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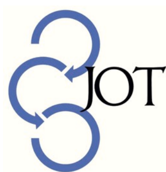

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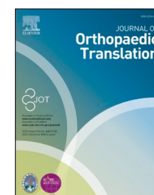

Review Article

Sclerostin inhibition in rare bone diseases: Molecular understanding and therapeutic perspectives

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ABSTRACT

Sclerostin emerges as a novel target for bone anabolic therapy in bone diseases. Osteogenesis imperfecta (OI) and X-linked hypophosphatemia (XLH) are rare bone diseases in which therapeutic potential of sclerostin inhibition cannot be ignored. In OI, genetic/pharmacologic sclerostin inhibition promoted bone formation of mice, but responses varied by genotype and age. Serum sclerostin levels were higher in young OI-I patients, while lower in adult OI-I/III/IV. It's worth investigating whether therapeutic response of OI to sclerostin inhibition could be clinically predicted by genotype and age. In XLH, preclinical/clinical data suggested factors other than identified FGF23 contributing to XLH. Higher levels of circulating sclerostin were detected in XLH. Sclerostin inhibition promoted bone formation in *Hyp* mice, while restored phosphate homeostasis in age-/gender-dependent manner. The role of sclerostin in regulating phosphate metabolism deserves investigation. Sclerostin/FGF23 levels of XLH patients with/without response to FGF23-antibody warrants study to develop precise sclerostin/FGF23 inhibition strategy or synergistic/additive strategy. Notably, OI patients were associated with cardiovascular abnormalities, so were XLH patients receiving conventional therapy. Targeting sclerostin loop3 promoted bone formation without cardiovascular risks. Further, blockade of sclerostin loop3-LRP4 interaction while preserving sclerostin loop2-ApoER2 interaction could be a potential precise sclerostin inhibition strategy for OI and XLH with cardiovascular safety.

The Translational Potential of this Article.

Preclinical data on the molecular understanding of sclerostin inhibition in OI and therapeutic efficacy in mouse models of different genotypes, as well as clinical data on serum sclerostin levels in patients with different phenotypes of OI, were reviewed and discussed. Translationally, it would facilitate to develop clinical prediction strategies (e.g. based on genotype and age, not just phenotype) for OI patients responsive to sclerostin inhibition. Both preclinical and clinical data suggested sclerostin as another factor contributing to XLH, in addition to the identified FGF23. The molecular understanding and therapeutic effects of sclerostin inhibition on both promoting

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bone anabolism and improving phosphate homostasis in *Hyp* mice were reviewed and discussed. Translationaly, it would facilitate the development of precise sclerostin/FGF23 inhibition strategy or synergistic/additive strategy for the treatment of XLH. Cardiovascular risk could not be ruled out during sclerostin inhibition treatment, especially for OI and XLH patients with cardiovascular diseases history and cardiovascular abnormalities. Studies on the role of sclerostin in inhiting bone formation and protecting cardiovascular system were reviewed and discussed. Translationaly, blockade of sclerostin loop3-LRP4 interaction while preserving sclerostin loop2-ApoER2 interaction could be a potential precise sclerostin inhibition strategy for OI and XLH with cardiovascular safety.

1. Introduction

Sclerostin, encoded by the gene *SOST*, is an osteocyte-secreted glycoprotein that was identified as a negative regulator of bone formation. Loss of function mutations in *SOST* are associated with sclerosteosis (MIM 269500) or van Buchem disease (MIM 239100), both of which are characterized by generalized hyperostosis or sclerosis of the skull and long bones [1,2]. In animal models, sclerostin deficiency is associated with increased bone mass and bone strength, while sclerostin overexpression is accompanied by decreased bone mass and bone strength [3]. Sclerostin has become a promising bone anabolic target for the treatment of common bone diseases such as osteoporosis [4].

Rare bone diseases, including osteogenesis imperfecta (OI) and X-linked hypophosphatemia (XLH), affect the musculoskeletal system and may cause severe mobility problems due to painful fractures, deformities, and bone pain [5,6]. Despite decades of researches and attempts to treat OI with anti-resorptive and osteogenic drugs [7–12], there is currently no satisfactory treatment. The conventional therapy for XLH patients was oral active vitamin D analogs and multiple dietary phosphate supplementation [6,13]. Although the conventional therapy improved rickets and skeletal deformities, the impaired linear growth in a large proportion of XLH patients were not improved [14–16]. Moreover, conventional therapy could cause several complications, including secondary hyperparathyroidism, gastrointestinal symptomatology and nephrocalcinosis [17,18]. Recently, the therapeutic anti-FGF23 antibody Burosumab was approved for treating XLH patients. However, long-term administration of Burosumab failed to restore serum phosphate levels in some XLH patients [19]. In addition, the bone phenotype of XLH patients treated with Burosumab treatment could not be improved to that of healthy individuals [15,19,20].

Elevated serum sclerostin levels were detected in young type I OI patients and XLH patients, in comparison with healthy individuals [21–24]. Genetic and pharmacologic evidences indicated the therapeutic potential of sclerostin inhibition for promoting bone formation in OI [25–31]. Sclerostin inhibition was demonstrated to promote bone anabolism and restore phosphate homeostasis in *Hyp* mice mimicking XLH [30,32]. However, severe cardiovascular events were found in phase III clinical trials (BRIDGE and ARCH) of the marketed humanized therapeutic sclerostin antibody Romosozumab for the treatment of postmenopausal osteoporosis [33,34]. Thus, Romosozumab for postmenopausal osteoporosis was approved by the U.S. Food and Drug Administration (U.S. FDA) with a black-boxed warning on the risk of heart attack, stroke and cardiovascular death (FDA Press Announcements), while it was approved by European Medicines Agency (EMA) with restriction to severe postmenopausal osteoporosis who had no disease history of heart attack and stroke (European Medicines Agency Documents). OI patients were associated with cardiovascular abnormalities [35,36], so were XLH patients receiving conventional therapy [37–40]. It indicated a growing cardiovascular concern for both OI and XLH patients during sclerostin antibody treatment, especially for those with cardiovascular abnormalities or with a cardiovascular disease history. Notably, it was found that sclerostin loop3 was critical in the antagonistic effect of sclerostin on bone formation, while the cardiovascular protective effect of sclerostin was independent of loop3 [41]. Targeting sclerostin loop3 could promote bone formation without increasing cardiovascular risk in *Col1a2*$^{+/G610C}$ mice [41,42]. However, molecular understanding for the role of sclerostin and its different loops in inhibiting bone anabolism, impairing phosphate homeostasis, and protecting cardiovascular system in the above disorders remain unclear.

Here, molecular understanding and therapeutic perspectives of sclerostin inhibition in OI and XLH were reviewed and discussed.

2. Molecular understanding and therapeutic perspectives for sclerostin inhibition in osteogenesis imperfecta

Osteogenesis Imperfecta (OI) is a rare hereditary heterogeneous skeletal dysplasia with an incidence of 1 in 15 000 to 20 000 live births [43,44]. It is characterized by various degrees of decreased bone mineral density (BMD), increased bone fragility, short stature, blue sclera, dentinogenesis imperfecta, hearing loss, and skeletal deformities [5].

2.1. Available clinical treatments for osteogenesis imperfecta

Bisphosphonates (BPs) are antiresorptive drugs that represent the prevailing standard of care for patients with OI [44], which have been shown to be effective in increasing BMD in several clinical trials [8,45,46]. BPs treatment mainly benefits trabecular bone and slightly improves cortical bone mass, without improving long bone strength and reducing fracture risk [7,47]. Long-term use of BPs could excessively inhibit bone remodeling, leading to atypical fractures and osteonecrosis of the jaw [48–50]. RANKL-antibody Denosumab, a reversible anti-resorptive compound, significantly elevated lumbar BMD in pediatric patients with type I, III, and IV OI, whereas had not effect on fractures [51]. Given symptoms in OI patients are most prominent in childhood [44], the use of antiresorptive drugs in OI patients may result in long-term suppression of bone turnover. Intermittent teriparatide was also used as an anabolic therapy to increase areal and volumetric bone mineral density (aBMD and vBMD) in adults with the mildest type I OI [9,52]. However, no benefit was observed in patients with severe OI (type III/IV), nor was a significant reduction in the number of self-reported fractures observed [52]. In addition, a risk of osteosarcoma was reported in rats treated with teriparatide [53], suggesting that teriparatide should be contraindicated in young patients. Recombinant human growth hormone (rGH) was also implemented as an anabolic therapy for pediatric patients with type I and IV OI, rather than type III OI [27,54]. The rGH slightly promoted bone formation but could not reduce fracture risk [27,54,55]. Up till now, there is no satisfactory treatment for OI (Fig. 1).

2.2. Molecular understanding for the role of sclerostin in impaired bone phenotype of osteogenesis imperfecta

Genetic mutation of *Lrp5*$^{p.A214V}$, which made LRP5 resistant to the endogenous inhibitor sclerostin, promoted bone formation and enhanced bone strength in *Col1a2*$^{+/p.G610C}$ mice [56]. Pharmacologic sclerostin inhibition by therapeutic sclerostin antibody (Scl-Ab) showed bone anabolic potential for mouse models of moderate type IV OI (*Col1a2*$^{+/G610C}$, *Brtl*/+), severe type III OI (*oim/oim*), severe type VII OI (*Crtap*$^{-/-}$) and severe type XV OI (*Wnt1*$^{sw/sw}$) [25–31]. Pharmacologic sclerostin loop3 inhibition by therapeutic sclerostin aptamer (Apc001)

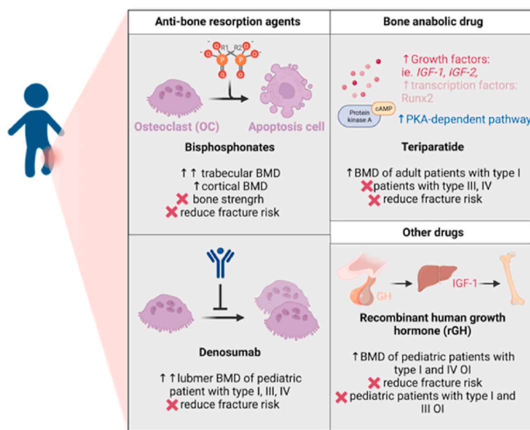

Figure 1. Available drugs for the treatment of osteogenesis imperfecta.

showed bone anabolic potential for mouse models of *Col1a2*$^{+/G610C}$ mice without cardiovascular risk (Tables 1 and 2) [41]. It indicated the critical role of sclerostin in OI.

Holdsworth et al. reported that sclerostin could bind to the YWTD repeats (β-propeller) within LRP5/6 of osteoblasts, thereby inhibiting bone anabolic Wnt signaling pathway [58]. Loop2 within sclerostin was reported as the binding domain to LRP5 according to the electrostatic potential map analysis [59–61]. The functional NXI motif within sclerostin loop2 was reported to bind to LRP6 on osteoblasts, subsequently antagonizing Wnt signaling [62]. Recently, Yu, Wang et al. found that sclerostin participated in inhibiting bone formation and protecting cardiovascular system via different loops [41]. Sclerostin loop3 was critical for the antagonistic effect of sclerostin on bone formation, while the cardiovascular protective effect of sclerostin was independent of sclerostin loop3 [41]. Based on the above molecular mechanism, one sclerostin aptamer specifically targeting sclerostin loop3 was developed and demonstrated to promote bone formation without increasing cardiovascular risk in *Col1a2*$^{+/G610C}$ mice [42]. Nevertheless, how sclerostin loop3 participates in the inhibitory effect of sclerostin on bone formation remains unclear. Sclerostin loop3 was reported to bind to LRP4 in osteoblasts by pull-down assay and BLI analysis [63]. LRP4 is a member of the LDL receptor family, whose mutations have been identified in patients with high-bone-mass disorders, such as sclerosteosis van Buchem disease [64]. *Lrp4* deficiency or conditional mutation in osteoblasts increased cortical and trabecular bone mass, which was associated with elevated bone formation and impaired bone resorption [64–66]. Osteoblastic LRP4 was found to be able to facilitate the binding of sclerostin to LRP5/6 for antagonizing bone formation [60,66,67]. Sclerostin loop3-LRP4 interaction was required by sclerostin to antagonize the Wnt signal and osteogenic potential in osteoblasts [63]. The pathophysiology of OI continues to be characterized as an inadequate osteoblastic synthesis of collagen type I, associated with inadequate bone matrix production, low bone mass and high fragility. Sclerostin was demonstrated to be an anti-osteoporosis target for promoting bone formation, increasing bone mass, and improving bone strength, whereas the role of sclerostin in regulating bone quality at the tissue level remained unclear. Sinder et al. reported that sclerostin inhibition not only promoted bone formation, but also increased tissue mineralization and altered the matrix chemistry of newly formed bone in *Brtl*/+ mice [25,27]. The relationships among sclerostin, bone matrix and bone mineralization warrant further investigation.

Table 1
Typical clinical classification of osteogenesis imperfecta and mouse model.

OI types	Disease phenotype in human	Mouse model (Inheritance)	Mutation genes, description and phenotypes
type III	Severe nonlethal progressive deforming phenotype	*Oim/oim* (AR)	*Col1a2*, a single nucleotide deletion (G) that alters the terminal approximately 50 amino acids of the pro-alpha 2 C-propeptide and prevents association with the pro-alpha1 chains; osteopenia, progressive skeletal deformities, lifetime fractures, cortical thinning, small body size
		Col1a1$^{jrt/+}$ (AD)	T to C transition in a splice donor of *Col1a1*
type IV	Moderate severity (intermediate between types I and III)	*Brtl*/+ (AD)	*Col1a1,* G349C; multiple features, smaller size, reduced BMD, more severe phenotype at young ages, increased bone brittleness, and increased bone turnover [25]
		Col1a2$^{+/p.G610C}$ (AD)	*Col1a2,* G610C
type VII	Severe to lethal (Similar to type II)	*Crtap*$^{-/-}$ (AR)	*Crtap* knockout; osteochondrodysplasia characterized by severe osteoporosis and decreased osteoid production, extraskeletal manifestations (skin, kidney, and lung abnormalities)
Type XV	Moderate to severe, central nervous system malformations	*Wnt1*$^{sw/sw}$ (AR)	G565 single nucleotide deletion in exon 3 of Wnt1, spontaneous tibial fractures, severe osteopenia, cerebellar defect, growth retardation [57]

Col1a2: alpha2 chain of type I collagen, Col1a1: alpha1 chain of type I collagen, Crtap: incartilage-associated protein; AD: autosomal dominant, AR: autosomal Recessive

2.3. Therapeutic perspectives of sclerostin inhibition in osteogenesis imperfecta

2.3.1. The bone anabolic potential of sclerostin inhibition for type IV osteogenesis imperfecta

In growing *Col1a2*$^{+/G610C}$ mice with a G610C point mutation in alpha2 chain of type I collagen (*Col1a2*), subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for six weeks) significantly enhanced bone mass and bone strength [68]. Subcutaneous administration of therapeutic sclerostin loop3-specific aptamer significantly promoted bone formation, enhanced bone mass, and improved bone mechanical properties in growing *Col1a2*$^{+/G610C}$ mice, without increasing cardiovascular risk [42].

In both growing and adult *Brtl*/+ mice with a G349C point mutation in alpha1 chain of type I collagen (*Col1a1*) [25], subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for two/five weeks) significantly enhanced trabecular bone mass, reduced long bone fragility and improved long bone strength in *Brtl*/+ mice [25–27,69].

Type IV OI with both G610C point mutation in *Col1a2* and G349C point mutation in *Col1a1* could be the response individuals to sclerostin inhibition strategies.

2.3.2. The bone anabolic potential of sclerostin inhibition for type III osteogenesis imperfecta

In growing *oim/oim* mice with a spontaneous mutation in the pro-alpha2 chain of type I collagen [70], subcutaneous administration of therapeutic Scl-Ab (50 mg/kg, once-weekly for nine weeks) significantly increased trabecular bone mass and cortical bone thickness [28,29]. Fracture is a severe clinical manifestation of OI. Type III OI patients sustain fractures throughout their lifespan [71]. Consistently in growing *oim/oim* mice, subcutaneous administration of therapeutic Scl-Ab dramatically enhanced bone strength, and reduced fracture rate in long bones, axial bones and appendicular bones [28,29].

In growing *Col1a1*$^{jrt/+}$ mice that mimic severe type III OI with T to C transition in a splice donor of *Col1a1* [72], intravenous administration of

Table 2
Preclinical studies of sclerostin inhibition in different OI mice.

Mice Model and Age		Brtl/+, male 8 weeks old [25]	Brtl/+, male 6 months old [26]	Brtl/+, male 3 week old [27]	Oim/oim (female) 5 weeks old [28,29]	*Col1a1*^{Jrt}/+(male) 4 weeks old [30]	*Col1a1*^{Jrt}/+(male) 12 weeks old [30]	*Crtap*$^{-/-}$ (female) 1 weeks old [31]	*Crtap*$^{-/-}$ (female) 6 weeks old [31]	*Col1a2*$^{+/G610C}$ 6 weeks old [42]
Dose and Duration		25 mg/kg, s.c., twice weekly, 4 weeks[a]	25 mg/kg, s.c., twice weekly, 5 weeks[a]	25 mg/kg, s.c., twice weekly, 5 weeks[a]	50 mg/kg, s.c.,once a week, 9 weeks[a]	100 mg/kg, i.v., once a week, 4 weeks[b]	100 mg/kg, i.v., once a week, 4 weeks[b]	25 mg/kg, s.c., twice a week, 6 weeks[a]	25 mg/kg, s.c., twice a week, 6 weeks[a]	12 mg/kg, s.c., twice a week, 6 weeks[a]
Circulating Parameter	OC or P1NP	+24.4 % (OC)	+47 % (OC)	↑ns (OC)	−69 % (P1NP)	↑ns	↑ns	N/A	N/A	N/A
	TRACP5b	↓ns	↓ns	↑ns	↑ns	↓ns	↓ns	N/A	N/A	N/A
Ct. parameters	Ct.Ar	N/A	+50 %	+25 %	N/A	N/A	N/A	+26 %	+31 %	
	Ct.Th	+17.6 %	+22.6 %	+24 %	+27 %	+18 %	↑NS	+32 %	+27 %	+18 %
Tb. parameters	Tb.BV/TV	↑ns	+119 %	↑NS	N/A	N/A	N/A	+26 %	+270 %	+118 %
	Tb.N	↑ns	+55 %	N/A	N/A	N/A	N/A	+45 %	+127 %	+42 %
	Tb.Th	+20 %	+29 %	+8.7 %	N/A	N/A	N/A	↑NS	+12 %	+24 %
Bone Strength	Ultimate load	+47.3 %	+127 %	+51 %	+86 %	N/A	N/A	+41 %	+17 %	+158 %
	Stiffness	+33.3 %	+38 %	+61 %	+172 %	N/A	N/A	+48 %	+36 %	+47 %
	Energy to failure	↑ns	+509 %	↑NS	+184 %	N/A	N/A	+39 %	↓NS	+110 %
Bone Formation	MS/BS	+50 %	+155 %	+62 %	N/A	N/A	N/A	NS	+65 %	+42 %
	MAR	↑NS	+180 %	↓NS	+128 %	N/A	N/A	NS	NS	+163 %
Fractures	N/A	N/A	N/A	N/A	Pelvic, tail, forelimb and hindlimb fractures↓	N/A	N/A	N/A	N/A	N/A

Ct. parameters: Micro-architecture (Cortical bone), Ct.Ar: cortical area, Ct.Th: cortical thickness, Tb. parameters: Micro-architecture (Trabecular bone), Tb.BV/TV: bone volume/total volume, Tb.N: trabecular number, Tb.Th: trabecular thickness, MS/BS: bone mineralization perimeter of femoral mid-shaft, MAR: mineral apposition rate of femoral mid-shaft, "NS" means not significant and was defined as $p > 0.05$, N/A: not avaliable
[a] Sclerostin antibody, Amgen Inc., [b] Sclerostin antibody, BPS804, Novartis Inc and and MorphoSys Inc, [c] Apc001PE, aptamer targeting sclerostin loop3

therapeutic Scl-Ab (100 mg/kg, once-weekly for four weeks) was associated with higher femoral trabecular bone volume and cortical bone thickness, while Scl-Ab had no effect on either trabecular bone or cortical bone in adult *Col1a1*$^{jrt/+}$ mice. Moreover, in either growing or adult *Col1a1*$^{jrt/+}$ mice, intravenous administration of Scl-Ab had no effect on fracture events [73].

Adult type III OI with T to C transition in a splice donor of *Col1a1* might not respond to sclerostin inhibition treatment, while the growing type III OI (*oim/oim*) with a spontaneous mutation in the pro-alpha2 chain of type I collagen could respond well.

2.3.3. The bone anabolic potential of sclerostin inhibition for type VII osteogenesis imperfecta

In pediatric and young adult *Crtap*$^{-/-}$ mice with inactivating mutations in cartilage-associated protein (*Crtap*) [74], subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for six weeks) was accompanied by significantly higher trabecular bone volume, trabecular and cortical bone thickness, as well as improved whole bone strength [31]. Pediatric and young adult type VII OI with inactivating mutations in *Crtap* might also respond to sclerostin inhibition treatment.

2.3.4. The bone anabolic potential of sclerostin inhibition for type XV osteogenesis imperfecta

In growing Swaying (*Wnt1*$^{sw/sw}$) mice with a G565 single nucleotide deletion in the third exon of Wnt1 [75], subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for six weeks) was associated with significantly higher trabecular bone volume and cortical bone thickness. Moreover, therapeutic Scl-Ab significantly decreased the fracture rate from 90 % (vehicle control) to 12.5 % [76]. Growing type XV OI with a G565 single nucleotide deletion in the third exon of Wnt1 could also be the response individuals to sclerostin inhibition strategies.

Accordingly, it is worth investigating whether the therapeutic response of OI to sclerostin inhibition strategies could be clinically predicted by genotype and age, rather than only by phenotype.

2.3.5. Potential predictive strategies for responsive populations to sclerostin inhibition

In the clinic, the serum sclerostin levels were reported to be higher in young patients with type I OI than the age- and sex-matched healthy controls, while were similar between young patients with type III, IV OI and the healthy controls [21,22]. The serum sclerostin levels were lower in adult patients with type I, III, and IV OI than the healthy controls [22]. It is desirable to investigate whether the therapeutic response of OI to sclerostin inhibition strategies could be clinically predicted by serum sclerostin level.

3. Molecular understanding and therapeutic perspectives for sclerostin inhibition in X-linked hypophosphatemia

Hereditary Hypophosphatemia is a series of disorders characterized by hypophosphatemic rickets/osteomalacia with impaired phosphate reabsorption in the proximal renal tubules. X-linked hypophosphatemia (XLH, MIM 307800) is the most common (~80 % of cases) hereditary hypophosphatemia, with an incidence of approximately 1 in 20,000–60,000 people worldwide [18]. XLH is caused by the loss-of-function mutation in the *phosphate-regulating gene with homology to endopeptidase located on the X chromosome* (*PHEX*) gene [77] and is characterized by high serum fibroblast growth factor 23 (FGF23), low serum phosphate, and inhibited skeletal mineralization [18]. Young XLH patients usually present with rickets, gait retardation, lower limb deformities, growth retardation, craniosynostosis and spontaneous dental abscesses [18]. Adults with XLH experience diffuse musculoskeletal pain (bone and joints), early osteoarthritis, pseudo-fractures, enthesopathy, spinal stenosis, muscle weakness, and severe dental damage [78].

3.1. Available clinical treatments for X-linked hypophosphatemia

Since the 1980s, conventional therapy for XLH entailed oral active vitamin D analogs and multiple dietary phosphate supplementation [79], which aims at correcting 1.25$(OH)_2$ vitamin D deficiency and compensating for renal phosphate wasting. Although the conventional therapy improved rickets and skeletal deformities, the impaired linear growth in a large proportion of XLH patients were not improved [80]. Previous reports suggested that conventional therapy in XLH patients was accompanied by an increase in circulating FGF23 concentrations, which may diminish the treatment efficacy or contribute to complications of therapy [11]. Moreover, conventional therapy is heavily medicated and have many complications, including secondary hyperparathyroidism, gastrointestinal symptoms, and nephrocalcinosis, which may be burdensome for patients with XLH, especially children [17]. Considering the persistence of rickets and short stature, some

Table 3
Preclinical studies of FGF23 inhibition and sclerostin inhibition respectively, in *Hyp* mice.

Item	Parameters	FGF23 antibody		Sclerostin antibody					
Mice Model and Age		*Hyp* mice (male) 6–8 weeks old [83]		*Hyp* mice (male) 4 weeks old [84]	*Hyp* mice (female) 4 weeks old [84]	*Hyp* mice (male) 4 weeks old [30]	*Hyp* mice (female) 4 weeks old [30]	*Hyp* mice (male) 12 weeks old [30]	*Hyp* mice (female) 12 weeks old [30]
Dose and Duration		4 mg/kg, once weekly for 4 weeks	16 mg/kg, once weekly for 4 weeks	25 mg/kg, twice weekly for 4 weeks		25 mg/kg, twice weekly for 4 weeks		25 mg/kg, twice weekly for 8 weeks	
Circulating Parameter	Phosphate	+49.0 %	+127.5 %	+69.4 %	+22.3 %	ns	ns	ns	ns
Micro-architecture (Cortical bone)	Ct.Ar	N/A	N/A	+55.5 %	+8.3 %	+75.5 %	+48.3 %	+28.0 %	+27.7 %
	Ct.Th	N/A	N/A	+15.2 %	+12.5 %	+42.9 %	+44.4 %	+12.5 %	+9.0 %
Micro-architecture (Trabecular bone)	Tb.BV/TV	+117.5 %	+80 %	+73.9 %	+90.3 %	+185.0 %	+10.4 %	+125.8 %	+3.0 %
	Tb.N	+133.3 %	+108.3 %	+12.3 %	ns	+23.3 %	−22.3 %	+13.9 %	−5.6 %
	Tb.Th	+4.3 %	−8.9 %	+13.8 %	+23.8 %	+24.1 %	+11.5 %	+52.3 %	+47.5 %
	Tb.Sp	N/A	N/A	−10.4 %	−1.7 %	−14.6 %	−25.0 %	−6.7 %	−8.5 %
Bone Strength	Peak load	N/A	N/A	+50.0 %	+25.0 %	+110.0 %	+108.0 %	+68.0 %	+48.0 %
	Bending stiffness	N/A	N/A	+25.0 %	+15.0 %	+274.0 %	+118.0 %	+41.0 %	+21.0 %
Bone Formation	Tb.MS/BS	N/A	N/A	N/A	N/A	+387.2 %	+73.9 %	+123.3 %	+73.3 %
	Tb.MAR	N/A	N/A	N/A	N/A	+500 %	+15.0 %	ns	ns
	Tb.BFR	N/A	N/A	N/A	N/A	+4210 %	+137.0 %	+605.3 %	+657.3 %

Ct.Ar: cortical area, Ct.Th = cortical thickness, Tb.BV/TV: bone volume/total volume, Tb.N: trabecular number, Tb.Th: trabecular thickness, Tb.Sp: trabecular spacing, Tb.MS/BS: trabecular mineralizing surface, Tb.MAR: trabecular mineral apposition rate, Tb.BFR: trabecular bone formation rate; "ns" means not significant and was defined as $p > 0.05$, N.A: not avaliable

patients require surgical intervention for lower extremity deformities. Although the administration of rGH led to a sustained increase in linear growth [81], it was not recommended as a routine treatment. Therapeutic anti-FGF23 antibody Burosumab emerges to be a novel therapeutic strategy for XLH. In the clinical trials, Burosumab could restore phosphate homeostasis in patients with XLH, thereby improving the prognosis for rickets, lower limb deformities and linear growth in children and pseudofracture healing in adults [15,16]. A real-world study conducted by Lnglart et al. and some case reports showed that not all patients achieved normal serum phosphorus levels and renal tubular maximum reabsorption rate of phosphate per glomerular filtration rate (TmP/GFR) after 160 weeks of treatment with Burosumab [19,20]. Besides, long-term Burosumab was unable to restore bone phenotype of XLH to that of healthy individual, especially standing height *Z*-score [15, 20].

3.2. Molecular understanding for the role of sclerostin in X-linked hypophosphatemia

Several cross-sectional controlled studies revealed significantly elevated serum sclerostin levels in both XLH patients and *Hyp* mice mimicking XLH [21–24]. Genetic sclerostin deficiency not only promoted bone formation, enhanced bone mass and bone micro-architecture, but also increased serum inorganic phosphorus levels in $Sost^{-/-}$ mice [82]. Pharmacological sclerostin inhibition by therapeutic sclerostin antibody (Scl-Ab) showed consistent effects on promoting bone anabolism and restoring phosphate homeostasis in *Hyp* mice [30,32] (Table 3). Sclerostin is emerging as a new target for XLH. Up till now, the molecular mechanisms underlying the role of sclerostin in regulating phosphate metabolism remain unclear.

3.2.1. Role of sclerostin in regulating FGF23 expression, iFGF23 cleavage, and levels of iFGF23/cFGF23 secreted in osteocytes

Sclerostin was reported to stimulate *Fgf23* mRNA expression in osteocytes *in vitro*. In detail, recombinant human sclerostin (rhScl) was found to remarkably enhance *Fgf23* mRNA expression in differentiated osteocytes (IDG-SW2) during the first 6 h of *in vitro* treatment, but dramatically reduced *Fgf23* mRNA expression from 6 h to 24 h [85]. Moreover, in differentiated IDG-SW2 cells *in vitro*, rhScl significantly decreased mRNA expressions of *Phex*, *Dmp1*, and *Enpp1*, which encoded the regulators for iFGF23 cleavage, while increased mRNA expression of *Galnt3*, which encoded N-acetylgalactosaminyl-transferase 3 (GalNAc-T3) for protecting iFGF23 from cleavage. However, secreted iFGF23 levels were determined to be unchanged after rhScl treatment, while secreted post-cleavage inactive c-terminal FGF23 (cFGF23) levels were determined to be significantly higher *in vitro*. Accordingly, it implied that rhScl could induce *Fgf23* mRNA expression during the first 6 h of *in vitro* treatment, and protect iFGF23 from cleavage in differentiated healthy osteocytes, but had no effect on iFGF23 secretion. Sustained accumulation of iFGF23 in cells might be the reason for the subsequent reduction of *Fgf23* mRNA expression from 6 h to 24 h.

Genetically, the serum iFGF23 levels in 8-week-old $sost^{-/-}$ mice were remarkably lower than those in age-matched wild-type (WT) mice [82]. Pharmacologically, subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly) for four weeks was accompanied by significantly lower serum levels of iFGF23 and higher serum levels of cFGF23 in male and female 8-week-old *Hyp* mice, followed by a compensatory increase in skeletal mRNA expression of *Fgf23* [32]. No changes were detected in gene expression of either *Galnt3* (encoding GalNAc-T3 which protects iFGF23 from cleavage via post-translational O-glycosylation of iFGF23) or *Fam20c* (encoding FAM20C which prevents post-translational O-glycosylation of iFGF23) in the above *in vivo* studies [32,86]. In another study, subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly) for eight weeks was associated with both lower serum levels of iFGF23 and lower serum levels of cFGF23 in 12-week-old *Hyp* mice and 20-week-old *Hyp* mice of both sex [30].

Scl-Ab treatment (25 mg/kg, twice-weekly) for four weeks significantly enhanced serum phosphorus levels in 8-week-old *Hyp* mice of both sexes [84], whilst Scl-Ab treatment (25 mg/kg, twice-weekly) for eight weeks had no effect on either serum phosphate levels or urine phosphate/urine creatinine ratios in 12-week-old/20-week-old *Hyp* mice of either sex [30]. The serum iFGF23 levels were decreased after Scl-Ab treatment in both 8-week-old *Hyp* mice and 12-week-old/20-week-old *Hyp* mice, while the serum cFGF23 levels were enhanced in 8-week-old *Hyp* mice but decreased in 12-week-old/20-week-old *Hyp* mice. The cFGF23 which could block iFGF23-Klotho-FGFR1c interaction was reported to alleviate hypophosphatemia [87]. Accordingly, the upregulated serum cFGF23 in 8-week-old *Hyp* mice after Scl-Ab treatment could be involved in enhancing serum phosphorus levels *in vivo*. The role of sclerostin in regulating circulating levels of cFGF23 remains unclear. Treatment of rhScl was reported to dramatically enhance secreted cFGF23 levels in differentiated osteocytes *in vitro*. It could be of interest to further investigate the role of sclerostin in regulating FGF23 expression, iFGF23 cleavage, and the levels of iFGF23/cFGF23 secreted in both osteocytes and osteoblasts of different developmental stages.

3.2.2. Role of sclerostin in regulating the renal expression of Na/Pi co-transporters

Notably, the *Sost* mRNA expression is highest in the kidney [88]. The role of renal sclerostin in regulating phosphate metabolism is also worthy of investigation. The renal sodium phosphate (Na/Pi) co-transporters, including NaPi-IIa and NaPi-IIc, regulate phosphorus reabsorption in kidney [89]. It was reported that the renal mRNA expression of genes (*Slc34a1* and *Slc34a3*) encoding NaPi-IIa and NaPi-IIc in male and female 12-week-old *Hyp* mice were significantly lower than their age- and sex-matched WT littermates [30]. However, therapeutic Scl-Ab treatment (25 mg/kg, twice-weekly) for either four weeks [32] or eight weeks [30] had no effect on the renal mRNA expression of *Slc34a1* and *Slc34a3* in 8-week-old [32] or 12-week-old [30] *Hyp* mice of either sex. In 20-week-old *Hyp* mice, the renal protein expression of NaPi-IIa, measured by immunohistochemistry (IHC), appeared to be sex-dependent: It was remarkably lower in *Hyp* females than in WT females, but not significantly different between *Hyp* and WT males. In female 20-week-old *Hyp* mice, the renal protein expression of NaPi-IIa was remarkably enhanced after Scl-Ab treatment (25 mg/kg, twice-weekly) for eight weeks, which was not detected in male *Hyp* mice [30]. Together, Scl-Ab could increase renal protein expression of NaPi-IIa only in female 20-week-old *Hyp* mice [84]. However, Scl-Ab significantly enhanced serum phosphorus levels in 8-week-old *Hyp* mice of both genders, but had no effect in 20-week-old *Hyp* mice of either sex [30]. The inconsistent results implied that there could be other molecular mechanisms by which sclerostin antibody restored phosphorus homeostasis in growing *Hyp* mice, rather than enhancing renal NaPi-IIa expression.

3.2.3. Role of sclerostin in regulating the level of bioactive $1,25(OH)_2D$ in kidney

The bioactive Vitamin D hormone, 1,25-dihydroxyvitamin D [$1,25(OH)_2D$], stimulates both intestinal and renal phosphorus reabsorption and decreases phosphate excretion. The 1α-hydroxylase, encoded by the *Cyp27b1* gene, is the is the crucial enzyme for activating Vitamin D to bioactive $1,25(OH)_2D$. The 24-hydroxylase, encoded by the *Cyp24a1* gene, is the inhibitor for activation of Vitamin D to the bioactive $1,25(OH)_2D$ [90]. Recombinant mouse sclerostin (rmScl) was reported to significantly decrease *cyp27b1* mRNA transcripts in cultured proximal tubule cells *in vitro* [82]. Genetically, sclerostin deficiency in 8-week-old $sost^{-/-}$ mice had significantly higher serum levels of bioactive $1,25(OH)_2D$, remarkably lower serum levels of inactive 24,25-dihydroxyvitamin D [$24,25(OH)_2D$], and higher renal mRNA expression of *Cyp27b1*, compared with age-matched WT mice [82]. Pharmacologically, therapeutic Scl-Ab (25 mg/kg, twice-weekly) treatment for eight weeks enhanced the serum levels of $1,25(OH)_2D$ in both male and

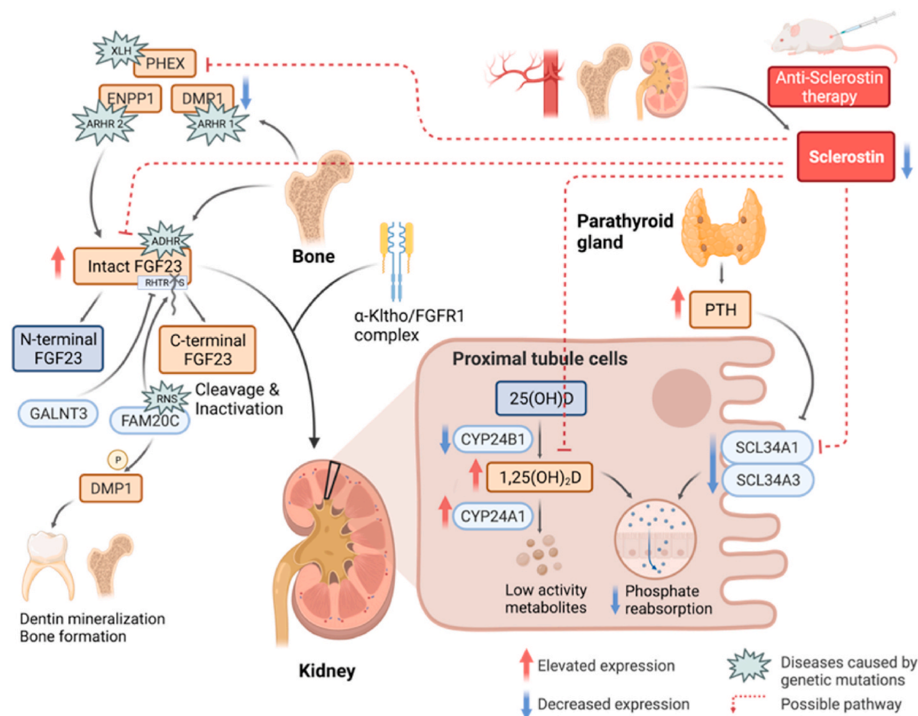

Figure 2. Mechanisms of phosphorus metabolism in the bone and kidney, which could be antagonized by sclerostin inhibition.

female 20-week-old *Hyp* mice, but not in 12-week-old *Hyp* mice [30]. For therapeutic outcome, Scl-Ab significantly enhanced serum phosphorus levels in 8-week-old *Hyp* mice of both sexes[13], but had no effect in either 12-week-old or 20-week-old *Hyp* mice of either sex [30]. It implied that sclerostin deficiency and inhibition could be involved in restoring phosphate homeostasis via improving mRNA expression of *cyp27b1*, enhancing circulating levels of bioactive 1,25(OH)$_2$D or reducing circulating levels of inactive 24,25(OH)$_2$D in growing mice, while the increased serum levels of 1,25(OH)$_2$D in 20-week-old *Hyp* mice had no effect on circulating phosphorus levels. In clinical studies, some XLH patients responseded poorly to supplemental bioactive 1,25 (OH)$_2$D therapy. It is desirable to study whether the therapeutic response of XLH patients to bioactive 1,25(OH)$_2$D-related treatments could be age-dependent. Fig. 2 showed the potential molecular mechanisms of both skeletal and renal sclerostin in regulating phosphate metabolism.

FGF23 is secreted by osteoblasts and osteocytes, and its secretion is downregulated by PHEX, DMP1, and ENPP1 all of which are expressed in bone. The activated intact FGF23 (iFGF23) (via the FGFR–KLOTHO complex) and PTH (via the PTH receptor) downregulate the activity of renal sodium-dependent phosphate (Na/Pi) co-transporter NTP2A (encoded by *SLC34A1*) and NTP2C (encoded by *SLC34A3*). The iFGF23 also reduces the expression of 25-hydroxyvitamin D1 α-hydroxylase) (encoded by *CYP29B1*) and increases the expression of 1,25-dihydroxyvitamin D 24-hydroxylase (encoded by *CYP24A1*), ultimately reducing phosphate reabsorption from renal proximal tubule cells through reduced active 1,25(OH)$_2$D. FAM20C phosphorylates iFGF23 directly on the Ser180 site, within the iFGF23 176RHTR179 (RXXR sequence) subtilisin-like proprotein convertase (SPC) motif, which inhibits O-glycosylation of iFGF23 by GALNT3, and promotes iFGF23 cleavage and inactivation by the SPC furin. Sclerostin may affect phosphorus homeostasis through the following four pathways: (1) sclerostin binds directly to the PHEX complex; (2) sclerotin regulate FGF23 expression, iFGF23 cleavage, and levels of iFGF23/cFGF23 secreted in osteocytes; (3) sclerostin regulates the renal expression of Na/Pi co-transporters in kidney; (4) sclerostin regulates the level of bioactive 1,25(OH)$_2$D in kidney.

PHEX: phosphate-regulating gene with homology to endopeptidase located on the X chromosome gene; DMP1: dentin matrix acidic phosphoprotein 1; ENPP1: ectonucleotide pyrophosphatase-phosphodiesterase family member 1; FAM20C: family with sequence similarity 20; XLH: X-linked hypophosphatemia, MIM 307800; ADHR: autosomal dominant hypophosphatemic rickets, 193 100, ARHR l: autosomal recessive hypophosphatemia 1, MIM 241520; ARHR 2: autosomal recessive hypophosphatemia 2, MIM 61331; RNS: Raine syndrome, MIM 259775.

3.2.4. Role of sclerostin in impaired bone phenotype of X-linked hypophosphatemia

Wnt proteins bind to Frizzled family members on the surface of the cell to regulate bone homeostasis [91]. Sclerostin is a bone tissue-specific inhibitor of the Wnt/β-catenin pathway, secreted by osteocytes, negatively regulating osteogenic differentiation and bone formation, and promoting osteoclastogenesis and bone resorption [1,2, 92–94]. Moreover, considering the effect of sclerostin inhibition on restoring phosphorus homeostasis in *Hyp* mice and the contribution of phosphate homeostasis to bone, the role of sclerostin in impaired bone phenotype of XLH is of great value to be investigated.

3.3. Therapeutic perspectives of sclerostin inhibition in X-linked hypophosphatemia

3.3.1. The effects of sclerostin inhibition on restoring phosphate homeostasis

In both male and female 8-week-old *Hyp* mice, the serum phosphate levels were significantly higher in the therapeutic Scl-Ab (25 mg/kg, twice-weekly for four weeks) treatment group, when compared to the vehicle treatment group [32]. Nevertheless, in either 12-week-old or 20-week-old *Hyp* mice of either sex, there was no significant difference in serum phosphate levels or urine phosphate/urine creatinine ratios between the therapeutic Scl-Ab (25 mg/kg, twice-weekly for eight weeks) group and vehicle group [30]**.** The serum phosphate levels in 8-week-old *Hyp* mice of both sexes were significantly lower than the age- and sex-matched WT controls [32], while no significant difference was

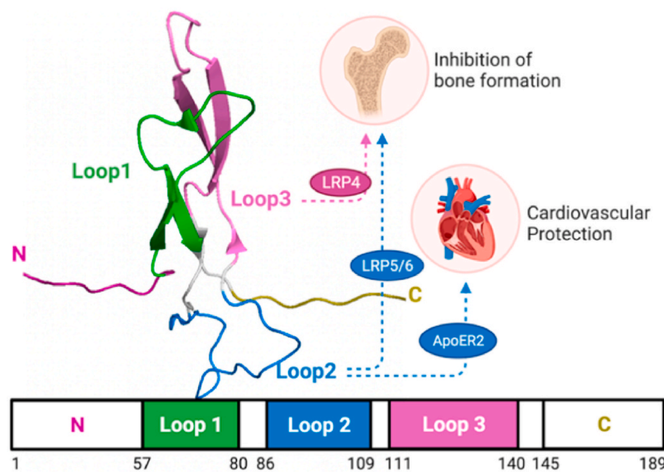

Figure 3. Distinctive role of sclerostin loops in bone and cardiovascular system.

detected in either serum phosphate levels or urine phosphate/urine creatinine ratios between 12-week-old/20-week-old *Hyp* mice and their WT controls of either sex [30]. Accordingly, it is worth further investigating whether the therapeutic response of XLH patients to restore phosphate homeostasis by sclerostin inhibition strategies could be clinically predicted based on age.

3.3.2. The bone anabolic effects of sclerostin inhibition

For bone anabolic potential, subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for four weeks) significantly enhanced trabecular bone mass in 8-week-old *Hyp* mice of both sex, but significantly increased cortical bone area and bone strength only in 8-week-old *Hyp* males [32]. Subcutaneous administration of therapeutic Scl-Ab (25 mg/kg, twice-weekly for eight weeks) significantly enhanced trabecular bone mass in both 12-week-old and 20-week-old *Hyp* males, but not females. Moreover, it remarkably increased cortical bone area in 20-week-old *Hyp* mice of both sex, but not 12-week-old *Hyp* mice. It merits further investigation whether the bone anabolic therapeutic response of XLH patients to sclerostin inhibition strategies could be clinically predicted according to age and sex.

3.3.3. Therapeutic perspectives of sclerostin inhibition in X-linked hypophosphatemia

Several clinical trails and clinical reports demonstrated that some patients with XLH showed poor response to the therapeutic anti-FGF23 antibody Burosumab treatment [15,16,19]. Increased skeletal mRNA expression of *Sost* was detected after Burosumab treatment [84]. The difference in sclerostin/FGF23 expression levels between the XLH patients with and without poor response to Burosumab treatment warrants further study for developing potential precise sclerostin/FGF23 inhibition stragety for XLH. Moreover, in patients with concomitantly elevated serum sclerostin and FGF23 levels, the combination of FGF23-Ab and sclerostin inhibition strategies might be a promising therapeutic approach.

4. The cardiovascular concern of sclerostin inhibition in osteogenesis imperfecta and X-linked hypophosphatemia

Cardiac valves and aortic wall abnormalities are relevant secondary features in patients with OI due to their connective tissue abnormalities [35–37,95]. Hypertension and left ventricular hypertrophy were observed in XLH patients during conventional therapy [38–40]. Up till now, it remains unclear whether the hypertension was caused by conventional therapy or cardiovascular abnormalities of XLH.

Romosozumab targeting sclerostin loop2 for postmenopausal osteoporosis caused severe cardiovascular events (CVEs) in phase III clinical trials (BRIDGE and ARCH) [33,34]. Several cross-sectional studies have shown that serum sclerostin levels are associated with vascular calcification, heart valve calcification and atherosclerosis [96–99]. Wnt signalling pathway is involved in the differentiation (to osteoblast-like cells) and mineralisation of vascular smooth muscle cells (VSMC) in the arterial wall [100]. As the Wnt pathway inhibitor, both *Sost* deficiency by genetic knockdown and sclerostin inhibition by the therapeutic sclerostin antibody Romosozumab exacerbate cardiac vascular, aortic and renal artery calcification in mice [101]. In our published work, aortic aneurysm and atherosclerosis development were inhibited, inflammatory cytokine and chemokine expression were significantly decreased in $hSOST^{ki}$. $ApoE^{-/-}$mice with AngII infusion, when compared to $ApoE^{-/-}$mice [41]. The data suggested a protective role of sclerostin against vascular calcification and cardiovascular events.

Accordingly, there is also a growing cardiovascular concern for both OI and XLH patients during sclerostin antibody treatment, especially for those with cardiovascular abnormalities or with a cardiovascular disease history. Sclerostin loop3 was recently found to be critical for inhibiting bone formation, while the cardiovascular protective effect of sclerostin was independent of sclerostin loop3 [41] (Fig. 3). Sclerostin loop3-specific aptamer Apc001 promoted bone formation in OI mice without increasing cardiovascular risks [42]. The reported *in vitro* data indicated that genetic and pharmacologic blockade of sclerostin loop2-ApoER2 interaction attenuated the inhibitory effect of sclerostin on inflammatory responses in macrophages [102], implying the crucial role of sclerostin loop2-ApoER2 interaction in the suppressive effects of sclerostin on aortic inflammatory responses and cardiovascular events progression [41,103]. It might contribute to developing the next-generation precise sclerostin inhibition strategy that targets sclerostin while preserving sclerostin loop2-ApoER2 interaction for promoting bone formation without increasing cardiovascular risk.

5. Discussion and conclusion

5.1. Molecular understanding and therapeutic perspectives for sclerostin inhibition in osteogenesis imperfecta

The $Lrp5^{p.A214V}$ mutation, which blocked the interaction of sclerostin to LRP5, increased bone mass, improved bone microarchitecture integrity and enhanced mechanical properties of $Col1a2^{+/p.G610C}$ mice [56]. The marketed therapeutic antibody Romosozumab targeting sclerostin loop2 showed bone anabolic potential for OI mice [25–31]. However, the severe CVEs found in phase III clinical trials limited the clinical usage of romosozumab [33,34]. Recently, it was notably found that sclerostin loop3 participated in the antagonistic effect of sclerostin on bone anabolism, while the protective effect of sclerostin on the cardiovascular system was independent of sclerostin loop3 [41]. Aptamer specifically targeting sclerostin loop3 promoted bone formation without increasing cardiovascular risk in OI mice [42]. Mechanistically, it was further found that sclerostin loop3-LRP4 interaction could participate in the antagonistic effects of sclerostin on Wnt signaling and osteogenic potential *in vitro* [63]. Sclerostin loop2-ApoER2 interaction could participate in the inhibitory effect of sclerostin on inflammatory responses in macrophages *in vitro* [41,103]. Translationally, blockade of osteoblastic sclerostin loop3-LRP4 interaction, rather than blockade sclerostin loop2-ApoER2 interaction, could be a potential precise sclerostin inhibition strategy to improve bone phenotype of OI with cardiovascular safety. In the future, in-depth studies of the different structural domains of sclerostin could provide further guidance and direction for sclerostin inhibition strategies. Therapeutically, according to the inconsistent bone anabolic effects of sclerostin inhibition in OI mice with distinctive genotypes/phenotypes, at different ages, as well as the uneven serum sclerostin levels of OI patients, it is desirable to investigate whether the therapeutic response of OI to sclerostin inhibition

strategies could be clinically predicted by serum sclerostin level, OI genotype and age, instead of only by phenotype.

5.2. Molecular understanding and therapeutic perspectives for sclerostin inhibition in X-linked hypophosphatemia

Several clinical trials have showed that long-term FGF23 antibody Burosumab treatment is unable to restore serum phosphate levels and bone phenotype of XLH patients to that of healthy individuals [15,19,20]. Genetically, FGF23 deficiency could not restore the bone phenotype of *Hyp* mice to the wild-type level [104]. In the cross-sectional studies, there was no significant difference in serum FGF23 levels between some XLH patients and healthy individuals [14,105]. Accordingly, elevated levels of FGF23 might be partially responsible for the disturbed phosphorus metabolism and impaired bone phenotype in XLH. High levels of circulating sclerostin were detected in both XLH patients and *Hyp* mice [21–24]. Moreover, sclerostin inhibition promoted bone formation and restored phosphate homeostasis in *Hyp* mice. For precision therapy of XLH, it is desirable to determine the correlation between serum FGF23/sclerostin levels and the response of XLH patients (*Hyp* mice) to FGF23 antibody treatment, as well as determine the correlation between serum FGF23/sclerostin levels and the response of *Hyp* mice to sclerostin antibody treatment. Further, sclerostin was proved to interact with the binding substance of PHEX directly [106]. Whether *PHEX* mutations contribute to the elevated levels of sclerostin remained unknown. Whether the co-elevated serum levels of sclerostin and FGF23 had a synergistic/additive effect in the pathogenesis of XLH warranted further investigation. Therapeutically, combination of FGF23-Ab and sclerostin inhibition strategies could be the promising therapeutic approach for XLH. Moreover, according to the inconsistent effects of sclerostin inhibition on promoting bone formation and elevating phosphate in *Hyp* mice with different ages and genders, it is desirable to investigate whether the therapeutic response of XLH to sclerostin inhibition strategies could be clinically predicted according to age and gender.

Credit author statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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