On the pathogenesis of osteogenesis imperfecta:
Some insights of the Utah paradigm of skeletal physiology

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Abstract

The pathogenesis of osteogenesis imperfecta (OI) baffled physiologists and physicians for over a century. Most past efforts to explain it depended heavily on cell and molecular biology and on changes in the material properties of affected bones (an old idea that OI patients could not make enough bone erred). To such views the still-evolving Utah paradigm of skeletal physiology can add a model for bone and bones that depends on errors in three genetically-determined features. The errors include, 1,2) elevated “set points” of the strain-dependent thresholds that help to control how lamellar bone modeling and remodeling adapt bone strength, architecture and “mass” to the voluntary loads on load-bearing bones; 3) and a reduced modeling-rate limit for the appositional rate of the lamellar bone formation drifts that can increase bone strength, outside bone diameters, cortical and trabecular thickness, and bone “mass”. If only abnormalities #1,#2 occurred, that should limit the eventual strength, architecture and “mass” of load-bearing bones, while if only #3 occurred that should prolong or delay how long it took to achieve the above limits, but without changing them. Equally, in driving from New York to Boston, stopping at New Haven would prevent reaching Boston no matter how rapidly one drove (a limited trip). But by not stopping one could reach Boston by driving very slowly (a prolonged but not a limited trip). This model concerns general features of bone and bones in OI that would need study and explanation at the tissue, cellular and molecular-biologic levels. Other places and people must discuss any devils in the details, as well as collagenous tissue, auditory, dental and other problems in OI, and the effects of treatment on the above features.

Keywords: Biomechanics, Bone, Fractures, Set Points, Modeling, Remodeling, Modeling-rate Limit

Introduction

This article would share with readers supplemental ideas about the pathogenesis of many bone features of OI (osteogenesis imperfecta). The ideas depend on insights into the Utah paradigm of skeletal physiology. That requires listing in Part II some bone features of OI that the Utah paradigm can explain plausibly, summarizing in Part III some pertinent features of that paradigm, and in Part IV presenting the paradigm’s explanations for the bone features in Part II. Table 1 defines abbreviations used below, and a short Glossary defines some terms.

II: Selected clinical-pathologic facts of OI

Below, a double asterisk (**) signifies a feature the Utah paradigm can explain plausibly (agreed, “plausibly” need not mean correct too).

1) OI has a genetic origin and is often but not always inherited*. A) Abnormal Type I collagens occur in most cases, B) but in some cases no abnormal collagens were found**. C) Different clinical Types of OI occur***. D) Different clinical Types of OI occur****.

2) Spontaneous fractures occur in OI and can affect both the spine and extremity bones**. “Spontaneous” means normal physical activities cause them, not any kind of trauma.

3) OI can occur in varied severities**. A) The more severe the disease, the younger the age at which spontaneous fractures appear**. B) In its severest forms fractures occur in utero and during vaginal deliveries***. Such infants seldom survive to adolescence and they make and/or keep little lamellar bone**, but they can produce abundant woven bone in fracture callus****. C) In some mild forms of OI spontaneous fractures only begin to occur in association with the
adolescent growth spurt**.

4) A) Spontaneous fractures usually decrease or stop in OI patients who reach skeletal maturity (around 16-20 years of age)**. B) In rare cases many bone features of OI may become apparent only in adult life**. Such a patient provided the first case of OI ever studied by dynamic histomorphometric analysis of tetracycline-labelled bone13. 

5) A) In OI, fractures of long bones like the tibia and femur can heal with angulations. B) X-rays of such angulated bones show evidence of the kinds of modeling drifts that could correct the angulations, but the drifts work too slowly to correct the angulations completely14**. Yet similar kinds of drifts can achieve complete or nearly complete corrections in normal children.

6) In OI patients who had reduced outside bone diameters in childhood, in adult life those diameters can finally approach if not reach normal values for otherwise comparable healthy people14**.

7) A) Increased volume-referent15 cortical and trabecular bone turnover and BMU-based remodeling occur in OI11,16**. B) Thus on OI increased BMU-based remodeling accompanies reduced bone modeling in the same bones at the same time**.

8) A) In children with OI, affected bones reveal an osteopenia characterized by less bone and weaker bones than normal, with reduced amounts of epiphyseal and metaphyseal spongiosa, and often with reduced outside bone diameter17 and thinned cortices14**. The reduced outside bone diameter would usually stem from reduced modeling-dependent expansion, not from periosteal bone losses**. B) In adults with OI, affected bones reveal an osteopenia with enlarged marrow cavities, thinned cortices, reduced amounts of spongiosa, and outside bone diameters that can approach if not reach normal**. C) The osteopenias in OI14,18 can reduce bone “mass” to 80%-40% of age-, bone- and sex-comparable norms11** (“mass” in quotes has its meaning in absorptiometry, not in physics).

9) Fractures heal well in OI, sometimes with excessive amounts of fracture callus12.

10) A) In many OI cases spontaneous fractures tend to affect the large bones in the lower but not the upper extremities **. B) Spontaneous fractures seldom affect finger and toe bones14*. C) Some children (and some adults) seem prone to frequent fractures without manifesting other recognized features of OI**. Many clinicians wondered if such patients had a very mild form of OI.

III: Pertinent features of the Utah paradigm

This summary concerns the physiology of healthy load-bearing mammalian bone and bones.

1) Modeling by formation and resorption drifts (not osteoblasts alone) increases whole-bone strength, in part by increasing bone “mass”, outside bone diameter and cortical and trabecular thickness5,19. “Whole-bone strength” distinguishes intact bones from bone as a material. Mechanically-controlled modeling normally turns on where bone strains exceed a modeling threshold range (MESm); otherwise it turns off.

The appositional rate of lamellar bone formation drifts (the thickness they can add to a bone surface in a day, month or year) has a “saturation limit”**. In the diaphyses of many mammals this modeling-rate limit (M-RL) lies in the region of 60 to 200 micrometers/month5,20. When something tries to make a formation drift exceed that limit, woven bone formation usually replaces lamellar bone formation. Woven bone drifts can add bone at well over 500 micrometers/month14. Reducing that M-RL should make modeling take longer to adapt bones to larger loads and strains by increasing bone strength and outside diameter (see Sections #7, #8 in Part III below).

2) BMU-based remodeling turns bone over in small packets but in two modes2. In its “conservation mode” BMUs turn bone over without appreciable net losses or gains. In remodeling’s “disuse mode” BMUs make less bone than they resorb so permanent bone losses occur, but only of endocortical and trabecular bone, and thus of bone next to or close to marrow2. This mode should cause all adult-acquired disuse-pattern osteopenias, which are characterized by losses of spongiosa and endocortical bone, and by marrow cavity expansion, cortical thinning and reduced whole-bone strength, but not by periosteal bone losses. When strains stay below a lower strain threshold range (the MESr) disuse-mode remodeling turns on2,21. As strains exceed that threshold mechanically-controlled remodeling begins to switch to its conservation mode. The centers of the MESm and MESr ranges can define their “set points”.

3) A) The modeling and remodeling thresholds make the largest bone loads control how bone modeling and remodeling affect whole-bone strength. Trauma excepted, muscle forces instead of body weight cause the largest bone loads (and strains)1,6, so muscle strength strongly influences whole-bone strength, especially during growth22-24. B) Sooner or later, lowering both thresholds should make bones stronger, since smaller loads and strains than before could turn modeling and conservation-mode remodeling on2. C) Sooner or later, raising both thresholds should cause a disuse-pattern osteopenia and weaker bones, since it would take larger loads and strains than before to make modeling increase bone strength and “mass”, and to make conservation-mode remodeling keep bone next to marrow4.

4) A) The modeling threshold (MESm) lies well below bone’s ultimate strength (Fx)3. By making healthy load-bearing bones stronger than needed for the voluntary loads on them, that arrangement would give such bones a strength-safety factor. Expressed as corresponding stresses (or unit loads), Fx approximately equals MESm could provide that factor’s value. Values cited in the Glossary suggest it approximately equals six in healthy young adult mammals2. B) Mildly raising only the MESm (so the M-RL is normal) should reduce a bone’s safety factor and make the bone proportionally weaker than normal relative to the peak voluntary loads
DEFINITIONS OF ABBREVIATIONS AND ACRONYMS

BMU: the basic multicellular unit of bone remodeling.
CIMI: cell-intercellular matrix interaction.
Fx: bone’s ultimate strength.
ICSE: intra- and/or intercellular signalling event.
M-RL: the modeling-rate limit for lamellar bone modeling formation drifts.
MDx: microdamage (microscopic fatigue damage) in bone.
MESr: the remodeling threshold strain range that helps to control the switching between disuse- and conservation-mode remodeling.
MESm: bone’s modeling threshold strain range, above which mechanically-controlled modeling turns on.
MESp: bone’s operational microdamage threshold.
OI: osteogenesis imperfecta.
ª: approximately equals; lies in the neighborhood of.

Table 1.

on it. This could increase fractures from low-energy trauma such as falls, and it might help to cause stress fractures not due to intensive physical activity or metabolic bone disease¹. A higher MESm should also limit the final correction of angulated malunions by modeling drifts. C) Making only the M-RL smaller (so the MESm and MESr are normal) should prolong how long it takes to increase whole-bone strength without limiting that strength. This phenomenon would retard modeling-dependent corrections of angulated fracture malunions. D) Equally, a small furnace would take longer than a large one to raise a room’s temperature to a higher thermostat setting, and that would take longer for large than for small rooms. Yet in each case the furnace would keep working until the thermostat indicated it had succeeded (see #9 in Part IV, and #1 in Part V). In that analogy the thermostat setting would be like the MESm set point, the furnace’s heating capacity would be like the M-RL, and the heat in small and large rooms (expressed in kilogram-calories) would be like the strength of small and large bones respectively.

5) Woven bone formation can depend on different kinds and/or intensities of stimuli than lamellar bone formation. Normally, woven bone is slowly removed if it does not carry significant mechanical loads; if it does carry them (as in healing fractures) lesser amounts of lamellar bone usually replace it¹⁴.

6) Repeated bone loads and strains cause microscopic fatigue damage (microdamage, MDx) that increases bone fragility. Large strains cause far more MDx than small ones¹. Normally remodeling BMUs can repair limited amounts of MDx¹³, but bone seems to have an operational MDx threshold (the MESp) such that strains above it can cause enough MDx to escape repair and begin to accumulate²⁵. Such accumulations can cause spontaneous fractures, stress fractures in athletes and special forces trainees, and pseudofractures in osteomalacia¹. Because the MESm normally lies below the MESp, modeling would normally make bones strong enough to limit MDx to amounts that remodeling BMUs can repair, which would tend to prevent spontaneous fractures¹³⁴. Most spontaneous fractures (including stress fractures) stem from accumulated MDx, so they are not really “spontaneous”³⁴. They usually affect lower more than upper extremity bones¹.

In principle six things could make MDx accumulate¹³: (i) reduced MDx detection and/or repair, (ii) reduced whole-bone strength due to inadequate modeling, so normal loads make strains exceed the MESp, (iii) reduced whole-bone strength due to excessive bone loss from disuse-mode remodeling, (iv) bone loads and strains that increase in size faster than the resulting MDx can be repaired, (v) a lowered MESp set point, (vi) or different combinations of (i-v).

7) During and shortly after the human adolescent growth spurt fractures from injuries tend to increase, but they decrease markedly near or after skeletal maturity⁷. This could stem from an increased adaptational lag in whole-bone strength as it adapts to growth-spurt-accelerated loading increases on bones from growing muscle forces and increasing body weight, presumably aided by the larger diaphyseal bending moments caused by the more rapidly increasing length of bones²⁵,²⁶.

8) A) The signalling mechanisms and cells that help to control all the above features now form separate fields of study¹⁶,²⁴,²⁵. B) The above physiology helps to explain how bone’s biologic machinery normally adapts a load-bearing bone’s strength to its peak voluntary loads, and why strong muscles would normally make strong bones and persistently weak muscles would usually make weaker bones. C) The above physiology also forms a subdivision of classical biomechanics that one might call “IO-biomechanics”, where “IO” signifies the skeleton’s Intermediary Organization, the realm of its tissue-level features and the current main focus of the Utah paradigm¹. D) Collectively the above features would form a mechanically-dedicated negative feedback system called the “mechanostat”²⁴,⁷,¹⁰. E) The relative roles in
the above things of genetics, humoral agents, muscle strength, aging, shear strains, strain-dependent signals and other features are under study.

IV: Synthesis

1) Three genetically-determined kinds of bone-physiologic errors in OI could combine to help to explain the facts listed in Part II above, 1, 2: Elevated MESm and MESr set points would limit final whole-bone strength, architecture (outside bone diameter, cortical and trabecular thickness, correction of angulated malunions), and bone “mass” 27. 3: A reduced M-RL for lamellar bone formation drifts would retard but not prevent achieving those modeling-dependent and remodeling-dependent final limits (Part III, Section #4C).

If those three abnormalities differed in severity in OI, that could help to explain its mild and severe forms (Part II, #3). If they could vary independently of each other that could help to explain some of the different Types of OI (Part II, #1C). How age and medications might affect those abnormalities needs study.

2) Abnormal collagens associate strongly with some genetically-determined skeletal diseases in which abnormal modeling of bone, collagenous tissue and/or cartilage occur. Besides OI, examples include Marfan’s syndrome, Ehlers-Danlos syndrome and some chondrodystrophies 9. That suggested skeletal modeling and remodeling responses to mechanical influences might depend on some kind of cell–intercellular matrix interaction 29. If so, disorders in that interaction in bone could help to raise the MESm and MESr set points and/or decrease the normal M-RL in OI. Those things would have predictable clinical, anatomical and radiographic effects described in some of the following sections. In principle an elevated MESm alone would tend to reduce outside bone diameter in affected children; an elevated MESr alone would let outside bone diameter increase in such children (because that is a modeling-dependent function) but it would cause severe cortical thinning due to losses of endocortical bone from disuse-mode remodeling.

3) In children with OI, an increased set point for the MESm and a reduced M-RL would reduce and delay increases in outside bone diameter, cortical thickness, whole-bone strength and bone “mass” (Part II, Section #8A).

4) The greater the MESm, and/or the smaller the M-RL, the younger the age at which their bone effects should become apparent (Part II, #3A). In the fetus a large set point increase and/or a very small M-RL could each sufficiently limit and/or retard increases in whole-bone strength to let developing fetal muscle forces cause intrauterine fractures, and to let vaginal deliveries cause fractures (Part II, #3B). Retarded bone strength increases would usually accompany retarded bone “mass” increases too (Part II, #8C).

5) A reduced M-RL and/or an elevated MESm could sufficiently retard and/or limit the correction of angulated malunions to let them persist throughout a child’s growth (Part II, #5B). In adults with OI, a reduced M-RL could let sluggish formation drifts keep increasing outside bone diameters after skeletal maturity, so the adult’s outside bone diameters could finally approach normal adult values (Part II, #6; also see Section #9C,D below).

6) An elevated MESr for turning conservation-mode remodeling on would let disuse-mode remodeling remove too much epiphyseal and metaphyseal spongiosa and too much endocortical bone. That would enlarge the marrow cavity and help to thin diaphyseal cortices. These phenomena, when combined with those in Section #5 above, should cause typical disuse-pattern osteopenias and increased bone fragility (Part II, #8A,B,C).

7) Reduced outside bone diameter and cortical thickness in long bones, and reduced amounts of spongiosa in vertebral bodies, would make normal muscle and other loads cause larger bone strains and more MDx. That would help to cause spontaneous fractures of such bones (Part II, #2).

8) That increased MDx should also increase the remodeling that tries to repair it in both cortical and trabecular bone (Part II, #7A).

9) A) A reduced M-RL could help to explain why some OI patients could develop spontaneous fractures in the larger bones of the lower but not of the upper extremities (Part II, #10A), and seldom in the small finger and toe bones (Part II, #10B). Why? To adapt properly to growing muscle and other loads assume the diaphysis of a child’s radius needed to increase in outside diameter by 0.5 mm/year, but the femur’s larger loads would require its diaphyseal diameter to increase by 1.0 mm/year. If the M-RL only allowed 0.7 mm/year to occur, the radius’s strength could keep up with growing mechanical demands, but the femur’s strength could not.

B) Ergo, a reduced M-RL could help to cause greater strength deficits and more spontaneous fractures in the femur and tibia than in the more slowly growing, smaller and less heavily loaded radius and ulna. Such strength deficits would exist relative to the size of the voluntary loads on a bone, and muscles cause the largest such loads 6. A reduced M-RL could also make spontaneous fractures occur much less often in the slowly growing and smaller finger and toe bones in OI (Part II, #10B) 3.

C) The smaller the M-RL, the earlier in life it should help to make spontaneous fractures occur (Part II, #3A). D) A mildly reduced M-RL plus the adaptational lag it would cause could help to make spontaneous fractures begin during or after the adolescent growth spurt instead of earlier, and then stop after skeletal maturity when muscle and body-weight loads on bones usually plateau (Part II, #3C, #4A).

In young adults, continuing slow increases in a bone’s outside diameter and strength could finally approach the needs of the plateaued mechanical loads (Part II, #6). E) The MESm set point and the M-RL might change independently of each other in different cases of OI. If so, in some OI Types the set point changes could be the major problem, in other Types the reduced M-RL could be the major problem, and
in still other Types each abnormality might contribute nearly equally to the cause of the bone features. Hence another basis for different OI Types (Part II, #1C), and perhaps a reason to reexamine their present classification.

10) The Utah paradigm can predict that some cases of OI could occur in the presence of normal kinds of collagen (Part II, #1B). How? Assume some cell-intercellular matrix interaction (CIMI) between bone matrix and its collagens on the one hand, with on the other hand some skeletal cells (osteocytes? bone lining cells?) helps to control bone’s modeling and remodeling responses to load-dependent strains. If so, cybernetic considerations suggest that monitoring strains of the intercellular bone matrix by some cell or cells should evoke several intra- and intercellular signalling events (ICSE) that eventually caused an appropriate bone modeling or remodeling response. Or:

\[
\text{CIMI} \rightarrow \text{ICSE}_1 \rightarrow \text{ICSE}_2 \ldots \rightarrow \text{ICSE}_n \rightarrow \text{Response}
\]

That idea has three interesting implications. (i) A genetic error in some “ICSE” event could have the same bone-architectural effects as a “CIMI” response to an abnormal bone matrix or collagen. If so, some bony features of OI could occur in the presence of normal bone collagens (Part II, #1B). (ii) Disorders in those “CIMI → ICSE” steps that developed in adults could explain why some OI features can appear in adults who seemed to have healthy bones in earlier life (Part II, #4B). (iii) Parenthetically, a similar phenomenon could explain some features of “idiopathic juvenile osteoporosis”.

11) Mild MESm set point elevations or/and M-RL decreases could reduce whole-bone strength (and a bone’s strength-safety factor) so little that no clinically-apparent problems occurred until the adolescent growth spurt, when the lag of bone strength relative to the accelerated increases in bone loads and flexural moments would fall farther behind mechanical needs than before. That decreased safety factor could increase fractures from low-energy trauma like falls, and make spontaneous fractures more likely too (Part II, #3C).

V: Comments, Conclusion

1) Why postulate a third defect as well as the MESm and MESr set point elevations suggested for OI in 1987? A) In principle and given a normal M-RL, elevated MESm and MESr set points should limit whole-bone strength similarly for all load-bearing bones relative to the size of the voluntary loads on them. That should tend to cause as many spontaneous fractures of upper extremity bones as of lower extremity bones, and of finger and toe bones too (yet those things are not always true). After skeletal maturity it should also make spontaneous fractures tend to continue at reduced rates but not stop (yet that is seldom true). B) An unusually small M-RL for lamellar bone formation drifts that accompanied elevated MESm and MESr set points could help to explain such “exceptions” (Part II, #10A,B).

2) Given a normal M-RL, a mildly elevated MESm might decrease bone’s strength-safety factor from say six, down to perhaps three. Such children (and adults) could have increased fractures from low-energy trauma without necessarily developing spontaneous fractures or other clinical features of OI (Part II, #10C).

3) To other proposed explanations for the bone features of OI that could each have merit, this article adds another that could also have merit. How aging, humoral agents, medications and other things might affect the MESm, MESr and MESp set points, MDx accumulations, and the M-RL are still unknown.

4) Some past explanations of OI proposed causative disorders in osteoblasts and/or osteoclasts, perhaps assuming that one did not need bone’s IO-biomechanics to explain those features. Nevertheless, in the same bone at the same time the osteoblasts and osteoclasts in modeling drifts and in remodeling BMUs can even respond oppositely to the same mechanical or endocrine influence. That occurs in OI too, where retarded modeling usually accompanies increased remodeling (Part II, #7B). Yet modeling and remodeling seem to use the same kinds of osteoblasts and osteoclasts in their work. It would seem difficult to explain the OI features in Part II without the IO-biomechanics in Part III. That excessive fracture callus can form in OI shows the old idea that osteoblasts in OI could not make enough bone erred (Part II, #9).

5) In conclusion: More than one hypothesis can explain most collections of facts, and in logic no hypothesis can invalidate another; only facts can do that. The above model and other ideas about the pathogenesis of OI are hypotheses, so more facts and help from others must determine their individual and relative merits.

Glossary

BMU: the Basic Multicellular Unit of bone remodeling that turns bone over in small activation-resorption-formation packets. In about 4 months a completed BMU turns over approximately 0.05 mm³ of bone. When it makes less bone than it resorbs, this tends to remove bone permanently, usually where bone touches or lies close to marrow. Healthy adult humans may create and complete about 3 million new BMUs annually, but in disease and some other circumstances that number can change over 5X.

Bone “mass”: here, the amount of bone tissue in a bone or skeleton, preferably viewed as a volume minus the volume of the soft tissues in the marrow cavity. In absorptiometry it does not mean mass as used in physics. It is often estimated as total body bone mineral content (TBBMC) by dual energy X-ray absorptiometry (DEXA), and sometimes by peripheral quantitative computed tomography (pQCT).

MDx: microscopic fatigue damage, known as microdamage when it occurs in bone, cartilage and collagenous tissue. megapascal: a force of one million Newtons applied to an area of one square meter. It would correspond to a unit load...
of M 0.1 kg/mm².

MESm: the genetically-determined Minimum Effective Strain range (or corresponding Stimulus or Signal) that can turn mechanically-controlled bone modeling on. Below it that modeling turns off. Its set point seems to center near 1000 (or 1500?) microstrain in healthy young adults. The 1000 microstrain value would correspond to a compression or tension stress of about 2 megapascals (or a unit load of about 2 kg/mm²). At that point woven bone formation usually also begins to replace lamellar bone formation.

MESr: the operational microdamage threshold. Above it more MDx can occur than its repair can cope with so it can begin to accumulate. It is a range, and its set point in lamellar bone seems to center near 3000 microstrain. That would correspond to a compression or tension stress of about 12 kg/mm² of bone).

unit load: the load on a unit cross section area of a bone. The unit area could = mm² or cm²; the load could = Newtons or kilograms of force.

References

14. A clinical and/or anatomical-pathologic observation by the author that proved consistent in the context cited, and which others probably recognized as such too so it need not be an original observation by the author. But in the past it was seldom thought important enough to deserve systematic study and a formal report.


