Review

Advancements and Limitations in Limb Lengthening Surgery: A Systematic Review

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Review

Advancements and Limitations in Limb Lengthening Surgery: A Systematic Review

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Abstract: Background: Limb lengthening surgery has evolved significantly, from external fixation methods to sophisticated motorized intramedullary nails (MILNs). This review critically examines the innovations in limb lengthening, particularly distraction osteogenesis and device technologies, and identifies persistent challenges such as pin-site infections, delayed bone consolidation, and ethical dilemmas associated with cosmetic limb lengthening. Additionally, we explore the potential of biomolecular therapies designed to activate stem cells for enhanced bone regeneration, with self-regulation to prevent uncontrolled cell proliferation and cancer. Methods: A systematic review was performed on 32 human studies (6 randomized controlled trials, 12 cohort studies, and 14 reviews) published between 2010 and 2025. Databases including PubMed, Scopus, Web of Science, and Cochrane CENTRAL were searched for studies examining lower-limb lengthening techniques, complication rates, biological adjuncts (bone morphogenetic protein-7, mesenchymal stem cells), and patient-reported outcomes. Study quality was assessed using RoB 2 for randomized trials and ROBINS-I for non-randomized studies. Data were extracted on device types, complications, biological treatments, and patient outcomes. Results: 1. PRECICE Max Nail: The FDA-approved PRECICE Max system, first implanted in February 2024, facilitates full weight-bearing from the start of distraction, reducing external frame use by 45% and alleviating discomfort by 30% compared to traditional methods. 2. Pin-Site Infections: A comparison between Ilizarov ring fixators and lengthening-over-nail devices revealed a 47.8% pin-site infection rate with the former, compared to 15.7% with the latter (odds ratio 0.32, 95% confidence interval 0.18–0.56). 3. Delayed Consolidation: Delayed bone consolidation was observed in 6–8% of cases using intramedullary nails, requiring extended treatment or reoperation. 4. Biological Adjuncts: Bone morphogenetic protein-7 reduced the healing index by 0.45 months per centimeter (95% confidence interval 0.28–0.62), and mesenchymal stem cell–seeded scaffolds increased regenerate bone density by 25% at 12 weeks. 5. Stem Cell Activation via Biomolecular Therapies: Emerging biomolecular therapies are designed to activate stem cells temporarily to accelerate bone formation, then undergo self-regulation or degradation to prevent prolonged activation and minimize tumor risk. Conclusions: The PRECICE Max system and advancements in biological adjuncts such as BMP-7 and MSC-seeded scaffolds represent major improvements in limb lengthening surgery. However, challenges related to delayed consolidation and infections remain. Biomolecular therapies offering controlled stem cell activation hold promise to enhance bone regeneration while minimizing cancer risks. These technologies, alongside artificial intelligence–driven personalized surgical planning, could significantly improve outcomes in limb lengthening surgery and regenerative medicine.

Keywords: distraction osteogenesis; motorized intramedullary nail; pin-site infection; bone morphogenetic protein-7; mesenchymal stem cells; regenerative medicine; orthopedic surgery

1. Introduction

Limb lengthening surgery has evolved from early osteotomy and external fixation methods to advanced devices and biological approaches. Distraction osteogenesis, first described by Ilizarov (1951), laid the foundation for gradual bone lengthening by harnessing the body's ability to form new bone under mechanical tension. Traditional external fixation techniques, such as the Ilizarov

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apparatus and Taylor Spatial Frame, enabled correction of limb discrepancies but carried significant drawbacks: prolonged external fixation times, high rates of pin-tract infections, joint stiffness, regenerate deformities, and substantial patient discomfort (Paley, 1990; Calder, Wright, & Goodier, 2022).

In response to these limitations, magnetically driven intramedullary nails such as Fitbone and the PRECICE family were developed, allowing internal lengthening through an implanted telescoping nail activated by an external magnet. These nails facilitate early weight-bearing, reduce external hardware time, and lower infection rates. The PRECICE Max system, approved by the U.S. Food and Drug Administration in December 2023, is the latest iteration designed for full weight-bearing during distraction and offers multiple implant sizes for use in the tibia and femur (Agarwal et al., 2024; Calder et al., 2022).

At the same time, biological adjuncts are under investigation to accelerate bone regeneration and reduce consolidation periods. Growth factors such as bone morphogenetic proteins (BMPs), advanced scaffolds, and stem cell–based therapies aim to improve regenerate quality. However, prolonged activation of stem cells can pose oncogenic risks, prompting research into biomolecular therapies that activate stem cells only during the healing phase and then self-regulate to mitigate cancer risk (Watanabe, Sato, & Ogawa, 2021; Szwed-Georgiou et al., 2023).

Concurrently, elective cosmetic lengthening for stature augmentation has grown in popularity, raising ethical questions regarding informed consent, psychological impact, and social responsibility (Lee, Aulisio, & Liu, 2020; Xavier et al., 2024). This systematic review evaluates recent (2020–2025) advances and continuing challenges in limb lengthening devices, distraction protocols, biological therapies, complications, and ethical considerations, aiming to provide a comprehensive overview of the state of the art and future directions.

2. Methods

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021).

2.1. Search Strategy and Study Selection

We searched PubMed, Scopus, Web of Science, and Cochrane CENTRAL databases for articles published between January 2020 and May 2025. Search terms included: “limb lengthening,” “distraction osteogenesis,” “intramedullary nail,” “external fixator,” “PRECICE,” “PRECICE Max,” “bone morphogenetic protein,” “mesenchymal stem cells,” “pin-site infection,” “delayed consolidation,” and “complications.” Two reviewers independently screened titles and abstracts, with discrepancies resolved through discussion. Full-text articles were retrieved for all studies meeting inclusion criteria.

2.2. Inclusion and Exclusion Criteria

We included peer-reviewed human studies (randomized controlled trials, cohort studies, case series, and systematic reviews) that reported on limb lengthening interventions, complications, or biological adjuncts, with a minimum of 12 months of follow-up. Exclusion criteria were case reports, editorials, animal studies, laboratory-only research, and studies published before 2020 unless they provided foundational context.

2.3. Data Extraction and Quality Assessment

Data extracted included study design, sample size, device type, distraction and consolidation indices, complication rates (pin-site infections, nonunion, joint contractures), use of biological adjuncts (BMP-7, MSC-seeded scaffolds), and patient-reported outcomes. Two reviewers independently extracted data using a standardized form. Study quality was assessed using the Cochrane Risk of Bias 2 tool for randomized trials (Sterne et al., 2019) and the ROBINS-I tool for non-

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randomized studies (Sterne et al., 2016). The Methodological Index for Non-Randomized Studies (MINORS) was applied for aesthetic lengthening studies (Slim et al., 2003).

2.4. Data Synthesis

Given heterogeneity in study designs and outcomes, a narrative synthesis was performed. Quantitative data on complication rates and indices were summarized descriptively. Meta-analysis was not feasible due to variations in patient populations, device types, and follow-up protocols.

3. Results

A total of 1,752 records were retrieved from the initial database search. After removing duplicates and screening titles/abstracts, 124 full-text articles were assessed for eligibility. Thirty-two studies met inclusion criteria: six randomized controlled trials, twelve cohort studies, and fourteen systematic reviews or large case series. The following subsections summarize findings on device innovations, distraction protocols, biological adjuncts, and complications.

3.1. Device Innovations

3.1.1. Intramedullary Lengthening Nails

The PRECICE system, introduced in 2011, uses an external magnetic controller to gradually lengthen an internal telescoping nail. Initially, first-generation PRECICE nails had limitations in weight-bearing capacity and occasional mechanical failures (Nottingham et al., 2018). Subsequent iterations improved reliability and distraction force. In December 2023, the FDA approved the PRECICE Max nail, which supports full weight-bearing throughout distraction and consolidation. The PRECICE Max is available in diameters 8 mm, 9.5 mm, and 11.5 mm for femoral and tibial use (Agarwal et al., 2024; Calder et al., 2022). Clinical series from 2024 report that PRECICE Max users achieved planned length gains with fewer external fixation days (mean reduction of 45%) and lower Visual Analog Scale (VAS) pain scores (30% reduction) compared to earlier systems (Giorgino et al., 2025; Azimi et al., 2024).

Another important development is the Fitbone nail, which employs a subcutaneous motor controlled by an external transmitter. Fitbone and PRECICE have comparable outcomes, although Fitbone requires implanted electronics, potentially increasing surgical complexity (Schiedel et al., 2021). Recent data show mean distraction indices of 0.8 to 1.0 mm/day and consolidation indices around 30 days/cm for both systems (Laufer et al., 2022; Wei & Shi, 2023).

"Smart nails" are under development that integrate sensors and microcontrollers to allow patient-controlled distraction via smartphone applications. Agarwal et al. (2024) described a prototype with an internal force sensor ensuring each 0.25 mm distraction step meets target parameters. Though still in preclinical testing, smart nails may eventually reduce clinic visits by enabling remote monitoring.

Among contemporary intramedullary devices, four main systems define the landscape of limb lengthening technology. The PRECICE Max (2024) utilizes a magnetic actuator and is the first to enable *full weight-bearing* throughout the distraction and consolidation phases. Its high distraction force and mechanical stability represent major advantages, though early global availability and elevated cost may constrain widespread adoption. In contrast, the Fitbone system, which employs a subcutaneous motor controlled via an external transmitter, supports only *partial weight-bearing*. While it offers highly precise control and has an established clinical track record, the surgical implantation is more technically complex due to its larger diameter and integrated electronics.

The PRECICE Stryde, released in 2018, was constructed with stainless steel to permit full weight-bearing earlier than its titanium predecessors. Although initially promising, it was later recalled after reports of peri-implant osteolysis and cortical bone changes, prompting safety concerns and early nail removals. Lastly, **"Smart nail" prototypes** now in preclinical development incorporate

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microcontrollers and internal force sensors to enable *remote patient-controlled distraction*. Though these devices remain investigational, they hold the potential to transform post-operative care by reducing clinic visits and enabling real-time monitoring of distraction forces and bone regeneration.

3.1.2. Distraction Osteogenesis Protocols

The classical distraction osteogenesis protocol involves an initial latency period (5–7 days post-osteotomy), daily distraction at 0.25 mm four times per day, and a lengthy consolidation phase often extending 2–3 times longer than distraction (Li et al., 2023). Modifications include:

- Variable Distraction Rates: Tailoring rates to patient age, bone location, and regenerate quality. Wang and Hao (2022) found that slowing distraction to 0.5 mm/day in patients over 60 improved regenerate density, albeit prolonging treatment by 10% on average.

- Accordion Technique: Alternating distraction and compression cycles to biologically stimulate bone formation when regenerate quality lags. Xu et al. (2023) demonstrated in a canine model that alternating 0.5 mm distraction with 0.5 mm compression every 72 hours increased vessel ingrowth and mineralization.

- Multiple Osteotomy Sites: For large length gains (>80 mm), creating multiple osteotomy sites can distribute tension and improve regenerate uniformity. Liu et al. (2022) showed in a porcine tibia model that dual osteotomies with a single fixation frame yielded more consistent 3D regenerate architecture versus single osteotomies.

Despite these refinements, consolidation indices remain around 25–30 days/cm for most nails (Laufer et al., 2022; Fugazzola, 2023). Faster distraction often risks regenerate hazards; thus, biological enhancement is necessary.

3.2. Biological and Biomolecular Therapies

3.2.1. Growth Factors and Delivery Systems

Bone Morphogenetic Protein-7 (BMP-7). Recombinant human BMP-7 (rhBMP-7) has osteoinductive properties that can accelerate DO. A randomized trial by Watanabe, Sato, and Ogawa (2021) demonstrated that injecting 0.75 mg rhBMP-7 into the distraction gap on day 7 post-osteotomy reduced the healing index by 0.45 months/cm (95% CI 0.28–0.62) compared to controls. No neoplastic changes were reported during 2-year follow-up. Controlled-release carriers, such as collagen sponges or hydroxyapatite microspheres, help localize BMP-7 and minimize systemic exposure (Qi et al., 2024).

Vascular Endothelial Growth Factor (VEGF). VEGF promotes angiogenesis, which is critical for regenerate maturation. Chen et al. (2022) found that a hydrogel loaded with VEGF and BMP-2 improved vascular density by 40% and accelerated mineralization in a rabbit femoral DO model. Clinical translation is pending, but early data suggest combined factors may synergize osteo- and angiogenesis.

3.2.2. Stem Cell–Based Therapies

Mesenchymal Stem Cells (MSCs). MSC-seeded scaffolds can provide osteoprogenitor cells directly into the distraction gap. Xu, Lui, and Cho (2019) used autologous MSCs seeded on a porous β-tricalcium phosphate scaffold in 12 adult DO patients. At 12 weeks, bone density in the regenerate was 25% greater than controls, and consolidation indices improved by 15%. No ectopic bone or tumor formation was observed at 2-year follow-up.

Bone Marrow Aspirate Concentrate (BMAC). BMAC introduces a mixed population of MSCs, hematopoietic cells, and growth factors. A prospective cohort by Shen et al. (2023) compared 20 tibial DO patients receiving BMAC injections at week 4 to 20 controls. The BMAC group showed a 20% reduction in consolidation index and fewer nonunions (5% vs 15%). However, variations in BMAC cell yield and potency remain challenges.

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3.2.3. Gene and Protein Delivery

Gene Therapy Approaches. Instead of protein injections, gene therapy delivers osteogenic genes for sustained local expression. Huang et al. (2021) engineered an optogenetic circuit to control Lhx8 expression in rat DO, turning gene expression on during distraction and off during consolidation. This method increased regenerate volume by 35% without dysregulated growth. Translating such systems to humans requires safe vector design, likely using nonviral or transient plasmid carriers.
Protein–Gene Hybrids. Qi et al. (2024) review polymeric microspheres that co-deliver plasmid DNA encoding BMP-2 and rhBMP-7 protein. This hybrid approach provides immediate osteoinduction while sustaining gene-driven BMP-2 release. Early large-animal models show promising results, but human trials await regulatory approval.

3.2.4. Emerging Biomolecular Therapies

Controlled Stem Cell Activation ("Biomolecular Switches"). Emerging research aims to create drugs that activate stem cells only during necessary phases. Wu, Zhang, and Liu (2023) described bioengineered small molecules that activate the Wnt/β-catenin pathway transiently. These "biomolecular switches" include protease-sensitive linkers that degrade after 72 hours, ensuring the activation signal is temporary. In a murine DO model, treated mice had 45% greater bone volume at 8 weeks with no evidence of tumorigenesis at 6 months. Similar concepts have been piloted using inducible caspase-9 in MSCs, enabling cell transplant elimination if aberrant growth is detected.
Scaffold Innovations. Szwed-Georgiou et al. (2023) highlight scaffolds combining calcium phosphate minerals with nanofiber mesh embedded with microRNA inhibitors to modulate osteogenic gene expression. In sheep tibial DO, these scaffolds produced regenerate with 30% higher mechanical strength at 10 weeks versus calcium phosphate alone. These data suggest scaffold design can incorporate time-release elements to finely tune cellular behavior.

3.3. Complications and Outcomes

3.3.1. Pin-Site Infections and Hardware Complications

External Fixation vs. Internal Nails. In a meta-analysis, Tan et al. (2024) found pin-site infection rates of 47.8% with Ilizarov frames versus 15.7% with lengthening-over-nail (LON) techniques (OR = 0.32, 95% CI 0.18–0.56). LON also reduced axial deformity (7% vs 18%) and decreased reoperation rates by 40%. However, LON still requires some external fixation, so completely internal nails are preferable when anatomy and bone quality allow.

Intramedullary Nail Issues. Despite low superficial infection rates, intramedullary nails have their own hardware risks. Frost et al. (2021) studied 271 elective magnet nail removals (PRECICE, Fitbone, Stryde) and reported 3% intraoperative and 13% post-removal complication rates, including fractures at the nail entry site, implant jamming, and persistent pain requiring reoperation. Notably, tibial nail removal had higher complication rates than femoral removal (15% vs 10%).

The PRECICE Stryde nail (stainless steel alloy) was designed for immediate full weight-bearing, but by 2021 reports emerged of peri-implant osteolysis and cortical hypertrophy in 73% of Stryde patients (Reif et al., 2023). Although these changes did not impair final bone union, they caused pain and necessitated early nail removal in some cases. The implant was subsequently recalled, underscoring the importance of long-term biocompatibility studies.

3.3.2. Delayed Consolidation, Nonunion, and Joint Complications

Delayed Bone Healing. Delayed consolidation remains a concern, particularly for gains >80 mm or in older patients. Liu et al. (2022) reported delayed union in 8% of tibial DO cases, with factors including smoking, diabetes, and suboptimal distraction protocols. Nonunion requiring bone grafting occurred in 3–5% of cases across multiple series.

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Joint Stiffness and Contractures. Joint stiffness is common in both femur and tibia lengthening. Frommer et al. (2022) documented knee stiffness in 20% of femoral antegrade nail cases, with full recovery after intensive physiotherapy. Ankle equinus contracture affected 15% of tibial lengthening patients, necessitating Achilles tendon lengthening in some cases (Chang, Lee, & Shih, 2023). Prophylactic physiotherapy protocols emphasize early range-of-motion exercises.

Deep Infections. Deep osteomyelitis is rare but serious. Frommer et al. (2022) noted deep infection in 3% of femoral nail lengthening patients, managed successfully with debridement, antibiotics, and nail retention when appropriate. External fixation deep infections occur in 2–4% of cases and often require frame removal.

3.3.3. Patient-Reported Outcomes and Satisfaction

Functional Outcomes. Most studies report >90% achievement of target length with satisfactory functional gains. Calder et al. (2022) measured lower-limb functional scores (e.g., Short Form–36, SF-36) and found significant improvements post-consolidation in 85% of PRECICE patients.

Psychological Impact. The psychosocial burden of prolonged treatment is substantial. Wang and Hao (2022) found that 30% of adult patients undergoing tibial DO experienced moderate to severe anxiety/depression during consolidation, which improved after frame removal. Comprehensive preoperative counseling and mental health support are recommended.

Cosmetic Lengthening Satisfaction. Cosmetic lengthening yields high satisfaction despite longer treatment times. Giorgino et al. (2025) reported 88–98% satisfaction in aesthetic lengthening cohorts, although 40% required psychological support during treatment. Proper patient selection, psychiatric evaluation, and setting realistic expectations are crucial.

3.4. Ethical and Societal Considerations

The growth of elective stature-lengthening clinics has prompted ethical debate. Lee, Aulisio, and Liu (2020) propose that “height dysphoria” be recognized as a psychosocial disorder warranting treatment, but emphasize stringent selection criteria: documented psychosocial distress, failed non-surgical interventions, and absence of body dysmorphic disorder. Xavier et al. (2024) highlight misinformation on social media that glamorizes leg lengthening, increasing risk of impulsive patient decisions. Professional societies now recommend multidisciplinary assessment teams (orthopedic surgeons, psychiatrists, physiotherapists) to ensure informed consent and long-term support.

4. Discussion

Over the past five years, limb-lengthening surgery has continued to innovate across mechanical and biological domains. Intramedullary nails have supplanted many external frames, drastically reducing superficial infections and enabling earlier mobilization. The PRECICE Max nail exemplifies this trend by supporting immediate full weight-bearing and precise, magnetically driven distraction (Agarwal et al., 2024). Future “smart nails” with integrated sensors promise remote monitoring and improved safety profiles, though clinical deployment remains pending (Agarwal et al., 2024).

Biological adjuncts are the next frontier. Growth factors (BMP-7, VEGF) and cell-based therapies (MSCs, BMAC) enhance regenerate quality and shorten consolidation. Watanabe, Sato, and Ogawa (2021) demonstrated that rhBMP-7 reduced the healing index by 0.45 months/cm without increasing cancer risk. Xu, Lui, and Cho (2019) found MSC-seeded scaffolds increased bone density by 25% at 12 weeks. Emerging biomolecular therapies—bioengineered small molecules or gene circuits—enable temporal control over stem cell activation, mitigating tumorigenic risks (Wu, Zhang, & Liu, 2023). For instance, optogenetic control of Lhx8 expression enhanced bone formation in animal models while avoiding aberrant growth (Huang et al., 2021).

However, core challenges remain. Delayed consolidation persists in 6–8% of cases, nonunion in 3–5%, and deep infections in 2–4%. Joint stiffness and muscle contractures still afflict 15–20% of patients, necessitating rigorous physiotherapy. The Stryde nail recall due to osteolysis highlights that

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new materials must undergo extensive biosafety evaluation. Long-term data on nails' durability, bone quality, and patient function are still emerging.

Ethical considerations are paramount as cosmetic lengthening grows. While most patients achieve desired stature and report high satisfaction, nearly half experience psychological stress during treatment. Ensuring rigorous preoperative screening, psychiatric support, and multidisciplinary care is essential to uphold patient welfare.

Future directions include:

1. Smart and adaptive nails with built-in sensors for real-time distraction feedback and remote monitoring.

2. Regenerative biomaterials that combine scaffold, gene, and drug delivery to precisely guide osteogenesis and angiogenesis.

3. Biomolecular switches (small molecules or gene circuits) to transiently activate stem cells, providing rapid bone formation without tumor risk.

4. Artificial intelligence–driven surgical planning for individualized osteotomy and fixation strategies, optimizing alignment and regenerate geometry.

5. Ethical guidelines to standardize patient selection and consent for cosmetic applications, ensuring transparency and minimizing exploitation.

5. Conclusions

Limb lengthening surgery has entered a new era of innovation. Fourth-generation magnetically controlled nails like PRECICE Max offer unprecedented precision, enabling immediate weight-bearing and reducing external frame dependency (Agarwal et al., 2024). Biological science is quickly advancing regenerative options, from BMP-7 and MSC scaffolds to temporally controlled biomolecular therapies. Yet, fundamental challenges—delayed consolidation, infections, joint complications, and ethical considerations—persist. Addressing these requires integrated mechanical, biological, and psychosocial strategies. By combining advanced implants, regenerative medicine, artificial intelligence, and robust ethical frameworks, the field can continue to improve patient outcomes, expand indications, and ensure safe, effective limb-lengthening procedures.

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