was found significantly higher in control group than Type I, III and IV patients. In opposite, a lower trabecular volumetric BMD was reported in Type I, III and IV OI than in control. This situation suggesting that high mineralization process occurs in cortical bone more than trabecular bone. Bone volume fraction (BV/TV) and bone trabecular number (Tb.N) observed to be significantly lower in OI Type I, III and IV compared to control ($P<0.001$). In addition, it has been noticed that compared to control group, the cortical thickness seems to be thinner in OI Type I but the cortical thickness does not appear the same in OI Type III and IV. The bone cortical thickness and intracortical porosity play a major role when it comes to bone fragility [25], [26]. This result indeed reflects how much the severity altered in OI patient ranging from mild OI Type I to moderate and severe OI Type III and IV.

Louis-Nicholas *et al* and Folketad *et al* investigated the bone mechanical properties of OI Type I and compared to normal control group [27] [28]. Louis-Nicholas *et al* in his study performed HR-pQCT on 30 OI type I patients and 30 healthy subjects. The scan was conducted on left tibia at 4% and 14% sites of tibia length which indicate the location of metaphysis the growth plate and metaphyseal-diaphyseal sites respective while muscle density and muscle size determined at 66% sites of tibia considering the calf muscle reached its maximum cross-sectional area [27]. It showed that tibia bone mineral content (BMC) at 4% and 14% were observed to be lower in OI type I patients with a value of 157 mg/mm and 132 mg/mm than a healthy subject with 200 mg/m and 161 mg/mm respectively. Total cross-sectional area (CSA) in OI type I and control group at 4% and 14% were shown on Table-1. These results suggest that the muscle bone strength between healthy group and OI Type I are almost identical, thus showed that OI Type I is the mildest type among all types. The cross-sectional study by Folketad *et al* showed that a lower volumetric BMD, altered bone microstructure, and altered bone geometry was found in OI Type I which contribute to an increased risk of bone fracture [28]. The study involving 39 OI Type I patients compared to age and gender-matched with 39 healthy people. Areal BMD in OI was 8% lower at the hip and 13% lower at the spine compared to control group. Trabecular volumetric BMD is 38% lower in tibia for OI patients. Cortical bone area was 18% lower in tibia in OI than control group. It was observed the number of trabeculae also low in OI group. Cortical bone area slightly low in the tibia of OI Type I patients, however, there is no differences in the total bone area and trabecular bone area as assessed through HR-pQCT method between both group. Besides that, OI Type I exhibit a thinner cortical bone, but the cortical porosity was noticed to be same with the control group. This result comes in agreement with previous study where the cortical bone in OI Type I seems to be thinner [21]. The high porosity in OI type I was because of the limitation of HR-pQCT to assess the smaller pores size differences [28] . In fact the BP treatment might cause the decrease in cortical porosity and an increase in BMD, trabecular and cortical thickness and total bone volume, where there is no exception in this study since the OI patients were treated with BP therapy [29]-[31].

A case study approach was used to allow a deeper insight into mechanical properties of OI bone especially Type II as conducted by Plachel *et al* [32]. In 2015, Plachel *et al* presented a case of a 33 years old male suffering from multiple fractures and typical radiographical and clinical characteristic of OI Type III. Through HR-pQCT method to analyze the severity of the bone fracture, a normal total volumetric BMD and a high cortical volumetric was recorded at the tibia. Furthermore, a high cortical thickness of 1.35 mm and high heterogeneous of trabeculae detected at tibia (0.716mm). Due to deformities of long bones and multiple fractures, these findings suggest the diagnosis of clinically severe OI Type III. To date, however, none study been done on OI Type II maybe because due to its nature where this type is considered to occur during pregnancy and even if the child is to be born usually would be able to survive even for a week. As an example, a case study reported by Akizawa1 *et al* involving a 32-year-old Japanese woman who is at 19 gestational weeks was observed to carry a fetus suffering from OI Type II [33]. A 3D CT images reveal a collapse and bowed long bone, a rib fracture and calvarial fracture which all lead to OI Type II symptom. The couple was given the advice to abort the baby as the best option. The fetus was then being observed to have curved limb and noticeable to be shorter compared to the normal fetus at the same age as can be seen in Figure-1. Table-1 summarize the CT scan techniques based on previous studies.

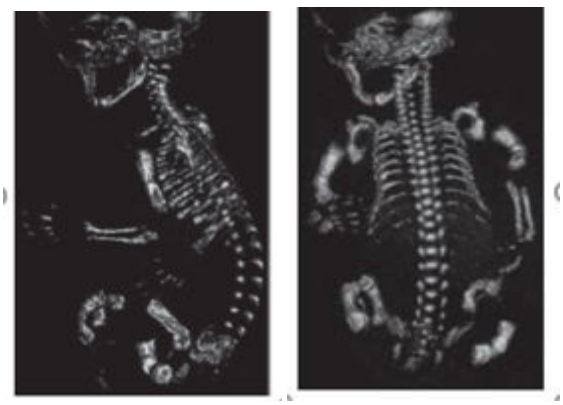

Figure-1. 3D CT of OI type II fetus with curved limbs. (a) side view: (b) front side [33].

Table-1. Recent studies on assessment of OI bone microstructure using CT scan techniques.

Study	No of samples	Type of CT	OI type	Anatomical site	Microstructural parameter observation	Finding
Jameson *et al* [8]	• 5 OI patients	µCT	• Type III • Type IV	• Femur • Tibia	• BMD result with median of 339.3 mg/cm^3 • Connectivity density and trabecular number highly correlated (R^2 =0.81)	• OI trabecular bone has less organized architecture • Patients with drug therapy treatment have high BMD, bone mineral content (BMC), bone volume fraction (BV/TV), trabecular number (Tb.N) and connectivity density (Eu.Conn.D) compared to those without the treatment.
Jameson *et al* [9]	• 13 OI patients • 5 healthy subjects	µCT	• Type I • Type III • Type IV	• Femur • Tibia • Humerus	• OI bone and control group statistically significant difference ($p<0.05$) in all microstructural parameter • OI bone saw an increase in cortical porosity, canal diameter, and connectivity.	• OI bone is more isotropic due to its high variability orientation of pores parallel to the direction of osteons.
Imbert *et al* [10]	• 5 OI patients • 3 healthy subjects	HR-pQCT	• Type I • Type III • Type IV	• Femur • Tibia	• Mean BMD ▪ OI = 0.819 gHA/cm^3 ▪ Control = 0.952 gHA/cm^3 • Mean TMD ▪ OI = 1.103 gHA/cm^3 ▪ Control = 0.988 gHA/cm^3 • Mean vascular intracortical porosity ▪ OI = 25.4% ▪ Control = 3.6%	• OI bone fragility mainly affected by both tissue quality and porosity
Albert *et al* [18]	• 9 OI patients	µCT	• Type I • Type III • Type IV	• Femur • Tibia	• High intervascular porosity range of 3% to 42% • Negative correlation between vascular porosity and longitudinal plane. • Not statically correlated between vascular porosity and transverse plane • Mean volumetric tissue mineral density is 1.63 g/cm^3	• OI bone is more anisotropic along the longitudinal plane compared to transverse plan
Kocijan *et al* [24]	• 30 OI patients • 30 healthy subjects	HR-pQCT	• Type I • Type III • Type IV	• Tibia	• High cortical volumetric BMD in control group than Type I, III and IV patients. • Lower trabecular volumetric BMD in Type I, III and IV OI than in control • Bone volume fraction (BV/TV) low in OI Type I, III and IV compared to normal ($P<0.001$) • Bone trabecular number (Tb.N) low in OI Type I, III and IV compared to normal ($P<0.001$) • Cortical thickness thinner in OI Type I	• Severity level increase from OI Type I to OI Type IV to OI Type III
Louis-Nicholas *et al* [27]	• 30 OI patients • 30 healthy subjects	HR-pQCT	• Type I	• Tibia	• Bone Mineral Content ▪ OI type I at 4%=157 mg/mm ▪ OI type I at 14 =132 mg/mm ▪ Control at 4% = 200 mg/mm ▪ Control at 14% =161mg/mm • Cross Sectional Area ▪ OI type I at 4% = 652mm^2 ▪ OI type I at 14% = 270 mm^2 ▪ Control at 4% = 681mm^2 ▪ Control at 14% = 296mm^2	• Muscle bone strength are identical for control group and OI Type I group
Folketad *et al* [28]	• 39 OI patients • 39 healthy subjects	HR-pQCT	• Type I	• Tibia	• Areal BMD OI < Control group • Trabecular volumetric BMD OI < Control group • Cortical bone area OI < Control group • Thinner cortical bone in OI ($p<0.05$) • Same cortical porosity in OI and control group ($p=0.75$)	• OI type I ▪ Lower volumetric BMD ▪ Lower trabeculae number ▪ Altered bone microstructure ▪ Altered bone geometry
Plachel *et al* [32]	• 1 OI patient	HR-pQCT	• Type III	• Tibia	• Total vBMD = 383.1 mg HA/ccm • Cortical vBMD = 968.0 mg HA/ccm • Cortical thickness = 1.35 mm • Heterogeneous of trabeculae high	• Diagnose with OI-III • Deformities of long bones • Multiple fracture

3. OTHER IMAGING TECHNIQUES (SEM, FTIR & MRI)

Others imaging methods including Scanning Electron Microscopy (SEM), Fourier Transform Infrared spectroscopy (FTIR) and Magnetic Resonance Imaging (MRI) are the technique used to observe and study the microstructure properties of OI bone. SEM provide the morphology and composition of the bone surface [34]. On the other hand, FTIR will characterize the chemical composition and bonding environment of the tissue constituents. Meanwhile, MRI provides the 3D images of the OI bone for more detail on bone geometry and microarchitecture.

In 2015, Katti *et al* used scanning electron microscopy (SEM) method to assess the microstructural of OI human cortical bone. A 20mm thick transverse section of the tibia was harvested from a 22 years old female suffering from OI Type I [35]. Through the SEM images, it was observed that all the medial, lateral, anterior and posterior section happen to experience the remodeling area with lateral, anterior and posterior seem to exhibit a larger remodeling area compared to medial. This is because these

three sections contain more Harvesian system with large resorption cavities. In addition, the anterior section appears to have less bone mass and more porous microstructural. Compared to lateral section, anterior, posterior and medial section contain fibrils bundles with a gap in one direction between adjacent lamellar. In contrast, lateral contains a bunch of mineralized fibrils position alternating within adjacent lamellae; however, both behaviors do resemblance to normal bone. Overall each section exhibits its own feature ranging from smooth microstructural to damaged area in OI bone specimen. Compared to all, the lateral section seems to exhibit more normal area. In the same study, Katti *et al* observed the microstructure and molecular composition of OI bone through Fourier Transform Infrared Spectroscopy (FTIR) [35]. They reveal that the anatomical section does have an effect on nanomechanical properties of OI bone. The FTIR images showed the anterior section of OI bone appears to be more heterogeneous as it is very porous and contains more non-collagenous proteins compared to others section. In contrast, the posterior section of OI bone seems to exhibit the same nanomechanical properties with the anterior section of normal bone. In addition, the result also showed that the nanomechanical properties of interstitial lamellae are greater than osteonal lamellae. Hence it can be concluded that the variation in nanomechanical properties correspond to its anatomical section showed the genetic mutation occur in OI bone and effectively cause the different microstructure behavior which eventually will cause the bone to be fractured.

Chunju *et al* run an experiment on OI Type I patients to study the mineral crystal structure, molecular differences, ultrastructure and nanomechanical properties using SEM [36]. The experiment target on the lower extremity of long bone harvested from a 22 years old female patients. SEM was performed on the transverse and longitudinal plane of OI bone specimen. The SEM result showed that particle and fiber in OI bone structure a bit loose and a weaker interaction which indicate the fragility of the OI bone itself. Apart from that, the OI bone specimen were noticed to have large porous structure, irregular osteons and large Haversian canal channel. This observation is in agreement with the previous study conducted by Katti *et al* [35]. In addition, it was noticeable that OI bone have abnormal collagen fiber hidden under crevices and abnormal deposition of the mineral region as a separate cluster. Together, this study clearly showed the unstable and weakened of OI bone microstructural behavior. In the same study, Chunju *et al* explained the structural and molecular of OI tibia bone Type I compared with the healthy bone through FTIR images. The images showed that OI bone contains abnormal collagen molecules than healthy bone which causing the effect on mineralization of OI bone [36]. This condition will ultimately lead to the altered material system that affects the bone remodeling process.

Pazzaglia *et al* used SEM to study the remodeling patterns and lamellar organization associated with major deformity [37]. In this study, osteon wedges are carried out to correct the long bone deformity in OI Type III. SEM is conducted on six osteotomy wedges obtain from the apex of tibia or femur angle compared to two cortical wedges of normal bone specimens. It was revealed that high percentage of nonosifed vascular area on OI bone with 44.3% compared to 13.6% in normal bone. In addition, OI bone show a high osteon total area, high central canal area, and high osteon bone area. In contrast, OI bone showed a low density of secondary osteons. These results suggested that abnormal remodeling pattern can possibly form from the result of altered load and tensile stresses on the deformed tubular bones.

A case study reported by Teng *et al* on the diagnosis of OI Type II using Magnetic Resonance Imaging (MRI) allowed a more detail on fetus bone geometry [38]. A 35 years old women who been found to have abnormal fetus development on her 22 weeks of pregnancy was further detected of suffering OI Type II of her fetus. The MRI images showed the multiple fractures, bowing and shortened bone observed. Through the cesarean section, the medical team was able to deliver the infant, however, due to respiratory issues and fracture all over the infant's bones, the infant was announced dead 10 hours' after postpartum. MRI diagnosis can be done to observe any abnormal fetus progress as the gestation starts at second-trimester with no radiation hazard to the fetus. The MRI diagnosis assists the parents and medical team to demonstrate the fetus condition in detail to the extent where it can help to detect the bone fracture. Table-2 sum up those mentioned techniques done previously.

Table-2. Other imaging techniques used on microstructural investigation of OI bones.

Study	No of OI patient	Type of imaging	OI type	Anatomical location	Microstructural observation
Katti *et al* [35]	• One	• SEM	• Type I	• Tibia	• Medial ▪ contain fibrils bundles with a gap in one direction between adjacent lamellar. • Lateral ▪ contains a bunch of mineralized fibrils position alternating within adjacent lamellae. ▪ display more normal area • Anterior ▪ have less bone mass and more porous microstructural ▪ contain fibrils bundles with a gap in one direction between adjacent lamella • Posterior ▪ exhibit a larger remodeling area. ▪ contain fibrils bundles with a gap in one direction between adjacent lamella
Chunju *et al* [36]	• One	• SEM	• Type I	• Tibia	▪ Particle and fiber bit loose and a weaker interaction. ▪ Have large porous structure. ▪ Irregular osteons. ▪ Large Haversian canal channel. ▪ Abnormal collagen fiber hidden under crevices. ▪ Abnormal deposition of the mineral region as a separate cluster.
Pazzaglia *et al* [37]	• Six (OI patients) patients • Two (Healthy subjects)	• SEM	• Type III	• Femur • Tibia	▪ Nonosifed vascular area 44.3%. ▪ High osteon total area. ▪ High central canal area. ▪ High osteon bone area ($p<0.001$, $p=0.028$, $p<0.001$ respectively). ▪ Low density of secondary osteons. ▪ Abnormal remodeling pattern can possibly from the result of altered load and tensile stresses on the deformed tubular bones.
Katti *et al* [35]	• One	• FTIR	• Type I	• Tibia	• Variation in nanomechanical properties indicates the genetic mutation occur in OI bone. ▪ Effectively cause the different microstructure behavior which eventually will cause the bone to be a fracture.
Chunju *et al* [36]	• One	• FTIR	• Type I	• Femur	▪ Contains abnormal collagen molecules. ▪ Causing the effect on mineralization of OI bone ▪ Altered material system that affects the bone remodeling process
Teng *et al* [38]	• One	• MRI	• Type II	• N/A	• MRI images showed the multiple fractures, bowing and shortened bone observed

4. CONCLUSIONS

Medial imaging is one of the well known techniques used to identify and to study on the bone microstrucutre and microarchitectural. It helps to provide a more detail and better image of the specific part in certain area. This is helpful especially for OI bone which is notable for its rupture and damage bone tissue. Thus these method is suitable to observed and analyse the connective tissue manifestations in OI. In conclusion, all the previous research discussed in this review do have some similarities where most of the researcher observed the chaarcteristic and properties of OI bone in different section to identify the diversity of the rupture bone structure.

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