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# Current concepts in osteogenesis imperfecta: bone structure, biomechanics and medical management

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## Abstract

The majority of patients with osteogenesis imperfecta (OI) have mutations in the COL1A1 or COL1A2 gene, which has consequences for the composition of the bone matrix and bone architecture. The mutations result in overmodified collagen molecules, thinner collagen fibres and hypermineralization of bone tissue at a bone matrix level. Trabecular bone in OI is characterized by a lower trabecular number and connectivity as well as a lower trabecular thickness and volumetric bone mass. Cortical bone shows a decreased cortical thickness with less mechanical anisotropy and an increased pore percentage as a result of increased osteocyte lacunae and vascular porosity.

Most OI patients have mutations at different locations in the COL1 gene. Disease severity in OI is probably partly determined by the nature of the primary collagen defect and its location with respect to the C-terminus of the collagen protein. The overall bone biomechanics result in a relatively weak and brittle structure. Since this is a result of all of the

above-mentioned factors as well as their interactions, there is considerable variation between patients, and accurate prediction on bone strength in the individual patient with OI is difficult.

Current treatment of OI focuses on adequate vitamin-D levels and interventions in the bone turnover cycle with bisphosphonates. Bisphosphonates increase bone mineral density, but the evidence on improvement of clinical status remains limited. Effects of newer drugs such as antibodies against RANKL and sclerostin are currently under investigation.

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**Keywords:** osteogenesis imperfecta; collagen I; hypermineralization; fracture; bisphosphonates

## Introduction

Osteogenesis imperfecta (OI) is a genetic disorder also known as 'brittle bone disease'. The primary defect lies in the disturbance of the production and/or subsequent assembly of collagen type I by osteoblasts. Collagen type I is present in many tissues. As a consequence, mutations in the COL1A1 or COL1A2 genes do not only affect bone but other tissues containing collagen type I as well. The prevalence of OI has been estimated to affect between 1:15 000 to 20 000 births. The clinical manifestations vary widely between the different types of OI ranging from patients who have mild symptoms with a normal life expectancy to intrauterine death.<sup>1-3</sup>

In clinical practice, the primary classification is still based on the phenotypical presentation.<sup>4</sup> The original clinically-based Sillence classification described just four OI types (OI type I to IV)<sup>5</sup> with the avalanche of reported collagen type I gene mutations in OI<sup>6,7</sup> providing molecular insights into these OI subgroups. In addition to collagen type I mutations, other gene mutations were found to result in OI. The genetic Sillence classification has already increased to 18 types of OI (OI types I to XVIII) and

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more genetic types are to be expected in the near future.<sup>8</sup> However, 85% of the OI population have an autosomal dominant inheritance leading to the common OI types I to IV due to the mutation in the COL1A1 or COL1A2 gene, and the rare OI type V in which Interferon Induced Transmembrane Protein 5 is mutated. The autosomal recessive OI types VI to XVIII make up the remaining 15% of the spectrum and commonly resemble the clinical presentation of OI type III or IV. The defects in OI type VI to XVIII are not in the COL1A1 or COL1A2 but in genes that play another role in the process of bone formation.<sup>8</sup>

This current concepts review is written in relation to the symposium on key aspects of OI at the 2018 Annual Meeting of the European Paediatric Orthopaedic Society and focuses on current knowledge related to the effects of COL1A1 and COL1A2 mutations on the intracellular formation of collagen type I, the alterations that occur in the cascade that leads to the formation of actual bone tissue on a matrix and architectural level and on the consequences of these alterations for the biomechanical properties of bone. Effects of medical treatment on the cascade of events present in OI patients with mutations in the COL1A1 or COL1A2 gene and future strategies for medication are discussed.

### Effects of COL1A1 and COL1A2 mutations on the intracellular formation of the collagen I triple helix

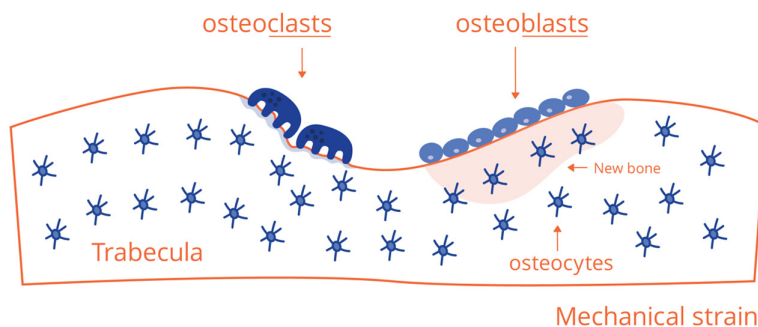
Bone formation and turn-over is primarily regulated by the basic multicellular unit (BMU) consisting of osteoblasts, osteocytes and osteoclasts (Fig. 1).

Amongst other proteins, osteoblasts produce collagen type I, the most abundant constituent of the bone matrix. Ribosomes in the osteoblast produce single alpha chains within the cell. A characteristic feature of collagens is the highly repetitive amino acid sequence with glycine (Gly), in the sequence Gly-X-Y-Gly-X-Y in each of the three alpha chains, where X and Y can be any amino acid. The

X is often a proline (Pro) and the Y often a lysine (Lys).<sup>9</sup> The three alpha-chains of collagen type I form disulphide bonds at the C-terminus end of the molecule. The three alpha-chains subsequently fold in a zipper-like fashion into a triple helix in the lumen of the endoplasmic reticulum.<sup>3,10</sup> The folding starts at the C-terminus part and ends at the N-terminus part of the molecule (Fig. 2).<sup>3,10</sup> Gly is the smallest amino acid and is always present in the centre of the triple helix, as there is no space to accommodate a larger amino acid. The procollagen thus formed is excreted by the osteoblast into the extracellular space and converted into collagen by cleaving off the propeptides<sup>11</sup> (Fig. 2).

During the zipper-like folding of the three alpha-chains, a hydroxy-group can be attached to certain proline and lysine amino acids in the alpha-chain, making hydroxyproline and hydroxylysine (Hyl), respectively (Fig. 2). Both amino acids are almost unique for collagen: they are seen in only a few other proteins. Additionally, sugar molecules (glucose and galactose) are attached to some of the Hyl molecules, resulting in galactosyl-Hyl and glucosyl-galactosyl-Hyl. The attachment of hydroxy-groups and sugar molecules in the alpha-chains is a time-dependent process and is carried out by various enzymes<sup>9</sup> (Fig. 2).

In OI type III and IV there is a mutation in the collagen protein and this causes a delay in the zipper-like folding of the triple helix<sup>12</sup> especially when the Gly in the sequence Gly-X-Y is substituted by a bulky amino acid in either the COL1A1 or COL1A2 chain, creating a molecular deformation within the triple helix<sup>13</sup> (Fig. 2). The prolonged helical folding results in more time for post-translational modifying enzymes to convert Lys into Hyl and Hyl into glycosylated Hyl (Fig. 2). In OI type I, there is no mutation in the collagen I and the zipper-like folding has a normal speed. However, in OI type I less than 50% of collagen is produced in an environment with a normal level of lysyl hydroxylating enzymes which results in an increased enzyme to collagen ratio and subsequent higher levels of hydroxylation and glycosylation as well.



**Fig. 1** Schematic view of the basic multicellular unit with interaction between bone resorbing osteoclasts and bone matrix producing osteoblasts, which become osteocytes over time.

## Effects of the COL1A1 and COL1A2 mutations on the extracellular formation of the collagen 1 triple helix

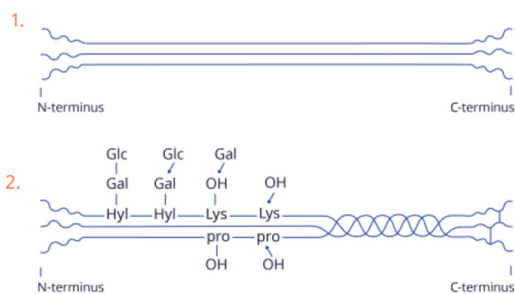
After the propeptides are cleaved off from the procollagen, the collagen molecules aggregate into a fibril. Due to the

formation of aldehydes in the telopeptides of collagen by lysyl oxidase, intermolecular covalent cross-links are being formed. The intrafibrillar collagen molecules are closely packed in characteristic quarter-staggered arrays, and it is this 3D packing that enables the formation of cross-links (Fig. 2).<sup>14-16</sup> Only molecules that are correctly aligned are

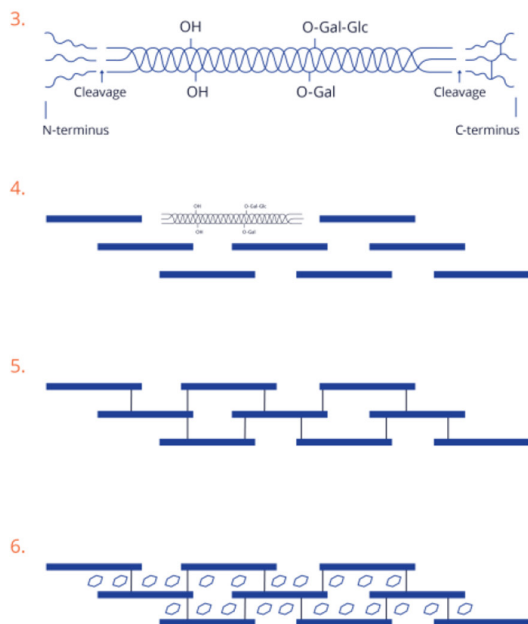
### Collagen production

#### Normal situation

#### Intracellular



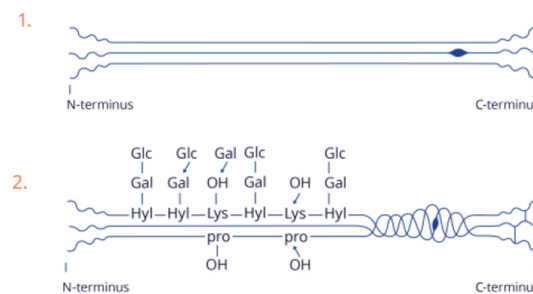
#### Extracellular



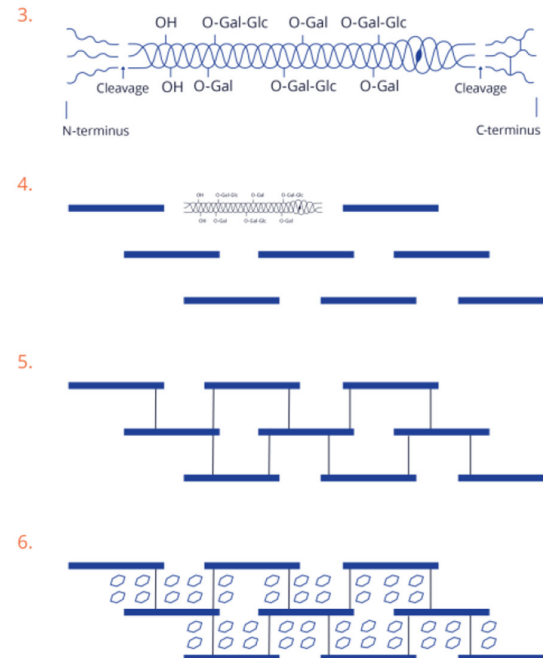
### Collagen production

#### Osteogenesis Imperfecta

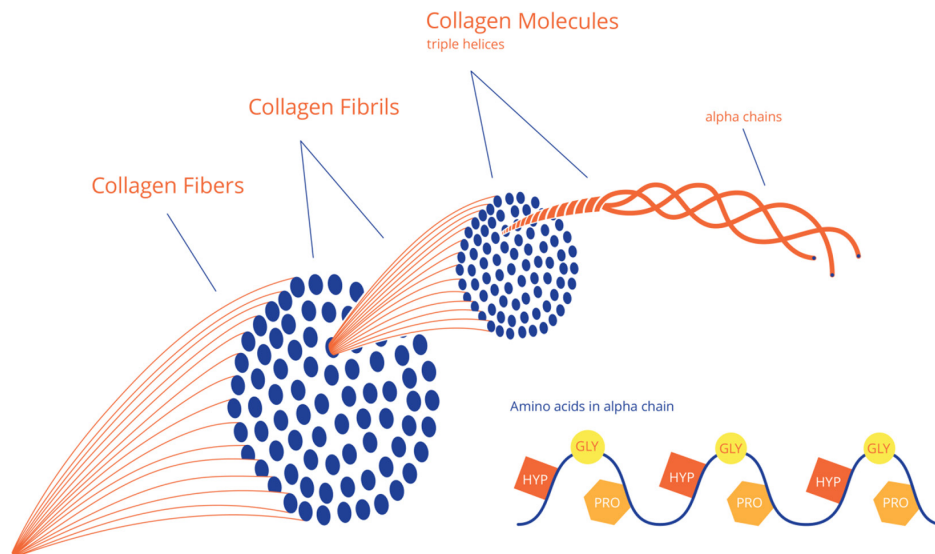
#### Intracellular



#### Extracellular



**Fig. 2** On the left side, a schematic view on the formation of collagen, both intracellular and extracellular. On the right side the same formation but with a mutation in one of the alpha chains as is seen in osteogenesis imperfecta (OI). Step 1: formation of three alpha chains by ribosomes (note the bigger amino acid in one of the chains in OI). Step 2: hydroxylation and glycosylation and the triple helix formation (note the slower folding in OI with increased hydroxylation and glycosylation: Glucose (Glc), Galactose (Gal), Lysine (Lys), Hydroxylysine (Hyl), Proline (Pro)). Step 3: extracellular cleavage of the C- and N-terminus. Step 4: quarter-staggered arrays (note the increased space between the molecules in OI). Step 5: the formation of cross-links which is unaffected in OI. Step 6: mineralization between the collagen molecules with an increased amount of mineral crystals of the same size in OI.



**Fig. 3** Multiple collagen fibrils form into collagen fibres. Amino acids on the alpha chain proline (PRO), glycine (GLY) and hydroxyproline (HYP).

able to form cross-links.<sup>17</sup> The total amount of pyridinoline cross-links in OI bone is similar to control bone, thus the packing geometry of intrafibrillar collagen molecules is not disturbed in OI.<sup>17</sup> The collagen molecules have regular distances with 'gap regions' as seen in electron micrographs. Multiple collagen fibrils form into collagen fibres (Fig. 3).

### Alterations that occur in the cascade that leads to the formation of bone matrix and bone architecture in OI: alterations in bone matrix

Bone tissue consists mainly of collagenous matrix (30%) and a mineral component (60%) that is located within and between the well-ordered collagen fibres. The mineralization process starts in the extracellular space as osteoblasts produce alkaline phosphatase causing the formation of mineral crystals on phosphate nucleation sites<sup>18-21</sup> in the gap regions between the collagen molecules. These crystals grow in and around the collagen resulting in mineralized bone matrix.

In OI an abnormally high bone matrix mineralization is found independent of the mutation type. Fratzl-Zelman et al<sup>22</sup> found a similar crystal size in bone of OI type 1 compared with the normal bone but the relative mineral volume fraction was increased by 12% due to a larger number of crystals in the same matrix volume. Thus, the size and shape of the hydroxy apatite (HA) crystals itself does not seem to be affected by the alteration of structure of the collagenous scaffold in OI. The previously mentioned increase of Hyl and glycosylated Hyl results in collagen fibrils with a smaller diameter,<sup>23</sup> and the individual

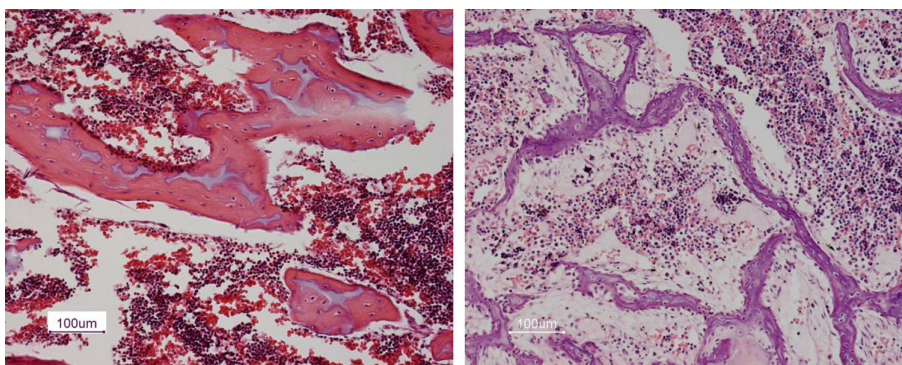
collagen molecules within the fibril are more widely spaced. The increased distance between two collagen molecules might be due to steric hindrance caused by over-hydroxylation and glycosylation (Fig. 2). Because of this increase in space more crystals can be accommodated between the collagen molecules, resulting in the abnormally high bone matrix mineralization (Fig. 2).

### Alterations that occur in cascade that leads to the formation of bone matrix and bone architecture in OI: alterations in bone architecture

Bone is composed of two distinct layers: cortical bone and trabecular bone. Cortical bone is compact and dense and consists of multiple microscopic columns of bone matrix, each called an osteon. Each column has multiple layers of osteoblasts and osteocytes around a central canal called the Haversian canal. Mineralized bone in the columns is constantly being remodelled by the BMUs synchronizing the action of osteoclasts and osteoblasts and adapting to mechanical loading by Wolff's law. The bone turnover in children with OI is increased compared with control bone and the bone shows an increased recruitment of these remodelling units.<sup>24</sup>

Trabecular bone is composed of a rod-like matrix that allows room for marrow, blood vessels and easy cell migration. In contrast to cortical bone, where BMUs can only start from an existing Haversian or Volkmann's canal,<sup>25</sup> the BMUs in cancellous bone lie on the surface of trabeculae.

The refinement of bone imaging technologies in recent years has improved the assessment of bone



**Fig. 4** Haematoxylin and eosin stain of both normal bone (left) and osteogenesis imperfecta (OI) bone (right). Note the difference in architecture between normal cancellous bone and cancellous bone in OI with a typical increased number of osteocytes and thinner trabeculae.

microarchitecture. Measures of bone microarchitecture, bone geometry and volumetric bone mass density (BMD) (vBMD) can be obtained by high-resolution peripheral quantitative computer tomography (HR-pQCT).<sup>26</sup>

Significant decreased cortical thickness was found at the tibia in type I OI patients with HR-pQCT but normal to increased cortical thickness in OI type III and IV.<sup>27</sup> Vascular porosity in OI cortical bone is significantly elevated compared with normal bone and there are also increases in canal connectivity and canal diameter. OI cortical bone porosity was also more isotropic than in healthy individuals. At the cellular level, osteocyte lacunar porosity was also increased in OI cortical bone; explained in part by an increase in lacunar density. Lacunae are more spherical in shape in OI cortical bone compared with normal bone.<sup>28-30</sup>

Both histomorphometric evaluation of cancellous iliac bone biopsies in patients with OI and HR-pQCT in OI bone show fewer and thinner trabeculae<sup>27,31,32</sup> (Fig. 4). Patients with OI type I have altered bone geometry (lower total bone area in the radius), altered bone microstructure (decreased trabecular number, increased trabecular spacing and greater trabecular inhomogeneity) and lower bone mass (decreased areal and volumetric BMD) compared with healthy controls.<sup>33</sup>

The Trabecular Bone Score (TBS) measured with HR-pQCT is related to trabecular connectivity and trabecular spacing. Low TBS in peripheral bone has a strong association with individual fracture risk.<sup>34</sup> In OI patients type III and type IV, lower TBS values were found.<sup>27</sup>

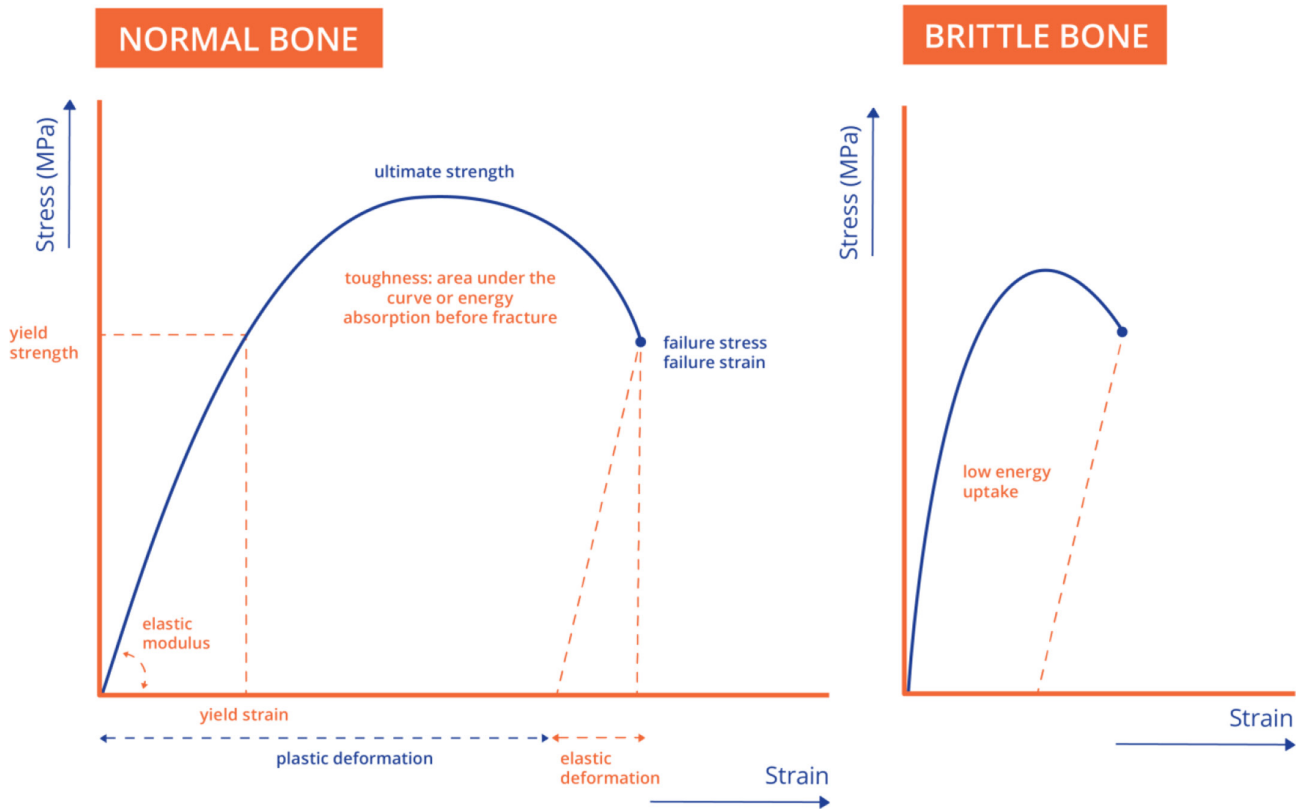
### Biomechanical consequences of alterations in bone matrix and architecture in OI

Bones fracture when external loading exceeds the load bearing capacity. However, this can occur for several different reasons. The bone matrix itself maybe weak with

inadequate physical properties such as a low ultimate strength or the geometry may be compromised by a thin cortex or low BMD. In order to differentiate between these two different reasons, mechanical tests can be performed on bone specimens of a standardized geometry to determine the true physical properties of a tissue, independent from its geometry. For bone this is often complicated. Firstly, because the bone specimen has to be reshaped or trimmed to a standardized shape that fits the actual mechanical test. Secondly, in case the bone is porous, the test has to correct for the porous geometry which is particularly important in the case of trabecular bone.

Bone matrix properties depend on the tissue characteristics within the calcified matrix also referred to as bulk tissue properties. They depend on the organization of collagen fibres, bone matrix mineralization, the constitution of the organic matrix and the interactions between mineral and organic phases. Geometrical properties of bone are related to either its micro-architecture (porosity or trabecular architecture) or its macro-architecture, the gross geometry (overall shape and cortical thickness). These geometrical aspects can be assessed by pore percentage, trabecular number and thickness, interconnectivity of trabecular bone, trabecular orientation (anisotropy), bone mass, cortical width and thickness or finally the overall shape of the entire bone.<sup>35-37</sup>

Bone matrix tensile strength and resistance to both traction and shearing forces is mainly determined by the collagen network with its intermolecular crosslinking, making up around 30% of the bone matrix.<sup>38,39</sup> The effects of fibril diameter reduction are associated with the clinical types of OI,<sup>40</sup> suggesting an association between the reduced diameter of the collagen fibrils and the (visco-)elastic and plastic properties of the bone matrix. The increased bone matrix mineralization found in OI<sup>41,42</sup> will result in a higher bone matrix elastic modulus and less ability for plastic deformation. As a consequence, the energy uptake under



**Fig. 5** Brittle bone. Hypothetical stress-strain curve of bone with some of the most essential mechanical properties. For cortical bone, the deformations at yield are up to 1%, whereas for cancellous bone this can reach 5% to 10% or even higher. Bone can absorb a substantial amount of energy and can be considered a relatively tough material (see area under the curve). Osteogenesis imperfecta bone is considered brittle which means that it cannot absorb much energy (small area under the curve, right side). In fact, brittleness represents a combination of low strength and little plastic deformation.

loading in patients with OI will be much lower, implying increased brittleness (Fig. 5).

Another determining factor in the biomechanics of OI bone is the altered geometry of the bone which occurs at various levels. An increased pore percentage in OI bone has been reported both at the level of osteocyte lacunae and vascularity.<sup>42,43</sup> It is known that a small rise in bone pore percentage leads to significantly increased crack propagation through bone, in particular with repetitive loading and accumulation of micro-damage. The combination of increased pore numbers with a higher elasticity modulus at the matrix tissue level will enhance this phenomenon with a substantial decrease of the peak stress threshold for fracture.

Pore percentage (porosity and pore size) are significantly related to tensile and shear fracture strength and there is a nonlinear relationship between porosity and pore size for tensile fracture toughness. For example, a bone pore percentage increase from 4% to 20% results in a three-fold lowering of the deformation abilities of bone before fracture,<sup>44</sup> whereas at the tissue (matrix/bulk) level the elastic modulus of OI bone is higher than normal and

at the architectural level the resistance to deformation is decreased.<sup>45</sup> Three-point bending tests on standardized bone samples of patients with OI showed lower strength and stiffness which was associated with an abnormally high vascular porosity within regions typically occupied by dense (high mineralized) cortical bone as measured by micro-CT.<sup>46,47</sup> In fact, these data are in line with the earlier finding of Boyde and co-workers who used backscatter electron microscopy.<sup>41,42</sup> There also appeared to be an effect of OI on bone anisotropy. Young's modulus is generally higher in the orientation longitudinal to the osteons compared with the transverse orientation.<sup>45-48</sup> However, differences between biomechanical properties in the longitudinal orientation and in the transverse orientation of cortical bone were lower in OI bone compared to normal bone, suggesting less anisotropy i.e. a less effective stress-related orientation of bone tissue.<sup>43</sup>

Biomechanical assessment at the level of whole bone can be considered as the optimal proxy of fracture incidence and fracture risk. Obviously, as these measures are destructive, clinical assessment must be by other means and mostly BMD as measured by dual-energy

X-ray absorptiometry (DXA) is used as a proxy for fracture risk. Therefore, many studies have been performed on the relationship between DXA-based BMD and the bone strength or fracture risk/incidence. Fracture risk is clearly related to BMD in the older population<sup>49</sup> although, to quote J. A. Kanis, "hip fracture prediction with BMD alone is as good as blood pressure readings alone to predict stroke".<sup>50</sup> However, other than postmenopausal osteoporosis, many clinical scenarios are not well related to bone volume alone as measured by DXA.<sup>51</sup> More recently, techniques that include information about trabecular microarchitecture such as trabecular spacing and connectivity density show an independent correlation to fracture incidence.<sup>52,53</sup> In children, using BMD in as a measure of biomechanical strength of bone is even more obscured in the individual patient as both micro and macro architecture are severely altered in children with OI and, even beyond the architectural issues of DXA-based BMD, the outcomes of DXA have to be adjusted for age, sex, height and weight.<sup>54</sup> Although an association between fractures and total body BMD as a measure for bone mass was found in studies in children and adults with OI, the specificity of the measurements with regard to bone strength and fracture risk in the individual patient remains very low.<sup>55,56</sup>

DXA is often considered as a measurement for bone volume or bone volume fraction but in fact it reflects a 2D image which is interpreted in a 3D manner thereby obscuring the discussed effects of micro and macro architecture. New methods that include geometric aspects such as, for example, patient-specific finite element models or geometrical measures from DXA<sup>36,57,58</sup> should be introduced as diagnostic tools in order to improve predictions of bone strength and fracture risk in the individual OI patient.<sup>59</sup>

## Effects of current medication on bone matrix and bone architecture in OI and future strategies

Medication for improving bone biomechanics in OI needs to address bone at both matrix and architectural levels.

As for all children, maintaining adequate vitamin D (vit D) concentrations is one of the basic prerequisites for normal bone mineralization and bone mass.<sup>60</sup> Children with OI seem to be at risk for vit D deficiency, especially those with more severe OI and/or a high body mass index.<sup>61</sup> Therefore, children with OI should have their vit D status monitored and be supplied with a dietary vit D supplement to ensure optimal levels.

The similarities in clinical presentation between OI and osteoporosis led to the introduction of treatment of OI patients with bisphosphonates (BPs) in order to increase BMD and reduce fracture rate. BPs primarily act on osteoclasts but as a result of the interaction of osteoclasts

with osteoblasts and osteocytes in the BMU of the bone turn-over cycle, all cells in the BMU are influenced by BPs.<sup>25, 62</sup>

BPs can be classified as nitrogen containing and non-nitrogen containing BPs. The non-nitrogen containing BPs like etidronate, clodronate and tiludronate cause apoptosis of osteoclasts by forming adenosine triphosphate (ATP) analogues. Nitrogen containing BPs like alendronate, risedronate, ibandronate, pamidronate and zoledronate interfere with the process of osteoclastic bone resorption without causing apoptosis. This group of BPs has a higher affinity to bind to HA<sup>63</sup>, is more potent and most used currently. The affinity to bind to HA is generally higher in trabecular bone as it is more active metabolically. Although BPs seem also to affect osteoblasts and osteocytes directly, the impact of these processes is not clear yet.<sup>25</sup> Therefore, the main effect of BPs in the treatment of OI lies in the modulation of osteoclast activity altering the structure and the architecture of bone.

In OI the decrease in bone strength is not only caused by alterations in the strength of the mutated collagen fibres and its effects on the collagen-mineral ratio in the bone matrix but also by consequent changes in quantity of bone per volume (BMD), the porosity of the bone and the architecture and connectivity within the structure. BPs cannot improve connectivity but do decrease pore percentage in osteoporotic bone<sup>64</sup> and increase BMD by increasing bone volume and trabecular thickness.<sup>65</sup> Increase in BMD after the start of BP treatment is usually highest in the first year due inhibiting osteoclasts in the BMU bone turn-over cycle to start new bone remodelling sites while filling of pre-existing remodelling sites by osteoblasts is ongoing and the positive effect on the net ratio bone resorption to bone formation is greatest.

In a study by Weber et al<sup>66</sup> of 14 OI patients before and after treatment with BPs, histomorphometry demonstrated increased bone mass. The amount of mineralization, the hardness and modulus of elasticity of bone tested with nanoindentation showed no statistical difference from before to after treatment and change in intrinsic bone properties secondary to BP treatment could not be established. These findings were similar to those found in OI mouse studies.<sup>67</sup>

Micro-cracks in trabecular and cortical bone are a normal phenomenon in bone biology under loading circumstances and BMUs actively repair the damage to the necessary bone strength. An interesting side effect of BP treatment is its potential negative effect on micro-crack repair by inhibiting bone remodelling by inhibiting bone resorption in the early phase of the BMU remodelling cycle. However, correlations between changes in micro-damage repair and bone toughness were not demonstrated in BP treated patients, probably due to the self-limiting nature of the process.<sup>68</sup>



Bone volume and porosity have a strong relationship with bone strength and resistance to deformation and the positive effect of BPs on bone biomechanics are explained mostly by the effect of BPs on these two determinants.<sup>69</sup>

The reports of effects of BPs on bone biomechanics and strength on a patient level in OI are derived from randomized clinical studies. The latest Cochrane Review (2016)<sup>70</sup> concluded that there was limited evidence that BPs increased BMD in children and adults with OI and multiple studies that reported a decrease in fracture rate as a measure of bone strength. In general, the BPs with the highest HA affinity<sup>63</sup> are prescribed (zoledronate, pamidronate iv and risedronate orally). Effects of BPs on radiological bone healing in OI are not clear due to different assessment techniques and medication regimes. Animal studies have shown some effect on callus remodelling but no negative clinical effects on fracture healing are reported.<sup>71,72</sup>

One of the disadvantages of BP treatment is the long half-life of BPs attached to bone which may be many years.<sup>73</sup> Therefore, newer drugs like the anti RANKL monoclonal antibody (Denosumab) were introduced in the treatment of OI. Denosumab inhibits osteoclast function but does not bind to bone and its half-life is only around 30 days.<sup>74</sup> A recent systematic review found that the quality of reports on the treatment effects on children with OI was poor, limited and inconclusive. Denosumab has been studied mostly in children with OI type VI known for a low response to BPs due to limited binding of BPs to the bone of OI type VI with the characteristic increase of unmineralized osteoid.<sup>75</sup> Current negative side effects are rebound effects on stopping treatment and hypercalcaemia and hypercalciuria during treatment.<sup>76</sup>

Apart from downregulating osteoclasts in the BMU bone turn-over cycle in OI, research is also focusing on anabolic agents that stimulate bone formation.<sup>77</sup>

Growth hormone (GH) is known to mediate bone strength in GH deficient children and was tested in children with severe OI. Only relatively small effects on BMD compared with treatment with BPs were found and use of GH has not been used therapeutically in children with OI.<sup>78</sup>

Teriparatide (synthetic parathyroid hormone (PTH 1-34)) is used in the treatment of postmenopausal osteoporosis.<sup>79</sup> For adults with OI only a few published studies have shown an increase in BMD.<sup>80,81</sup> There are no studies in children yet due to the increased osteosarcoma risk reported in animal studies.<sup>82</sup>

More recently, anti-sclerostin (Romozosumab), a glycoprotein stimulating osteoblasts by inhibiting the WNT signalling of osteocytes in the bone turn-over cycle of the BMU unit, has also shown an increase in BMD and reduction in fractures in postmenopausal women.<sup>83</sup> Results of an open label phase 2a study in adults with OI were recently published, showing increased BMD and blood markers

indicating increased bone formation and decreased bone resorption.<sup>84</sup>

Transforming growth factor-beta (TGF-beta) is known to have effects on both osteoblasts and osteoclasts.<sup>85</sup> The current status in OI is that excessive TGF-beta signalling was found in OI mouse models as well as anabolic and anti-catabolic effects on bone with treatment with anti TGF-beta antibodies. This makes anti-TGF-beta antibody a promising treatment in patients with OI.<sup>86,87</sup> Currently, losartan, an angiotensin-receptor blocking agent with anti-TGF-beta properties is being considered as an alternative agent.

## Summary and conclusion

Mutations in the COL1A1 or COL1A2 gene result in over-modified collagen molecules, thinner collagen fibres and a hypermineralized bone matrix at a tissue level. Individual variation of disease severity and effectiveness of medical treatment in OI is probably partly determined by the nature of the primary collagen defect and its location with respect to the C- terminus of the collagen protein. This has final repercussions at the tissue level of the bone matrix and on the micro- and macro-level of the architecture. These architectural alterations include a lower trabecular number and connectivity as well as lower trabecular thickness and volumetric bone mass. At the macro-scale there is a decreased cortical thickness with less mechanical anisotropy and with increased pore percentage from osteocyte lacunae and vascular porosity. The overall bone biomechanics are a result of all the above factors as well as their interactions. In patients with OI, these properties and interactions are altered in varying degrees, making accurate predictions on bone strength in the individual patient with OI very difficult. Current treatment of OI focuses on intervening in both the catabolic and anabolic phases of the bone turnover cycle of the BMU. However, appropriate diagnostics and treatment efficacy are not well founded on bone biomechanical criteria that primarily refer to the brittleness of bone, and diagnostic tools would certainly benefit from improved methodologies that could identify such criteria in an individual patient.

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WHN: Drafted article: all sections.

DME: Editing/grammar of all sections; Effects of current medication on bone matrix and bone architecture in osteogenesis imperfecta (OI) and future strategies.

JA: Effects of current medication on bone matrix and bone architecture in OI and future strategies.

IH: Biomechanical consequences of alterations in bone matrix and architecture in OI.  
HHW: Alterations that occur in cascade that leads to the formation of bone matrix and bone architecture in OI and alterations in bone architecture; Biomechanical consequences of alterations in bone matrix and architecture in OI.

RAB: Effects of COL1A1 and COL1A2 mutations on the intracellular formation of the collagen I triple helix; Effects of the COL1A1 and COL1A2 mutations on the extracellular formation of the collagen I triple helix; Alterations that occur in the cascade that leads to the formation of bone matrix and bone architecture in OI and alterations in bone matrix.

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