Neurofibromin in bone disease: Mechanisms and therapeutic implications (Review)

SHUHONG ZHANG[1,2] and GE YANG[1]

[1]Department of Orthopedics, Key Laboratory of Pediatric Orthopedics of Hunan Province, Hunan Children's Hospital, Affiliated Children's Hospital of Xiangya School of Medicine, Central South University, Changsha, Hunan 410007, P.R. China; [2]Department of Orthopedics, The Second Xiangya Hospital of Central South University, Changsha, Hunan 410011, P.R. China

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Abstract. Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder caused by pathogenic mutations in the NF1 gene, which encodes neurofibromin, a critical tumor suppressor and regulator of intracellular signaling. NF1 is a multisystem disease characterized by café-au-lait macules, neurofibromas, learning disabilities and prominent skeletal abnormalities. Accumulating evidence has demonstrated that neurofibromin is essential for maintaining skeletal homeostasis and a loss of neurofibromin results in dysregulated signaling pathways, particularly RAS/MAPK and PI3K/AKT. This dysregulation leads to NF1-associated skeletal diseases, such as low bone mineral density, osteoporosis, congenital pseudarthrosis of the tibia and scoliosis through disordered bone remodeling. Despite substantial progress being made in elucidating the molecular and cellular mechanisms underlying NF1-associated skeletal diseases, clinical management remains challenging. Skeletal abnormalities often present early in childhood and may progress despite intervention, highlighting the need for timely and effective assessment strategies. Current treatments for NF1 rely largely on complex surgical reconstruction and supportive medical therapy, with variable long-term outcomes. The present review summarizes the current understanding of the role of neurofibromin in bone homeostasis, discusses the cellular and molecular mechanisms driving NF1-associated skeletal diseases, and examines emerging assessment tools and therapeutic strategies. Furthermore, future directions aimed at translating mechanistic insights into improved clinical outcomes for patients with NF1-associated skeletal diseases are outlined.

Contents

1. Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disorder with an estimated global incidence of ~1 in 2,500-3,000 live births (1,2). NF1 is caused by variants in the NF1 gene, which is located on chromosome 17q11.2 and encodes neurofibromin, a multifunctional tumor suppressor protein that negatively regulates RAS signaling (3,4). Loss of neurofibromin leads to hyperactivation of downstream signaling cascades, resulting in widespread effects on cell proliferation, differentiation and tissue homeostasis (5). Clinically, NF1 is characterized by café-au-lait macules, cutaneous and plexiform neurofibromas (PNs), optic pathway gliomas and a broad spectrum of skeletal abnormalities, which substantially contribute to morbidity and reduced quality of life (6).

Skeletal manifestations are among the earliest and most debilitating complications of NF1 and are increasingly recognized as essential features of the disease (7). NF1-associated skeletal diseases comprise a heterogeneous group of abnormalities, including congenital pseudarthrosis of the tibia

Correspondence to: Professor Ge Yang, Department of Orthopedics, Key Laboratory of Pediatric Orthopedics of Hunan Province, Hunan Children's Hospital, Affiliated Children's Hospital of Xiangya School of Medicine, Central South University, 86 Ziyuan Road, Yuhua, Changsha, Hunan 410007, P.R. China
E-mail: yangge@zju.edu.cn

Abbreviations: NF1, neurofibromatosis type 1; CPT, congenital pseudarthrosis of the tibia; BMD, bone mineral density; MSCs, mesenchymal stem cells; GRD, GAP-related domain; cAMP, cyclic adenosine monophosphate; RANKL, receptor activator of nuclear factor-κB ligand; TGF-β1, transforming growth factor-β1; MEK, mitogen-activated protein kinase kinase; rhBMP-2, recombinant human bone morphogenetic protein-2; BMP, bone morphogenetic protein

Key words: neurofibromatosis type 1, bone homeostasis, pathological mechanism, treatment strategies

(CPT), scoliosis and low bone mineral density (BMD) (8-10). These conditions frequently present in early childhood, often progress despite intervention, and can result in fractures, deformities and long-term functional impairment (9). Notably, multiple lines of evidence have indicated that NF1-associated skeletal diseases reflect intrinsic defects in skeletal development and remodeling, rather than mechanical or secondary effects, emphasizing the central role of neurofibromin in skeletal biology (11,12).

Over the past few decades, substantial advances have been achieved in elucidating the molecular and cellular mechanisms underlying NF1-associated skeletal diseases. Neurofibromin is now recognized as a key regulator of osteoblast differentiation, osteoclast activity and the fate of mesenchymal stem cells (MSCs), thereby coordinating bone formation and resorption (11-13). Dysregulation of these processes results in abnormal bone remodeling and impaired skeletal integrity. Despite these mechanistic insights, the clinical management of NF1-associated skeletal diseases remains challenging. Current treatment strategies are largely surgical and supportive, particularly for severe manifestations. For example, surgical reconstruction of CPT is technically demanding, often requiring multiple procedures over a number of years with risks of nonunion and refracture (14). Pharmacological interventions have also been explored to address fracture risk and low BMD, but their efficacy in promoting bone healing and modifying disease progression has been inconsistent (15).

Collectively, NF1-related skeletal diseases represent a complex intersection of developmental biology, signal transduction dysregulation and clinical orthopedic pathology. An improved understanding of how neurofibromin regulates skeletal homeostasis is essential to bridge the gap between molecular mechanisms and effective therapies. The present review synthesizes the current knowledge on the function of neurofibromin in bone homeostasis, summarizes advances in mechanistic and translational research, discusses emerging assessment and therapeutic strategies, and proposes future directions aimed at improving skeletal outcomes in patients with NF1.

2. NF1 gene and neurofibromin protein

The human NF1 gene is located on chromosome 17q11.2, representing a large genomic locus spanning ~350 kb (16,17) (Fig. 1). The NF1 locus contains an upstream promoter/regulatory region, followed by the 5' untranslated region and a complex gene body composed of 60 exons separated by introns (18). The alternative splicing exons contribute to transcript diversity, including exon 9a, exon 10a-2, exon 23a and exon 48a. For example, alternative splicing of exon 23a results in two types of transcripts, with type I encoding neurofibromin, a tumor suppressor protein comprising 2,818 amino acids (19,20). Neurofibromin contains several functional domains, including a cysteine/serine-rich domain, a central GAP-related domain (GRD), a Sec14 domain, a pleckstrin homologous domain and a C-terminal domain (18,21). Among these domains, the GRD primarily accelerates the conversion of active RAS-guanosine triphosphate (GTP) to its inactive RAS-guanosine diphosphate (GDP) form, thereby negatively regulating RAS signaling and cell growth (22-24).

RAS acts as a central negative upstream regulator of the RAF/mitogen-activated protein kinase kinase (MEK)/ERK signaling cascade, which governs essential cellular processes including development, differentiation, proliferation and apoptosis (25,26). In addition, neurofibromin modulates other RAS-dependent pathways; loss of neurofibromin leads to hyperactivation of the PI3K/AKT/mTOR axis, thereby influencing cell survival, metabolism and lineage commitment (27). Beyond RAS-dependent mechanisms, accumulating evidence has indicated that neurofibromin exerts important RAS-independent functions (3). In particular, neurofibromin deficiency reduces cyclic adenosine monophosphate (cAMP) levels and alters protein kinase A (PKA) activity, thereby impairing osteogenic differentiation and extracellular matrix mineralization (28,29), revealing an additional layer of metabolic and transcriptional regulation relevant to skeletal homeostasis.

Neurofibromin is widely expressed across multiple tissues during development, providing a molecular basis for the multisystemic manifestations of NF1 (30). At the molecular level, pathogenic NF1 variants result not only in sustained MAPK activation but also in widespread disruption of interconnected intracellular signaling networks. These signaling abnormalities impair skeletal development, bone remodeling and tissue repair, highlighting neurofibromin as a central integrator of the signaling pathways essential for bone homeostasis (11). Accordingly, loss-of-function mutations in NF1 lead to neurofibromin deficiency and dysregulated downstream signaling, thereby contributing to the development of NF1-associated skeletal diseases (31).

3. Cellular impact of neurofibromin deficiency

The pathogenesis of skeletal diseases, including those associated with NF1, is fundamentally rooted in the disruption of bone homeostasis. Loss of neurofibromin disrupts this balance, thereby predisposing patients with NF1 to localized skeletal lesions (32-34). The present review examines the cellular effects of neurofibromin deficiency on bone homeostasis (Fig. 2).

Mineralization gap in osteoblasts. While complete loss of NF1 allows for the initial osteogenic commitment of stromal cells, it profoundly hinders their functional maturation (35). Even NF1 haploinsufficiency in MSCs is sufficient to impair osteoblast differentiation and subsequent mineralization (36). Mechanistically, this differentiation defect is largely RAS-dependent, as re-expression of the NF1 GRD can restore osteogenic differentiation (12). Consistent with this mechanism, complete loss of NF1 suppresses the expression of key mineralization-related genes (35); however, pyrophosphate accumulation and the resulting inhibition of hydroxyapatite formation likely represent downstream mineralization abnormalities rather than direct RAS-dependent events (37). This chemical imbalance directly impairs hydroxyapatite formation, creating a 'mineralization trap' that underlies the clinically observed low BMD.

Accelerated bone resorption by osteoclasts. In contrast to the braking effect on osteoblasts, both neurofibromin

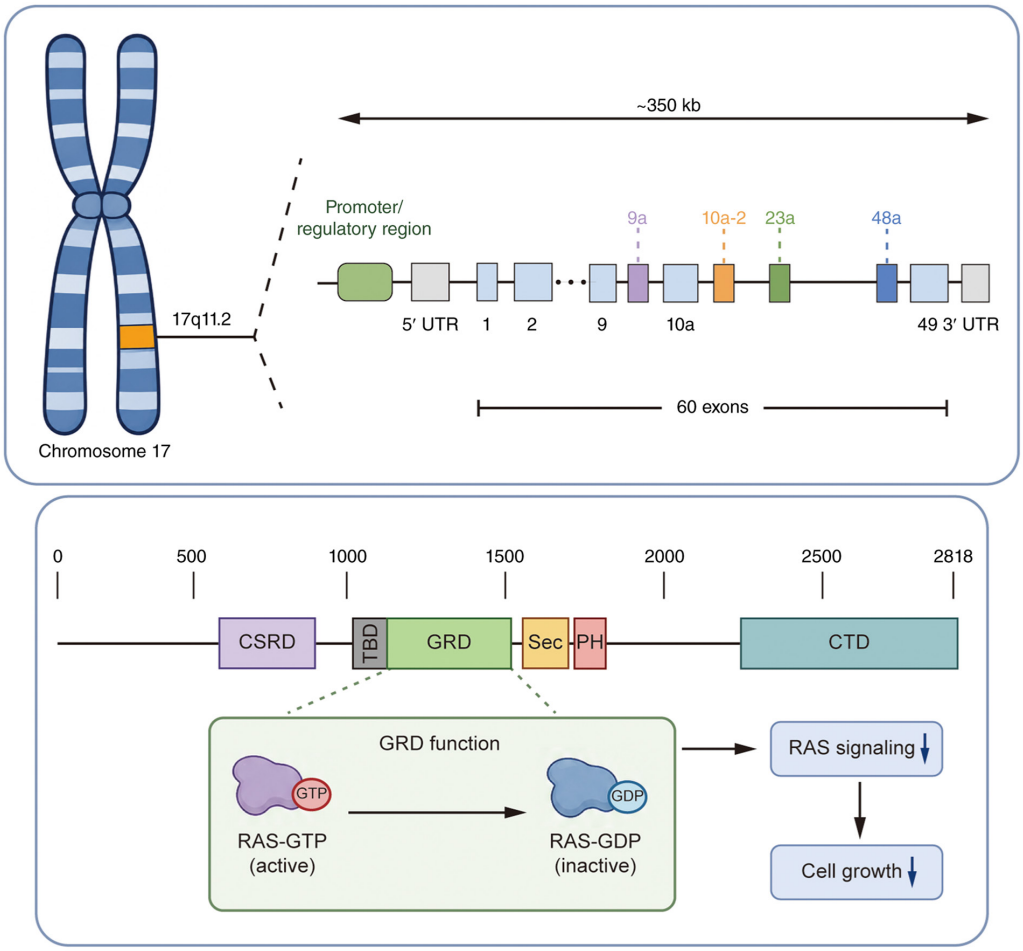

Figure 1. Schematic representation of the human NF1 gene and domains within the neurofibromin protein. The upper image shows the structure of the human NF1 gene, which is located at chromosome 17q11.2 and spans ~350 kb. The locus comprises an upstream promoter/regulatory region, followed by the 5' UTR and a complex gene body containing 60 exons separated by introns (not shown). Several alternatively spliced exons, including exon 9a (light purple), exon 10a-2 (orange), exon 23a (green) and exon 48a (blue), contribute to NF1 transcript diversity. Neurofibromin contains multiple functional regions, including a CSRD, a GRD, a Sec, a PH and a CTD. The GRD functions as a GTPase-activating domain that accelerates conversion of active RAS-GTP to inactive RAS-GDP, thereby negatively regulating RAS signaling and suppressing cell growth. NF1, neurofibromatosis type 1; UTR, untranslated region; CSRD, cysteine/serine-rich domain; GRD, GAP-related domain; Sec, Sec14 domain; PH, pleckstrin homologous domain; CTD, C-terminal domain; GTP, guanosine triphosphate; GDP, guanosine diphosphate; TBD, tubulin-binding domain.

deficiency and complete loss promote osteoclast formation and activity, thereby accelerating skeletal degradation (38,39). In NF1-haploinsufficient mice, osteoclasts were found to be more numerous, larger, and contained more nuclei (40). Moreover, NF1 haploinsufficiency enhances the responsiveness of osteoclasts to macrophage colony-stimulating factor and receptor activator of NF-κB ligand (RANKL) through hyperactivation of RAS-dependent signaling, particularly the RAS/PI3K pathway, thereby promoting osteoclastogenesis and bone-resorptive activity (41). This excessive osteoclastogenesis highlights a specific requirement for neurofibromin in restraining osteolytic activity within the myeloid lineage (13).

Disruption of growth framework in osteocytes and chondrocytes. Beyond the classic osteoblast-osteoclast axis, neurofibromin is essential for maintaining the cellular architecture and growth plate dynamics of the skeleton. A complete loss of neurofibromin disrupts the terminal differentiation of osteoblasts into osteocytes through RAS-dependent mechanisms. Osteocytes with a complete loss of neurofibromin exhibit cytoplasmic vacuolization and a failure to properly organize the perilacunar matrix, which disrupts calcium-phosphorus homeostasis and contributes to defective osteoid mineralization (42,43).

Neurofibromin deficiency also disrupts chondrocyte function and endochondral ossification through RAS-dependent mechanisms. A complete loss of neurofibromin impairs chondrocyte proliferation and maturation, thereby disrupting endochondral ossification (44). Moreover, neurofibromin restrains RAS-ERK1/2 signaling and inhibits RANKL expression, undermining the proper organization of proliferative chondrocyte columns (45,46). Without this regulation, the developmental program of endochondral ossification is fundamentally dismantled. Collectively, these findings establish neurofibromin as a critical regulator of skeletal homeostasis and provide a mechanistic foundation for the development of NF1-associated skeletal diseases.

Currently, research on RAS-independent mechanisms remains largely focused on the nervous system, such as neuronal excitability (47). Although the cAMP/PKA pathway has been reported to function in NF1-knockdown osteoblasts, it remains unclear whether this effect is RAS-independent (29).

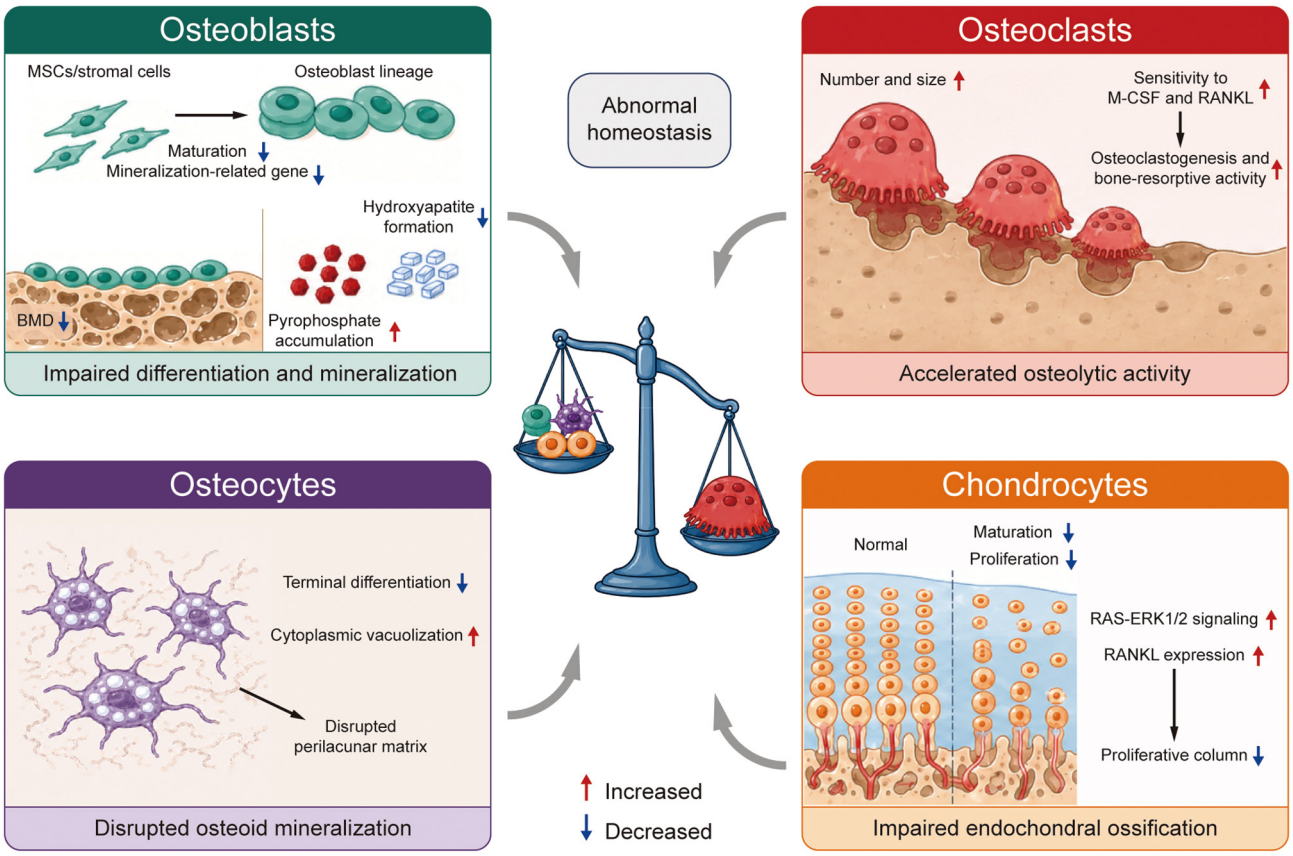

Figure 2. Cellular impacts of neurofibromin deficiency on bone homeostasis. Neurofibromin deficiency disrupts bone homeostasis through cell-type-specific effects on osteoblasts, osteoclasts, osteocytes and chondrocytes. Research using fracture-derived stromal cells from patients with NF1 and with somatic NF1 loss show that a complete loss of NF1 allows early osteogenic specification, but impairs later functional maturation, indicating a block in the transition from lineage commitment to mature bone-forming activity. NF1-haploinsufficient mesenchymal stromal cells derived from human-induced pluripotent stem cells display impaired osteoblast differentiation and reduced matrix mineralization, demonstrating that partial NF1 loss is sufficient to compromise osteogenic capacity. In mouse models with osteoblast-specific Nf1 ablation, neurofibromin deficiency causes pyrophosphate accumulation, which inhibits hydroxyapatite crystal formation and contributes to reduced bone mineral density. NF1 loss also affects bone-resorbing and matrix-embedded skeletal cells. In murine NF1-haploinsufficient osteoclasts, hyperactivation of RAS/PI3K signaling increases responsiveness to M-CSF and RANKL, resulting in enhanced osteoclast differentiation and accelerated osteolytic activity. Osteocytes with a complete loss of Nf1 in mice exhibit cytoplasmic vacuolization and disorganization of the perilacunar matrix, suggesting impaired osteoid mineralization. In cartilage, unrestrained RAS-ERK1/2 signaling inhibits chondrocyte maturation and endochondral ossification, thereby interfering with normal skeletal growth and repair. Together, these findings from patient-derived cells and genetically engineered mouse models indicate that neurofibromin deficiency impairs both bone formation and bone resorption control, providing a cellular basis for the diverse skeletal abnormalities observed in NF1. NF1, neurofibromatosis type 1; M-CSF, macrophage colony-stimulating factor; RANKL, receptor activator of NF-κB ligand; MSCs, mesenchymal stem cells.

Therefore, further studies are needed to elucidate the roles of RAS-independent mechanisms in bone homeostasis.

4. NF1-associated skeletal diseases

Osteopenia and osteoporosis. Notably, approximately half of individuals with NF1 develop osteopenia or osteoporosis, which substantially increases their risk of fractures and contributes to notable skeletal morbidity (48-50) (Fig. 3). Patients with NF1 typically exhibit lower BMD compared with the general population, particularly in the lumbar spine and femur (51,52). Additionally, vitamin D deficiency has been observed in these patients, and it is considered to contribute to the clinical severity of neurofibromas (53,54). Low vitamin D levels are associated with a more aggressive phenotype and larger neurofibromas, and likely underlie the impaired bone status in NF1 (15). This deficiency may also serve a role in the reduced BMD observed in NF1, further exacerbating skeletal fragility (55,56).

NF1-associated osteopenia often progresses to osteoporosis, as BMD continues to decline with age, even in young patients (57), and patients with NF1 have an increased age-dependent fracture risk (58). Histological analysis of bone samples from patients with NF1 has revealed marked disruption of bone microarchitecture, driven primarily by reduced trabecular bone (59). Furthermore, children with NF1 exhibit increased urinary excretion of pyridinium crosslinks, reflecting increased bone resorption and suggesting excessive osteoclast activity in NF1 progression (32). Moreover, increased osteoclast activity has been considered to partly account for osteopenia and osteoporosis (39). Hyperactive TGF-β1 signaling has a pivotal role in the pathogenesis of osteoporosis in NF1 (60). Additionally, the elevated osteoblast-secreted osteopontin in NF1 activates intrinsically hyperresponsive osteoclasts, promoting osteopenia and osteoporosis (61). ERK signaling downstream of the RAS/MAPK cascade in osteoprogenitors is required for normal skeletal development and bone maintenance, and loss of MEK in these cells induces severe osteopenia (62).

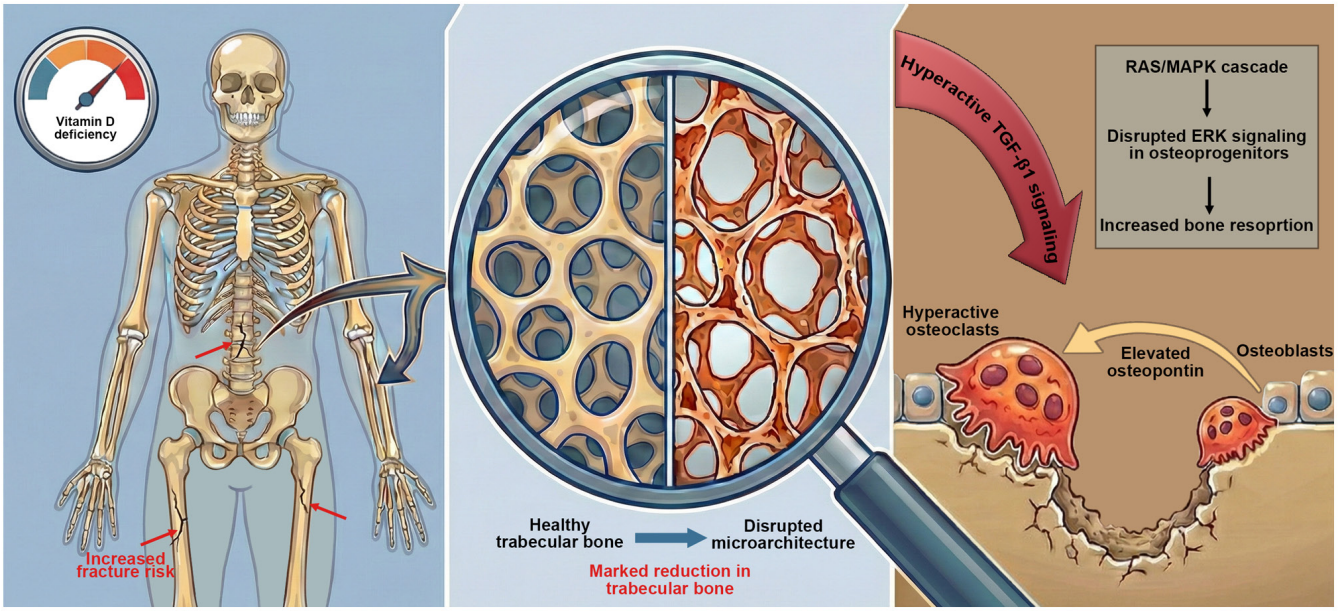

Figure 3. Pathogenesis of osteopenia and osteoporosis in patients with NF1. Individuals with NF1 frequently exhibit reduced BMD, particularly in the lumbar spine and femur, which contributes to increased fracture susceptibility and often co-occurs with vitamin D deficiency. Histological and microarchitectural analyses of NF1-associated osteopenia and osteoporosis have demonstrated impaired bone structure, including reduced trabecular bone. Mechanistic research using NF1-related mouse and cellular models has further indicated that bone loss is associated with increased bone turnover and enhanced osteoclast activity. In $Nf1^{flox/-}$; Col2.3Cre mice, hyperactivation of TGF-β1 signaling promotes osteoclast activation and pathological bone resorption. $Nf1^{+/-}$ osteoblasts secrete elevated levels of osteopontin, which further stimulates osteoclasts and contributes to excessive bone degradation. Additional evidence from adult osteoprogenitor-specific MAPK pathway models, including $Mek1^{Osx\text{-}ERT}Mek2^{-/-}$ mice, has shown that disruption of downstream ERK signaling within the RAS/MAPK cascade markedly reduces BMD, highlighting the importance of NF1-regulated signaling in maintaining skeletal homeostasis. Together, these findings support a pathogenic model in which NF1-associated dysregulation of osteoblast-osteoclast coupling drives high-turnover bone loss, reduced BMD and increased fracture risk. NF1, neurofibromatosis type 1; BMD, bone mineral density.

CPT. CPT, which is characterized by anterolateral bowing deformities and refracture, is a rare and challenging skeletal disease in children (63). Currently, the Crawford classification is the predominant system for CPT, dividing patients with CPT into four progressive types (64).

The hallmark of NF1-associated CPT is the presence of a markedly thickened, pathogenic periosteum surrounding the pseudarthrosis site (65) (Fig. 4). Exome sequencing has shown that somatic NF1 mutations are concentrated in soft tissue at the pseudarthrosis site but are absent from cortical bone (66). CPT appears to originate from fibrous hamartoma formed by aberrantly expanding NF1-haploinsufficient periosteal cells, which fail to complete terminal osteoblastic differentiation and exhibit an enhanced ability toward osteoclastogenesis (67,68). Critical histological analysis has revealed that these abnormal cells are misdirected toward alternative lineages, including myofibroblasts or chondrocytes (69). This cellular reprogramming results in a highly proliferative fibrous tissue that actively invades the fracture site (70). Consequently, NF1 deficiency drives a dual pathology: It promotes fibrotic invasion while simultaneously compromising the osteogenic homeostasis required for repair, creating a mechanical and biological barrier to union.

Although CPT shows a strong association with NF1 (71), mutations or complete loss of NF1 are insufficient to fully explain the pathogenesis of pseudarthrosis (69). While biallelic NF1 inactivation and subsequent clonal expansion may contribute to fibrous hamartoma formation in a subset of CPT cases, NF1 haploinsufficiency has also been identified in patients without clinical NF1, suggesting that even partial neurofibromin deficiency can trigger localized pathological bone and soft-tissue remodeling (72,73). Notably, proteomic profiling has revealed shared dysregulated proteins in NF1-CPT and non-NF1-CPT periosteum, highlighting core pathogenic mechanisms such as disorganized extracellular matrix architecture, aberrant PI3K/AKT signaling and vascular narrowing (74). Furthermore, previous research expanded both the genotypic spectrum of NF1 variants and the phenotypic spectrum of CPT, underscoring substantial heterogeneity within this disorder and the need for improved mechanistic characterization in future research (75). Collectively, these findings indicate that CPT arises from convergent biological pathways rather than a single genetic etiology, emphasizing the importance of integrated genetic, cellular and microenvironmental investigations in future studies.

Scoliosis. Spinal deformity is the most common orthopedic manifestation in NF1, and is broadly classified into dystrophic and non-dystrophic types (76,77) (Fig. 5). Dystrophic scoliosis represents a hallmark skeletal feature, characterized by early onset, rapid progression and difficult clinical management (78). The etiology of dystrophic scoliosis is multifactorial, with somatic NF1 mutations contributing to its development (79), and dystrophic curves predominantly involve the upper thoracic spine (80). By contrast, non-dystrophic scoliosis behaves similarly to adolescent idiopathic scoliosis, but tends to present earlier and exhibits a higher risk of pseudarthrosis (81).

Patients with NF1 exhibit substantially reduced BMD, with the lumbar spine being more severely affected than the whole skeleton (50); this reduction appears to be even

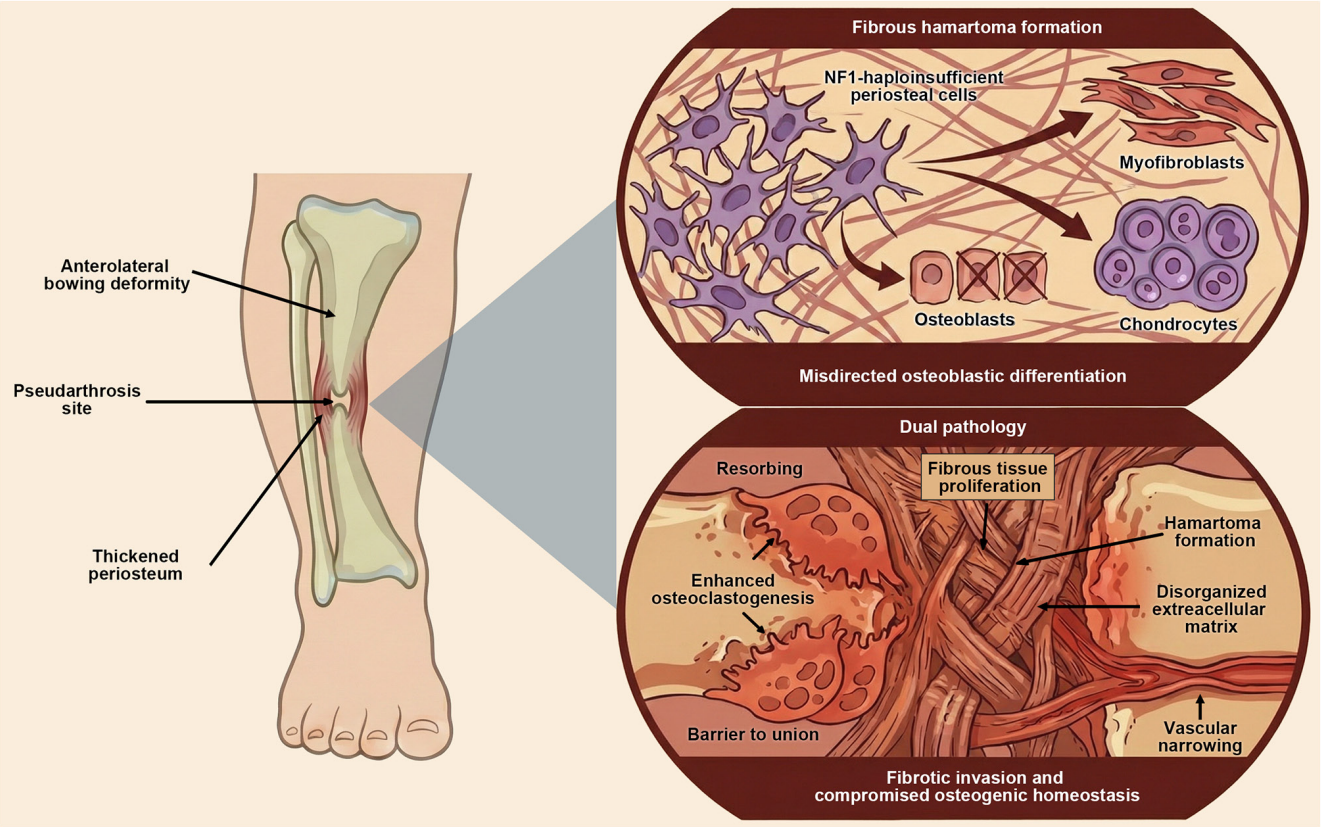

Figure 4. Pathology and molecular mechanisms driving NF1-associated CPT. CPT is characterized by anterolateral bowing deformity, pseudarthrosis and thickened periosteum, which gives rise to fibrous hamartoma tissue that mechanically and biologically interferes with fracture repair. Cellular and molecular research have indicated that this lesion originates from aberrant NF1-haploinsufficient periosteal cells, which exhibit impaired terminal osteoblastic differentiation, and a phenotypic shift toward myofibroblastic and chondrogenic lineages. These defects reduce the osteogenic capacity of the periosteum and promote fibrotic tissue accumulation at the nonunion site. Genetic and histological analyses have further suggested that somatic NF1 inactivation is enriched in the soft tissue component of CPT lesions. In addition to impaired bone formation, enhanced osteoclastogenesis and increased bone resorption contribute to cortical erosion and create a biological barrier to union. Proteomic and molecular profiling studies have identified dysregulated signaling pathways and tissue abnormalities, including aberrant PI3K/AKT signaling, vascular narrowing and disorganized extracellular matrix architecture. Together, these findings indicate that NF1-associated CPT results from the convergence of defective periosteal osteogenesis, fibrotic hamartoma invasion, excessive osteoclast-mediated bone resorption, abnormal vascular supply and disrupted matrix organization. NF1, neurofibromatosis type 1; CPT, congenital pseudarthrosis of the tibia.

more pronounced in patients with NF1 and with scoliosis requiring surgical intervention (51). At the molecular level, neurofibromin deficiency disrupts RAS and TGF-β1 signaling cascades, promoting abnormal osteoclast proliferation, impairing osteoblast differentiation and altering collagen biosynthesis, collectively contributing to structural abnormalities in the spine (8). Consistent with these clinical observations, mouse models with a complete deletion of periosteal or osteoblastic NF1 exhibit defective vertebral remodeling, frequent segmental fusion and obliteration of the intervertebral disc, which closely parallels human cases (82). Taken together, these findings demonstrate that NF1-associated scoliosis originates from intrinsic cellular dysfunction that disrupts vertebral homeostasis and induces a predisposition to progressive spinal deformity.

Other skeletal diseases. Hypophosphatemic osteomalacia has been reported in patients with NF1, even in the presence of additional congenital anomalies such as intracranial glioma and unilateral renal agenesis, highlighting the broad systemic involvement of NF1 (83). Among the craniofacial skeletal manifestations, sphenoid wing agenesis represents a distinctive and progressive NF1-associated skeletal defect. This defect is typically associated with intraorbital PNs or progressive temporal lobe herniation, often necessitating surgical intervention (84). More broadly, NF1-associated skull defects frequently coexist with adjacent PNs or dural ectasia, underscoring the close relationship between osseous abnormalities and soft-tissue pathologies in this condition (85). Additionally, epidemiological data have suggested that individuals with NF1 may have a markedly higher risk of developing bone sarcomas; however, further large-scale studies are required to more precisely characterize this association and its underlying mechanisms (86).

5. Assessment of bone disease in NF1

Follow-up and assessment during childhood are important for implementing preventive strategies to maximize peak bone mass for children with NF1 (10). The current review presents established and emerging assessment modalities.

Patients with NF1 frequently exhibit vitamin D insufficiency, emphasizing the need for routine evaluation of bone status and timely vitamin D replacement (53). Furthermore, low BMD is markedly more common in NF1 and occurs more frequently than in the general population, largely due to the

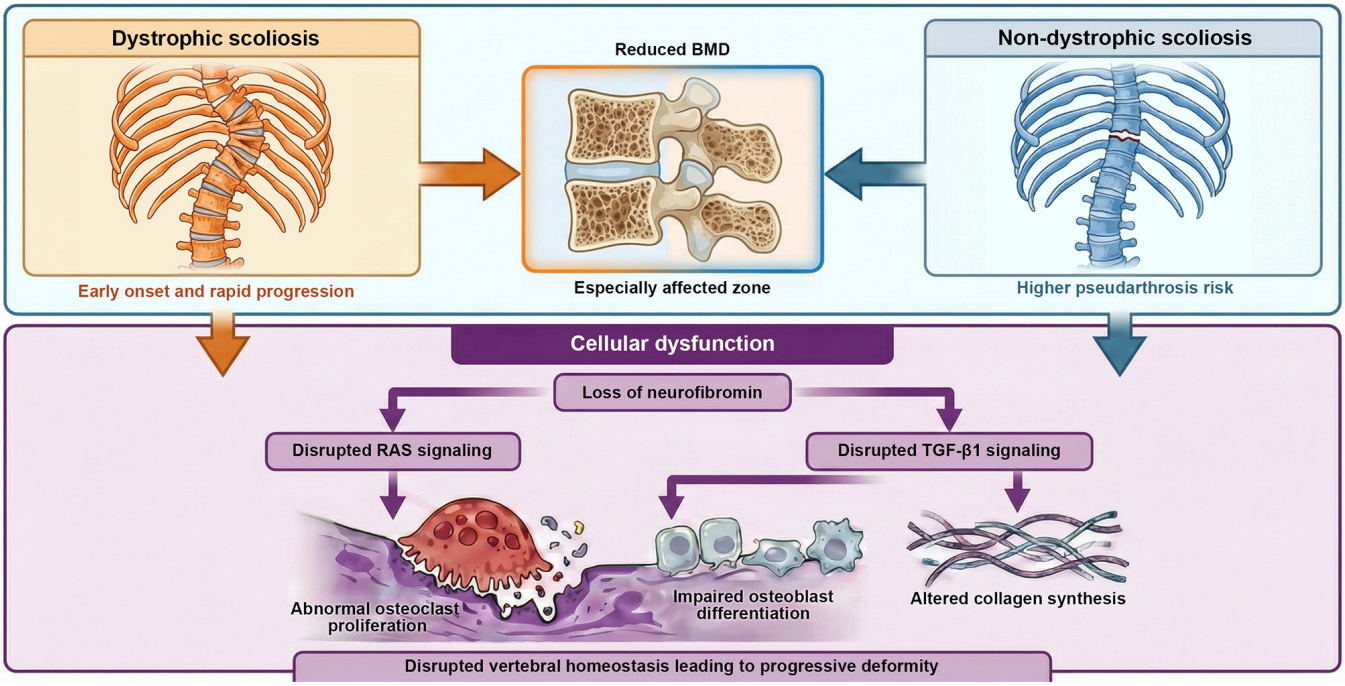

Figure 5. Clinical classification and cellular pathogenesis of NF1-associated scoliosis. NF1-associated scoliosis is generally classified into dystrophic and non-dystrophic forms, which differ in radiographic features, progression pattern and clinical risk. Dystrophic scoliosis represents the characteristic spinal deformity in NF1, and is typically marked by early onset, rapid progression and frequent involvement of the upper thoracic spine. By contrast, non-dystrophic scoliosis may initially resemble adolescent idiopathic scoliosis but can progress. Non-dystrophic scoliosis is associated with an increased risk of complications, including pseudarthrosis after spinal fusion. In addition to focal spinal deformity, patients with NF1 often exhibit systemic reduced BMD, with the lumbar spine disproportionately affected, suggesting that spinal instability occurs in the context of generalized skeletal fragility. At the cellular and molecular levels, neurofibromin deficiency disrupts key signaling pathways that regulate vertebral bone remodeling, including RAS/MAPK and TGF-β1 signaling cascades. These changes promote abnormal osteoclast proliferation, impair osteoblast differentiation and alter collagen biosynthesis. Together, these abnormalities disturb vertebral bone homeostasis, and provide a mechanistic basis for reduced BMD, progressive spinal deformity, impaired fusion biology and the clinical severity of NF1-associated scoliosis. NF1, neurofibromatosis type 1; BMD, bone mineral density.

secondary hyperparathyroidism associated with vitamin D deficiency (56). Notably, supplementation of vitamin D has been shown to markedly improve BMD, underscoring the clinical importance of monitoring and correcting vitamin D deficiency in NF1 (87).

The evaluation of bone pathophysiology is complemented by a range of instrumental modalities that offer more direct information than plasma assessments. Beyond conventional dual-energy X-ray absorptiometry, which aids in identifying patients with NF1 at risk of clinical bone complications and monitoring therapeutic responses, qualitative parameters such as trabecular bone scores further enable longitudinal monitoring and finer characterization of bone impairment (10,49). Quantitative computed tomography has a unique value in separately evaluating trabecular and cortical bone compartments (88). Furthermore, radiation-free ultrasound techniques, specifically bone waveform and average ultrasound modalities, have demonstrated high sensitivity in detecting adverse bone matrix alterations in preclinical models, indicating considerable promise as non-invasive biomarkers for the early detection of bone fragility in pediatric NF1 (89). At the molecular level, exome sequencing has emerged as an essential tool for delineating complex skeletal phenotypes resulting from dual molecular diagnoses, thereby revealing underlying genetic complexity (90). Together, these approaches are advancing the assessment of skeletal diseases into an integrated and multidimensional framework.

6. Treatment methods of NF1-associated skeletal diseases

The management of NF1-associated skeletal diseases remains challenging due to the complex interplay between intrinsic cellular defects, aberrant signaling pathways and mechanical instability. Current treatment strategies can be broadly divided into conservative approaches and surgical interventions. While conservative therapies aim to modulate the dysregulated bone microenvironment and enhance skeletal regeneration, surgical treatment remains indispensable for severe deformities and nonunion.

Conservative approaches

Targeting pharmacological therapies. Emerging evidence has indicated that NF1-associated skeletal abnormalities are driven by profound disturbances in the local bone microenvironment, including impaired osteoblast differentiation, dysregulated RAS/ERK and β-catenin signaling, excessive pyrophosphate accumulation and increased cortical porosity (82,91,92). These mechanistic insights have revealed multiple potential molecular targets for pharmacological intervention (Table I).

In preclinical models, MEK inhibition has been shown to attenuate fibrotic differentiation and enhance bone regeneration (93), particularly when combined with Src homology 2 domain-containing protein tyrosine phosphatase-2 inhibitors or recombinant human bone morphogenetic protein-2 (rhBMP-2) (94,95). Additional signaling pathways have also

Table I. Targeting pharmacological therapies for NF1-associated skeletal diseases.

Category	Representative medicine	Functions	Clinical status	(Refs.)
MEK inhibitor	Trametinib, selumetinib, binimetinib, and cobimetinib	Inhibiting fibroblast proliferation, and improving bone regeneration	Approved use for NF1 PN; investigational relevance to NF1-associated skeletal diseases	(93,95, 99,142)
JNK inhibitor	SP600125	Increasing osteogenesis	Preclinical	(96)
WNT promoter	β-catenin, and anti-DKK	Increasing osteoblastogenesis, and improving fracture healing	Preclinical	(97,98)
BMPs	BMP-2, rhBMP-2, and rhBMP-7	Accelerating osteogenesis and bone repair	Early clinical experience in CPT; limited efficacy when used alone	(94,100-102, 143)
cAMP activator	Icariin	Promoting osteogenic differentiation	Preclinical	(29)

NF1, neurofibromatosis type 1; MEK, mitogen-activated protein kinase kinase; DKK, Dickkopf; BMPs, bone morphogenetic proteins; rhBMP-2, recombinant human bone morphogenetic protein-2; cAMP, cyclic adenosine monophosphate; CPT, congenital pseudarthrosis of the tibia.

demonstrated therapeutic relevance. Modulation of β-catenin signaling was shown to restore osteogenic differentiation, while inhibition of c-Jun N-terminal kinase was demonstrated to enhance osteogenesis in NF1-deficient progenitor cells, particularly when combined with BMP-2 (96,97). In addition, inhibition of Dickkopf-related protein 1, an inhibitor of WNT signaling, was shown to promote endochondral ossification (98). Furthermore, icariin was found to activate the cAMP/PKA/CREB pathway, promoting osteoblast differentiation in NF1-deficient models and supporting its potential role as an anabolic adjunct targeting bone metabolism (29).

Although MEK inhibitors are currently being evaluated in clinical trials, their application has primarily focused on NF1-associated PNs (99). Their efficacy in NF1-associated skeletal disease remains to be further investigated through systematic clinical trials. BMPs have been explored in the treatment of CPT, with some early clinical evidence suggesting potential therapeutic value (100-102); however, their efficacy appears to be limited when used alone and their efficacy for other NF1-associated skeletal diseases remains unknown. By contrast, other candidate therapeutic agents remain largely at the preclinical stage and their clinical utility has yet to be established through systematic studies.

Cell-based and regenerative therapies. Cell-based and regenerative strategies represent a promising option for addressing the intrinsic osteogenic defects characteristic of NF1-associated skeletal diseases. Stem cell-based interventions have demonstrated potential in enhancing mineralization capacity in refractory CPT, and dental pulp stem cells derived from patients with NF1 retain regenerative capability, supporting their prospective utility in skeletal repair (103,104). Additional studies have further highlighted the potential of MSC-based therapy. Notably, MSCs in the iliac crest have been reported to exhibit stronger osteogenic capacity than those at the lesion site in patients with CPT (105). Moreover, MSC transplantation has been shown to normalize bone remodeling, suppress excessive bone resorption, and improve bone mineral content and structural integrity in experimental models (106).

Adjunctive biological strategies. Adjunctive biological strategies have shown strong promise. Combined anabolic and anti-resorptive therapy, specifically rhBMP-2 with zoledronic acid, has been shown to notably increase callus bone volume, reduce fibrous tissue infiltration and restore mechanical properties to near-normal levels in NF1-associated pseudarthrosis models (107-109). Clinical experience similarly suggests that integrating anti-resorptive agents with anabolic stimulation may improve bone healing and postoperative consolidation in pediatric patients with NF1 (110). Additional pharmacological adjuncts have also shown benefit. Local delivery of low-dose lovastatin was demonstrated to enhance callus maturation and mechanical strength during fracture repair in NF1-deficient models, highlighting its potential as an intraoperative adjunct (111). Enzyme replacement therapy with asfotase-α was also found to improve bone growth, mineralization and strength in NF1 mouse models, suggesting potential translational relevance for perioperative optimization (112).

Metabolic and physical interventions. Metabolic modulation represents an additional therapeutic aspect in NF1-associated skeletal diseases. Altered lipid metabolism contributes to skeletal fragility, and supplementation with L-carnitine and medium-chain fatty acids reduces cortical porosity, while protein restriction improves bone formation (113). Classical metabolic treatments have also exhibited therapeutic value. Vitamin D3 supplementation has been reported to improve BMD in adults with NF1 (114,115). Bisphosphonates were also shown to exert measurable anti-resorptive effects, although NF1-derived osteoclasts

demonstrated relative resistance *in vitro*, underscoring the need for combination strategies (116).

Non-pharmacological interventions may also contribute to skeletal health. Promotion of muscle development and physical activity has been associated with partial mitigation of progressive lower-limb bone mass deficits observed during childhood, emphasizing the functional interdependence of muscle and bone in NF1 pathophysiology (117).

Collectively, these findings support a promising and expanding therapeutic framework that includes targeting pharmacological therapies, cell-based and regenerative therapies, adjunctive strategies, and metabolic and physical interventions, offering multiple approaches for treating NF1-associated skeletal diseases.

Surgical techniques. Despite ongoing advances in conservative therapy, surgical intervention remains the cornerstone of treatment for severe NF1-associated skeletal diseases. Conservative approaches alone are often insufficient to achieve durable correction, particularly in cases involving nonunion, progressive deformity or mechanical instability.

Management of CPT. Surgical management of CPT aims to address both the biological and mechanical barriers to bone union. A large single-center database built at Hunan Children's Hospital (Changsha, China) has substantially improved the clinical understanding and management of CPT (118). Techniques such as the 'Four-in-One' or 'Three-in-One' integrate resection of the pathological periosteum, intramedullary fixation, autologous iliac crest bone grafting and Ilizarov external fixation to simultaneously enhance osteogenesis and provide mechanical stability (119-121). Vascularized fibular grafting is an effective option for managing severe bone defects and in cases with previous treatment failure (122,123); this option offers high union rates when combined with complete resection of the diseased bone and stable compression plating (124). Notably, intramedullary vascularized fibular grafting combined with Ilizarov distraction has achieved primary union in all reported cases within certain cohorts (125). Autologous bone grafting remains critical for large tibial defects, with iliac crest grafts widely used due to their robust osteogenic and cellular properties (126,127). Limb-lengthening procedures may also be chosen in select patients with complex growth disturbances, as reported in NF1 cases with concurrent hemihypertrophy and longitudinal growth retardation (128).

Management of scoliosis. Surgical correction is essential for severe NF1-associated spinal deformities, particularly dystrophic scoliosis, which is characterized by an early onset, rapid progression and technical complexity (129). Selection of the stable vertebra is critical in non-dystrophic scoliosis to reduce postoperative complications (130). Multiple corrective strategies have demonstrated efficacy across different clinical scenarios. Traditional growing rods represent a safe and effective option for early-onset dystrophic scoliosis with intraspinal rib head dislocation, allowing partial rib head reduction during distraction (131). Compared with posterior fusion, growing-rod constructs may better preserve trunk growth in early-onset cases (132). Other techniques, including halo-gravity traction combined with dual growing rods, have shown promising deformity correction, although long-term outcomes require further evaluation (133).

Advances in fixation techniques have improved outcomes in patients with pedicle dysplasia. Segmentation correction achieves superior deformity correction compared with traditional methods and may serve as an alternative in patients lacking apical pedicles (134). Sectional correction using a concave domino connector effectively restores coronal balance while reducing implant failure risk (135). For severe and rigid deformities, a one-stage posterior pedicle screw approach is both safe and effective, with posterior vertebral column resection recommended for curves demonstrating <35% flexibility, and fusion to stable vertebrae advised to ensure durable alignment (136). In addition, a recent comparative analysis demonstrated that both three-column osteotomy and halo-gravity traction combined with posterior column osteotomy provide notable postoperative improvement in coronal and sagittal parameters, supporting tailored selection of surgical pathways based on the severity of the deformity and patient characteristics (137).

Other NF1-associated orthopedic diseases. For other orthopedic manifestations, such as NF1-associated osteoarthritis, standardized surgical protocols are currently lacking. Management decisions should therefore be individualized based on preoperative functional status, disease severity and patient-specific considerations (138).

Collectively, the management of NF1-associated skeletal diseases requires comprehensive surgical approaches. Existing surgical options offer a wider range of therapeutic possibilities, ensuring improved outcomes and enhancing the quality of life for patients.

7. Future directions and perspectives

NF1-associated skeletal diseases represent one of the most complex manifestations of NF1, arising from the convergence of genetic alterations, dysregulated intracellular signaling, cellular dysfunction and biomechanical instability. Although notable progress has been made in elucidating the role of neurofibromin in skeletal biology, multiple knowledge gaps remain between mechanistic insights and durable clinical solutions. Addressing these gaps will require coordinated advances across genetics, molecular therapeutics, surgical innovation and longitudinal patient management.

Advances in genetic and molecular characterization. Recent advances in genetic research have expanded both the genotypic and phenotypic spectrum of NF1-associated skeletal diseases. Novel NF1 mutations and modifier genes have been implicated in CPT, providing new insights into disease heterogeneity and potential therapeutic targets (139). In addition, emerging evidence has suggested that non-coding regulatory elements, including long non-coding RNAs, participate in the pathogenesis of CPT by modulating osteogenic differentiation and extracellular matrix organization (140). In NF1-associated dystrophic scoliosis, transcriptomic and network-based analyses have identified dysregulated immune and osteoimmunological pathways, highlighting an underappreciated role of immune-bone interactions in disease progression (141). Taken together, these findings underscore the need for integrative genomic and multi-omics approaches to further define disease mechanisms, identify high-risk patients and uncover actionable molecular targets.

Translating mechanistic insights into therapeutic strategies. Targeting dysregulated signaling pathways remains a promising option for improving outcomes in NF1-associated skeletal diseases. While MEK inhibitors have demonstrated clinical efficacy in NF1-associated tumors, their effects on bone formation, remodeling and fracture healing require systematic investigation (93). Future studies should continually evaluate how targeting drugs influence osteoblast and osteoclast function, bone regeneration and the unique pathophysiology of NF1-associated skeletal lesions.

Surgical intervention will continue to serve a central role in the management of severe skeletal manifestations; however, current surgical strategies are associated with substantial complication rates and inconsistent long-term outcomes. For example, vascularized fibular grafting, despite high union rates, remains technically demanding and carries a marked risk of morbidity (124). Future directions should therefore prioritize the development and refinement of surgical strategies that can improve long-term outcomes and minimize morbidity.

Longitudinal surveillance and risk stratification. As an autosomal dominant disorder, NF1 typically manifests in early childhood, making timely surveillance critical for preventing progressive skeletal morbidity. Longitudinal follow-up beginning in early childhood is therefore essential to identify early reductions in BMD, vitamin D deficiency, progressive bowing deformities and evolving spinal pathology. However, an improved clinical understanding of the diseases requires multicenter research and collaboration. Future surveillance frameworks should move beyond phenotype-based assessment toward multidimensional risk stratification models, which integrate genetic data, molecular biomarkers, imaging parameters and validated clinical predictors.

8. Conclusion

NF1-associated skeletal diseases represent a multifaceted disorder arising from neurofibromin deficiency and the consequent dysregulation of key signaling pathways that govern skeletal development, remodeling and repair. Accumulating evidence has demonstrated that NF1 mutations disrupt the coordinated function of osteoblasts, osteoclasts, osteocytes and chondrocytes, resulting in uncoupled bone remodeling, defective mineralization, abnormal endochondral ossification and a permissive microenvironment for fibrotic tissue invasion. Together, these intrinsic and microenvironmental abnormalities underlie the diverse skeletal manifestations observed in NF1, including osteopenia and osteoporosis, CPT, scoliosis and other less common but clinically important bone defects.

Despite substantial progress being made in the mechanistic understanding of NF1, clinical management remains challenging. Current therapies rely heavily on complex surgical interventions and supportive metabolic strategies, which are often associated with high complication rates and incomplete efficacy. Emerging translational studies targeting dysregulated RAS/MAPK, PI3K/AKT and cAMP/PKA signaling pathways, together with regenerative and cell-based approaches, offer promising opportunities to develop mechanism-based and biologically informed treatments. However, robust clinical evidence supporting these strategies is still limited.

In the future, integrating mechanistic insights with advances in genetics, biomaterials, pharmacology and surgical innovation will be essential to improve outcomes for patients with NF1-associated skeletal diseases. Early risk stratification, longitudinal surveillance and personalized treatment strategies based on molecular and clinical features are likely to serve central roles in improving outcomes. Ultimately, coordinated multicenter efforts and standardized outcome frameworks will be essential to translate biological discoveries into effective and durable therapies that meaningfully improve skeletal health and quality of life in individuals with NF1.

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Authors' contributions

SZ and GY designed the scope and structure of the review, performed structured literature searches, as well as wrote and revised major sections of the manuscript. SZ critically synthesized and interpreted the findings. Both authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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